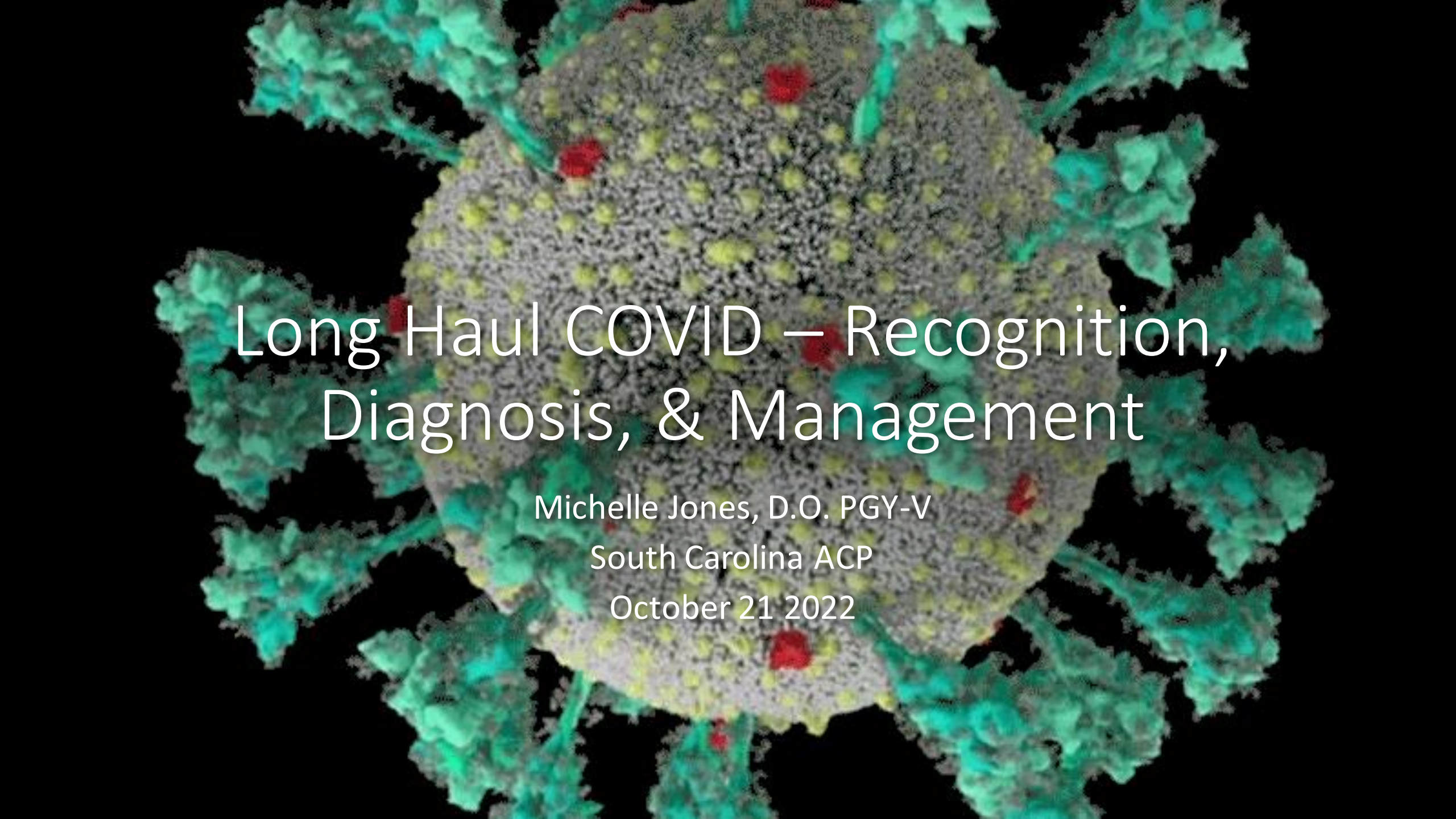

Long Haul COVID – Recognition, Diagnosis, & Management

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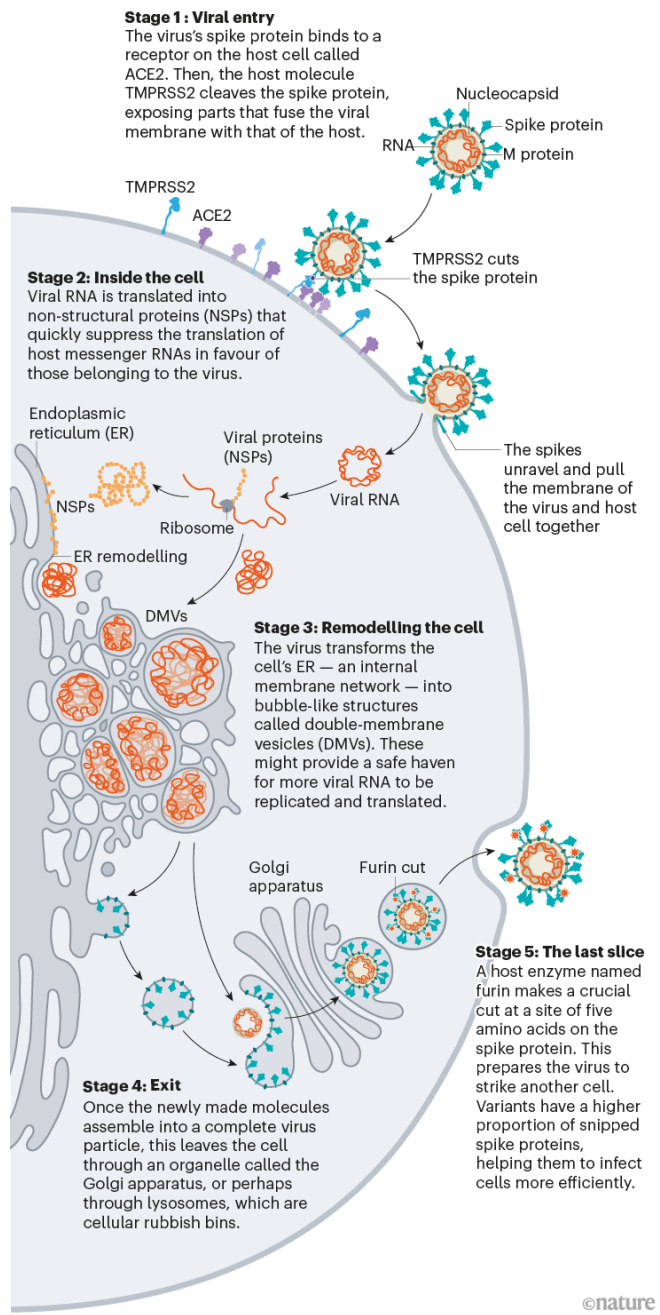
LIFE CYCLE OF THE PANDEMIC CORONAVIRUS

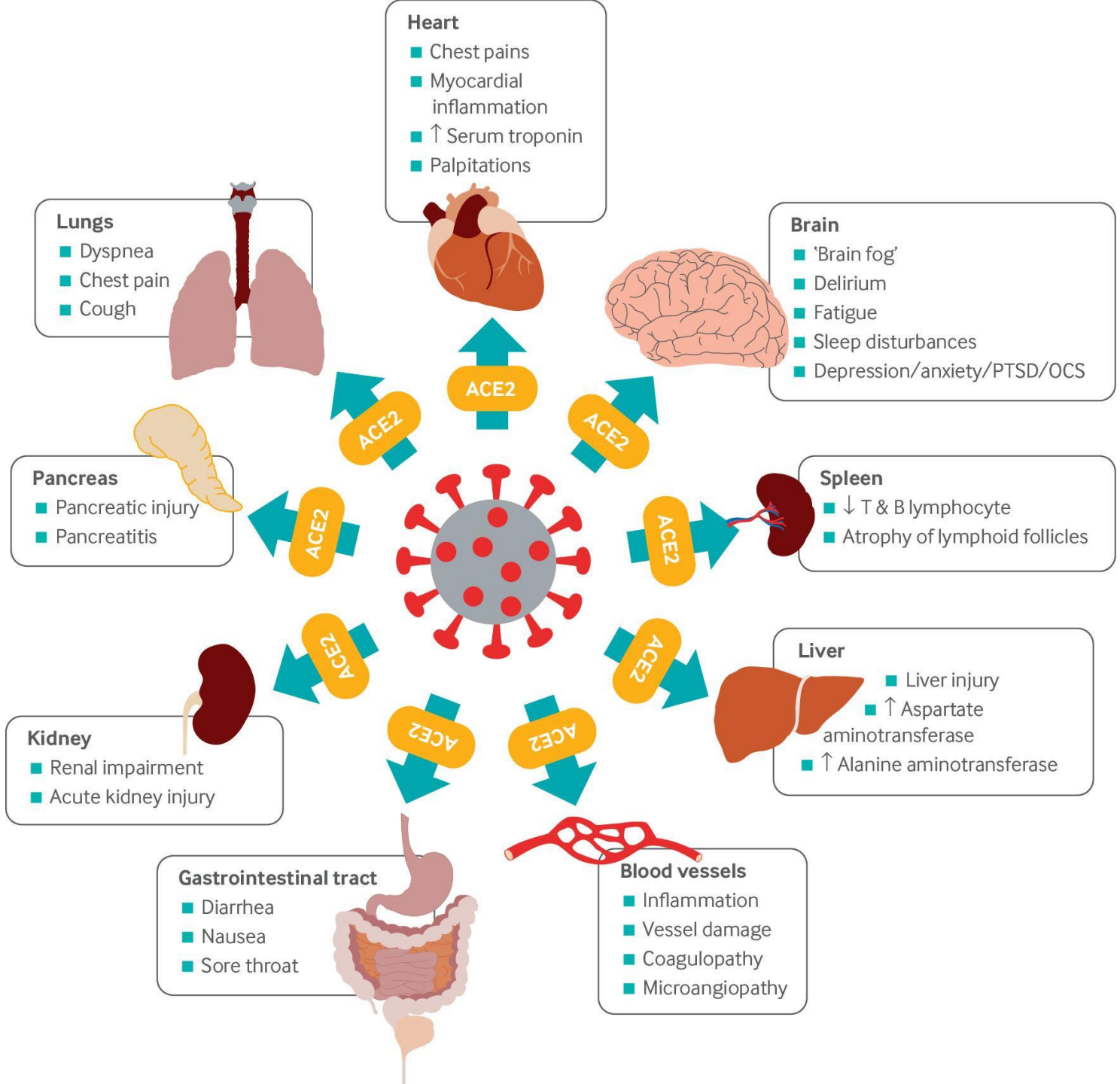
A simplified account of how SARS-CoV-2 enters and exits cells.



What is Long Haul COVID?

Persistent symptoms after an acute COVID-19 infection. Most common:

- Fatigue & Dyspnea
- Other symptoms: cognitive and mental impairments, chest and joint pain, palpitations, myalgia, smell/taste impairments, cough, headache, GI and cardiac concerns
- How Long? Many different groups have proposed different timelines, most commonly symptoms >1-3 months after initial symptoms
- Affects patients who had all levels of initial infection – from asymptomatic or mild, to severe and life threatening
- 10-30% of patients who had COVID may have persistent symptoms


Heart
Chest pains
Myocardial inflammation
↑ Serum troponin
Palpitations
Lungs
Dyspnea
Chest pain
Cough
Brain
'Brain fog'
Delirium
Fatigue
Sleep disturbances
Depression/anxiety/PTSD/OCS
ACE2
Pancreas
Pancreatic injury
Pancreatitis
Spleen
↓ T & B lymphocyte
Atrophy of lymphoid follicles
Liver
Liver injury
↑ Aspartate aminotransferase
↑ Alanine aminotransferase
Kidney
Renal impairment
Acute kidney injury
Gastrointestinal tract
Diarrhea
Nausea
Sore throat
Blood vessels
Inflammation
Vessel damage
Coagulopathy
Microangiopathy

Long Term SARS-CoV 1

- SARS-CoV 1 outbreak occurred in 2003
- 80 medical staff in Beijing were infected, 78 survived and 71 were followed. Survivors had residual pulmonary fibrosis and osteonecrosis (suspected to be due to high dose steroids)
- CT scans
- PFTs in 2006 and 2018:
  - 2006: 21.7% of patients had restrictive defect, 34.8% had mildly reduced DLCO
  - 2018: 1 patient had obstructive defect, none had restrictive defects, 38.5% had reduced DLCO

Long Term SARS-CoV 1

Survivors of SARS-CoV 1 have been followed, and many had long term symptoms including:

- Dyspnea, Fatigue (60% at 12 months), Myalgia, Cognitive impairment, Headache, Palpitations, Chest pain, Femoral Head Necrosis

These symptoms lasted for longer than 6 months in some cases, and at 7 and 15 year follow ups, some patients had pulmonary and bone radiographic evidence of their prior infections.

Patients with normal baseline chest imaging were more likely to have symptomatic improvement compared to those with abnormal chest CT. If I patient was going to recover pulmonary function, that was evident around the 2 year mark after infection when things stabilized.

Zhang, P., Li, J., Liu, H. *et al.* Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. *Bone Res* **8**, 8 (2020). https://doi.org/10.1038/s41413-020-0084-5

Exploring Symptoms of Long-COVID

Fatigue

In one study, nearly 94% of patients report fatigue 79 days after initial infection, regardless of severity of infection.

- Proposed Mechanisms:
  - Inflammatory response pathways (follow up studies found no correlation between pro-inflammatory markers and long term fatigue)
  - Congestion of the glymphatic system and toxin build up in the CNS - this occurs due to resistance to CSF drainage through the cribiform plate
  - Hypometabolism in frontal lobes and cerebellum d/t systemic inflammation - unclear if this causes long COVID fatigue
  - Negative psychosocial factors associated with COVID
  - Myopathy, neuropathy from direct muscle infection

Dyspnea

- 4.6% of patients have SOB at 5 weeks after infection regardless of infection severity
  - Dyspnea is extremely complex in COVID patients
- Mechanisms: direct damage to endothelial cells, substantial immune reaction and inflammation after infection, Chest wall & diaphragm weakness from mechanical ventilation, cardiomyopathy, pulmonary fibrosis, anemia of inflammation, steroid induced myopathy, bacterial or fungal pneumonia, ARDS
- Think broadly about their dyspnea – review their chart, imaging, PFTs, labs, etc. Their history/physical may be the best clue

Cardiac Abnormalities

- One study showed that 21.7% of patients had chronic chest pain after COVID
- Increased incidence of POTS

Cardiac Complications

- One study showed that 21.7% of patients had chronic chest pain after COVID
- Increased incidence of POTS
- Dysrhythmia/Palpitations
- Myocarditis
- Pulmonary Hypertension
- Myocardial Infarction
- Takotsubo’s CM
- Congestive Heart Failure/Cardiomyopathy
- Sudden Cardiac Death

Neurologic Complications

- CVA
- cognitive impairment
- post-ICU delirium
- seizures
- hypoxic brain injury

What can we do about this?

Initial Approach Post-COVID

1. Allow time for the patient to get through their acute illness
2. At follow up, the PCP/Internist can begin the workup for persistent symptoms
    1. PFTs
    2. 6MWT
    3. HRCT
    4. Echo
    5. EKG
3. If persistent abnormal lung imaging, continued need for oxygen, signs of right heart strain, abnormal PFTs, or grossly abnormal 6M walk distance, consider pulmonary referral.

Treatment Options

RECOVERY: CompREhensive Post-COVID CentER at Yale

Referral Pathway

Inpatients (pre-discharge)

Respiratory Assessment
- Ambulatory oximetry
- Pulse oximeter & incentive spirometry training

Functional Assessment
- Physical & occupational therapy evaluation
- Swallow evaluation

Care Coordination
- Arrange home services
- Address care barriers

Outpatients (ongoing sx)
- Referral by outpatient provider, occupational medicine provider, health system COVID-19 hotline, or self

Initial Assessment

Visit 1 (telehealth)
- Pulmonary consultation
- Subjective sx assessment
- Assess for extrapulmonary complications

Initial Diagnostics
- Repeat imaging (HRCT)
- PFTs, 6MWT
- Repeat selected labs

Visit 2 (face-to-face)
- Ongoing pulmonary care
- PT/OT assessment
- Subjective sx assessment
- Neurocognitive screening
- Mental health screening
- Additional subspecialty involvement

Subsequent Care

MD visits
- Planned 3, 6, and 12 mo or as needed per severity
- Extrapulmonary consultation as needed

Rehab
- PT/OT outpatient care
- Pulmonary rehabilitation

Lung function testing
- PFT & 6MWT at 3, 6, 12 mo
- CPET for selected patients

Additional diagnostics
- VQ or CTA chest
- Transthoracic Echo
- Cardiac event monitoring
- Functional cardiac imaging
- Neurocognitive testing

Disposition

Sx resolve & PFT normal
- Transition to primary care

Sx persist or PFT abnormal
- Non-specific phenotype → continue RECOVERY clinic
- Phenotype consistent with specific disease process → appropriate advanced lung disease program (e.g. interstitial lung disease, airways disease, pulmonary vascular disease)

Multi-disciplinary discussion of active cases
Translational research efforts
Revision of clinic processes to meet patient needs and evolving evidence

Take From What We Already Know

- IPF Guidelines
- Heart Failure/PH/MI Guidelines
- Treatments for Chronic Fatigue Syndrome, Fibromyalgia, POTS

- Treat the underlying organ dysfunction based on already established practices
- Supportive Care in many instances

PFT Findings

- Most commonly can see restriction from pulmonary fibrosis (TLC)
  - Mild ≥70%
  - Moderate 60-69%
  - Severe <60%

- Low DLCO
  - High >140% predicted
  - Normal 76-140% predicted
  - Mildly reduced 61-75% predicted
  - Moderately reduced 40-60% predicted
  - Severely reduced <40% predicted

Hi-Resolution CT Chest

Most Common findings:

- Ground Glass
- Reticulation
- Bronchial Dilation/Bronchiectasis

Do Inhalers Work?

- There is no current evidence for any type of inhaler to be used – should be used case by case
- Can give a trial of SABA (albuterol, levalbuterol) if it helps with acute symptoms
- If SABA helps, can give a trial of ICS/LABA

Supplemental Oxygen

- Treat similar to any other cause of hypoxic respiratory failure

Pulmonary Rehab

Has the best evidence to treat the multiple causes of dyspnea

- Deconditioning
- Hypoxemia
- Dealing with Breathlessness

Prognosis

- Unclear at this time, more data needed
- NIH study for Long COVID

Prevention

- Prevention is the best management strategy at this time
- Masking (to prevent large droplet spread)
- Hand washing
- Social Distancing
- Vaccination + Boosters

Multiple Choice Questions

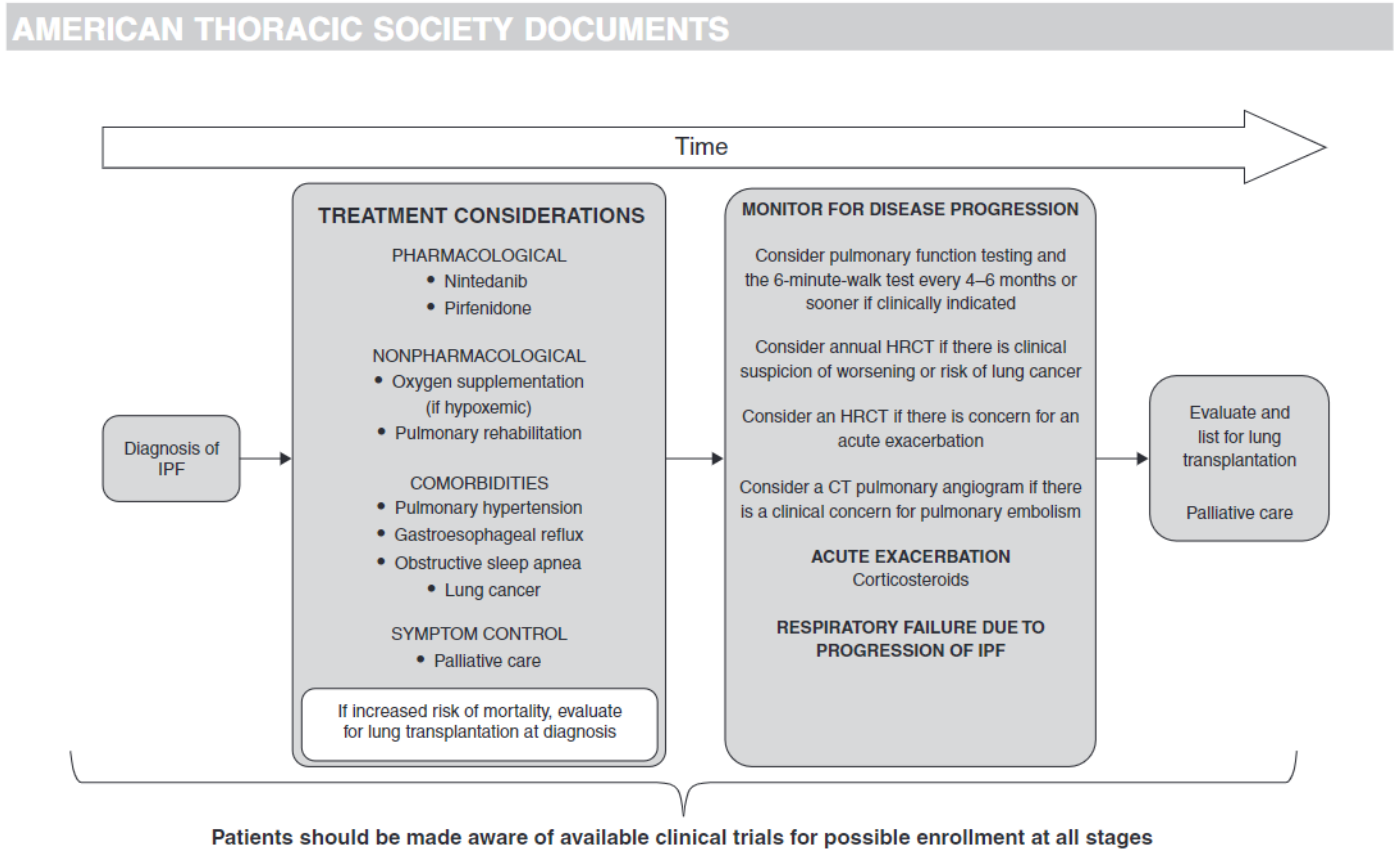
Question 1

A 42 year old male presents to your office for a hospital follow up. He was recently hospitalized for acute hypoxic respiratory failure due to COVID-19. He received supplemental oxygen, remdesivir, and tocilizumab. He was discharged on 2L NC 2 weeks ago, and a repeat 6 minute walk test in your office shows that he still requires 2L. He describes significant dyspnea on minimal exertion and wonders if an inhaler might help him.

Which of the following inhalers has been shown in a clinical trial to improve dyspnea in long COVID-19?

1. Beclomethasone
2. Budesonide- Formoterol
3. Fluticasone – Umeclidinium – Vilanterol
4. Albuterol HFA
5. **None**

Explanation



There have been no studies looking at the effectiveness of any inhaler in the management of long COVID. The BMJ recommends treating long COVID similar to IPF. We can try SABA, but there is no evidence to support this. We may also try ICS/LABA if the SABA helps

Question 2

A 65 year old female with no know medical history presents to your office as a hospital follow up. She was diagnosed with, and hospitalized for, COVID-19 eight months ago. Her hospital stay was complicated by acute hypoxemic respiratory failure requiring mechanical ventilation and subsequent tracheostomy, gram positive bacteremia, acute pulmonary embolism, ventilator associated pneumonia, and acute renal failure requiring HD. She was discharged to an LTACH, but has been back at home now for four months. Her tracheostomy was decannulated at the LTACH and she is swallowing well. She is still very short of breath with minimal exertion and wants to understand why she isn't feeling better.

Which tests/set of tests are the best to order now?

1. Chest X-Ray only
2. PFT, 6 minute walk test
3. **PFT, 6 minute walk test, Hi-Res CT, EKG, Echocardiogram**
4. EKG
5. Cardiopulmonary Exercise Test

Explanation

A chest XR will only look for pulmonary causes of her DOE.

PFT and 6MWT will be helpful, but may not reveal every cause of her DOE.

EKG will assess for any cardiac ischemia or right heart failure, but will not look for all pulmonary causes of DOE.

CPET will look at lung and cardiac function while exercising, but will not look at lung parenchyma, LVEF, RVSP.

Answer 3 is the most comprehensive – can look for obstruction/restriction, DLCO, cardiac ischemia, PH, CHF, pulmonary fibrosis/bronchiectasis and exertional hypoxemia.

Resources

Long-Term Outcomes after Severe COVID-19 Infection: A Multicenter Cohort Study of Family Member Outcomes (atsjournals.org)

Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for COVID-19: A Longitudinal Study of Respiratory, Physical, and Psychological Outcomes (atsjournals.org)

Effectiveness of the BNT162b2 Vaccine after Recovery from Covid-19 | NEJM

INFD_0_1924397.pdf (nih.gov)

Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study | Bone Research (nature.com)