

Post-acute Sequelae of COVID-19 (long COVID-19): What Treatments are Being Used and Why

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Disclosures

I (Alice Hemenway) do not have any financial conflicts to disclose.

Objectives

At the end of this presentation, **pharmacist** participants should be able to:

- Review the proposed pathophysiologic mechanisms behind post-acute sequelae of COVID-19 (PASC).
- Discuss the proposed mechanisms of action and data supporting use of non-pharmacologic treatment options for PASC.
- Explain the proposed mechanisms of action and data supporting use of pharmacologic treatment for PASC.



Pre-test Question 1

What is NOT an overarching pathophysiologic mechanism for PASC symptoms?

- A. Virus specific
- B. Psychosomatic
- C. Immune mediated/Inflammatory damage
- D. Post-critical illness



Pre-test Question 2

Based on data for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), what may be the best non-pharmacologic treatment for PASC fatigue?

- A. Graded exercise therapy
- B. Cognitive behavioral therapy
- C. Pacing
- D. Meditation



Pre-test Question 3

TW is a 55 year old male with dyspnea that has continued for 10 weeks after a mild acute COVID infection. His follow up tests do not indicate lung damage.

His past medical history includes hypertension and hypercholesterolemia for which he takes amlodipine and atorvastatin daily. He drinks ~1 drink daily and smokes ½ pack per day.

Go to next slide for question



Pre-test Question 3

Which suggestion is most appropriate?

- A. Oral prednisolone
- B. Inhaled fluticasone
- C. Low dose morphine
- D. Offering smoking cessation counseling and medications



Pre-test Question 4

What medication should be avoided in a patient with a new diagnosis of PASC associated postural orthostatic tachycardia syndrome (POTS)?

- A. Atorvastatin
- B. Lisinopril
- C. Bupropion
- D. Sertraline



Caveats

- There are no FDA approved medications for treatment of post-acute sequelae of COVID-19 (long COVID)
- Mechanisms mentioned have varying levels of data
- Pharmacologic treatment data continues to evolve, but is currently quite limited
- All treatment information in this talk related to long COVID is off-label, and any data to support or refute will be discussed



Abbreviations

- CBT= Cognitive behavioral therapy
- FEV= Forced expiratory volume
- FVC= Forced vital capacity
- GET= Graded exercise therapy
- IDSA= Infectious Diseases Society of America
- MCAS= Mast cell activation syndrome
- ME/CFS= Myalgic encephalomyelitis/chronic fatigue syndrome
- MeSH= Medical Subject Headings
- NICE= National Institute for Health and Care Excellence (UK)
- PE= Pulmonary embolism
- PFTs= Pulmonary function tests
- POTS= Postural orthostatic tachycardia syndrome
- RCT= Randomized controlled trial
- SIBO= Small intestine bacterial overgrowth



Definitions

- NIH/CDC: Sequelae that extend beyond 4 weeks after initial infection
- NICE: Symptoms that continue or develop after acute COVID-19 infection, and which cannot be explained by an alternative diagnosis
 - Ongoing symptomatic COVID-19 (4-12 weeks post-infection)
 - Post-COVID-19 syndrome (beyond 12 weeks post-infection)

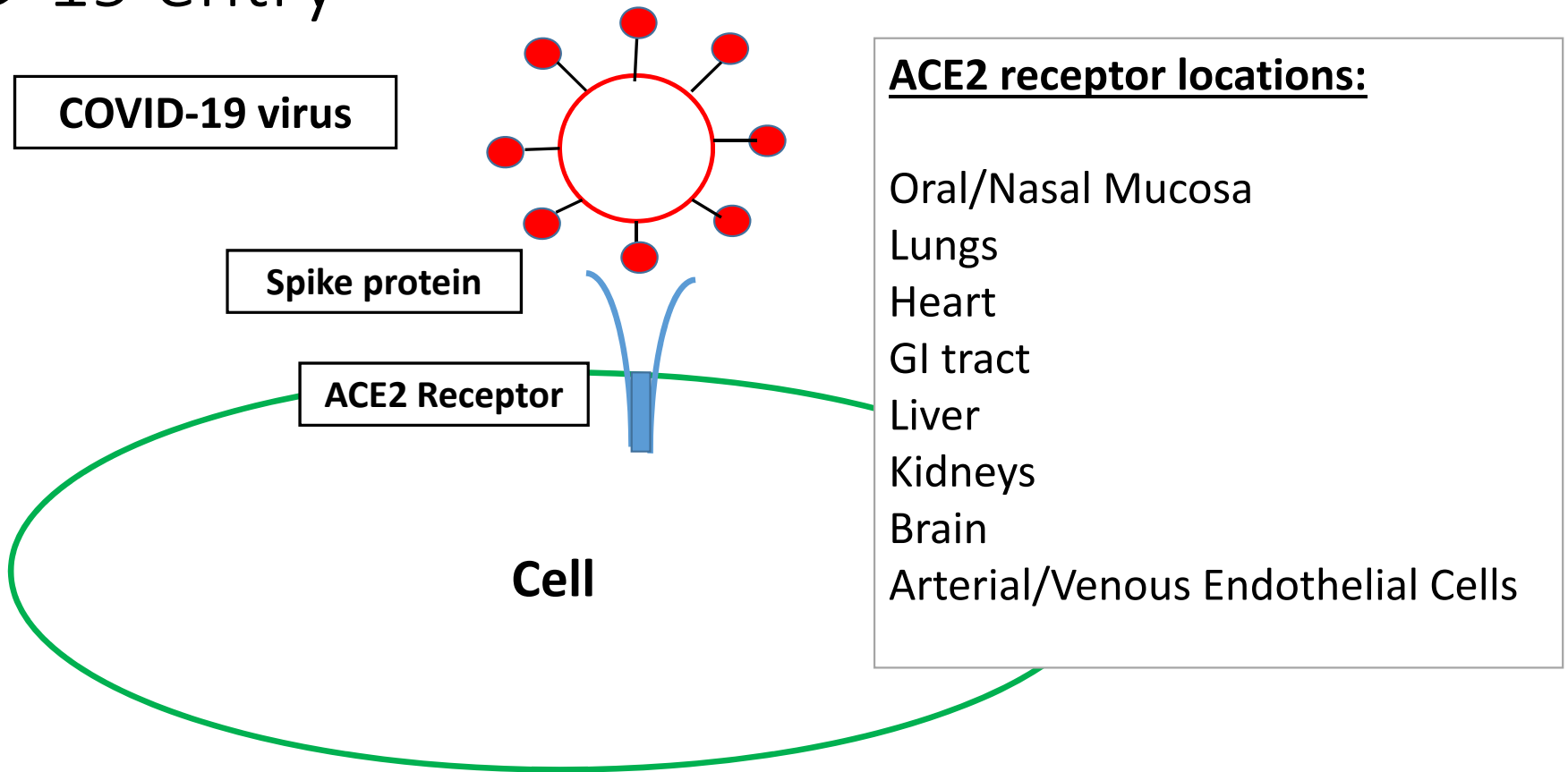


Terminology

- Long-COVID
 - Term created by a patient and infectious diseases professor
- Long-haul COVID/COVID long-haulers
 - Often used by lay public
- Post-acute COVID-19 syndrome
 - MeSH term
 - IDSA
- Post-acute sequelae of COVID-19 (PASC)
 - Dr. Fauci in February 2021



COVID-19 entry



COVID multi-organ complications- acute and long term

Lungs:

- Dyspnea
- Chest pain
- Cough

Heart

- Chest pains
- Myocardial inflammation
- Increased troponin
- Palpitations

Brain

- Brain fog
- Delirium
- Fatigue
- Sleep disturbances
- Depression/anxiety

Pancreas

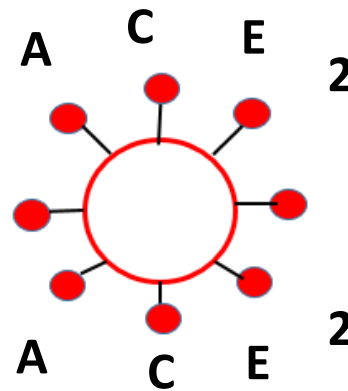
- Injury
- Pancreatitis

Liver

- Liver injury
- Increased AST/ALT

Kidney

- Renal impairment
- Acute kidney injury



GI Tract

- Diarrhea
- Nausea
- Sore throat

Blood vessels

- Inflammation
- Vessel damage
- Coagulopathy
- Microangiopathy



Case Question #1

TT is a 45 year old female who has experienced fatigue that has continued 8 weeks past her diagnosis of moderate COVID-19. She asks if you know how common it is to experience symptoms of long COVID.

Based on published studies what is an accurate answer of the incidence of long COVID?

- A. 32.6% of patients at 60 days
- B. 76% of patients at 6 months
- C. 96% of patients at 90 days
- D. All of the above



Epidemiology

- Reported incidence of long COVID is difficult to accurately ascertain:
 - Variation of acute COVID rates and mortality between countries
 - Accuracy of diagnosis and self-reporting
- Range of incidence rates:
 - 32.6% at 60 days up to 96% at 90 days
- Differences in length of follow-up period and symptoms examined also play a role
- Prevalence study:
 - 5 week prevalence of any symptom: 22.1%
 - 12 week prevalence: 9.9%



Question #2

Which patient is most likely to experience the most severe symptoms of PASC?

- A. 70 year old male who had mild acute COVID
- B. 70 year old female who had severe acute COVID
- C. 37 year old male who had moderate acute COVID
- D. 55 year old female who had moderate acute COVID



Risk Factors

- Compared to the risk factors known for severe COVID (male sex, older age, non-white ethnicity, BMI, etc.) the risk factors for PASC are less elucidated
- Male sex, age, pre-existing conditions including obesity and CV disease were not associated with risk of PASC
- Different survey found increased rates in women and in patients between 35-49 years.
- Severe COVID infection was associated with more severe symptoms of PASC
- However, PASC has been reported in patients with mild infection



PASC Symptoms

Fatigue

Dyspnea

Cardiac abnormalities

Cognition and mental health

Taste or smell alterations

Headache

Muscle/Joint pain

Sore throat

Many additional others



Guidelines

- IDSA, CDC, WHO have not released guidelines for PASC
- NICE guidelines from the UK
 - No suggestions for pharmacologic therapies
 - Focus is on process for evaluation and patient support



What have you heard/read/seen patient's use for PASC?



What are patients using for PASC?

A search of patient-focused media (Facebook, Reddit, Twitter, Pinterest, Instagram, patient support groups, Google news, and a general Google search) was performed in March 2021.

List of commonly reported medications	Possible PASC mechanisms
Anti-histamines	Inflammation, MCAS
Aspirin (low-dose)	Inflammation, MCAS
Beta-blockers	POTS
Corticosteroids	Inflammation, MCAS
COVID vaccine	Unknown
Deupirfenidone (LYT-100)	Inflammation, Fibrosis
Histamine H2 receptor antagonists	Inflammation, MCAS
Ivabradine	POTS
Leronimab	Neuroinflammation
Low dose naltrexone/NAD+	Immune modulation
Montelukast	Inflammation, MCAS
Rintatolimod	Immune modulation, anti-viral
Ruconest	Inflammation
Vitamins (B3, C, D, Selenium, Zinc)	Deficiencies



Case question #3

RW is a 52 year old female who has chronic fatigue 12 weeks after an acute COVID-19 diagnosis. She asks if there is any medication she can take to decrease her fatigue.

Which pharmacologic option would you recommend for her COVID-19 related chronic fatigue?

- A. Methylphenidate
- B. Prednisone
- C. Levothyroxine
- D. None of the above

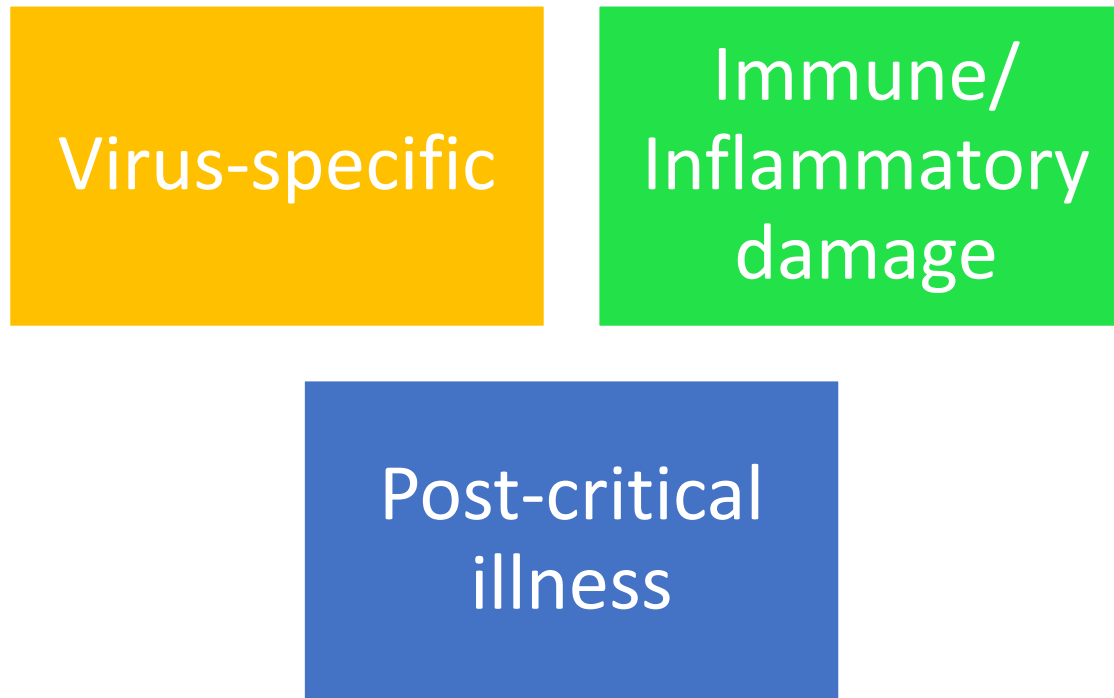


Fatigue

- Has been reported also after SARS-CoV-1 infections
 - 60% at 12 months
- One of the most reported sequelae
 - ~93% of patients at 79 days
 - Similar rates for hospitalized and non-hospitalized patients



Overarching PASC pathophysiologic mechanisms



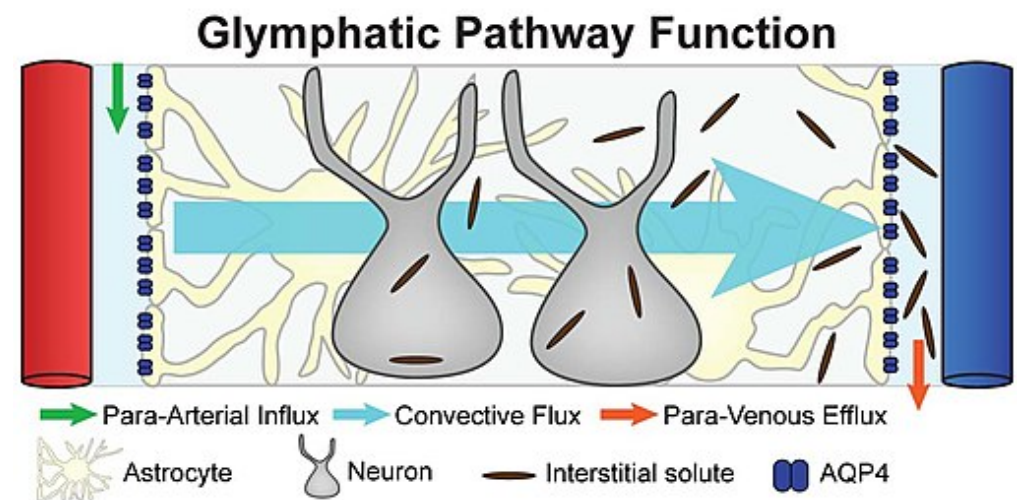
Post-intensive care syndrome

- Symptoms
 - ICU acquired weakness
 - Cognitive dysfunction
 - Mental health problems
- Proposed pathophysiology
 - Microvascular injury
 - Immobility
 - Metabolic alterations



PASC Fatigue- possible mechanisms

- No association between pro-inflammatory markers and long term fatigue
- Combination of central, peripheral and psychological factors?
- Central:
 - Glymphatic system congestion
 - Hypometabolism in frontal lobe/cerebellum



BMJ.2021;374:n1648; Neurochem Res.2015; 40(12):2583–99

Image credit (open source):

https://commons.wikimedia.org/wiki/File:Glymphatic_system_schematic.jpg



PASC Fatigue- possible mechanisms

- Peripheral
 - Skeletal muscle damage (direct infection)
 - Neuromuscular junction damage and inflammation
- Psychological
 - Negative psychological factors associated with fatigue during COVID quarantines
 - Negative social factors also associated with fatigue
- Overlap with ME/CFS?



ME/CFS and PASC chronic fatigue similarities

- ME/CFS includes symptoms such as fatigue, pain, dizziness and problems with sleep and concentration symptoms
 - Overlap with other PASC symptoms
 - ME/CFS and PASC chronic fatigue both have long durations
- There is no laboratory test that will diagnose ME/CFS
 - There is currently no COVID or inflammatory marker associated with COVID-19 fatigue
- The mechanisms are not well understood
 - Post-viral fatigue can precede ME/CFS
 - Mechanistic similarities (or differences!) are still unknown
 - Can/should we treat them similarly?



Non-pharmacologic treatment of PASC fatigue

- The NICE long COVID guidelines do not provide specific information
- NICE guidelines for ME/CFS recommend CBT, GET, and pacing
- The ME Association posted a statement disagreeing with CBT and GET
 - Cochrane review questioned effectiveness and showed high incidence of adverse events
 - Concern for GET is that it may cause post-exertional malaise (additional concern during COVID-19 recovery)
 - A statement of caution was released by NICE regarding GET
- US ME/CFS Clinician Coalition non-pharmacologic recommendations for ME/CFS fatigue are focused on pacing and assistance devices

NICE guidelines; <https://www.nice.org.uk/guidance/cg53>; ME Association Statement: <https://meassociation.org.uk/2020/10/me-association-statement-on-the-nice-clinical-guideline-for-me-cfs-and-the-nice-guideline-for-post-long-covid-19/>; US ME/CFS clinician coalition: <file:///C:/Users/aliceh/Downloads/MECFS%20Clinician%20Coalition%20Treatment%20Recs%20V1.pdf>



Pharmacologic treatment for PASC fatigue?

- There are no suggested pharmacologic treatments for PASC fatigue in the NICE long COVID guidelines
- NICE ME/CFS guidelines list several medications that should NOT be used for ME/CFS
 - Steroids
 - Amphetamines/methylphenidate
 - Levothyroxine
- Insufficient evidence for supplements
- Other medications as needed for symptom control
 - Tricyclic antidepressants for chronic pain/sleep issues
 - Melatonin for sleep



US ME/CFS Clinician Coalition treatment guidance

In contrast to the UK based NICE guidelines, the US ME/CFS Clinician Coalition has pharmacologic recommendations for common ME/CFS symptoms/possible mechanism

- Pain
 - Low dose naltrexone*
- Orthostatic intolerance
- Sleep
- Immune dysfunction
- SIBO
- Fatigue and cognitive dysfunction
 - Methylphenidate (with a caution warning and caveats)
 - Modafinil/Armodafinil
 - Amantadine

*= noted in search of patient-focused media for PASC



Scoping review of pharmacologic treatments for PASC

- A scoping review was performed, includes data through June 12, 2021
- This review looked at any data source- case reports up to RCT
- An initial 1,319 records were found, but only 26 met inclusion criteria
 - 3 prospective, open-label studies
 - 5 case reports/series
 - 1 survey
 - 1 correspondence
- 16 studies in progress
 - Most appear to be RCTs



In the pipeline for PASC fatigue?

- There is no current, published data for pharmacologic treatment of PASC fatigue
- Treatments with ongoing RCTs include:
 - Low dose naltrexone plus nicotinamide
 - Ruconest (C1 esterase inhibitor FDA approved for hereditary angioedema)
 - Leronimab (Investigational HIV medication- CCR5 antagonist)
 - Various supplements



Question #4

Which medication has the most published data to support its use in patients with post-acute COVID-19 interstitial lung disease?

- A. Inhaled fluticasone
- B. Oral prednisolone
- C. Intravenous methylprednisolone
- D. Inhaled budesonide



Dyspnea

- One of most common symptoms
 - Incidence of 42-66% at 60-100 day follow up
- Breathlessness had an estimated prevalence of 4.6% at 5 weeks
 - Regardless of acute respiratory symptoms or disease severity
- Abnormalities noted in multiple lung functions
 - Diffusion capacity, total lung capacity, FEV, FVC



PASC Dyspnea- possible mechanisms

- Viral dependent
 - Direct damage to alveolar epithelial and endothelial cells
- Viral independent
 - Fibrotic changes in patients who experience ARDS (provoked by IL-6)
 - Immunologic/inflammatory damage
- Pulmonary vascular thromboembolisms (micro and macro)
 - Observed in 20-30% of patients

- Also, long term breathing difficulties reported not associated with lung damage
 - Unknown mechanism(s)



Treatment of PASC dyspnea- targeted assessment

Severe

4-6 weeks: phone or in person assessment
PE assessment, post-ICU care, holistic assessment

12 weeks: CXR, face to face assessment, consider full PFTs, walk test, sputum sampling, echocardiogram

If abnormal CXR: CT, CTPA, specialist referrals if needed

Mild to Moderate

12 weeks:
Part 1: CXR and virtual clinic

Part 2: Clinical assessment and PFTs

If abnormal: CT/CTPA, consider walk test, consider echocardiogram



Non-pharmacologic treatment for PASC dyspnea

Based on data for non-COVID dyspnea:

- Self-management techniques
 - Stopping smoking
 - Avoiding pollutants
 - Avoiding extremes in temperature
- Breathing exercises
- Pulmonary rehabilitation



Pharmacologic treatments for PASC dyspnea?

- Cohort study of patients with symptoms 4 weeks after discharge
 - 4.8% with interstitial lung disease
 - Those treated with prednisolone had significant improvement
- There can also be suggestions in high-level reviews that might be questionable if implemented without nuance
 - BMJ review article mentions use of opioids as treatment for breathlessness
 - Data cited is a meta-analysis that showed a statistically significant decrease in sensation of breathlessness in advanced COPD
 - It is often used for end of life care, but use in patients with an estimated life expectancy of > 5 years may cause long term issues

Pharmacists have an important role of reviewing overall appropriateness of suggestions
Especially important with evolving data.



In the pipeline for PASC dyspnea?

- The prednisolone cohort study is the only currently published study evaluating pharmacologic treatment for PASC dyspnea
- Treatments with ongoing RCTs:
 - Deupirfenidone (Investigational cytokine inhibitor)
 - Montelukast*
 - Prednisone*

*= noted in search of patient-focused media for PASC



Question #5

What medication has the most data to support it's use in PASC associated POTS?

- A. Midodrine
- B. Fludrocortisone
- C. Propranolol
- D. Ivabradine



Cardiovascular abnormalities

- 21.4% of patients experienced chest pain 60 days after acute COVID symptoms
 - Possibly owing to myocarditis
- Myocarditis has also been found in young, low risk patients
- Emerging trend of POTS/autonomic dysfunction post-COVID infection
 - POTS is characterized by dizziness, palpitations, tachycardia
 - POTS is diagnosed by HR increase of > 30 bpm within 10 minutes of upright posture, with absence of orthostatic hypotension and associated symptoms of orthostatic intolerance, for at least 3 months
 - Other symptoms include weakness/fatigue, “brain fog”, shaking/sweating



PASC Cardiac abnormalities- possible mechanisms

- ACE2 receptors are highly expressed in the heart
 - Direct route of infection
 - Intense local immune response occurs in cardiomyocytes
- Sustained immune activation can lead to damage
 - Heart is bystander of injury instead of direct target
- Viral infection has been seen to precede POTS
 - ACE2 receptor expression on neurons
 - Consequences on autonomic nervous system



Non-pharmacologic treatment of PASC CV abnormalities

- Clinical evaluation and EKG, echocardiogram at 4-12 weeks
 - Patients with CV complications during acute infection
 - Persistent CV symptoms
- Abstinence from competitive sports/aerobic activity for 3-6 months
 - Competitive athletes with CV complications
- Non-pharmacologic treatments based on POTS guidelines:
 - Regular, structured, progressive exercise program
 - Up to 2–3 L of water and 10–12 g of NaCl daily may be considered



Pharmacologic treatments for PASC CV

- Treatments recommended for non-PASC myocarditis
 - ACEI, Beta-blockers*, mineralocorticoid receptor antagonists as needed
- Non-PASC POTS guidelines
 - Fludrocortisone (increase Na and plasma volume)
 - Midodrine, pyridostigmine, low-dose propranolol*, ivabradine* (decrease orthostatic tachycardia)
 - Avoid drugs that block norepinephrine reuptake
 - Bupropion, methylphenidate, venlafaxine, duloxetine
- RCT for ivabradine in non-PASC POTS
 - Small study (22 patients), compared ivabradine* to placebo
 - Improved reduction in HR but also QoL and physical functioning

*= noted in search of patient-focused media for PASC



In the pipeline for PASC CV abnormalities

- Six publications assessing use of ivabradine (or beta-blockers) in PASC related POTS/tachycardia
 - 5 are case reports/case series
 - 1 is a prospective, randomized, open label study that found benefit with both carvedilol and ivabradine for HR reduction in patients with persistent tachycardia after acute COVID diagnosis
- Treatments with ongoing RCTs
 - No RCTs found in clinicaltrials.gov as of June 2021 for PASC associated POTS
 - Studies with supplements that include chest pain as an outcome



Case Question #6

AB is a 45 year old female who was diagnosed with POTS. She is also experiencing brain fog, and her physician wants to try medications that have shown effect for “chemo brain”. Which medication used for “chemo brain” should be avoided?

- A. Modafinil
- B. Methylphenidate
- C. Memantine
- D. Donepezil



Cognitive and mental health impairments

- Symptoms include brain fog (concentration, memory), depression, anxiety, PTSD, insomnia
- After 30 days, 56% of screened patients had at least 1 psychiatric sequelae
- In a separate study anxiety, depression, sleep difficulties were present in ~25% of patients at 6 months
- Large study estimated incidence of 18.1% (between 14 and 90 days after diagnosis)



Possible mechanisms of PASC cognitive and mental health impairments

- Direct viral infection, neurodegeneration, microvascular thrombosis
 - Changes to brain parenchyma and vessels seen on autopsy
- Severe systemic inflammation, neuroinflammation
 - Levels of immune activation correlate with cognitive changes
- Dysautonomia
 - Contribution to brain fog



Non-pharmacologic treatment of cognitive and mental health impairments

- Identification and evaluation
 - Use of standard screening tools
- Good sleep hygiene
- Holistic approach to cognitive impairment
 - SLP, OT to address changes
- Using compassion and understanding when discussing with patients



Cognitive impairment treatments- comparison to “chemo brain”

- Non-pharmacologic strategies
 - Repeating exercises
 - Stress relief and coping strategies
- Pharmacologic treatments
 - Methylphenidate
 - Donepezil
 - Modafinil
 - Memantine
- Full assessment of other symptoms to prevent worsening



In the pipeline for PASC cognitive and mental health impairments

- Survey showed greater improvement in PASC symptoms, including brain fog, in patients who received COVID-19 vaccine
- Luteolin has in vitro data in PASC
 - Alleviation of cognitive impairment by inhibiting mast cell activation
- Treatments with ongoing studies
 - Atorvastatin (prospective, observational cohort)
 - Supplements



Olfactory/gustatory disturbances

- 5 week prevalence of ~8% for both loss of smell and taste
- Though there is a large range seen in studies: 11-45%
- Mechanisms include entry into olfactory support cells, stem cells and perivascular cells
 - Local infection could lead to inflammatory response that reduces function
 - Could also indirectly reduce signaling to the brain
- Also, ACE2 receptors are on mucous membranes of oral cavity
 - Direct route for cellular injury

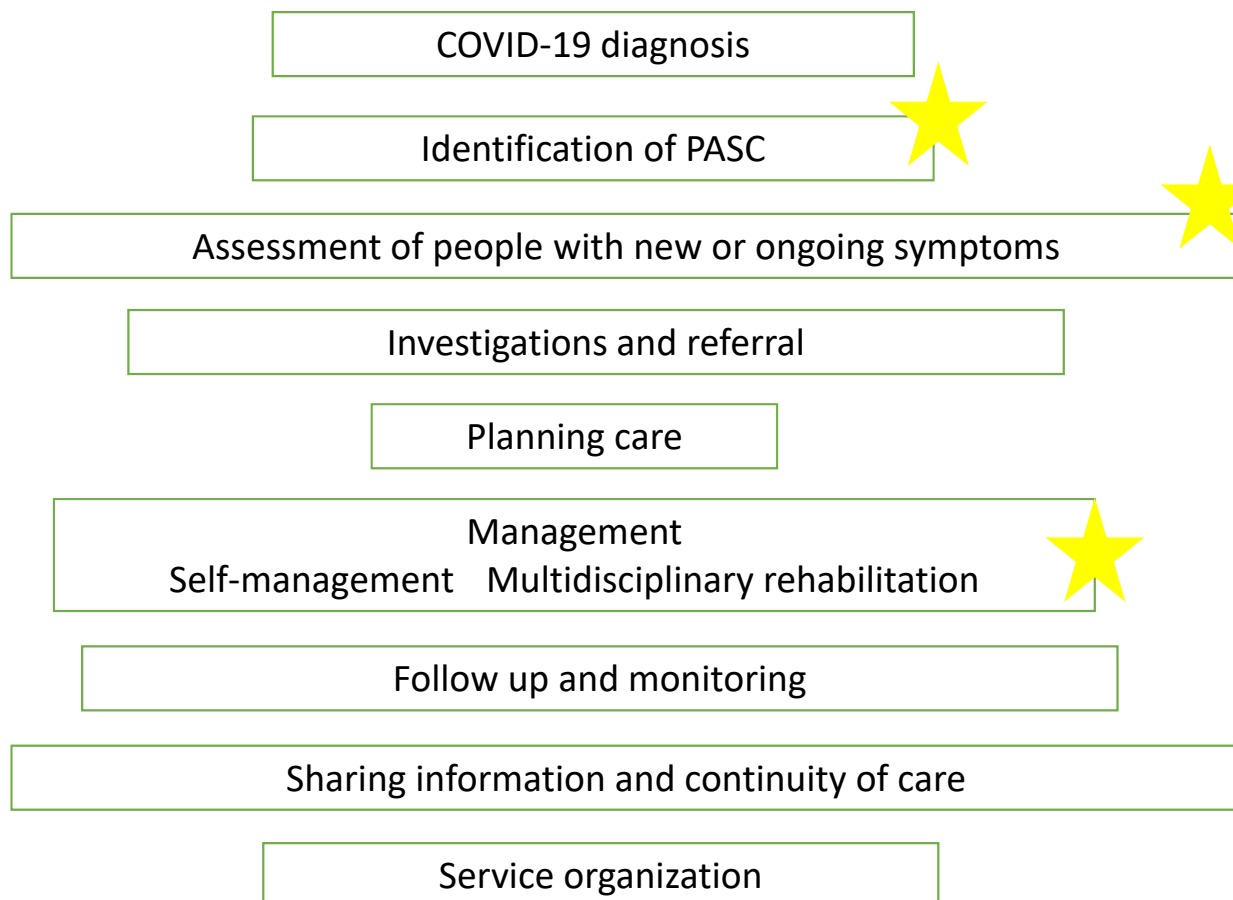


Treatment of olfactory/gustatory symptoms

- No non-pharmacologic treatments currently recommended
- Prospective, randomized, open label trial the compared systemic prednisone plus a nasal irrigation with betamethasone, ambroxol, and rinazine to untreated controls
 - Improved olfactory scores in treatment group at 20 days (40 vs 10; $p=0.011$) and 40 days (60 vs 30; $p=0.024$)
- In the pipeline
 - Supplements for olfactory symptoms



Overall management guidance



Patient resources

- Online support groups
 - Longcovid.org
 - Survivorcorps.com
- Multidisciplinary treatment centers
 - Map at: <https://www.survivorcorps.com/pccc>
 - Most states have at least 1
 - Illinois has 7, all located within Chicago region



Best practices for pharmacists

- Patients desire providers that have understanding, empathy and support
- Awareness and identification of patients who would benefit from follow-up
- Thorough medication histories should be a priority
 - Supplements
 - OTCs
- Assess possible adverse effects and drug/disease interactions
 - And weight against level of data regarding efficacy
- Assistance with self-management opportunities like tobacco cessation



Post-test Question 1

What is NOT an overarching pathophysiologic mechanism for PASC symptoms?

- A. Virus specific
- B. Psychosomatic
- C. Immune mediated/Inflammatory damage
- D. Post-critical illness



Post test Question 1 Answer

What is NOT an overarching pathophysiologic mechanism for PASC symptoms?

- A. Virus specific
- B. Psychosomatic**
- C. Immune mediated/Inflammatory damage
- D. Post-critical illness

PASC symptom pathophysiology have mechanisms based in either direct viral damage, indirect damage due to inflammation, or can be associated with post-intensive care syndrome



Post-test Question 2

Based on data for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), what may be the best non-pharmacologic treatment for PASC fatigue?

- A. Graded exercise therapy
- B. Cognitive behavioral therapy
- C. Pacing
- D. Meditation



Post-test Question 2 Answer

Based on data for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), what may be the best non-pharmacologic treatment for PASC fatigue?

- A. Graded exercise therapy
- B. Cognitive behavioral therapy
- C. Pacing**
- D. Meditation

GET and CBT are controversial treatments for ME/CFS, while pacing is a well-accepted therapy that could have benefit for PASC fatigue. Meditation is not a non-pharmacologic treatment option discussed for ME/CFS



Post-test Question 3

TW is a 55 year old male with dyspnea that has continued for 10 weeks after a mild acute COVID infection. His follow up tests do not indicate lung damage.

His past medical history includes hypertension and hypercholesterolemia for which he takes amlodipine and atorvastatin daily. He drinks ~1 drink daily and smokes ½ pack per day.

Which suggestion is most appropriate?

- A. Oral prednisolone
- B. Inhaled fluticasone
- C. Low dose morphine
- D. Offering smoking cessation counseling and medications



Post-test Question 3 Answer

TW is a 55 year old male with dyspnea that has continued for 10 weeks after a mild acute COVID infection. His follow up tests do not indicate lung damage.

His past medical history includes hypertension and hypercholesterolemia for which he takes amlodipine and atorvastatin daily. He drinks ~1 drink daily and smokes ½ pack per day.

Which suggestion is most appropriate?

- A. Oral prednisolone
- B. Inhaled fluticasone
- C. Low dose morphine
- D. Offering smoking cessation counseling and medications**

Oral prednisolone was shown efficacious in patients with interstitial lung disease, which our patient doesn't have. Inhaled fluticasone doesn't have any supporting data for PASC. Low dose morphine has shown to help with chronic breathlessness, but there is no data in PASC and it could cause long-term issues in non-hospice patients. The best option is to offer to assist with smoking cessation.



Post-test Question 4

What medication should be avoided in a patient with a new diagnosis of PASC associated postural orthostatic tachycardia syndrome (POTS)?

- A. Atorvastatin
- B. Lisinopril
- C. Bupropion
- D. Sertraline



Post-test Question 4 Answer

What medication should be avoided in a patient with a new diagnosis of PASC associated postural orthostatic tachycardia syndrome?

- A. Atorvastatin
- B. Lisinopril
- C. Bupropion**
- D. Sertraline

Norepinephrine reuptake inhibitors can worsen symptoms of POTS and should be avoided.



In Summary

- There is still much to be learned about PASC, including the underlying mechanisms
- There may be other, similar diseases that can be used to help guide patient evaluation
- It is yet unknown whether treatments for these other disease will show efficacy in PASC
- There are no approved medications for PASC, and there is very little data for supporting use of any pharmacologic treatment.
- Pharmacists should consider patients with PASC a priority for medication histories, given possible supplement, vitamin and OTC use



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Questions?

