Post COVID Syndrome: An Overview and Approach to Management

March 30, 2021

AETC AIDS Education & Training Center Program Midwest

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AETC AIDS Education & Training Center Program South Central

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Speakers

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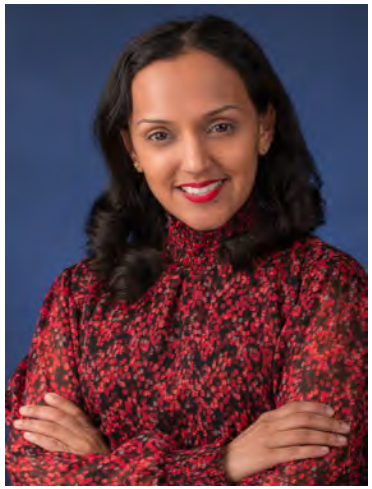

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Disclosures

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- Dr. Swindells reports research grants to her institution from ViiV Healthcare
- Drs. Yusuff and Kulkarni have no conflict of interests to disclose

Learning Objectives

- Define post COVID syndrome and describe its clinical characteristics
- Review useful strategies for the diagnosis and management of post COVID syndrome

Post Acute Sequelae of COVID-19

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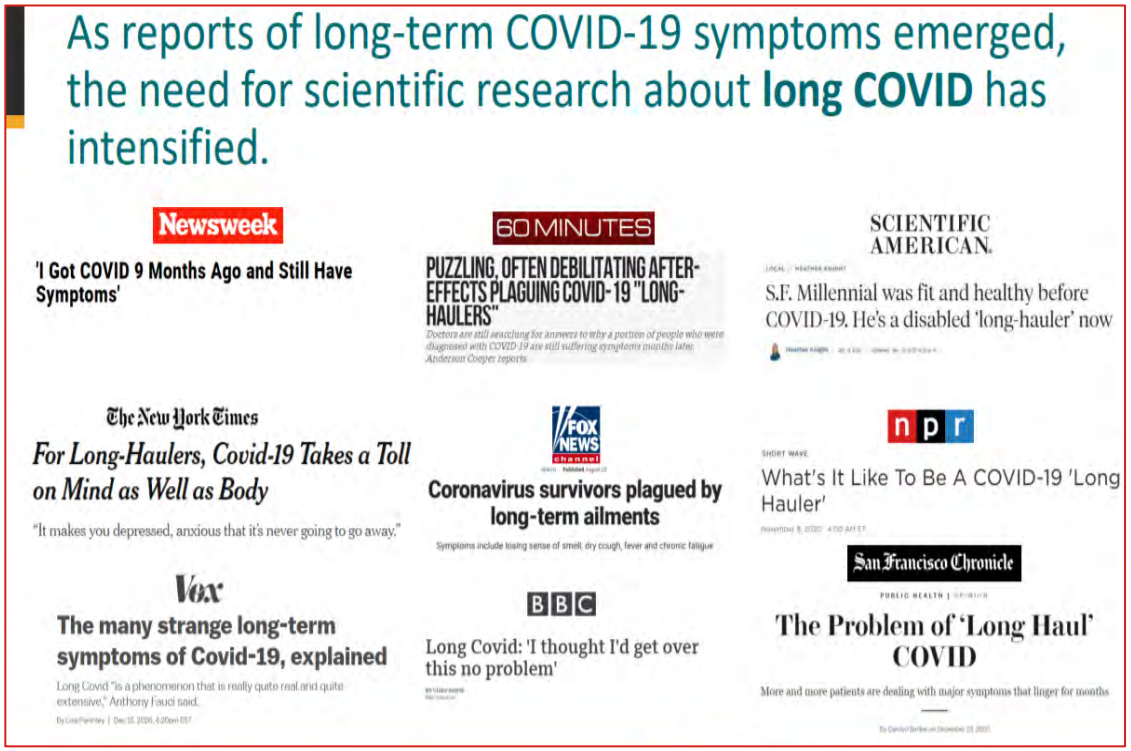
OUTLINE

- What is Post-Acute Sequelae COVID-19 (PASC)?
- What are the predominant sign/symptoms
- What are the specific end organ disease?
- What are the management strategies?
- What are areas for further research?

Long COVID = Long Hauler = PASC



Often referred to as “Long COVID”, these symptoms, which can include fatigue, shortness of breath, “brain fog”, sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression, can persist for months and **can range from mild to incapacitating**. In some cases, new symptoms arise well after the time of infection or evolve over time. **-NIH**

Preliminary reports indicate some patients may develop a so-called “post-acute COVID-19 syndrome,” in which they experience persistent symptoms after recovering from their initial illness. **The syndrome appears to affect those with mild as well as moderate-to-severe disease.** The incidence, natural history and etiology of these symptoms is currently unknown -**CDC**

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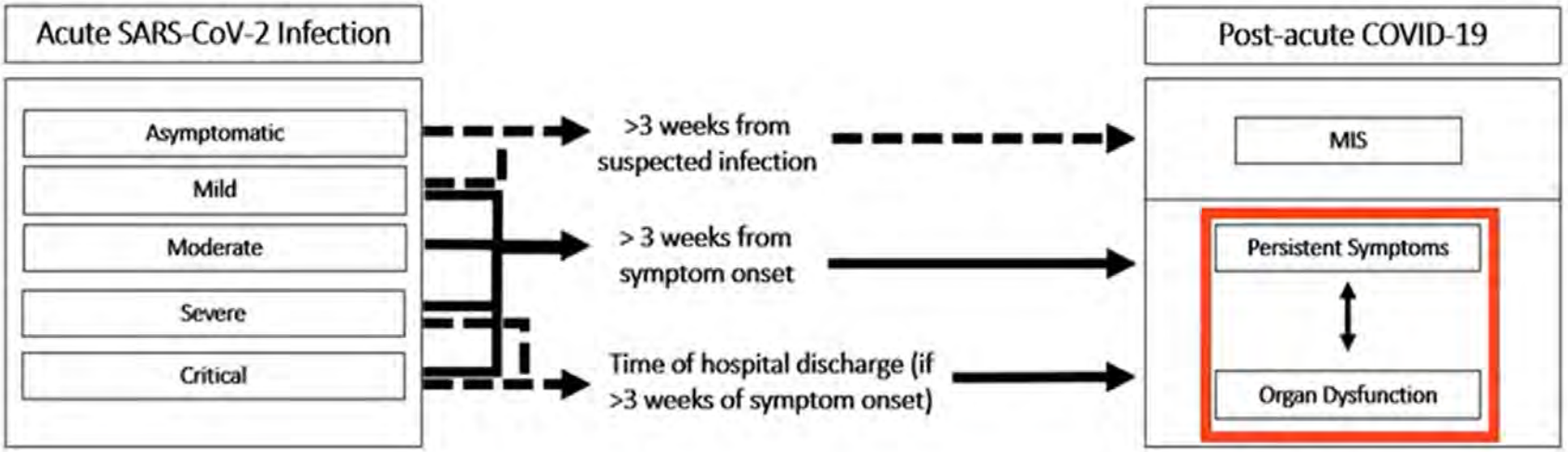
Framework for Categorizing PASC



MIS = Multisystem Inflammatory Syndrome

There is likely a relationship between organ dysfunction and persistent symptoms that is not yet completely understood.

Ameta EM et al. OFID. 2020 Oct 21;ofaa509.

Varying Definitions of When PASC Starts

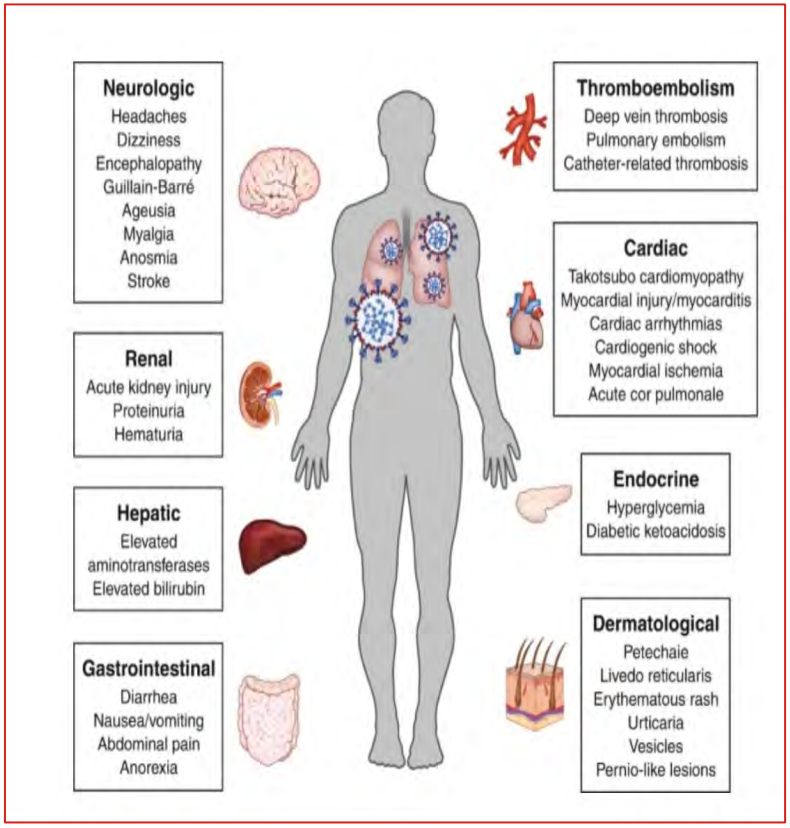
- OFID: Framework of PASC estimated 3 weeks post infection
- CDC JAMA: Proposed Framework of Timeline: suggests 4 weeks post infection
- Guidelines from the UK's National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP).
- Their breakdown is as follows:
  - **Acute COVID-19**: signs and symptoms of COVID-19 for up to 4 weeks.
  - **Ongoing symptomatic COVID-19**: signs and symptoms of COVID-19 from 4 to 12 weeks.
  - **Post-COVID-19 syndrome**: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis

https://www.nice.org.uk/guidance/NG188

Open Forum Infect Dis. 2020 Oct 21;7(12):ofaa509. doi: 10.1093/ofid/ofaa509. PMID: 33403218
JAMA. 2020 Dec 8;324(22):2251-2252. doi: 10.1001/jama.2020.22717. PMID: 33206133.

Long-Term Sequelae of COVID-19

- Limited peer reviewed data
- Severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infection long term complications not uncommon
  - Depression, anxiety, post-traumatic stress disorder (PTSD) and post-intensive care syndrome (PICS)
- Entry receptor angiotensin-converting enzyme 2 (ACE2) expressed in extrapulmonary tissue



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Symptom Persistence

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Symptom Persistence Among Inpatients

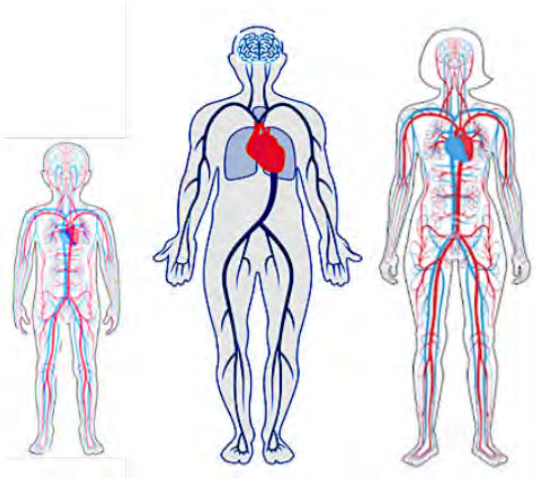
COVID-19: Persistent Symptoms in Hospitalized Patient

A Multi-Organ, Multi-System Clinical Presentation

120 patients (mean = 111 days post admission)

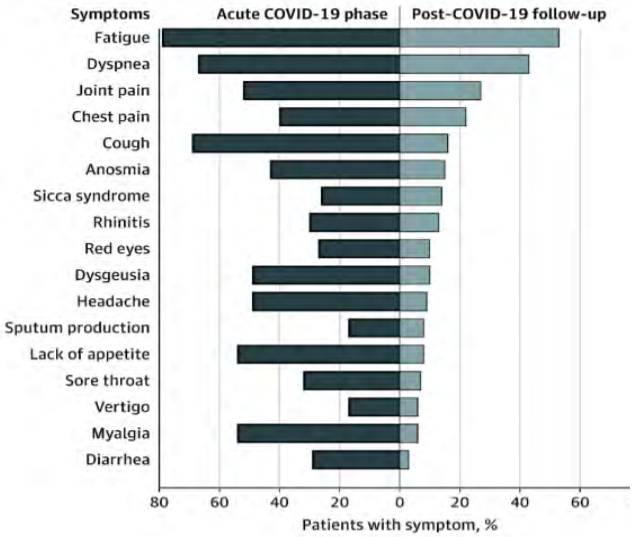
Persistent symptoms

- Fatigue 55%
- Difficulty breathing 42%
- Memory loss 34%
- Sleep disorder 32%
- Attention disorder 27%
- Significant hair loss 20%
- Cough 17%
- Loss of smell 13%
- Chest pain 11%
- Loss of taste 11%



Garrigues et al. Infect. 2020 Aug 25:S0163-4453
https://doi.org/10.1016/j.jinf.2020.08.029

143 patients (mean 60 days post onset)



Carifi, et. al. JAMA. 2020;324(6):603-605.
doi:10.1001/jama.2020.12603

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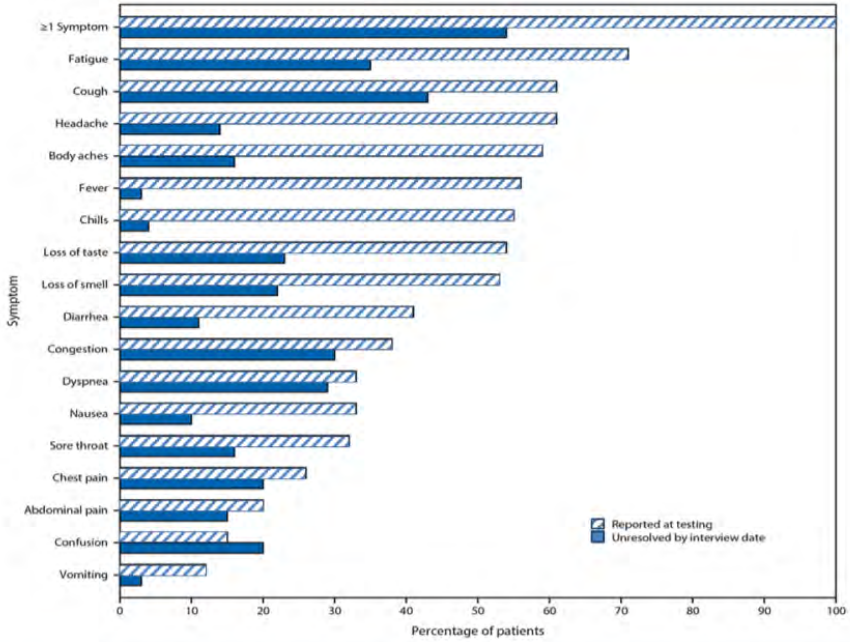
Symptom Predominance Among Outpatients

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
July 31, 2020
Morbidity and Mortality Weekly Report (*MMWR*)

Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020

MW Tenforde, LR Feldstein et al. for the IVY Network Investigators and CDC COVID-19 Response Team



Among symptomatic <u>non hospitalized</u> patients with positive test for SARS-CoV-2, 35% not returned to baseline health <u>2-3 weeks</u> after testing

- Older age and comorbidities associated with lack of return to baseline health
- 19% of young adults (18-34) with no comorbidities had not returned to baseline health
- In contrast 90% of influenza outpatients recover within 2 weeks

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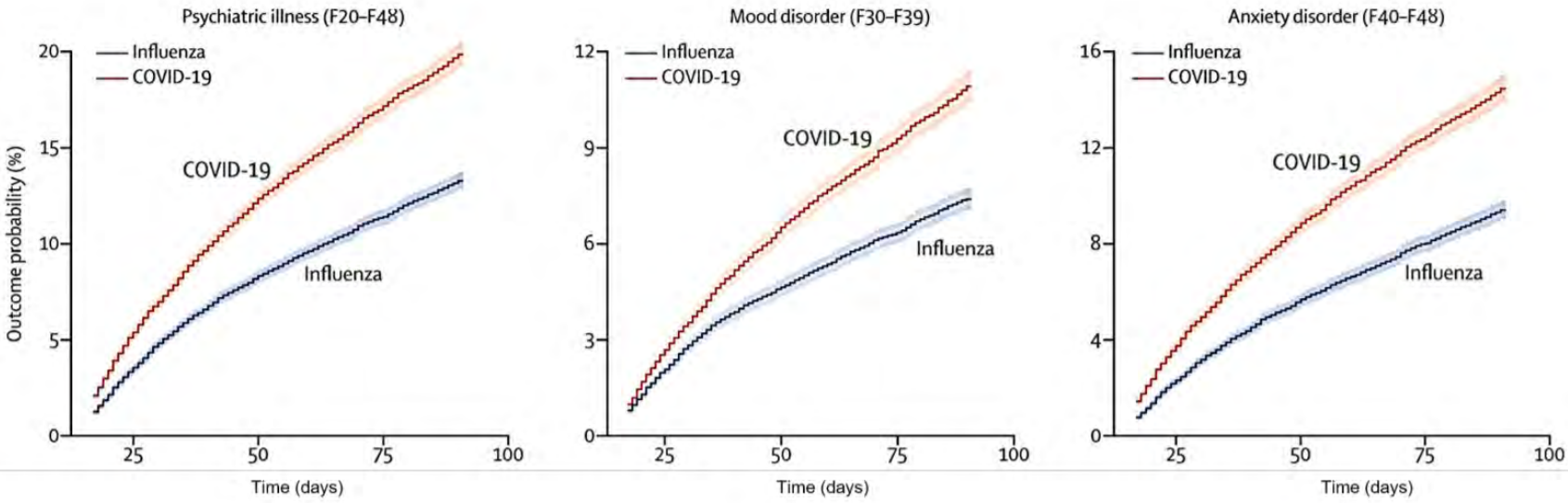
New diagnoses of anxiety, insomnia, dementia, and mood disorders, as well as psychiatric disorders in general, were increased after COVID-19 illness



www.thelancet.com/psychiatry Published online November 9, 2020 https://doi.org/10.1016/S2215-0366(20)30462-4

ORGAN DYSFUNCTION

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NEUROLOGIC INVOLVEMENT

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Neurologic Sequelae

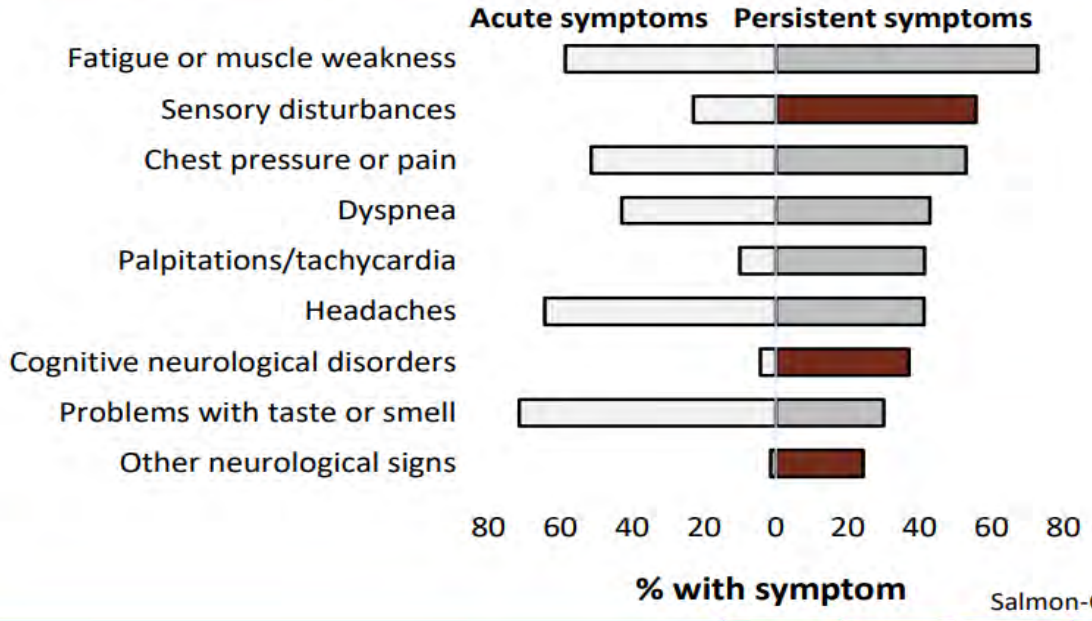
- Acute Manifestations
  - Headache, vertigo, weakness, anosmia, ageusia
  - Encephalopathy, seizures, strokes,
  - Guillain Barre

- Post-Acute Manifestations
  - Major Mood swings-depression/anxiety
  - “Brain Fog”
  - Dysautonomia
  - Paresthesias
  - Headaches

Long Term Neurologic Symptoms

More than one quarter of patients **developed new neurological symptoms** after their acute COVID-19 illness.

COVID-19 symptoms among 70 non-hospitalized patients, France



Salmon-Ceron et al., J Infect. 2020

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Possible Neurologic Workup for Symptoms

- History/Physical Exam:
  - Age, comorbidities, course of COVID, other screening for PTSD, depression and psychiatric screening
- Lab:
  - Standard labs, HIV, HgbA1c, B12, TSH, Rheum w/u
- Imaging:
  - Consider MRI, MRA
- Other testing:
  - EMG, EEG, Orthostatic, tilt table

https://emergency.cdc.gov/coca/calls/2021/callinfo_012821.asp, Allison Nevis Mt. Sinai

Possible Treatment Modalities

- **Brain fog**: – No specific treatment – Address any abnormalities in bloodwork – Address contributing factors – If attention is major issue: Atomoxetine, dextroamphetamine/amphetamine, methylphenidate, modafinil
- **Dysautonomia**: – Hydration, increase salt intake, compression stockings – Meditation, breathwork – Postural Orthostatic Tachycardia Syndrome (POTS): consider adding in midodrine or fludrocortisone – Hyperadrenergic POTS: betablocker
- **Small fiber neuropathy:** – Address any abnormalities in bloodwork – Symptomatic treatment of paresthesias: gabapentin, pregabalin, tricyclics, duloxetine – Dysautonomia as above
- **Fatigue:** Pacing of exercise: low-impact, short duration exercise with gradual increase. Do not push to recondition quickly.
- **Sleep:** – Sleep hygiene – Assess for possible sleep apnea – Sleep aids: melatonin, mirtazapine, gabapentin or amitriptyline (if paresthesias or headaches also present)
- **Mental Health**: Depression, anxiety and PTSD can affect cognition; Anti-depressants like duloxetine or venlafaxine may be beneficial in also treating paresthesias and/or headaches

https://emergency.cdc.gov/coca/calls/2021/callinfo_012821.asp, Allison Nevis Mt.Sinai

PULMONARY INVOLVEMENT

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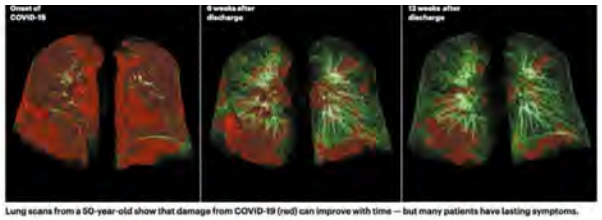
Pulmonary

- Acute Manifestations
  - Pneumonia
  - Acute respiratory distress syndrome (ARDS)
  - Hypoxic respiratory failure
- Post-Acute Manifestations
  - Signs and symptoms of chronic fibrosis and restrictive lung disease

Pulmonary Sequelae

- In 55 COVID survivors symptoms of restrictive lung disease common among those hospitalized
  - 30 days: 53% DLCO
  - 3 months: 25% DLCO
  - 3 months: 71% evidence of interstitial thickening



Lung scans from a 50-year-old show that damage from COVID-19 (red) can improve with time — but many patients have lasting symptoms.

Zhao YM et al Eclinical Medicine 2020:25:100463

- 150 patients with noncritical COVID were followed 2 months found:
  - 30 days: 36.7% with dyspnea
  - 60 days: 30% with dyspnea

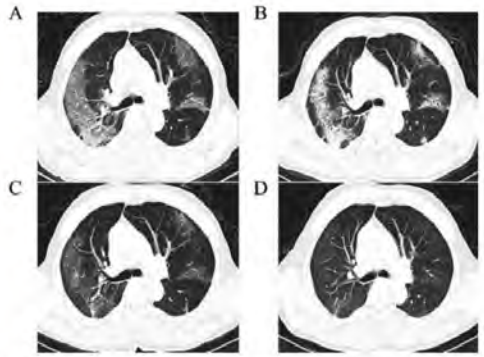


Fig. 2. Follow-up thin-section CT imaging of 63-year-old man with confirmed COVID

Huang Y, Respir Res, 2020;21(1):163

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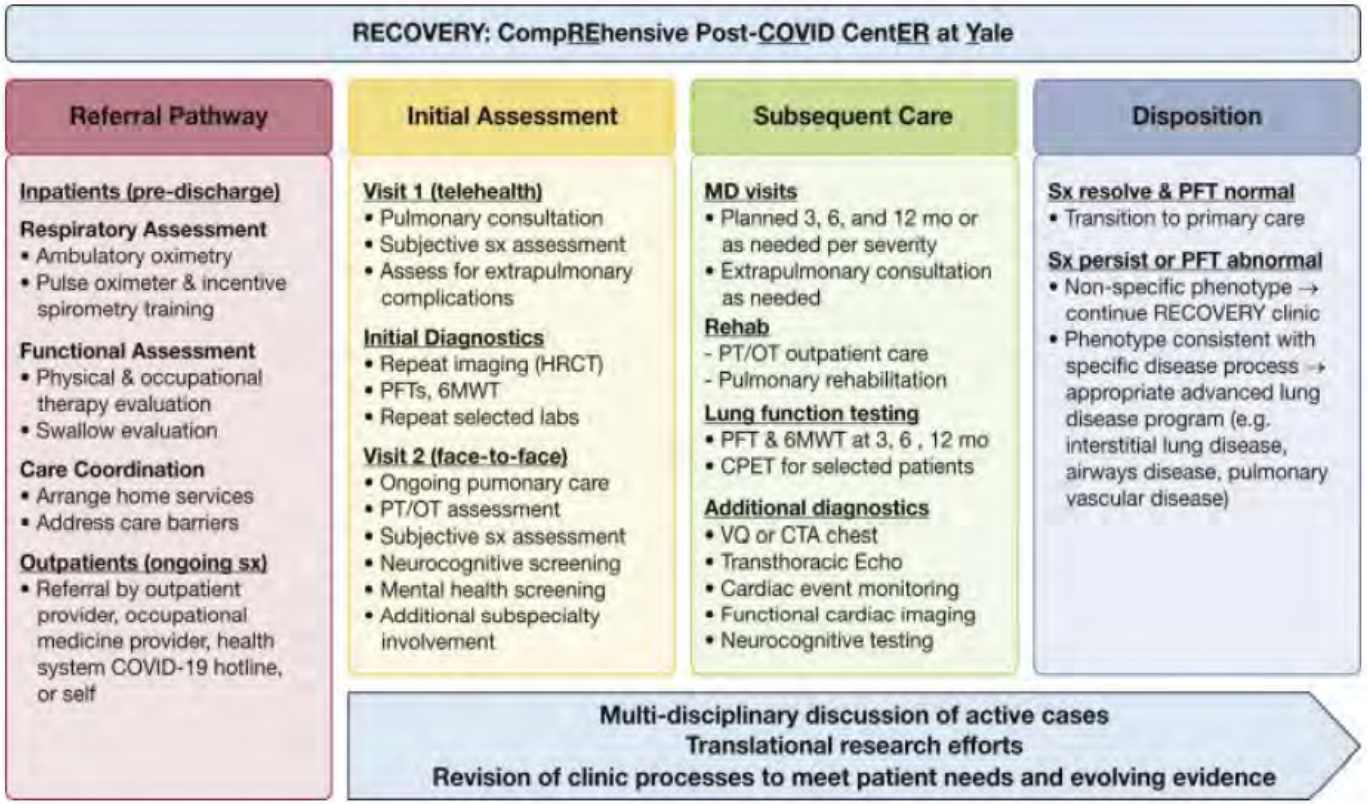
Our initial clinical model: Post COVID Clinic Pathway at Yale



Lutchmansingh et al, Chest 2020

CARDIAC INVOLVEMENT

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Cardiovascular

- Acute Manifestations
  - Cardiac injury
  - Myocarditis
  - Arrhythmias
  - Cardiogenic shock
- Post-acute manifestations
  - Myocarditis
  - Arrhythmia
  - Cardiomyopathy

MRI Outcomes in Patients Recovered

JAMA Cardiology | Original Investigation

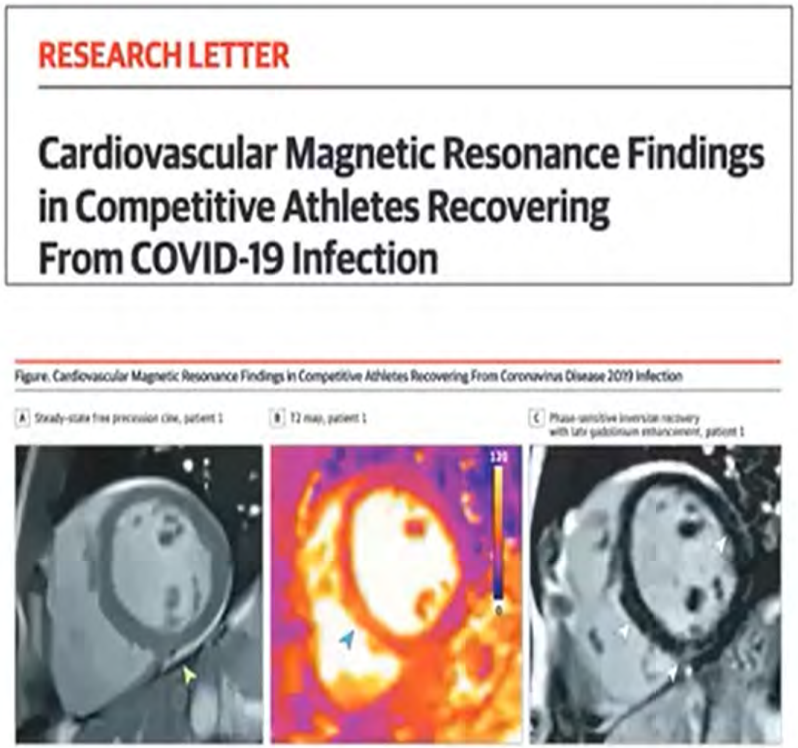
Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

- German study, n=100
- Cardiac MRI done in median 71 days after COVID-19 diagnosis
- Cardiac involvement in 78%
- Ongoing myocardial inflammation in 60%
- Presence of chronic comorbidities, duration and severity of acute COVID-19 time since original diagnosis did not correlate with findings

Non-random sample likely biased toward cardiac findings.

Puntmann VO et al. JAMA Cardiol. 2020 Jul 27;e203557.

MRI Findings in Athletes


RESEARCH LETTER

Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection

Figure. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From Coronavirus Disease 2019 Infection

A Steady-state free precession cine, patient 1 B T2 map, patient 1 C Phase-sensitive inversion recovery with late gadolinium enhancement, patient 1

- 26 competitive college athletes diagnosed with COVID-19
- None were hospitalized
- Majority had no symptoms
- 12 (46%) had evidence of myocarditis or prior myocardial injury by cardiac MRI (12-53 days)

Rajpal s et al JAMA cardiol 2020 Sep 11; e204916

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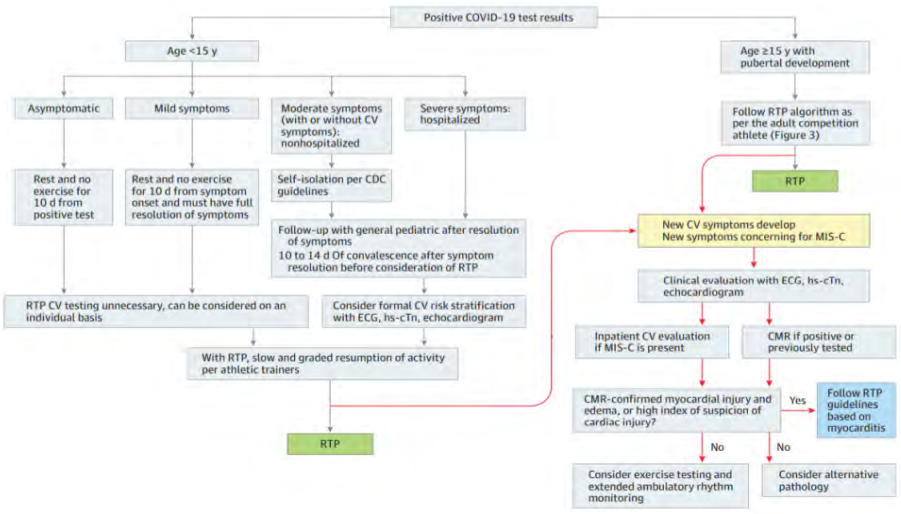
Cardiac Algorithms for Athletes

JAMA Cardiology

Coronavirus Disease 2019 and the Athletic Heart
Emerging Perspectives on Pathology, Risks, and Return to Play

Jonathan H. Kim, MD, MSc; Benjamin D. Levine, MD; Dermot Phelan, MD, PhD; Michael S. Emery, MD, MS; Mathew W. Martinez, MD; Eugene H. Chung, MD, MSc; Paul D. Thompson, MD; Aaron L. Baggish, MD



JAMA Cardiology

Return to Play for Athletes After Coronavirus Disease 2019 Infection—Making High-Stakes Recommendations as Data Evolve

James E. Udelson, MD; Michael A. Curtis, MEd, CSCS; Ethan J. Rowin, MD

- Complex algorithms published for high school athletes, adult engaged in recreational sports, and professional athletes
- Slow escalation of activity recommended for those with mild COVID and no CV symptoms
- Aggressive work-up (ECG, troponins, echocardiogram) for those with CV symptoms (particularly syncope), progressing to CMR as needed

RECOVERY AND FOLLOW-UP

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Other Aspects of Recovery

- Provide multidisciplinary clinics
  - Respiratory, Cardiology and Neurology specialty care
  - Rehabilitation requirements
  - Case management support for housing and food
- Listen to our patients
  - Mental health care for anxiety and depression
    - Referrals for counseling and peer support
  - Self management for disease monitoring
- Public Health Messaging for young people to avoid infection—it's not all about COVID Mortality

Management of post-acute covid-19 in primary care | The BMJ

Recovery…what we still don't know..

- What is the spectrum of clinical "recovery" from COVID-19?
- What interventions might enhance or hasten recovery?
- What is the spectrum of tissue injury due to COVID-19 infection?
- Will unabated symptoms lead to chronic illness in a subset of people?
- Will COVID-19 predispose to other disease in the future?

FUTURE STUDIES

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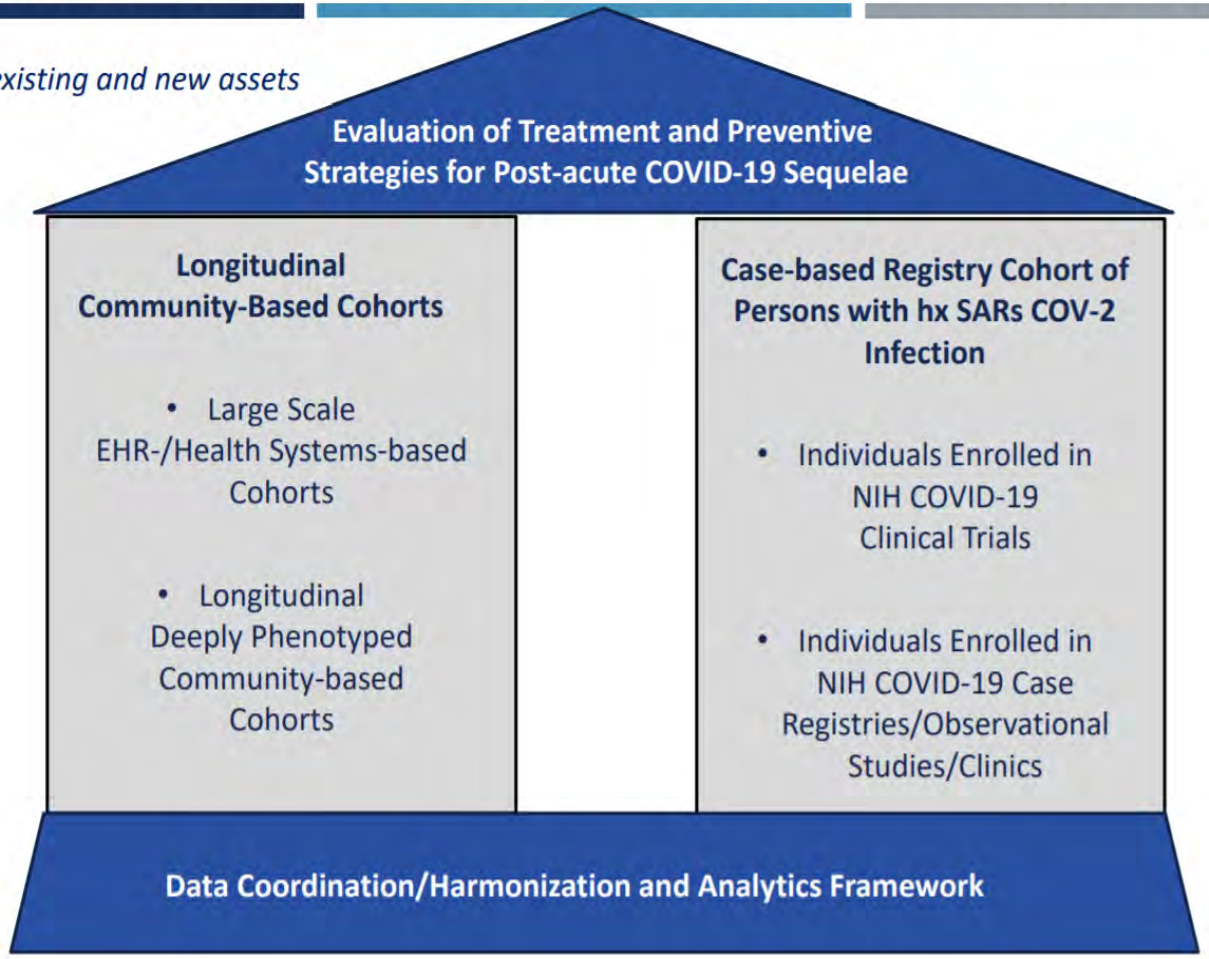
NIH Clinical Research Strategy to Understand and Treat Post-acute Sequelae of COVID-19

Note: Includes existing and new assets



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Resources

- **CDC webpages on PASC:**
  - **For the general public**:
    https://www.cdc.gov/coronavirus/2019- ncov/long-term-effects.html
  - **For clinicians:**
    https://www.cdc.gov/coronavirus/2019- ncov/hcp/clinical-care/late-sequelae.html

    Webinar January 28, 2021 - Treating Long COVID: Clinician Experience with Post-Acute COVID-19 Care (cdc.gov)

- **NIH Workshop on PASC:**

  Day 1: https://videocast.nih.gov/watch=38878

  Day 2: https://videocast.nih.gov/watch=38879

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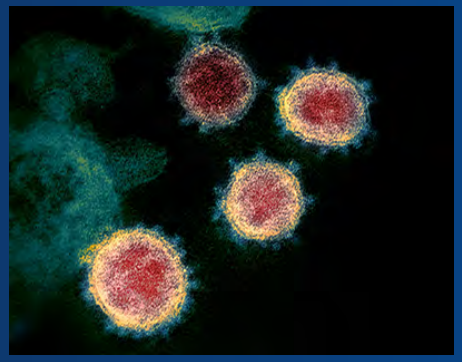

Post COVID Syndromes: Cases

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Case 1

Mario R, aged 22, and his brother live in Chicago. Their father worked in meat packing plant, and he became ill with fever and shortness of breath (SOB) in April, 2020

- Found to be COVID+, hospitalized & died in 2 weeks

Mario and his brother both had anosmia. His brother also had a URI and tested SARS-CoV-2 positive in April, 2020; Mario tested negative, and had no repeat testing, no other symptoms

- Mario's brother recovered fully; 2 cousins in the same building also tested positive, and had no symptoms

Mario developed SOB, fatigue, and joint pain after 3 weeks

- Increasing fatigue, post-exertional exhaustion for 3 months that prevented him from working and attending classes
- Noticed increasing lack of concentration, HA from June – Sept
- Improved but 'still not right' as of Oct, 2020, 6 months later

Case 1: Questions

CASE SUMMARY:

22 yo man w/ likely false negative PCR

Initial anosmia only

Post COVID Syndrome with Chronic fatigue, arthralgia, post-exertional exhaustion, HA, & poor concentration x 6 mos

Does Mario require a positive Ag test for the diagnosis of Post COVID Syndrome?

- Is a + SARS-2 Ab test needed?

What is the pathogenesis of this form of post-COVID syndrome?

What medical evaluation should be conducted?

- Differential diagnosis
- Role of PFTs; exercise testing; OT/PT; CT/MRI

What are the options for treatment and management?

What to tell Mario re: prognosis?

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Case 2

Jane P., a 79-year-old ambulatory African-American female presenting to the ED 11/30/20 with 3 days of cough & dyspnea.

- Dry cough and shortness of breath 3 days PTA
  - Symptoms have worsened
- Abdominal pain and decreased appetite for the past 1 week, has been able to tolerate fluids
  - Abdominal pain is intermittent, non-radiating and localized around the periumbilical region

Contact w/ son who is CTA bus driver, currently at UCM w/ SARS-CoV-2

Case 2

PMHx: Colon CA 1987, HTN, DM, Obesity

On multiple meds

PE: BP 158/114, Pulse 97, RR 24

T 37.5c, SpO2 99% on RA, alert, in NAD, exam unremarkable

CXR: no infiltrates

Initial Labs

CBC

WBC	8.0
Hgb	12.8
Plt	165
Neutrophils	72
Lymphocytes	18
Monocytes	10
Eosinophils	0
Basophils	0
Immature Grans.	0.1

Cardiac Markers

hsTrop	**17 -> 19 -> 21** (Ref. <14)
proBNP	442 (Ref. <450)

CMP

Na	**131**
K	4.2
Cl	**94**
CO2	23
BUN	14
Cr	1.4
Gluc	**261**
Ca	8.6
Total protein	7.4
Albumin	3.9
Tbili	0.3
Bili, conj	<0.1
Bili, unconj	-
Alk Phos	96
AST	35
ALT	30

HgbA1c	**10.7**

Inflammatory Markers

Fibrinogen	**433** (Ref. 180-409)
D Dimer	**0.6** (Ref. <0.40)
Ferritin	**549** (Ref. 10-220)
ESR	**56** (Ref. 1-53)
CRP	**85** (Ref. <5)
LDH	**312** (Ref. 116-245)
CK	**254** (Ref. 9-185)

Infectious Disease

Blood Cx	Negative
MRSA Screen	Negative
HIV Ab/Ag	Non-reactive
Legionella Urine Ag	Negative
S. pneumo Ag	Negative
RVP	Negative
C. dif PCR	Negative
SARS-COV-2	**POSITIVE on 3/29/20**

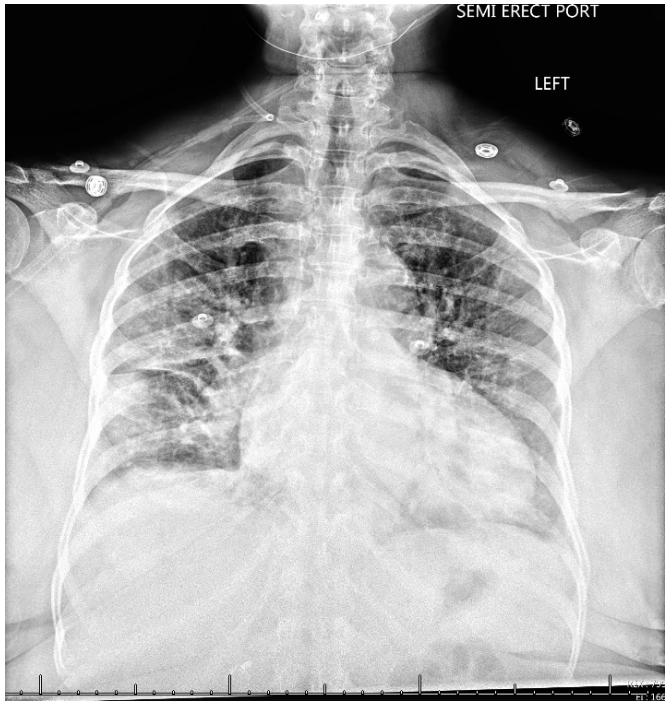
Influenza A/B — Negative

Initial Assessment & Plan

1. Viral pneumonia due to SARS-CoV2
   - Oxygen support as needed
   - Remdesivir, dexamethasone held due to NL CXR, no O2 requirement
   - Antibiotics held, given afebrile, NL CXR, neg strep/legionella
   - Abdominal pain: Likely related to viral infection
2. Prophylaxis: Started prophylactic dose of LMW Heparin
3. Admitted to COVID unit

Hospital Course: Day 2

- Interval history
  - Spiked a **fever of 39.5** C overnight
  - WBC ct 14.1 (from 8.9 on HD 2)
  - Na+ 128, creat 3.4
  - Increasing 02 needs: **4 L NC -> 40L HFNC**
  - Started **remdesivir** 200 mg IV for 5 days
  - Started **dexamethasone** 6 mg po x 10d
  - Started cefdinir & azithromycin



HD 2: Increase in hazy mid and lower lung opacities consistent with atypical infection given history.

- Assessment/Plan
  - Hypoxic respiratory failure: Hold intubation for now
  - Hyponatremia: Fluid restrict + high-dose furosemide
  - Nephrology consult: Confirmed ATN w/ urine sediment
  - ***Transferred to COVID ICU***

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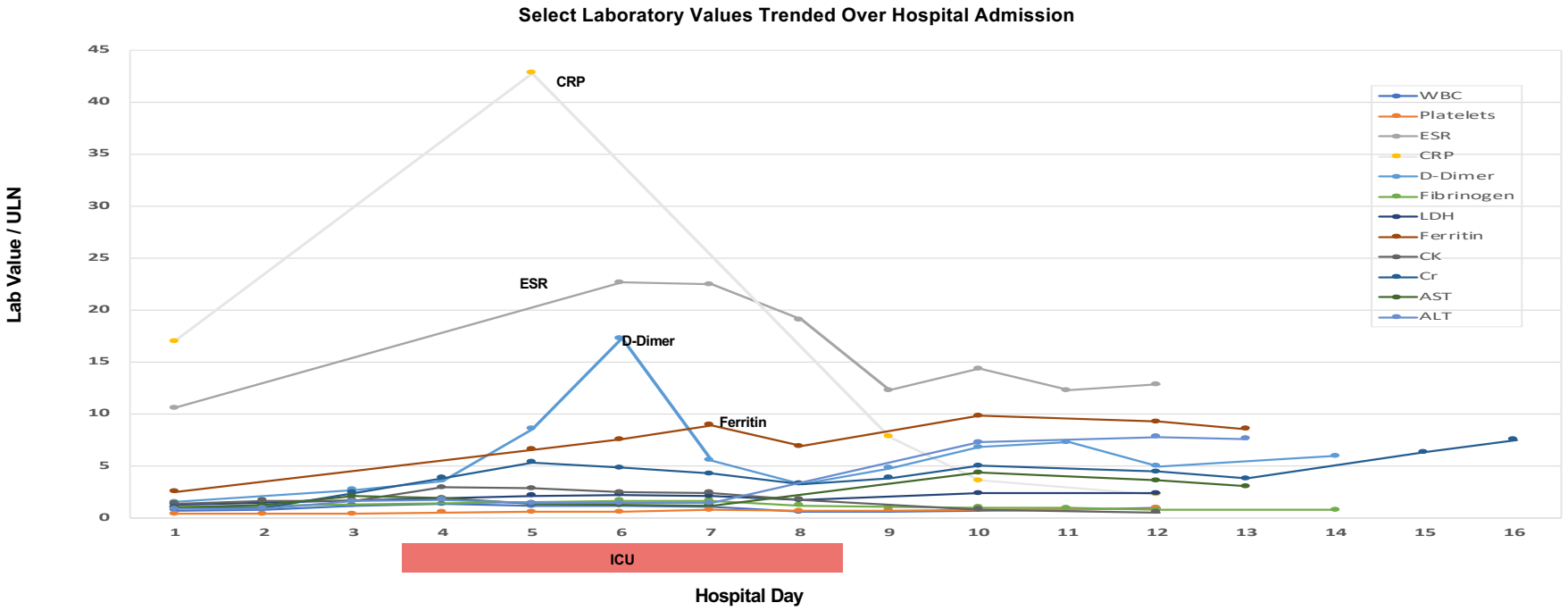
Hospital Course: Days 4 – 5

- Interval history
  - Hypothermia, AMS, agitation
  - 40L HFNC, 80% FiO2
  - D-DIMER 6.9, CRP 125, creat 5.2
  - Doppler shows bilat DVT
- Assessment/Plan
  - Poss SIADH; Continuous dialysis (CVVHD) begin
  - Hypoxic respiratory failure not improved
  - Cytokine release syndrome likely
  - Tocilizumab 400 mg IV given
  - Full anti-coagulation begun



Hospital Day	One	Two	Three	Four	Five	Six	Seven	Eight	Nine	Ten	Eleven	Twelve	Thirteen	Fourteen	Fifteen	Sixteen
Location	ED	Floor	Floor	ICU	ICU	ICU	ICU	ICU	Floor	Floor	Floor	Floor	Floor	Floor	Floor	Floor/Home
Respiratory Support	2 L NC	4 L NC	5 L NC	15 L NRB	55 L HFNC 60% FiO2	40 L HFNC 80% FiO2	40 L HFNC 40% FiO2	5 L NC	2 L NC	1 L NC	2 L NC	2 L NC	1 L NC	1 L NC	1 L NC	1 L NC
Fever	afebrile	febrile (39.5 C)	afebrile	afebrile	hypothermic (34.3 C)	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile
Dialysis					Start CVVHD			Transitioned to IHD								
HCQ																
Lopinavir/Ritonavir																
Tocilizumab																
Other Events			AKI	Confirmed ATN		Intermittent AMS		AMS resolved								

Hospital Course: Days 6 -10

- Interval history
  - Clinically improving, mentation clear
  - Respiratory req: 2 L NC
  - New transaminitis
- Labs
  - **AST: 160**
  - **ALT: 255**
  - ESR: 76
  - CRP: 18
  - D-dimer: 2.71
  - Ferritin: **2162**
- Assessment/Plan
  - **RUQ ultrasound**: Likely liver pathology – fatty liver - with clear biliary tree
  - Discharge home on 2L 02; **out pt dialysis**

Case 2: Questions

CASE SUMMARY:

79 yo w/ severe illness:

Pneumonia, respiratory failure, AKI -> CKD and dialysis, DVTs, high troponins, transaminitis

Issues at discharge:

- HTN, DM, obesity
- Post ARDS pulm. fibrosis
- CKD & dialysis
- DVT & anticoagulation
- F/u liver enzymes
- Post AMS, mental health

- Is Jane's post COVID syndrome the same as case #1?
  - End organ damage vs. immunologic mediation? Both?
- What is the pathogenesis of this form of post COVID syndrome? Was tocilizumab useful in this patient?
- What *additional* medical evaluation should be conducted?
  - Differential diagnoses? Repeat SARS-2 Ag or Ab tests useful?
  - What cardiac evaluation should follow elevated troponins?
  - Role of PFTs and exercise testing?
  - Is CKD reversible?
  - Expected duration of anticoagulation?
  - Does transient AMS require follow up diagnostic evaluation?
- What are the options for treatment and management?
  - Role of rehab, OT/PT, mental health support?
- What to tell Jane re: prognosis?

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Summary

- Post COVID syndrome has been recognized as an important clinical entity during the COVID-19 pandemic
- Currently no universally accepted or agreed upon definition or criteria
- Can be thought of as including persistent symptomatology and/or persistent organ dysfunction
- Future work will aim to clarify the specifics of the syndrome further, as well as underlying pathophysiology and evidence-based management approaches

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https://aidsetc.org/resource/hiv-sars-cov-2-webinar-series

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