Post-Acute COVID Syndrome and Its Many Faces

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Learning Objectives

Upon completion of this learning activity, participants should be able to:

- Define post-acute COVID syndrome and recognize its range of clinical presentations.
- Review and compare the immune mechanisms underlying acute COVID infection and post-acute COVID syndrome.
- Identify potential upper and lower airway complications associated with post-acute COVID and assess if and when patients should be referred for further care.

What is Post-Acute COVID Syndrome?

- AKA long COVID syndrome, COVID long haulers, long-haul COVID, chronic COVID, post-acute sequelae of SARS CoV-2 infection (PASC), etc. (1)
- Rates vary according to individual studies, but PACS affects a significant proportion of patients after acute infection (11)
  - Can also affect patients who had asymptomatic COVID infection.
- According to the CDC, the term refers to a wide range of physical and mental health sequelae experienced by patients 4 or more weeks after acute COVID infection. (1)
  - Symptoms can be persistent, or they can wax and wane
  - Can last several weeks to months, potentially years
  - About half of cases resolve within 3-4 months (6) but the overall course can be highly dependent on the specific symptoms

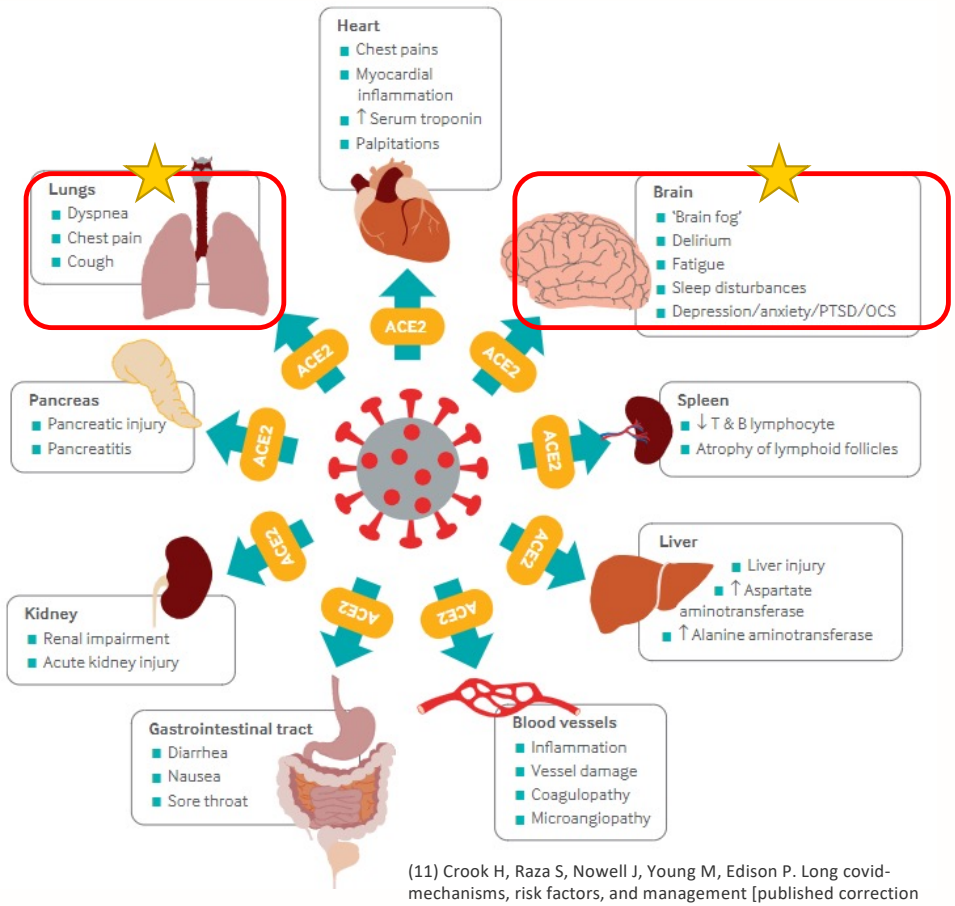
What is Post-Acute COVID Syndrome?

World Health Organization definition:

- "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 and that **last for at least 2 months** and **cannot be explained by an alternative diagnosis**. 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 or persist from the initial illness. Symptoms may also fluctuate or relapse over time." (2)

What is Post-Acute COVID Syndrome?

- Can affect multiple organ systems (3, 4, 11, 12)
- Can also occur in children and the fully vaccinated but much less commonly (1, 13, 14)
  - More common in older children >11yo, and many had mild obstructive PFTs that were bronchodilator reversible (13)
- Most commonly reported symptoms are (4):
  - Fatigue
  - Dyspnea
  - Cognitive dysfunction



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Acute vs Post-Acute COVID and Potential Risk Factors

Common associations (12, 15, 16):

- Unvaccinated status
- # of reinfections
- SARS-CoV-2 viremia
- Presence of autoantibodies (correlated with anti-SARS-CoV-2 antibodies)

Acute Severe COVID / Hospitalization	Post-Acute COVID Syndrome
Male predominance	Female predominance
Age >/= 50 years	Age 35-69 years
<u>Associated comorbidities:</u> Obesity, Diabetes mellitus, Cardiovascular disease, Chronic kidney disease, etc	<u>Associated comorbidities:</u> Asthma, Type 2 diabetes, EBV reactivation/viremia
	(11, 12, 15)

Our Case

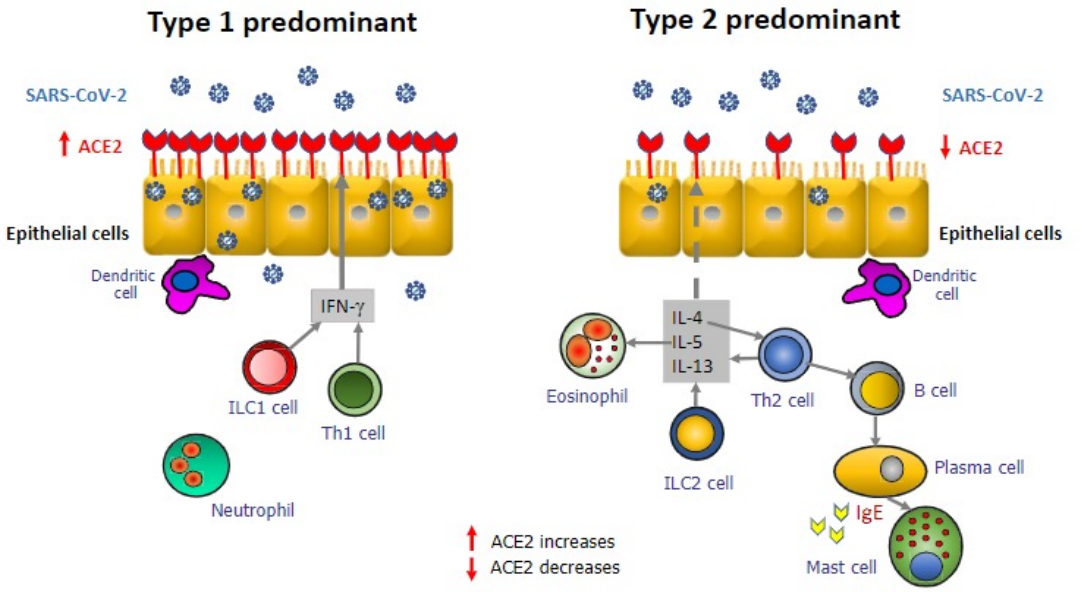
37yo F with history of chronic rhinosinusitis without nasal polyposis, allergic rhinitis, and COVID infection x2 presented with persistent dyspnea and chronic dry cough x2 months since last COVID infection.

- Did not need hospitalization or oxygen during either COVID infections
- Has never had chronic cough or any other respiratory issues prior
- Allergic Rhinitis, CRSsNP
  - + sensitivity to multiple indoor and outdoor environmental aeroallergens
  - s/p immunotherapy 2015-2020 with recurrence of symptoms upon stopping
  - History of multiple antibiotic courses for acute on chronic sinusitis
  - Past CT sinus showed clear sinus passages

Pathophysiology of COVID

SARS-CoV-2 infects cells via the ACE2 receptors.

Evidence has shown that T1 and T2 inflammation regulate ACE2 expression in the upper and lower airway epithelium (5, 7).



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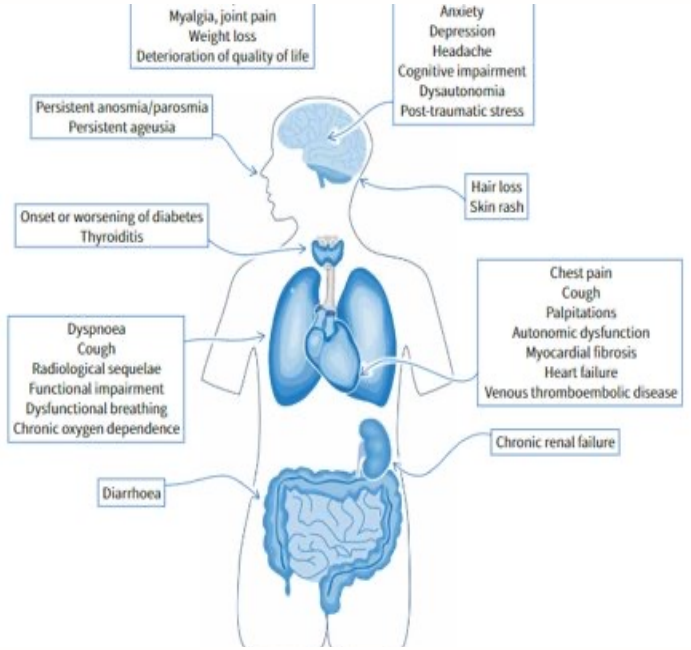
Pathophysiology of Post-Acute COVID

Cellular injury due to the mechanism of viral infection may be responsible for the persistence of symptoms after the acute phase.

- SARS-CoV-2 has a propensity to affect nerves, their support cells, and surrounding structures via cell receptors other than ACE2 (7, 10, 11)

Cellular injury due to the immune response to SARS-CoV-2 infection may also contribute to the persistence of many symptoms.

- Endothelial damage and immune activation, including production of IL-6, result in fibrotic changes and disruption of normal coagulant pathways (11).



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Pathophysiology of Post-Acute COVID

Persistence of virus or viral antigens may contribute to a chronic hyperinflammatory state (12).

- SARS-CoV-2 antigens have been detected throughout body tissues months after acute infection.
- Chronically increased levels of certain cytokines, antibodies, and specific T-cell populations have been detected in post-acute COVID patients.
- Some patients have evidence of EBV reactivation.

Certain populations are less able to mount a timely and effective antiviral response which promotes viral persistence and prolonged tissue damage (12, 15).

At-Risk Populations
Older individuals
Immunosuppressed
Chronic inflammatory diseases (e.g. obesity, type 2 diabetes mellitus, metabolic syndrome)
Autoimmune conditions*
T2-predominant conditions (?)

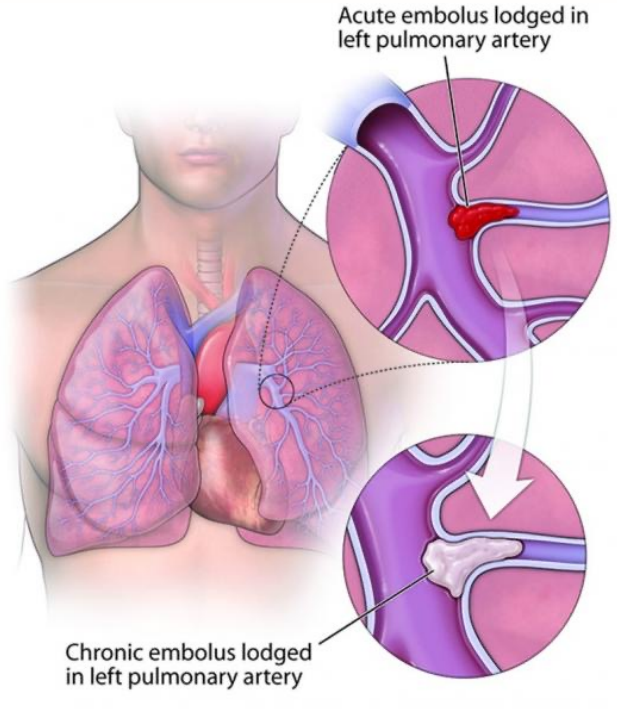
Post-Acute COVID in the Lungs

Chronic dyspnea is not associated with the severity of acute COVID disease (3, 4).

Patients with a severe disease course are more likely to have physiologic changes apparent on imaging and pulmonary function testing.

- Reduced diffusion capacity is the most commonly reported, though both restrictive and obstructive defects have been observed as well (4, 13).
- Pulmonary fibrosis is more typically seen in patients who required intensive care.

Post-Acute COVID in the Lungs



The incidence of pulmonary embolism is 14-25% in acute COVID cases (3).

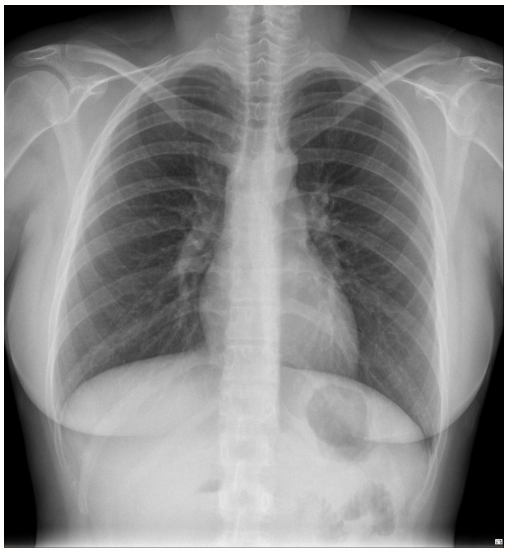
Based on this high incidence, there is a theoretical risk of developing **chronic thromboembolic pulmonary hypertension (CTEPH)** in post-COVID patients (3).

- Can initially present with fatigue and dyspnea and later develop into heart failure, but there is often a honeymoon period.
- Can be screened for with echocardiography and ventilation/perfusion lung scans.

The risk of post-COVID CTEPH is currently not known (3, 4).

Our Case

37yo F with history of chronic rhinosinusitis without nasal polyposis, allergic rhinitis, and COVID infection x2 presented with persistent dyspnea and chronic dry cough x2 months since last COVID infection.



- Pulmonary Function Testing:

FVC	FVC %	FEV1	FEV 1 %	Ratio Value	FeF 25-75	FeF 25-75%	Post test
2.92	72	2.29	68	93	1.92	52	
3.54	88	2.74	81	92	2.25	66	yes

  - FEV1 reversible by 450mL (20%)
- Chest X-ray clear

Symptoms improved on mometasone furoate HFA

Our Case

A few months later, this same 37yo F patient returns with the complaint of recurrent rhinosinusitis symptoms worse than her prior baseline.

- CRSsNP and Allergic Rhinitis
  - Long history of moderate/severe perennial rhinosinusitis symptoms
  - + sensitivity to cat, dog, oak, olive, walnut, alder, cottonwood, elm, ragweed, pigweed, russian thistle, mugwort, Bermuda, Timothy, Johnson grasses
  - Improved control on immunotherapy (2015-2020) but worsened upon stopping in March
  - Initially reported near-resolved symptoms for a few months after recovery from most recent COVID infection
  - Symptoms then recurred and the patient was treated with antibiotics for acute on chronic rhinosinusitis which did not resolve her symptoms

Post-Acute COVID in the Upper Airway

Olfactory and Taste Disorders:

- Includes anosmia, hyposmia, cacosmia, ageusia
- In patients with mild COVID-19, the estimated prevalence ranges from 56.5% to 85.9% (3).
- The exact pathophysiology remains to be elucidated, but local mucosal inflammation and olfactory epithelial destruction appear to be the main mechanisms.
- Most (95%) patients recover by 6 months (3).
- Olfactory training may be beneficial in these patients.

Post-Acute COVID in the Upper Airway

Invasive Fungal Rhinosinusitis

- Though rare, it is the most aggressive form of fungal infection (8).
- Usually affects immunocompromised individuals (e.g. diabetes mellitus, liver/renal dysfunction, immunosuppressive drugs, and leukemia)

Table 1
Incidence of acute invasive fungal rhinosinusitis per year (AIFRS).

Year of study	Males		Females		Total	
	No.	%	No.	%	No.	%
2017	3	33.3	6	66.7	9	16.07
2018	4	50.0	4	50.0	8	14.29
2019	4	40.0	6	60.0	10	17.86
2020	19	65.5	10	34.5	29	51.78
Total	30	53.57	26	46.43	56	100

Fig. 1. A photo of an endoscopic examination with ischemic changes in the middle turbinate suggesting AIFRS.

Post-Acute COVID in the Upper Airway

Invasive Fungal Rhinosinusitis (9)

Figure 1. Different patterns of skin necrosis/ulceration and eye involvement in invasive fungal infection. (A) Left eye chemosis and proptosis and small skin ulceration below left lower eye. (B) Severe right eye proptosis and necrosis over right cheek area. (C) Right eye proptosis and right lower motor neuron facial palsy with angle of mouth deviated to left.

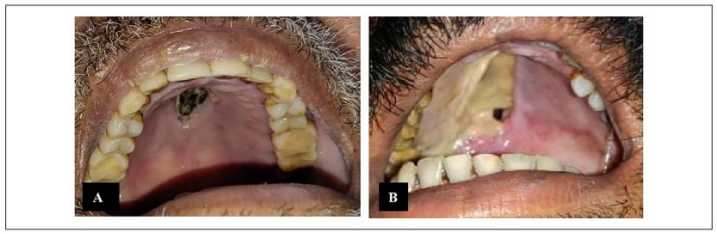


Figure 2. Different pattern of palatal involvement in post COVID-19 AIFRS. (A) Small central palatal ulceration with necrosis. (B) Extensive necrosis involving right side palate.

Table 2. Presenting Signs and Symptoms Among Post COVID-19 AIFRS Patients.

Sign or symptom	Number	Frequency (%)
Headache/facial pain/periorbital pain	18	85.71
Facial/periorbital swelling	13	61.90
Blurred vision	5	23.81
Restricted extraocular movement	4	19.05
Nasal blockage	4	19.05
Facial/periorbital/gingival numbness	3	14.29
Proptosis	3	14.29
Conjunctival redness	3	14.29
Chemosis	3	14.29
Jaw/gingival/tooth pain	2	9.52
Loose tooth	2	9.52
Nasal discharge/CSF rhinorrhea	2	9.52
Skin ulceration/necrosis	2	9.52
Palatal ulceration/necrosis	2	9.52
Altered mental status	1	4.76
Facial nerve palsy	1	4.76
Otalgia	1	4.76

Our Case

37yo F with history of chronic rhinosinusitis without nasal polyposis, allergic rhinitis, and COVID infection x2 presented with recurrent rhinosinusitis symptoms worse than baseline 4 months after last COVID infection in August 2021.

- CRSsNP and Allergic Rhinitis
  - Patient was treated with 4 different antibiotic courses over the next few months by different providers for acute on chronic rhinosinusitis which did not resolve her symptoms
    - Doxycycline, Azithromycin, Augmentin, Clindamycin
  - Rhinoscope exam by ENT was unremarkable
  - Repeat CT sinus was stable (negative) compared to pre-pandemic images

Evolution of Post-Acute COVID Care

In the US alone, there are have been >87,000,000 cases of COVID as of June 2022, and the CDC estimates post-acute COVID prevalence at ~7.5%.

Since July 2021, “long COVID,” also known as post-COVID conditions, can be considered a disability under the Americans with Disabilities Act (ADA).

There is a paucity of data available regarding post-COVID specific disease and its management, so management often relies on treating the signs/symptoms similarly to other known conditions.

Multidisciplinary long COVID clinics are becoming increasingly prevalent.

- Can include social services, occupational and behavioral therapists, several different medical subspecialists, etc.

Several long COVID support groups are also available.

Key Points

- Post-acute COVID syndrome is an umbrella term for the constellation of symptoms that can persist or present >4 weeks after the acute infection.
- Symptoms are nonspecific as it can affect nearly any organ system. However, the most common are respiratory and neuropsychiatric complaints.
- Post-acute COVID syndrome is thought to be the result of cellular injury from acute infection, a hyperinflammatory state, and/or the sequelae of critical care.
- Due to the associated physiological alterations, patients are at increased risk for pulmonary fibrosis, thromboembolic events such as CTEPH, invasive fungal rhinosinusitis, and other complications.
- Though atopic patients do not appear to be at greater risk for severe COVID infection, they may be more likely to develop post-acute COVID symptoms.
- Overall, prognosis and treatment depend on the specific signs and symptoms for each patient. Management oftentimes involves multidisciplinary care.

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