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Long COVID: Exploring Advancements & Management

Avindra Nath, M.D.

Senior Investigator and Clinical Director – National Institute of Neurological Disorders and Stroke at the National Institute of Health

Collaborators

More resources available at:
https://dchealth.dc.gov/dcrx

Course Overview

- This educational module is tailored for healthcare professionals seeking to deepen their understanding the emerging challenge of Long COVID.
- In order to receive completion credit, you must receive a passing score on the knowledge checks and complete the evaluation.
- This module will be approximately 60 minutes in length for viewing and completion of the evaluation.
- This module is approved for CME.

Instructors

Leonard H. Calabrese, DO

Professor of Medicine at the Cleveland Clinic Lerner College of Medicine

RJ Fasenmyer Chair of Clinical Immunology

Department of Rheumatic and Immunologic Disease Cleveland Clinic

Eric Wisotzky, MD

Medical Director, COVID Recovery Program

MedStar Health

Moderator/Advisor

Avindra Nath, M.D.

Senior Investigator and Clinical Director at National Institute of Neurological Disorders and Stroke at the National Institute of Health

Conflict of Interest

Dr. Calabrese is a speaker for, Amgen, UCB, GSK, Janssen, Sanofi, and AstraZeneca.

Dr. Wisotzky is a medical advisory board member for ImpediMed.

Dr. Nath has no financial disclosures or conflicts.

The course planners have no financial disclosures or conflicts.

All relevant financial relationships have been mitigated.

Anti-discrimination Policy

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Long COVID: Advances in Case Definition, Diagnosis, and Pathogenesis

Leonard H. Calabrese

Professor of Medicine at the Cleveland Clinic Lerner College of Medicine

RJ Fasenmyer Chair of Clinical Immunology

Department of Rheumatic and Immunologic Disease Cleveland Clinic

Learning Objectives

- To describe the current case definitions used for Long COVID and their limitations in care and research
- To describe the pathophysiology, risks and protective factors for developing Long COVID
- To recognize common clinical manifestations of Long COVID
- To critically appraise the major therapies and evidence for Long COVID

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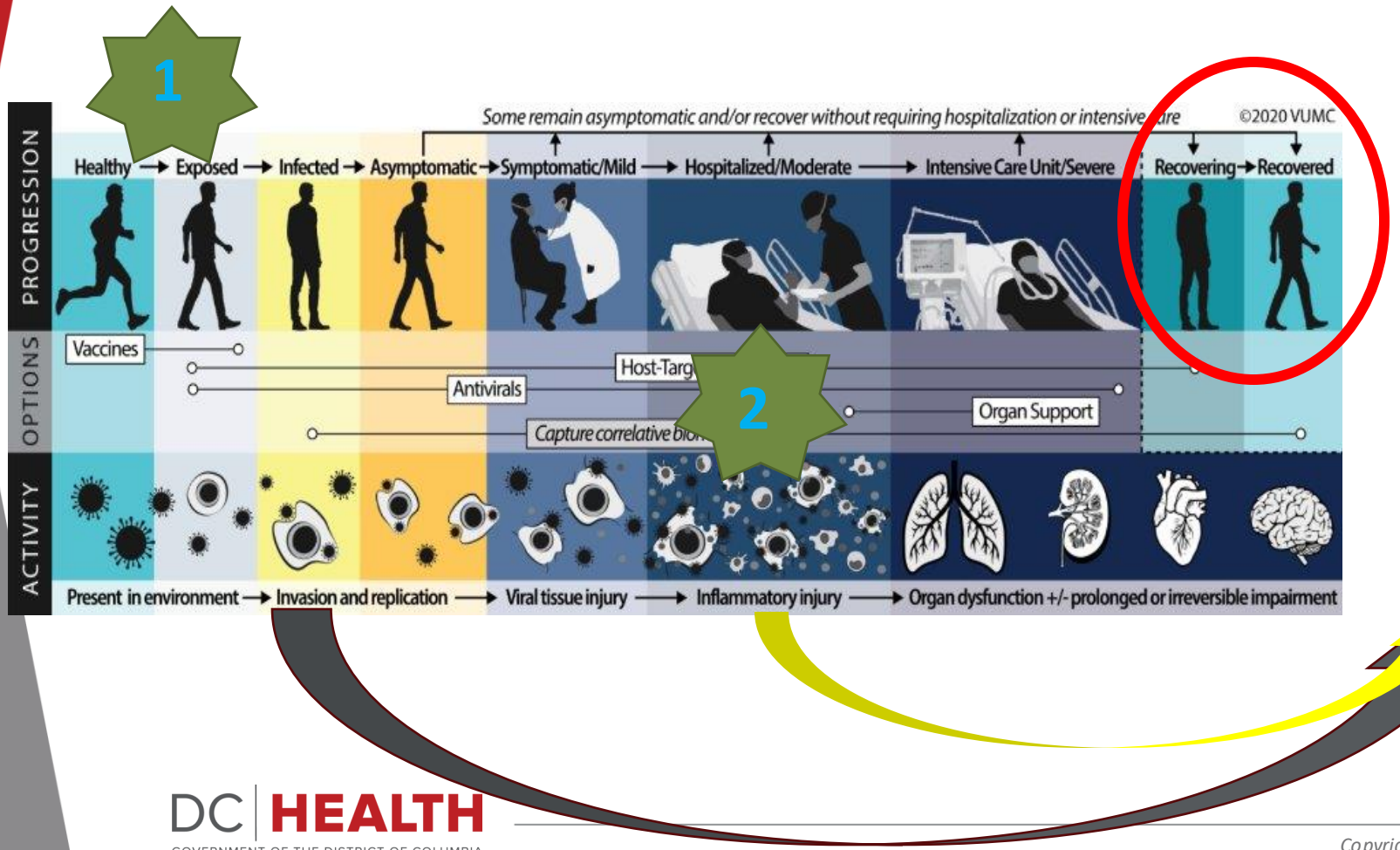
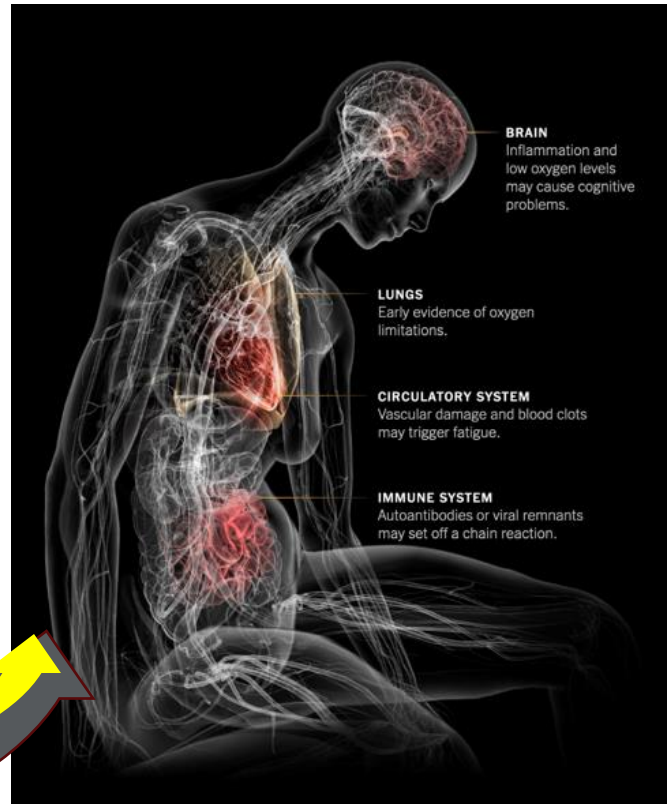
Learning Objective #1

To describe the current case definitions used for Long COVID and their limitations in care and research

COVID-19 Clinical Continuum

- Sequela: A condition which is the consequence of a previous disease or injury
- Disease Course: Self limiting in 80%, Severe in 15-20%, Fatal in 1-2%





Keller, NYT, 2022

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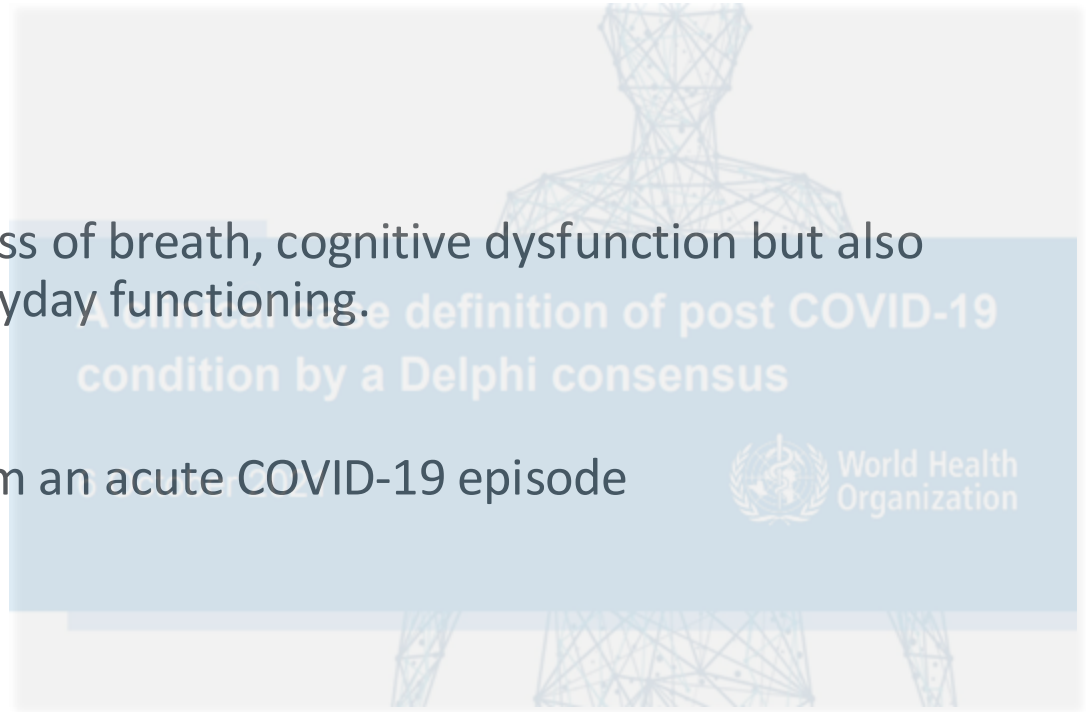
Post Acute Sequelae of COVID-19 (PASC)

- Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, **usually 3 months** from the onset of COVID-19 with symptoms that last for at least **2 months** and cannot be explained by an alternative diagnosis:
  - CDC definition: 1 month
  - WHO definition: 3 months
- Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning.
- Symptoms may be:
  - New onset following initial recovery from an acute COVID-19 episode
  - Persisting from the initial illness
  - Fluctuating or relapsing over time



CDC, 2023. WHO, 2023.

2024 NASEM Long COVID Definition

- **Long Covid (LC) manifests in multiple ways.**
  - A complete enumeration of possible signs, symptoms, and diagnosable conditions of LC would have hundreds of entries. Any organ system can be involved, and LC patients can present with:
    - **Single or multiple symptoms, such as:** shortness of breath, cough, persistent fatigue, post exertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea
    - **Single or multiple diagnosable conditions such as:** interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), fibromyalgia, connective tissue diseases, hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjogren's syndrome

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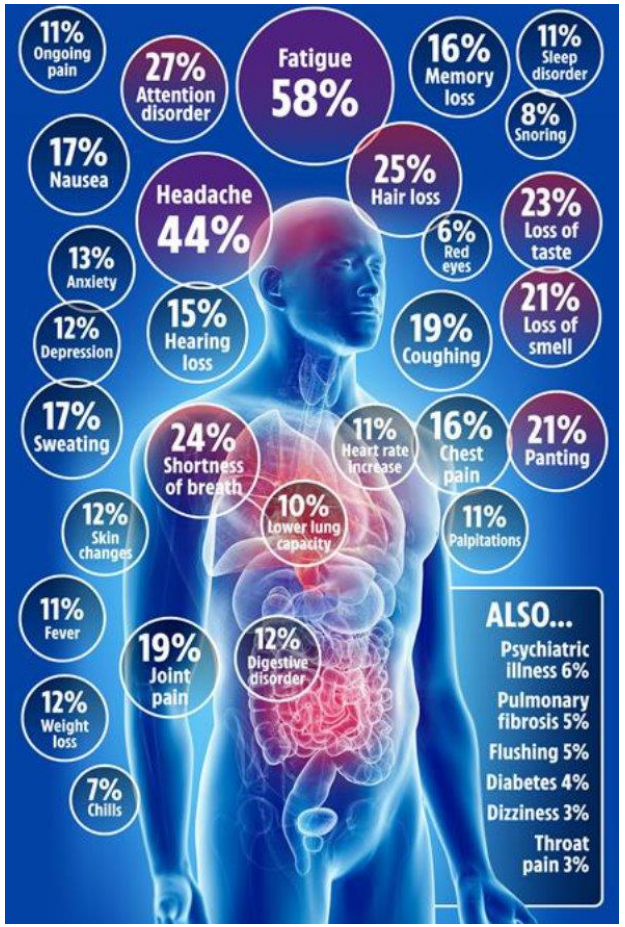
Learning Objective #2

To describe the pathophysiology, risks and protective factors for developing Long COVID

Long COVID at a Glance

- **Symptoms:**
  - Diversly affects multiple systems:
    - Respiratory
    - Nervous
    - Cardiovascular
    - Musculoskeletal



- **Most common symptoms:**
  - Fatigue
  - Shortness of breath
  - Muscle pains
  - Chest pain
  - Brain fog
  - Headache
  - Depression

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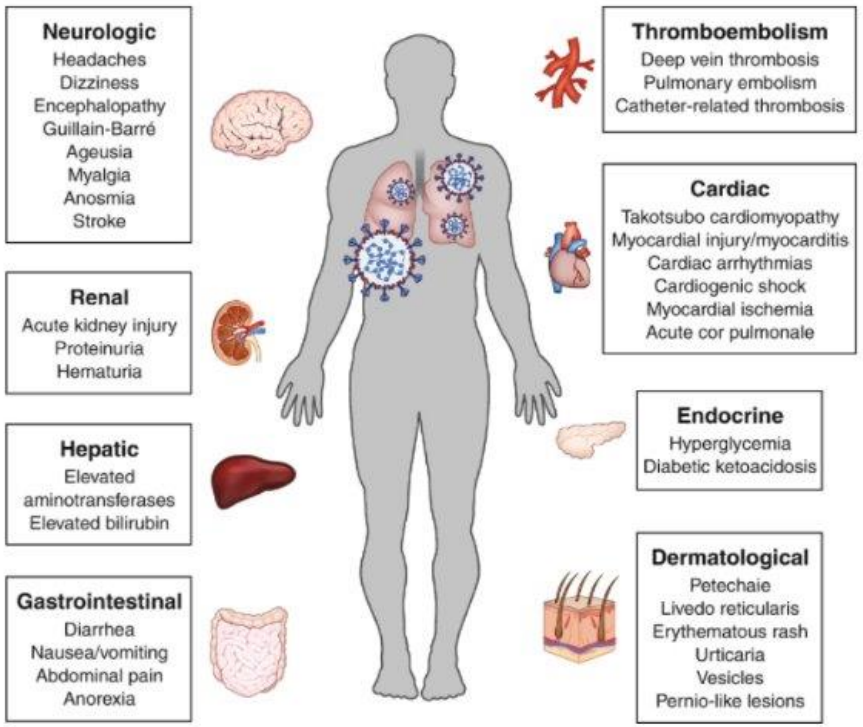
Sudre, 2024

Documented Post COVID Pathologic Entities

- Syndromic
  - Persistent symptoms without defined pathology
  - Long COVID "Long Haulers"
- Non-syndromic
  - Persistent symptoms secondary to defined pathology
  - Defined pathology without associated symptoms

Fig. 2: Extrapulmonary manifestations of COVID-19.

From: Extrapulmonary manifestations of COVID-19



Gupta, 2020

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Household Pulse Survey

Measuring Social and Economic Impacts During the Coronavirus Pandemic

125 million infected
53 % of USA >18yo have had COVID by positive test

35 million
28%
ever experienced Long COVID (>3months)
35 million

7.3 million
5.9% currently experiencing Long COVID

1.9 million
25% of LC significant limitations of activity

Among TEST+ adults 30%

"Do you have symptoms for 3 months after COVID that you have never had before?"

United States® Census Bureau

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US Census Bureau, 2023

Learning Objective #3

To recognize common clinical manifestations of Long COVID

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Are There Risk Factors or Endotypes?

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Risk Factors for Long COVID

Observational study in a primary care population using data from Platform C19

Risk Predictors of Long COVID +

- Age ≥40 years
- Female sex
- Severity of acute COVID (symptom number burden), hospitalization
- Minority race, social determinants of health
- Frailty / Premorbid state of health

Protective Mitigating Factors

- Younger age*
- Milder acute COVID-19 illness*
- Vaccination decreases, but variable effect 15-50%) depending on study*
- Previous infection (limited data)
- Omicron
- Use of antiviral therapy/metformin*

***Aggregate Summary of extant literature of which there are general agreement**

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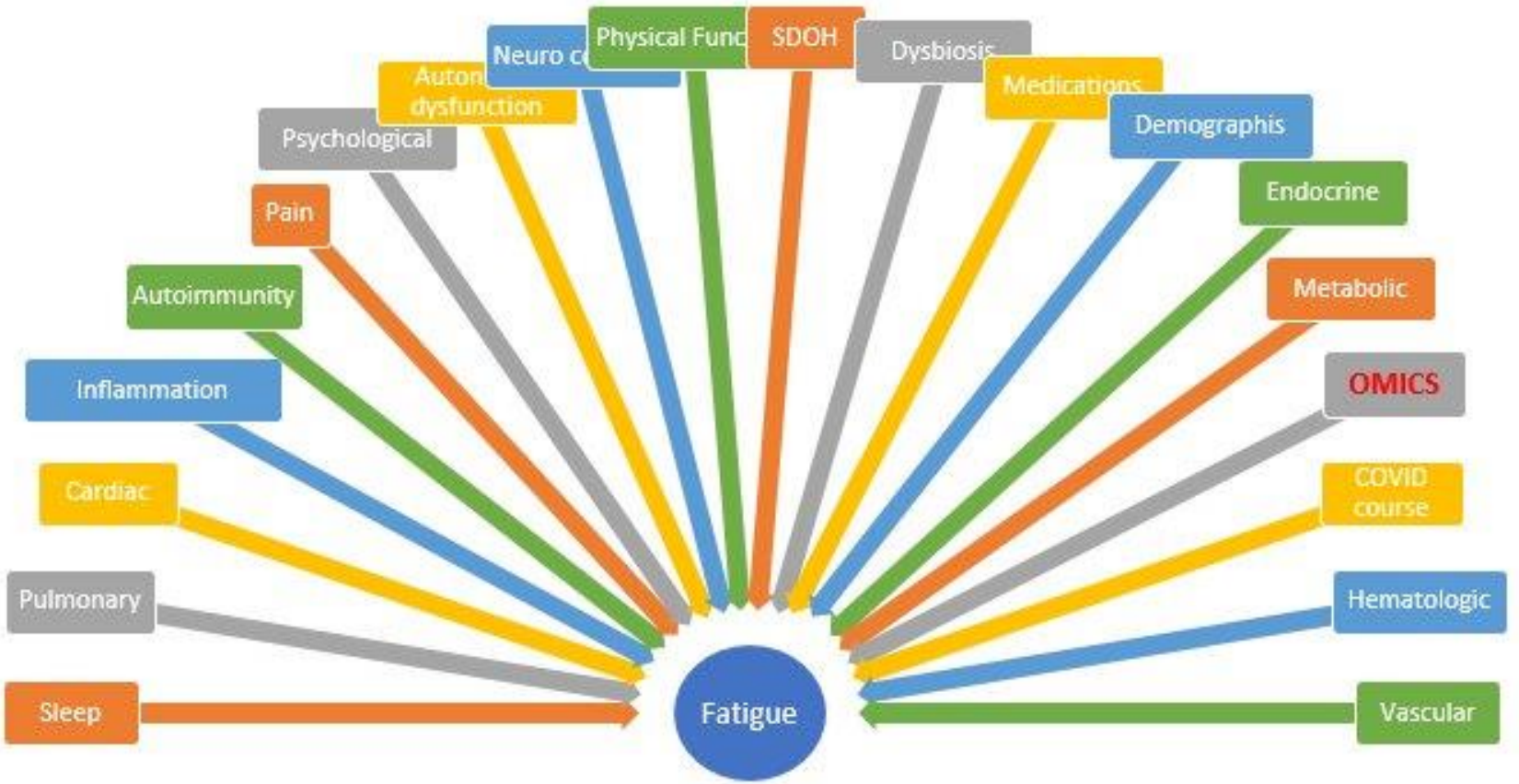
Calabrese, 2023

Clinical Endotypes

- Chronic fatigue
- Brain Fog
- Autonomic dysfunction
  - POTS
  - Dysrhythmias
- Pain Fibromyalgia
- Pulmonary pattern

All evaluations for possible Long COVID must begin with a rigorous assessment of defined underlying disorders, whether related or unrelated, that explain the patient's signs, symptoms, complaints, and concerns, and for which established therapies may exist.

Fatigue Post COVID-19 Matrix



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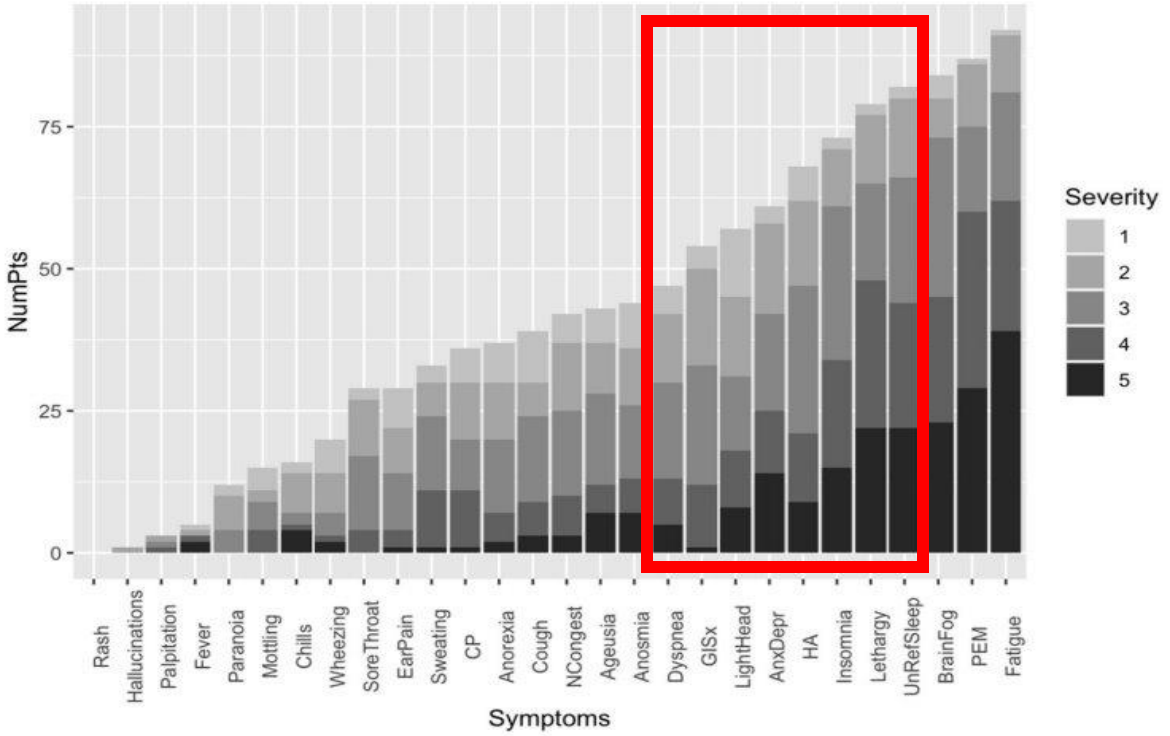
Study 1

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome is Common in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): Results from a Post-COVID-19 Multidisciplinary Clinic



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Bonilla, 2023

Post-Exertional Malaise (PEM)

Define: A worsening of ME/CFS symptoms and/or the appearance of new symptoms after physical or cognitive exertion which was **previously tolerated**, and is often delayed 24-72 hours or more

Symptoms

- Fatigue/exhaustion, cognitive function, pain, flu like feeling, further exercise intolerance

Triggers

- Physical activity, Mental activity, psychologic stressors, orthostatic

Infections as Triggers for Chronic Pain

- Chronic pain as a result of COVID-19
- Well documented in epidemiologic studies, confounded by:
  - Psychological factors
  - Critical illness (ICU-related events)
- Exacerbation of chronic pain in the absence of actual infection
- New onset pain related to psychological stressors
- Epidemiologic studies reveal in Long COVID:
  - Pain in 11-90% of cases
  - Myalgia in 13-70% of cases
  - 'Joint pain' in 5-55% of cases

J Pain D.J. Clauw et al.·161 (2020) 1694–1697

{Davis, 2021 } {Michelen, 2021 }{O'Mahoney, 2023 }{Lopez-Leon, 2021 }{Natarajan, 2023

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Long COVID and Impaired Cognition

GROUNDTRUTHS
A SUBSTACK FROM ERIC TOPOL

Facts, data, and analytics about Covid and other biomedical matters.

Long Covid and Cognitive Deficits

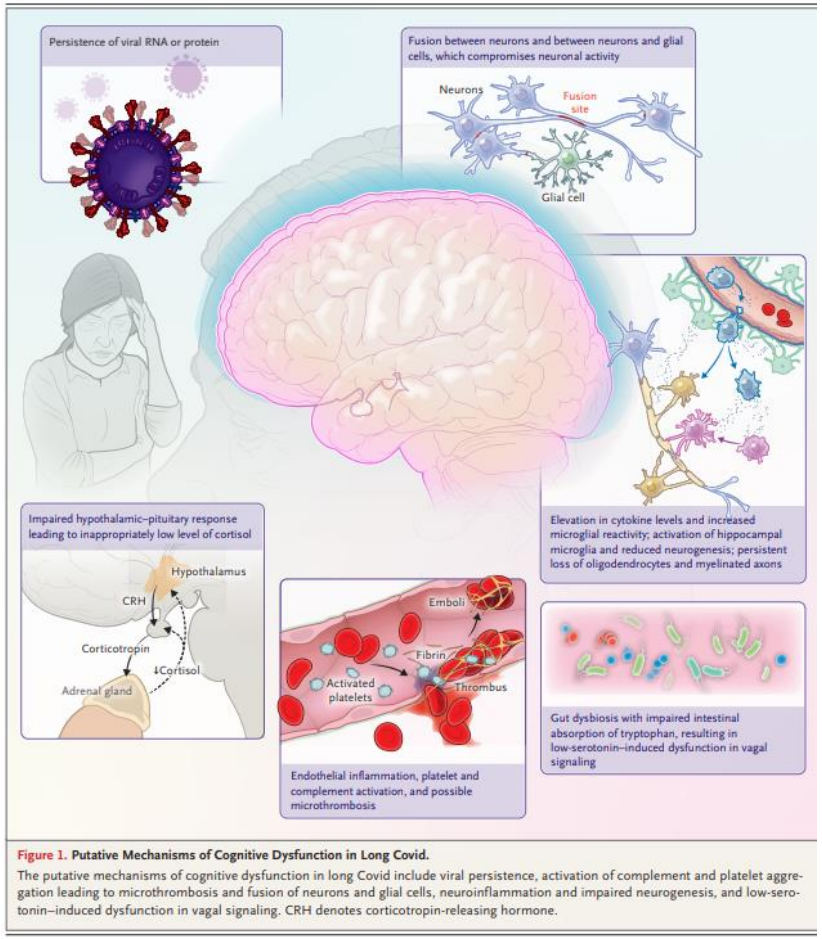

Figure 1. Putative Mechanisms of Cognitive Dysfunction in Long Covid.
The putative mechanisms of cognitive dysfunction in long Covid include viral persistence, activation of complement and platelet aggregation leading to microthrombosis and fusion of neurons and glial cells, neuroinflammation and impaired neurogenesis, and low-serotonin–induced dysfunction in vagal signaling. CRH denotes corticotropin-releasing hormone.

Study 3

Sleep Disturbances are Highly Prevalent Among People with Long COVID

- 962 patients referred from ReCOver Clinic
- Assessed using PROMIS Sleep & select studies instruments
  - Scores standardized on T-scale (mean = 50, SD = 10)
  - Scores ≥ 60 indicate moderate disturbance
  - Scores ≥ 70 indicate severe disturbance

Patient Characteristics

- Predominantly female (74.9%)
- Mean age: 49.6 years

Sleep Disturbance

- Mean T-score: 57.8 +/- 8.4
- **41% with moderate disturbances**
- **8% reporting severe sleep disturbances**
- Black race and hospitalization associated with greater sleep disturbances

Fatigue

- Mean T-score: 62.7 +/- (.1
- 67% with at least moderate fatigue
- 22% with severe fatigue

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J Gen Intern Med . 2023 Jun;38(8):2015-2017. doi: 10.1007/s11606-023-08187-3. Epub 2023 Apr 4.

Learning Objective #4

To critically appraise the major therapies and evidence for Long COVID

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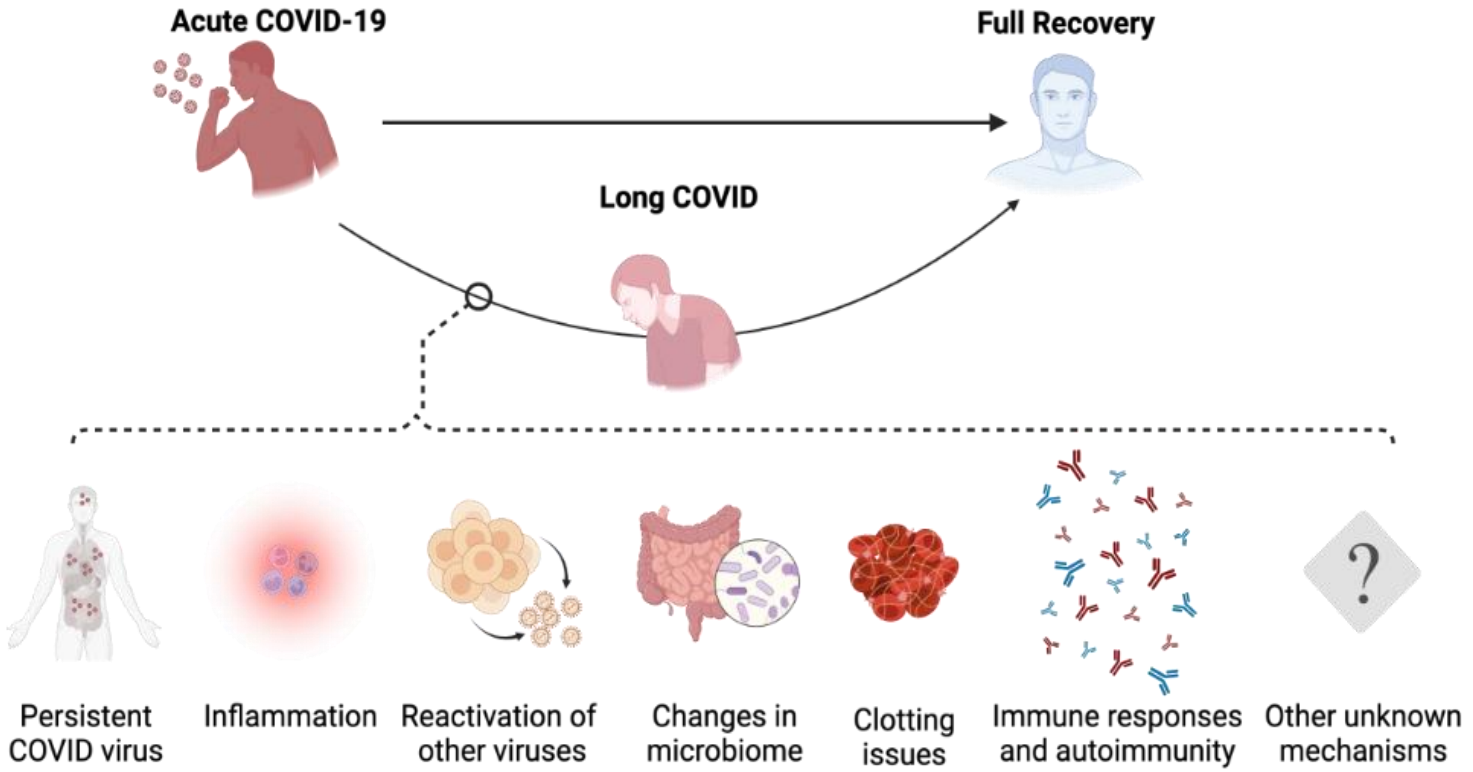
Mechanisms That Could Underly Long COVID

- **Predictors:**
  - Female sex
  - Middle age
  - Diabetes
  - Obesity
  - Lower Sick Euthyroid Syndrome
  - HIV?



Peluso & Deeks Trends in Immunology 2022

Conclusion

- Long COVID is a Post Acute Infectious Sequelae (PAIS) that affects a significant portion of SARS CoV-2 infected patients.
- These sequelae can include both tissue based (pathologic) disorders (non-syndromic), but is more frequently present with an array of symptoms not readily explained based on classic tissue pathology dominated by fatigue, pain, neurocognitive dysfunction, breathlessness sleep disturbances as well as possibly numerous other complaints.
- Numerous pathogenic mechanisms have been proposed as contributing to both syndromic and non-syndromic Long COVID, though our current understanding remains incomplete.

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Post Acute Sequelae of COVID-19 (Long COVID)

Diagnostic Workup and Treatment

Eric Wisotzky, MD, FAAPMR

Medical Director, COVID Recovery Program

MedStar Health

Learning Objective

- Review **diagnostic workup** and **treatment options** for various long COVID related symptoms including diagnostic workup of:
  - Neurologic/autonomic symptoms
  - Cardiovascular/pulmonary symptoms
  - Cognitive/mental health symptoms
  - ENT symptoms
  - Fatigue

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American Academy of PM&R: National Call to Action

- Mental Health Guidance Statement
- Neurological Symptoms Guidance Statement
- Autonomic Dysfunction Guidance Statement
- Pediatrics Guidance Statement
- Cardiovascular Complications Guidance Statement
- Cognitive Symptoms Guidance Statement
- Breathing Discomfort Guidance Statement
- Fatigue Guidance Statement

Stand with AAPM&R in Our Long COVID National Call to Action

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Neurologic/Autonomic Symptoms

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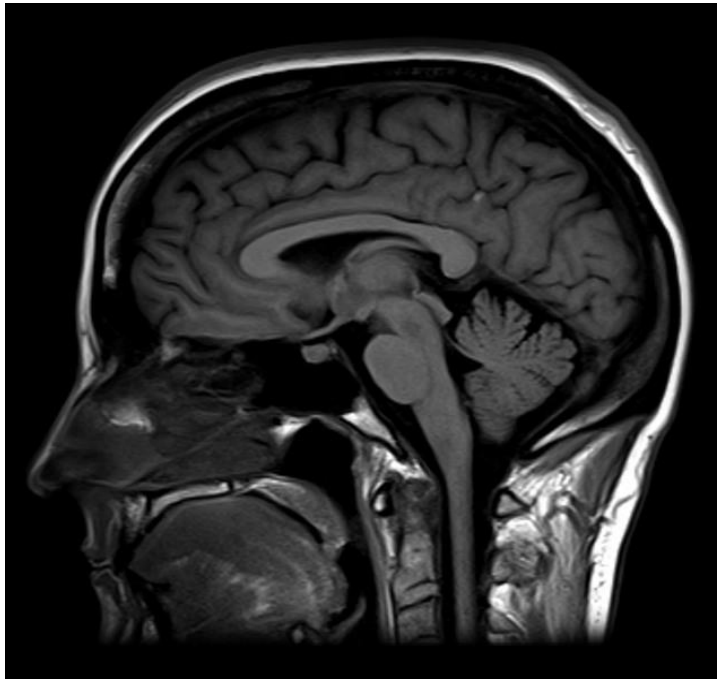
Neurologic Symptoms

Multidisciplinary Collaborative Consensus Guidance Statement on the Assessment and treatment of Neurologic Sequelae in Patients with Post Acute Sequelae of SARS-CoV-2 infection (PASC)



Gaillard F., Radiopaedia, 2008

Melamed et.al., PM&R., 2023

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Neurologic Symptoms: Diagnostic Workup

- **Symptom epidemiology**
  - **Headache** in 21.5% of non-hospitalized patients, 2 months after illness
- **Diagnostic Workup**

Headache:

- Consider brain MRI
- Fundus exam for papilledema
- Cerebral venous thrombosis is of concern in this population which can manifest as headaches

Neuropathy:

- Consider appropriate laboratory workup (r/o pre-existing diabetes)
- Consider electrodiagnostic studies
- Usually, small fiber so may need skin biopsy

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Bell ML et al., PONE, 2021

Neurologic Symptoms: Treatment

- **Headache:**
  - Tension-Type: acetaminophen, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)
  - Migraine: acetaminophen, NSAIDs, tricyclic antidepressants (TCAs), topiramate, triptans, gepants/calcitonin gene-related peptide (CRG) antagonists
  - Neurology referral if refractory
- **Neuropathy:**
  - Physical/occupational therapy
  - Assistive device
  - Medications for neuropathic pain

Autonomic Symptoms

Multi-disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Autonomic Dysfunction in Patients with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

Saint Luke's, 2024

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Blitshteyn S. et al., PM&R., 2022

Autonomic Symptoms and Diagnostic Workup

- **Symptoms**
  - Dizziness, Syncope, Fatigue
    - Some of these symptoms could be autonomic, vestibular, or other causes
- **Diagnostic Workup**
  - Postural Orthostatic Tachycardia Syndrome (POTS):
    - Sustained HR increase ≥30 bpm within 10 min for adults (≥40 bpm for adolescents 12–19 years of age) of standing or on tilt table
    - Absence of orthostatic hypotension
    - Symptoms of orthostatic intolerance for ≥6 months
  - Orthostatic Hypotension:
    - Sustained drop in blood pressure ≥20/10 mm Hg within 3 min of standing or on tilt table

Autonomic Symptoms and Diagnostic Workup Continued

- **Labs:**
  - Complete Blood Count (CBC)
  - Complete Metabolic Panel (CMP)
  - Thyroid Function Test (TFT)
  - Vitamin B12
  - Ferritin
  - Morning cortisol
  - Antinuclear Antibody (ANA), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP)
- **Cardiac workup**: to be discussed later
- **Vestibular evaluation**: ENT, Vestibular Physical Therapist

Autonomic Symptoms: Non-Pharmacologic Treatment

- >3 Liters of fluid per day
- >10 grams of salt per day (4 mg of sodium)
- Compression garments
- Personalized autonomic rehabilitation program
- Deep breathing exercises

Autonomic Symptoms: Pharmacologic Treatment

First line:

- Beta-blockers
- Fludrocortisone
- Midodrine

Second line:

- Pyridostigmine
- Ivabradine
- Clonidine
- Methyldopa
- Modafinil
- Methylphenidate
- SSRIs/SNRIs

Cardiovascular/Pulmonary Symptoms

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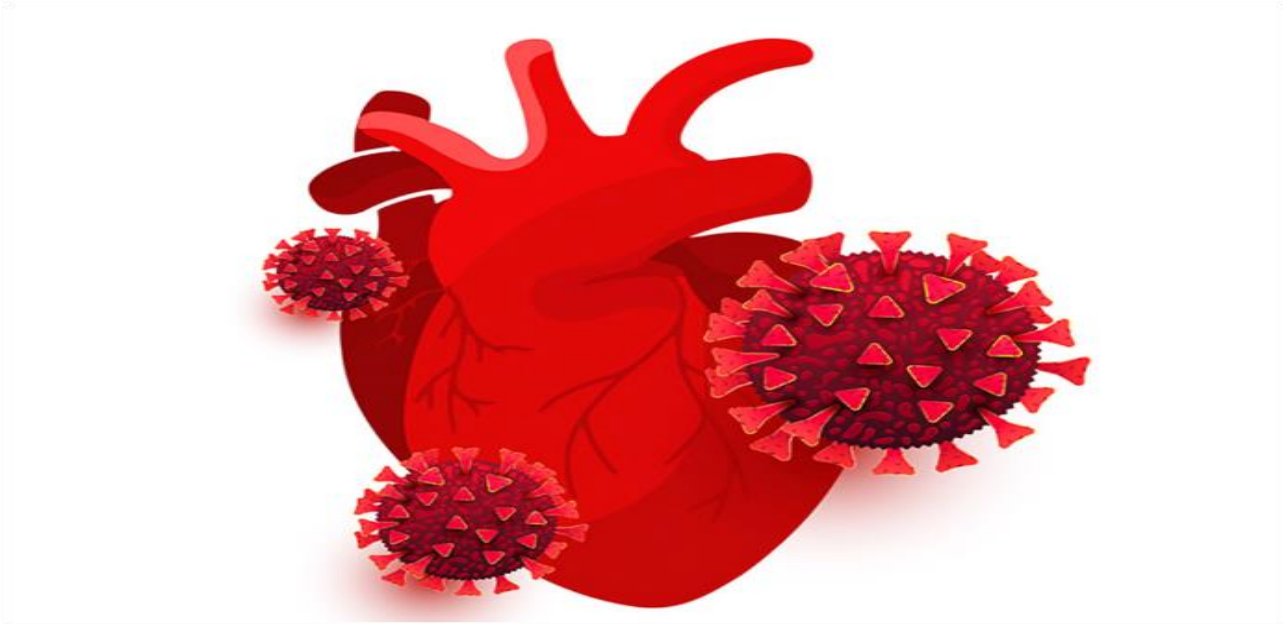
Cardiovascular Symptoms

Multi-disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Cardiovascular Complications in Patients with Post-Acute Sequelae of Sars-CoV-2 Infection (PASC)



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Whiteson JH et al., PM&R., 2022

Cardiovascular Symptoms

- Chest pain
  - Prevalence ranges from 10-20%
  - Differential diagnosis (DDx): Cardiac, pulm, MSK, GI
- Palpitations
  - Prevalence up to 10%
  - Heightened sense of awareness of heartbeat
  - May be persistent or transient
  - With rest or activity
- Fatigue
- Dyspnea
- Dizziness

Cardiovascular Symptoms: Diagnostic Workup

- For more urgently concerning symptoms consider:
  - EKG
  - Echocardiogram
  - CTA chest
- Labs:
  - CBC
  - Basic Metabolic Panel (BMP)
  - Troponin
  - Brain Natriuretic Peptide (BNP)
  - D-dimer
  - CRP/ESR

Cardiovascular Symptoms: Diagnostic Workup

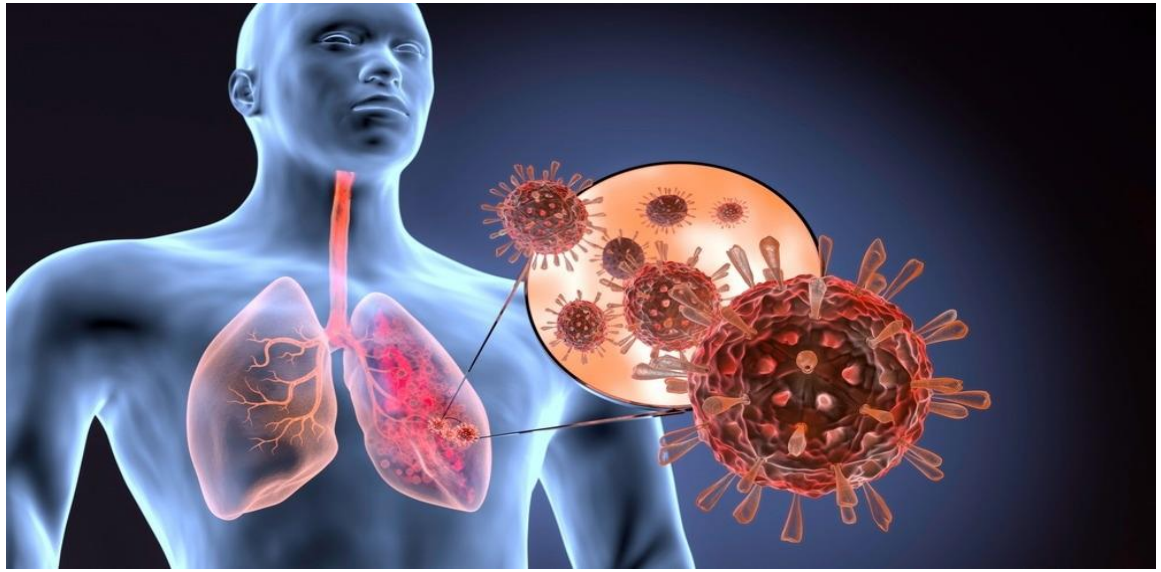
- Palpitations
  - EKG
  - Echocardiogram
  - Holter monitor
- Chest pain
  - Similar to above
  - Consider stress test

Cardiovascular Symptoms: Treatment

- Palpitations:
  - Antiarrhythmic drugs
- POTS symptoms (see autonomic symptoms above)
- Cardiac rehabilitation
- Chest pain of musculoskeletal origin
  - Anti-inflammatories
  - Physical therapy

Pulmonary Symptoms

Multi-disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Breathing Discomfort and Respiratory Sequelae in Patients with Post-Acute Sequelae of Sars-CoV-2 Infection (PASC)



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Maley JH et al., PM&R., 2022

Pulmonary Symptoms: Diagnostic Workup

- Pulse oximetry
- Pulmonary function tests
- Chest imaging
- Echocardiogram
- Stress test

Pulmonary Symptoms: Treatment

- Oxygen (as indicated)
- Pulmonary rehabilitation
- Breathing exercises
- Medications:
  - Oral or inhaled corticosteroids
  - Inhaled bronchodilators
  - Montelukast

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Cognitive/Mental Health Symptoms

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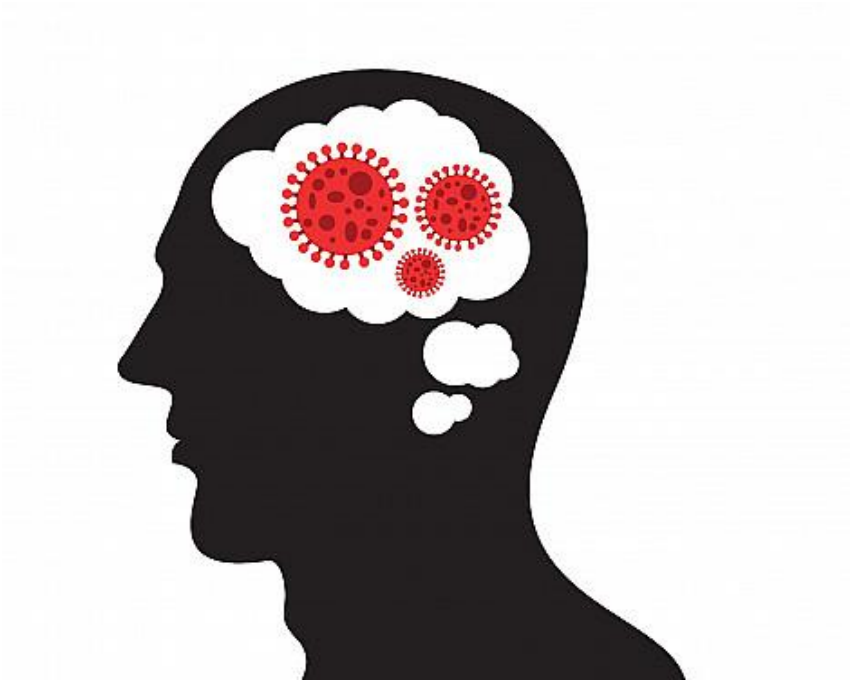
Cognitive Symptoms

Multi-disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Cognitive Symptoms in Patients with Post-Acute Sequelae of Sars-CoV-2 Infection (PASC)



Budson, Harvard Health Publishing, 2021

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Fine JS et al., PM&R., 2022

COVID-19 and Alzheimer's Study

Association of COVID-19 with New Onset Alzheimer's Disease

- Retrospective cohort study of 6,245,282 older adults (age ≥65 years) with COVID-19
  - At significantly increased risk for new diagnosis of Alzheimer's disease within 360 days after the initial COVID-19 diagnosis
    - Especially in people age ≥85 years and in women

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Wang L et al., Journal of Alzheimer's Disease. 2022

Cognitive Symptoms: Diagnostic Workup

- **Symptoms**: 30.8% of non-hospitalized patients, 2 months after illness
- **Diagnostic Workup**
  - Cognitive screen (MOCA, MMSE)
  - Neuropsychology testing
  - Lab workup:
    - CBC
    - Vitamin B12
    - Thiamine/Folate
    - Homocysteine
    - Vitamin D
    - Magnesium
    - Liver function tests
    - Thyroid testing

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Bell ML et al., PLoS One. 2021

Cognitive Symptoms: Treatment

- Sleep assessment/treatment
- Mood assessment/treatment
- Speech language pathologist (cognitive rehabilitation)
- Structured return to physical activity
- Medications ***could*** be considered:
  - Guanfacine with N-acetyl cysteine (NAC)
  - Stimulants: modafanil, methylphenidate, etc.

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Mental Health Symptoms

Multi-disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Mental Health Symptoms in Patients with Post-Acute Sequelae of Sars-CoV-2 Infection (PASC)

NCBHS, 2024

Cheng AL et al., PM&R, 2023

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COVID-19 and Anxiety Meta-Analysis

Mid and Long-term Neurological and Neuropsychiatric Manifestations of Post-COVID-19 Syndrome

- Meta-analysis found that approximately 23% of participants reported experiencing anxiety 3 months or more after a COVID-19 infection

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Premraj L et al., Journal of the Neurological Sciences. 2022

Mental Health Symptoms: Diagnostic Workup

- Symptom screens
  - Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7 (GAD-7), etc.
- Comprehensive patient history

Mental Health Symptoms: Treatment

- Referrals:
  - Supportive psychotherapy
  - Psychiatry
  - Cognitive behavioral therapy
- Medications
  - SSRIs or SNRIs

ENT Symptoms

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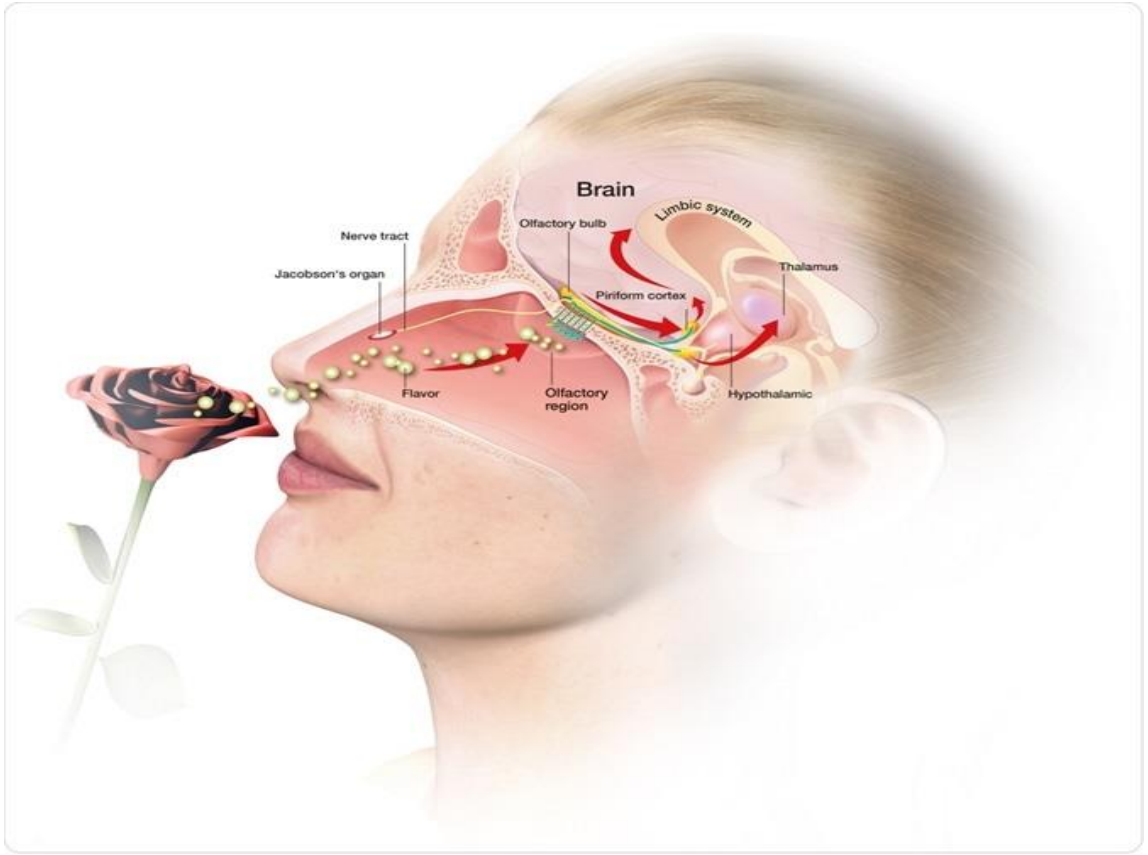
ENT Symptoms

- Loss of taste/smell
- Dizziness/vertigo (vestibular)



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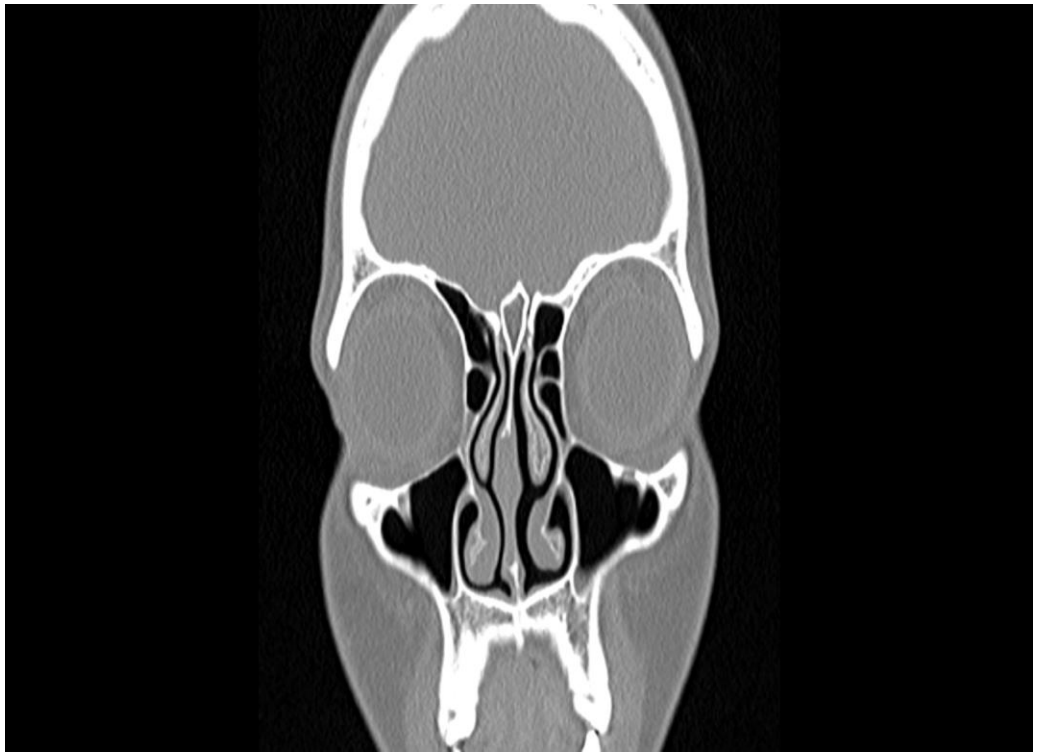
ENT Symptoms: Diagnostic Workup

- Rhinoscopy
- Imaging of sinuses
- Vestibular evaluation



Rogalskyi V., Radiopaedia 2024

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ENT Symptoms: Treatment

- Antihistamines
- Intranasal corticosteroids
- Smell training
- Vestibular rehabilitation

Galper, NY Institute of Aromatherapy, 2021

Fatigue

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Fatigue

Multi-disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Fatigue in Post-Acute Sequelae of Sars-CoV-2 Infection (PASC)

O'Connell, Healthline, 2023

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Herrera JE et al., PM & R. 2021

Fatigue

- Frequency: 37.5% of non-hospitalized patients, 2 months after illness
- Etiology: multifactorial
- Presentation: central or peripheral
    - Post-exertional malaise (PEM)

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Bell ML, PLoS One. 2021

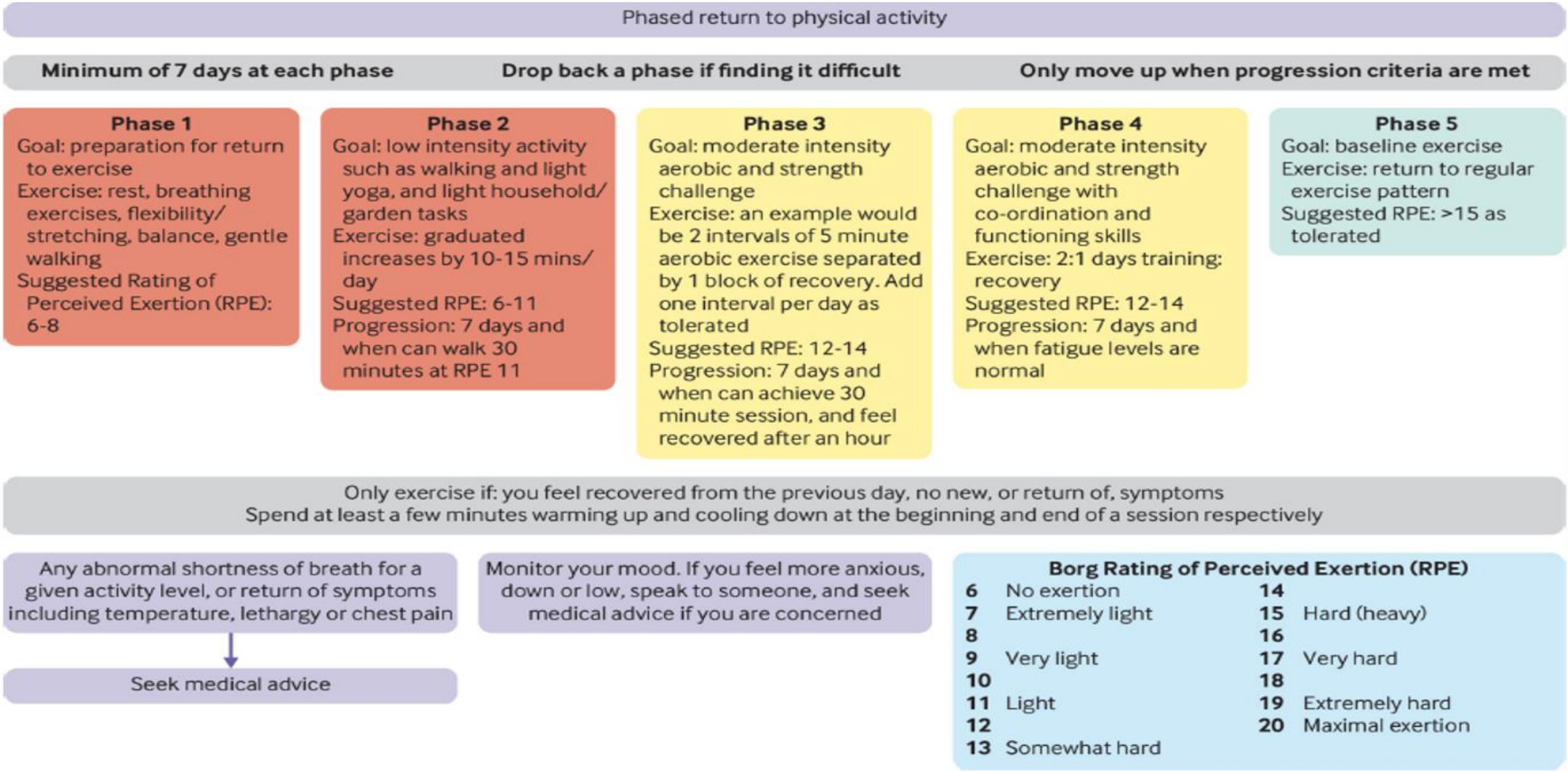
Fatigue: Diagnostic Workup

- Detailed history and physical exam
  - Sleep --> consider **sleep apnea!**
  - Mood
  - Cardiopulmonary
  - Medications
- Labs:
  - CBC
  - CMP
  - Thyroid-Stimulating Hormone (TSH)
  - CRP
  - Creatine Kinase (CK)
- Consider functional assessment (6 min walk test)

Fatigue: Treatment

- Slow return to activity
- Energy conservation
- Pharmacologic treatment
- Pacing
  - Rate the intensity of most significant symptoms (e.g., fatigue, headache) from 1 to 10 prior to beginning a task, and use this scale to decide when symptoms worsen, and it is time for a break.
  - When symptom severity increases by three units (e.g., increased from a 2 to a 5) it is moment to take a break.
  - Focus on decreasing the symptom (e.g., for headaches take medication; for fatigue lay down, practice relaxation exercises).
  - When the symptom has decreased to its initial baseline, continue your activity.
  - Repeat as needed throughout the day.

Fatigue: Treatment



Salman et al., BMJ, 2021

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Future Directions for Treatment

- Paxlovid
- Metformin
- Low dose naltrexone
- Intravenous Immunoglobulin (IVIG)
- Hyperbaric oxygen
- Stellate ganglion block
- Nicotine patch

Summary

- Long COVID can present with a myriad of symptoms
- There is no single well-established treatment for underlying pathophysiology to this point
- Appropriate medical workup should be considered based on presenting symptoms
- There are many available supportive treatments for various symptoms
- Hope for future directions in care

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