

Post-acute Sequelae of COVID-19 (PASC):

“long-haulers” and pulmonary disease

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Disclosures

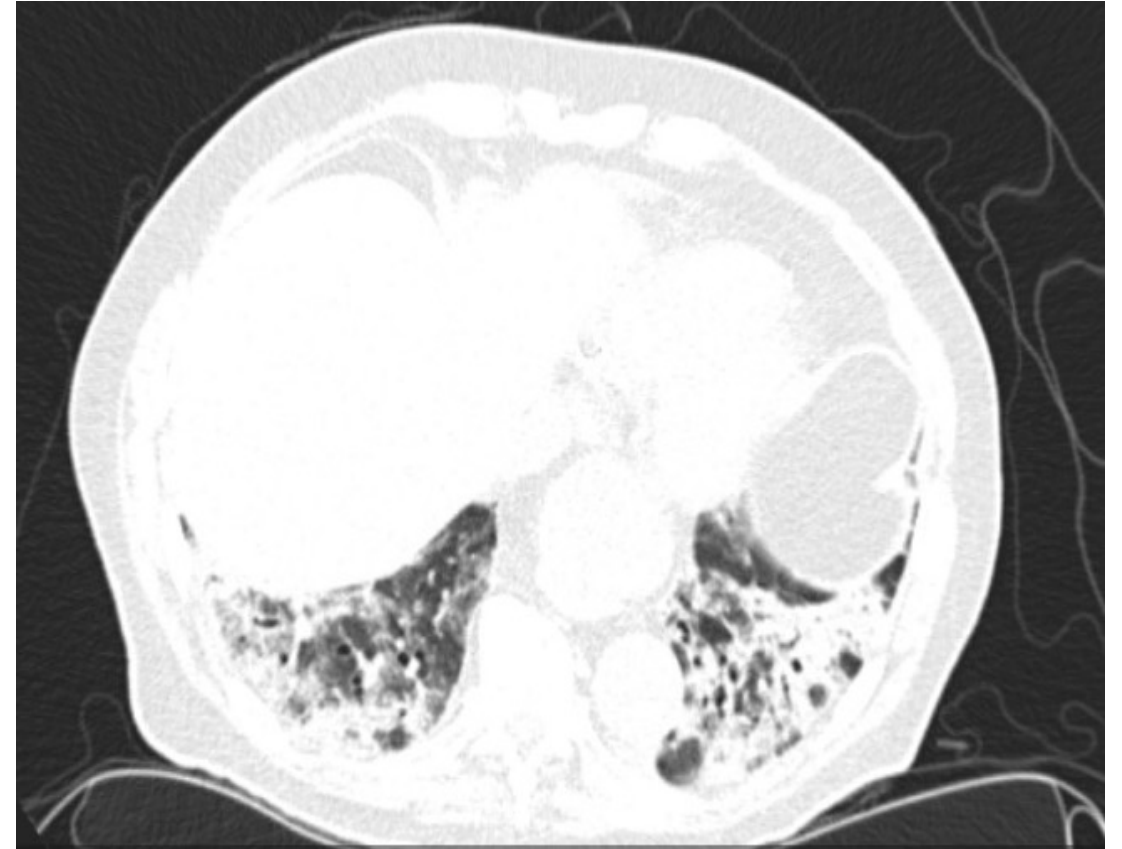
Clinical Research:

- RECOVER: Researching Covid and Recovery; NIH
- TETON: Inhaled Trepostinil in PPF; United Therapeutics

- RNAi-investigational drug in patients with IPF; Nitto Denko Corporation
- Starscape: Evaluation of Safety and Efficacy of Recombinant Human Pentraxin-2 in IPF; Roche



79 yo man, 4 weeks after COVID pneumonia with persistent hypoxemia



Peripheral predominant mixed ground glass and consolidative opacities bilaterally, some with a perilobular morphology, seen in all lung lobes. Associated mild bronchial dilation, particularly in the lower lobes. There is also associated architectural distortion and cicatricial atelectasis.

PASC; Long COVID

- Ongoing sx, acute COVID-19
- Sx persist 4-12 weeks
- Post-acute syndrome at 12 weeks after onset of acute syndrome
- Seen with all variants



PASC-The Hidden Pandemic

Estimate: At least 65 million individuals world-wide

>770 million cases of COVID -19 worldwide

Incidence estimated:

10-30% of non-hospitalized cases

50-70% of hospitalized cases

10-12% of vaccinated cases



PASC

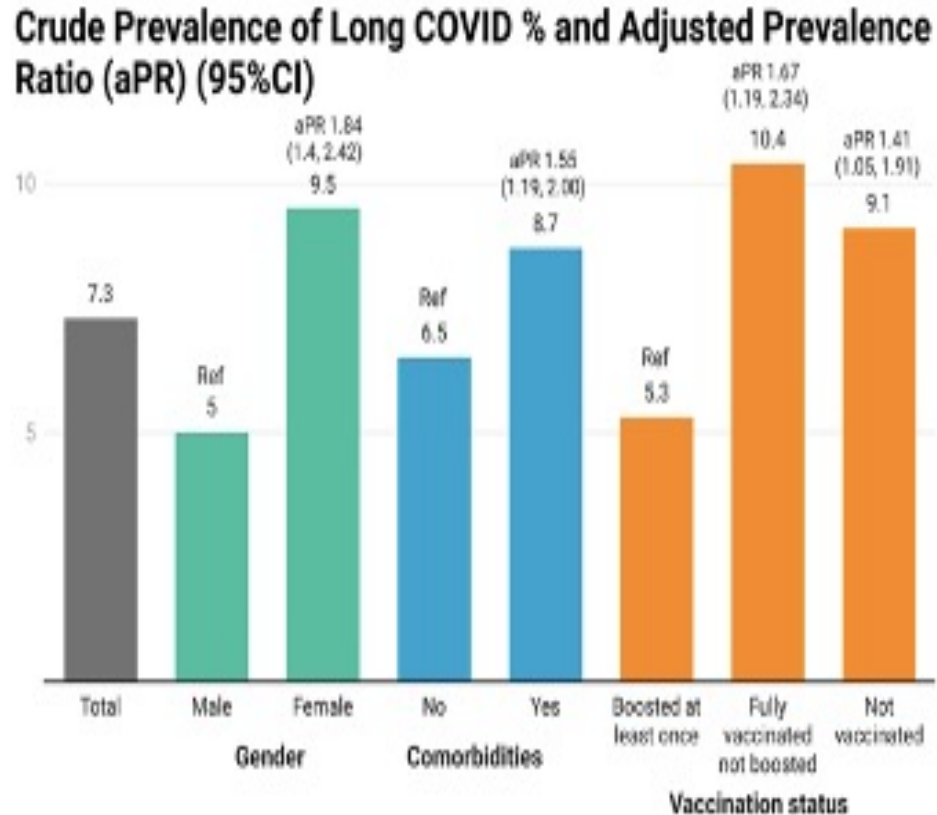
Associated with all ages and acute disease severities;
highest %: 36-50 y.o.

Most long-COVID seen in non-hospitalized pts with
mild acute illness



Epidemiology of long COVID in US adults

In a population-representative sample, we estimated **7.3%** of US adults, approximately **18 million adults**, had symptoms of long COVID during the two-week study period ending July 2, 2022.



- 25% reported day-to-day activities impacted “a lot”
- >28.9% had SARS-CoV-2 > 12 months ago

Robertson et al Clin Infect Dis 2022 Dec 21

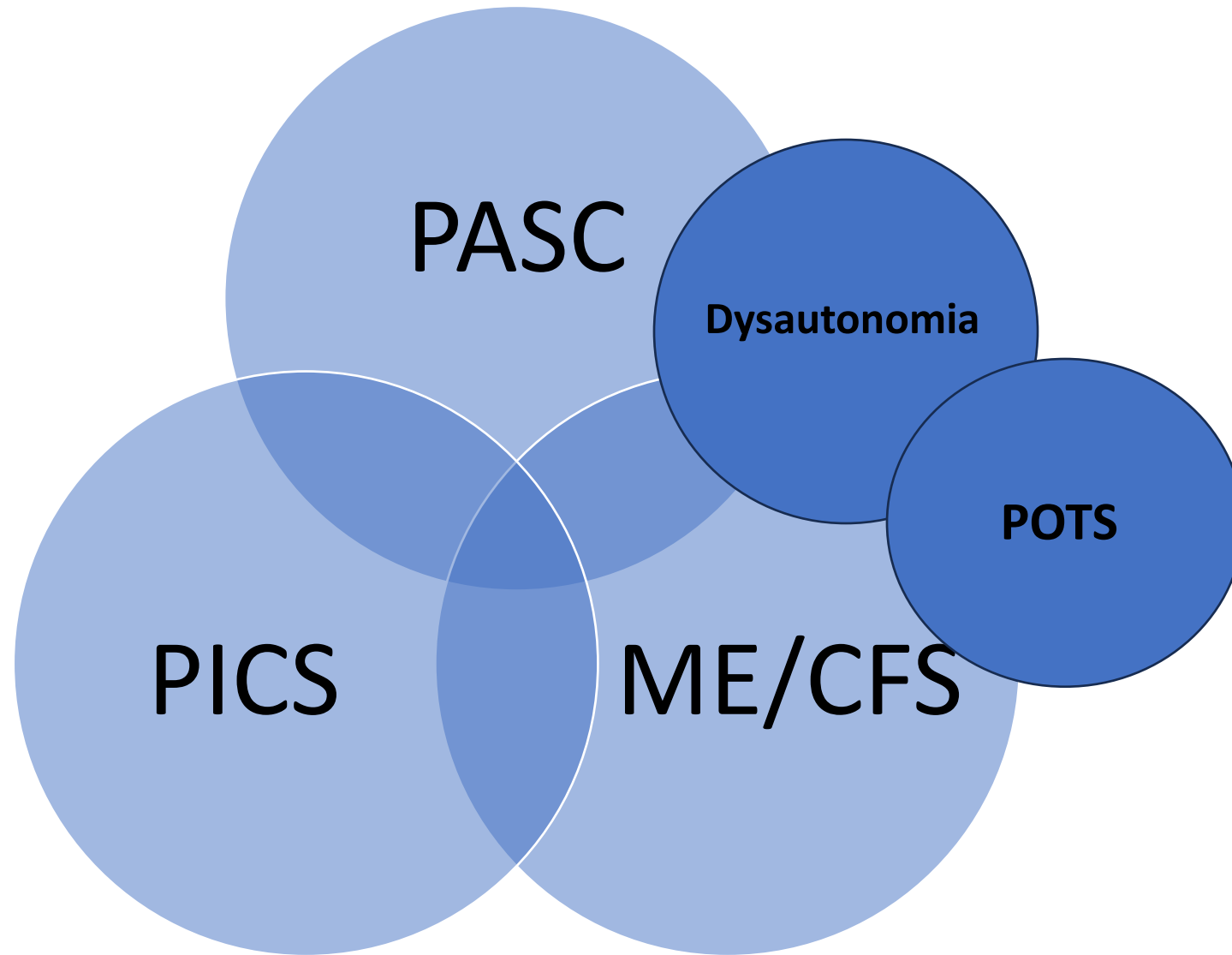


PASC: A wide clinical spectrum

- Multiple organs effected; more than 200 sx
- Common new onset conditions: Pulmonary, cardiovascular, thrombotic, type 2 DM, ME/CFS, Dysautonomia, POTS
- Sx can last for years
- *No validated effective therapies*



Overlap:



PASC: Gaps in Our Clinical Knowledge

- Inconsistencies in definition of Long-COVID
- Many studies are retrospective in design
- Relatively small sample size studies
- Reliance on self reports
- Single or limited multisite studies
- Many reports with limited follow up period
- The most impacted populations are inadequately represented



PASC and Respiratory sx

May persist for extended duration

- Cough in 20% of pts >6 months
- Dyspnea in 40% of pts >6 months

↑ IL-1 *Beta*, IL-6, IL-8

Activated T-cells



Who gets Post-COVID Pulmonary Fibrosis (PCPF)?

- Meta-analysis to investigate prevalence of PCPF
- 13 studies: 2,018 pts; prev 44.9%
- Sx: dyspnea, cough, chest pain, fatigue
- Assoc. Factors: COVID severity; mech vent; Rx with steroids, antibiotics, immunoglobulin; COPD

Amin et al. Ann Med Surg (Lond) 2022, May 7



Natural history of PCPF

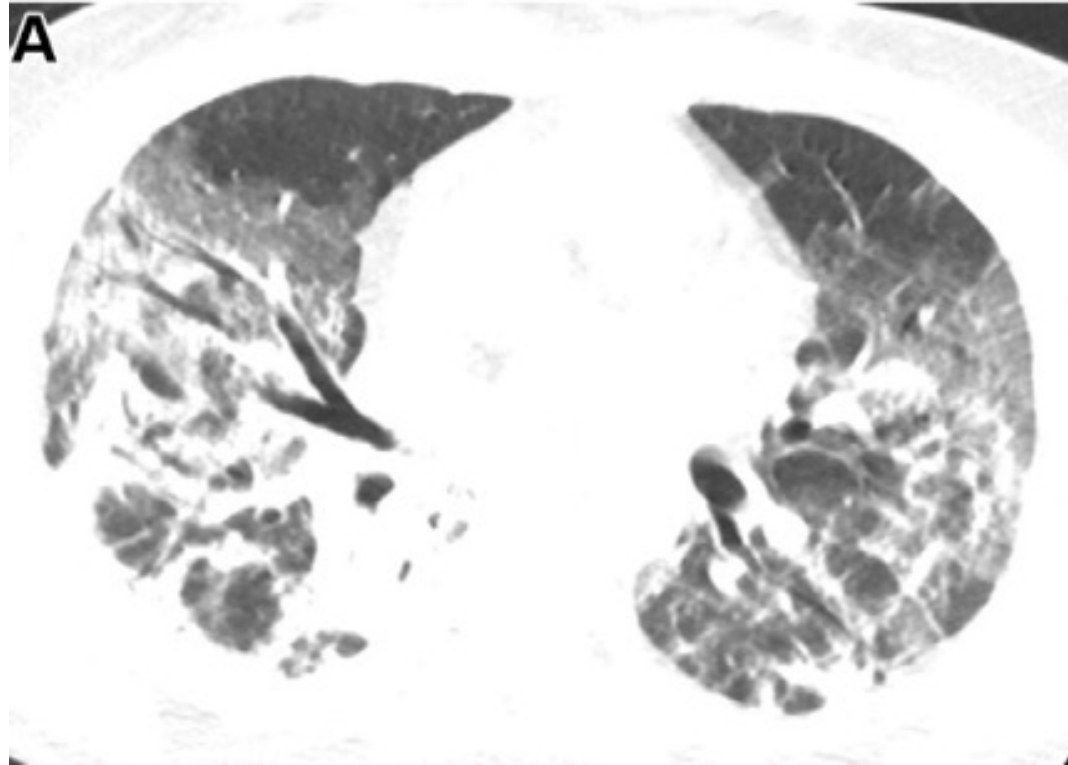
- Prospective cohort study-76 pts-4.4 mos p hosp
- Fibrotic patterns-chest ct: mech vent; male; more severely ill; ↑↑LDH; shorter telomere length
- Fibrosis: cough, DLCO, fragility
- Dyspnea: frailty score, ↓ grip strength

McGroder et al Thorax 2021 Dec



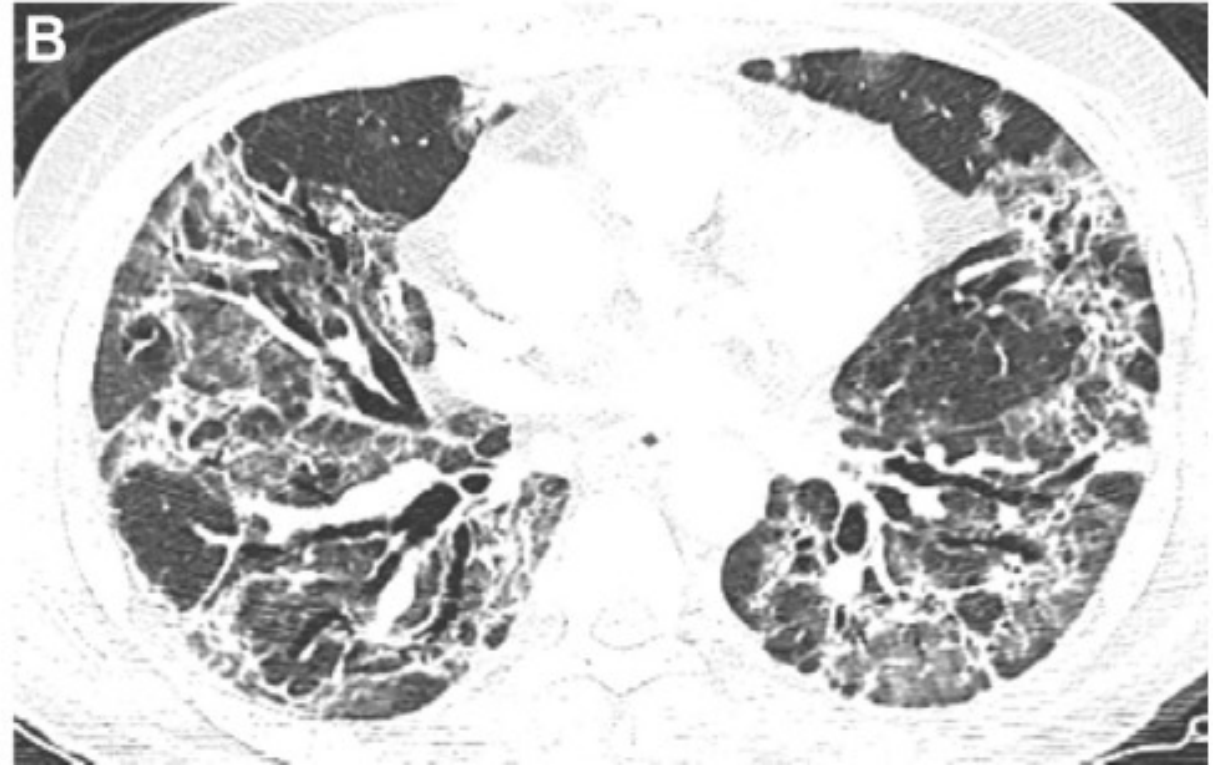
PASC-CT chest- Fibrosis

2 weeks p admission



Diffuse GGO; Retic

6 months p admission



GGO; traction bronchiectasis; architectural distortion; air trapping (?? Honey-comb)

Organizing Pneumonia

- Common with many infections
- Viral-induced damage to alveolar epithelial cells and endothelial cells, associated with inflammation, intra-alveolar edema
- Fibroproliferative process
 - without major disruption of lung architecture
 - potentially reversible



PASC-Etiology and Pathophysiology

- Organ damage from acute infection phase
- Ongoing viral activity associated with a host viral reservoir
- Vagus nerve dysfunction
- Mitochondrial dysfunction
- Gut dysbiosis
- Persistent inflammatory state
- Serotonin reduction
- Immune dysregulation
- Autoimmunity
- Blood clotting and Endothelial dysfunction



PASC & Pulmonary Fibrosis-3D imaging and multi-omics analysis

- Widespread microvascular occlusions
 - microvascular thrombi of pulm and bronchial vessels
 - Lobular ischemia
- Intussusceptive neo-angiogenesis
 - Proangiogenesis and profibrotic signaling
- Fibrotic remodeling
- Associated plasma markers

Ackermann et al EBioMedicine 2022



Dynamic Contrast-enhanced MRI: Pulmonary Microvascular Abnormalities

DCE-MRI: continuous dynamic imaging before, during, and after injection of gadolinium-based contrast

10 pts with hx (non-severe) COVID; \approx 8 mos, prior vs 10 controls

Pts: \downarrow pulmonary microvascular perfusion (NI DLCO in 90%)

Zhou et al Am J Crit Care Med 2023



Management of PCPF

- Observe: patients improving on their own
- Anti-fibrotics
 - **Pirfenidone**—blocks fibroblast prolifer, myofibroblast differentiation, collagen deposition; anti-inflammatory; ↓ expression ACE-2 receptor
 - short term course → with improvement in uncontrolled reports



Clinical Trials for Rx PCPF

- Pirfenidone; Deupirfenidone
- Nintedanib
- Fuzheng Huayu
- Sirolimus
- Canrenoate potassium
- Nirmatrelvir-ritonavir (Paxlovid)
- Longidaze
- Collagen-polyvinylpyrrolidone
- Antifibrotic monocyte
- Treamid
- Tetrandrine
- Genistein nanoparticles



Current treatment for Post COVID OP (PCOP)

- No approved treatments
- Most pts with PCOP recover within 1 yr
- 5-25% need specialized Rx
- Steroids → response in majority
 - Limited by high relapse frequency
 - Adverse Side effects
- “Steroid-sparing” agents – limited data



Persistent Post COVID-19 Inflammatory ILD: An Observational Study of Steroid Treatment

- 837 pts screened by phone for sequelae of Covid19 pneumonia @ 4 weeks post discharge
- Pts with sx had out-pt eval @ 6weeks
- 39% reported ongoing sx
- 4.8% - dx with ILD, predominantly org. pneumonia
- Objective: to prevent fibrosis with permanent deficit
- 30 pts received steroid treatment
- Result: ↑ in transfer factor of 32%; ↑ in FVC of 10%

Improvement in sx and imaging

Caveats: small group; not RCT; ? Spontaneous recovery; ?

Long-term

Annals ATS Jan 12, 2021



Can PASC be Prevented with Rx during Acute COVID?

Rx with Paxlovid among vaccinated, non-hosp pts during acute COVID-not assoc with lower prevalence of long-COVID sx after 90 days.

No relationship to rebound

Limitations: biased; not RCT; retro; self report quest.

Chung et al Journal of Medical Virology 2023



Long-COVID: Pulmonary Fibrosis Evaluation

Comprehensive history, exam, routine screening studies. Serologies for autoimmunity.

PFTs; CPET if sx are disproportionate

HRCT chest

Screen for PEM; Exclude cardiac impairment; O₂ desaturation; Autonomic dysfunction



New Diagnoses – MGH Pulmonary CORE Clinic

- Auto- immune disorders
- ANCA+ disease
- Asthma
- Bronchiectasis
- Bronchiolitis
- Organizing pneumonia
- Pulmonary fibrosis
- + ANA
- Small fiber neuropathy
- Dysautonomia
- Fibromyalgia
- Sleep-related breathing problem
- Laryngeal abnormalities
- Malignancy



CORE Clinic & Lessons Learned

- Avoid cognitive bias
- Consider differential diagnosis as usual
- Do not assume that sx that occur post-COVID-19 are necessarily secondary to COVID -19
- Speculation: Auto-immune (and other) disorders may become more apparent following the immune/inflammatory disorder associated with acute COVID



RECOVER

- REsearching COVID to Enhance Recovery
- NIH-sponsored initiative seeking to understand, prevent, and treat PASC
- Award of nearly \$470 million
- More than 30 institutions utilizing a set of main protocols
- Build a study population of Tens of thousands
- Big Data

