"Post-Acute Covid Syndrome"

Janet A. Jokela, MD, MPH, FACP, FIDSA

Acting Regional Dean

University of Illinois College of Medicine at Urbana-Champaign

November 10, 2020 | Denver Health COVID ECHO Program

UIUC Photos: Illinois.edu

UNIVERSITY OF ILLINOIS SYSTEM

No financial or other conflicts of interest

What we'll discuss

- Resources & Acknowledgements
- Background
- Data
- The heart
- Patient advocacy
- Concluding comments

- *FREE* COVID-19: An ACP Physicians Guide www.acponline.org
- https://www.cdc.gov/coronavirus/2019-ncov/hcp/index.html
- For clinicians: 800-CDC-INFO (800-232-4636)

Society for Healthcare Epidemiology of America

https://www.shea-online.org

David Jay Weber, M.D., M.P.H.

https://www.idsociety.org

Infectious Disease Society of America

Background

Humility

We are still learning

What we think is true today may not be true tomorrow...

Impressively wide clinical spectrum

- Asymptomatic—understanding still evolving
- Mild-Moderate—
  - Mild: fever, cough, muscle pain, nasal congestion, sore throat
  - Moderate: cough plus moderate dyspnea consistent with moderate pneumonia
- Severe acute disease—severe pneumonia with severe dyspnea, hypoxia
- Critical—respiratory failure, septic shock, organ failure
- Recovery: *we are still learning…*

- Persons of *all ages* are at risk for infection and severe disease
- Fatal disease risk greatest in those > 65 years, living in a nursing home or long-term care facility, or underlying conditions: obesity, HTN, diabetes, cardiovascular disease, renal disease, chronic respiratory disease, renal disease
- Pediatric multisystem inflammatory syndrome—persistent fevers and features of Kawasaki disease and/or toxic shock syndrome

ACUTE INFECTION (COVID-19) | POST-ACUTE HYPERINFLAMMATORY ILLNESS | LATE SEQUELAE

Immunologic characteristics

Clinical signs and symptoms

Laboratory testing profile

Approx. 8.5mil cases in US
Approx 225,000 deaths

In children, national reporting approx. 1000 cases (20 deaths)
In adults, unknown

Not yet quantitated

Illness start — Week 1 — Week 2 — Week 3 — Week 4 — ?
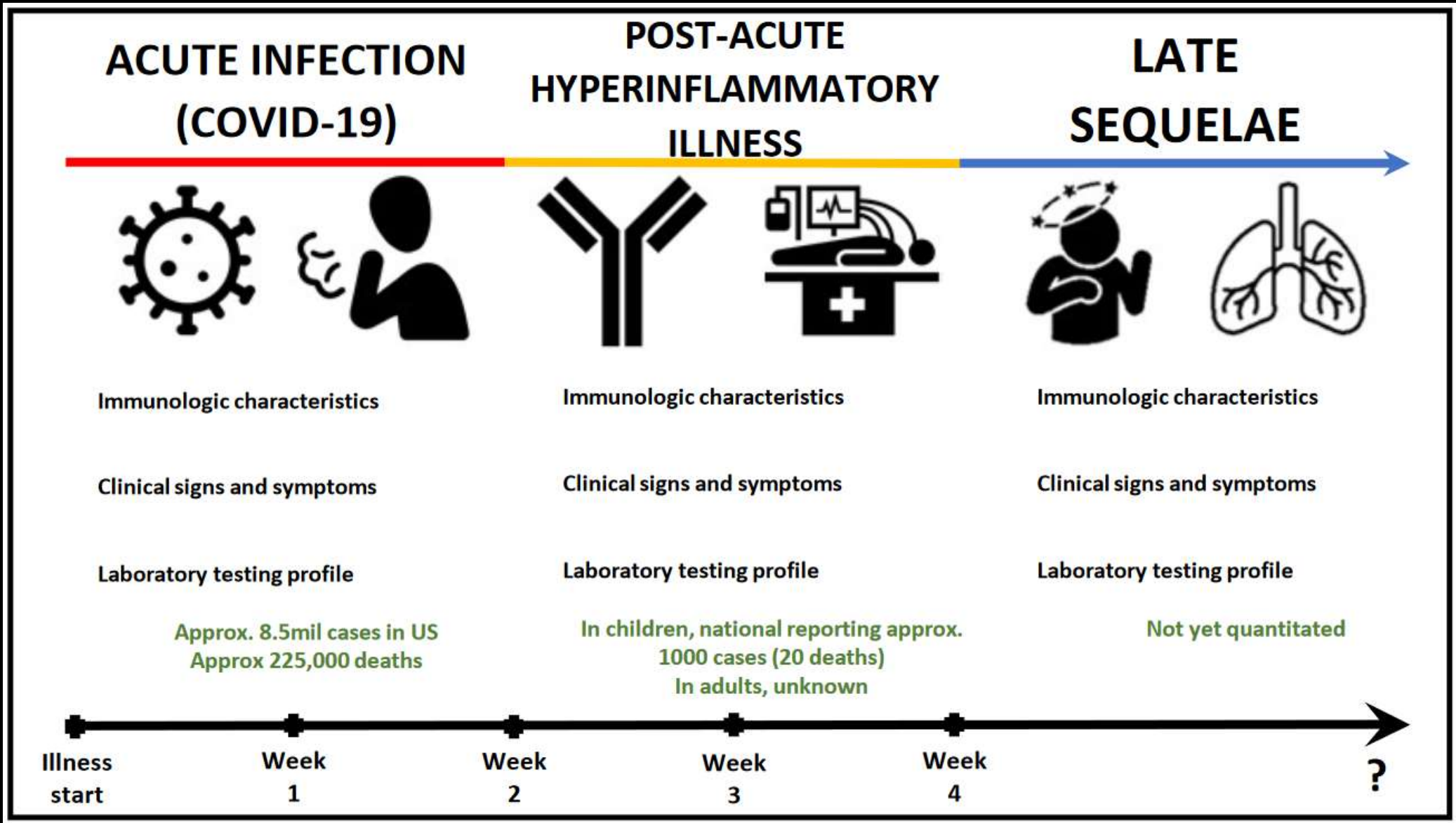
S. Deblina Datta, MD, FIDSA, Clinical Team Lead CDC COVID 19 Response, 23 October 2020

Long-hauler

19 August 2020 | Ed Yong
Long-Haulers Are Redefining COVID-19
Without understanding the lingering illness that some patients experience, we can't understand the pandemic

https://www.theatlantic.com/health/archive/2020/08/long-haulers-covid-19-recognition-support-groups-symptoms/615382/

JAMA October 5, 2020

Opinion

VIEWPOINT

Carlos del Rio, MD
Division of Infectious Diseases, Department of Internal Medicine, Emory University School of Medicine, Atlanta, Georgia.

Lauren F. Collins, MD
Division of Infectious Diseases, Department of Internal Medicine, Emory University School of Medicine, Atlanta, Georgia.

Preeti Malani, MD, MSJ
Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor; and Associate Editor, JAMA.

Audio

Long-term Health Consequences of COVID-19

With more than 30 million documented infections and 1 million deaths worldwide, the coronavirus disease 2019 (COVID-19) pandemic continues unabated. The clinical spectrum of severe acute respiratory syndrome coronavirus (SARS-CoV) 2 infection ranges from asymptomatic infection to life-threatening and fatal disease. Current estimates are that approximately 20 million people globally have "recovered"; however, clinicians are observing and reading reports of patients with persistent severe symptoms and even substantial end-organ dysfunction after SARS-CoV-2 infection. Because COVID-19 is a new disease, much about the clinical course remains uncertain—in particular, the possible long-term health consequences, if any.

Epidemiology
Currently, there is no consensus definition of postacute COVID-19. Based on the COVID Symptom Study, in which more than 4 million people in the US, UK and Sweden have entered their symptoms after a COVID-19 diagnosis, postacute COVID-19 is defined as the presence of

> Longer-ranging longitudinal observational studies and clinical trials will be critical to elucidate the...health consequences attributable to COVID-19 and how these may compare with other serious illnesses.

tion among a random sample of 292 adults (≥18 years) who had a positive outpatient test result for SARS-CoV-2 by reverse transcriptase–polymerase chain reaction, 35% of 274 symptomatic respondents reported not having returned to their usual state of health 2 weeks or more after testing, including 26% among those aged 18-34 years (n = 85), 32% among those aged 35-49 years (n = 96), and 47% among those aged 50 years or older (n = 89).[4] Older than 50 years and the presence of 3 or more chronic medical conditions were associated with not returning to usual health within 14 to 21 days after receiving a positive test result. Notwithstanding, 1 in 5 individuals aged 18-34 years without chronic medical conditions had not yet achieved baseline health when interviewed at a median of 16 days from the testing date.

Manifestations
The most commonly reported symptoms after acute COVID-19 are fatigue and dyspnea. Other common symptoms include joint pain and chest pain.[3] In addition to these general symptoms, specific organ dysfunction has been reported, involving primarily the heart, lungs, and brain. From a pathogenesis standpoint, these complications could be the consequence of direct tissue invasion by the virus (possibly mediated by the presence of angiotensin-converting enzyme 2 receptor), profound inflammation and cytokine storm, related immune system dam-

13

Data

MMWR: Symptom Duration & Risk Factors for Delayed Return to Usual Health, March–June 2020

- Assess prolonged symptoms among **<u>outpatients</u>**; 14 US academic health systems, 13 states

- April-June 2020; adults > 18 yrs; first + RT-PCR; random sample; phone interviews; median **<u>16 days after test date</u>**

- Results:
  - 292 respondents: 94% (274) reported experiencing one or more symptoms at the time of testing; **<u>35% of symptomatic persons had not returned to usual state of health </u>** by the date of the interview (median—16 days since test)
    - 18-34 yrs: 26%
    - 35-49 yrs: 32%
    - >50 yrs: 47%
  - Continued symptoms: cough 43%, fatigue 35%, shortness of breath 29%

MMWR: Symptom Duration and Risk Factors for Delayed Return to Usual Health, March–June 2020

- Persistence of symptoms correlated with presence of comorbidities:
  - 0-1 comorbidities: 28%
  - 2 comorbidities: 46%
  - 3 comorbidities: 57%
- Age and comorbidities: independent predictors of continued symptoms
- Among 274 symptomatic outpatients, median number of symptoms: seven
  - Fatigue (71%), cough (61%), headache (61%) most common

FIGURE. Self-reported symptoms at the time of positive SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) testing results and unresolved symptoms 14–21 days later among outpatients (N = 274)* — 14 academic health care systems,[†] United States, March–June 2020
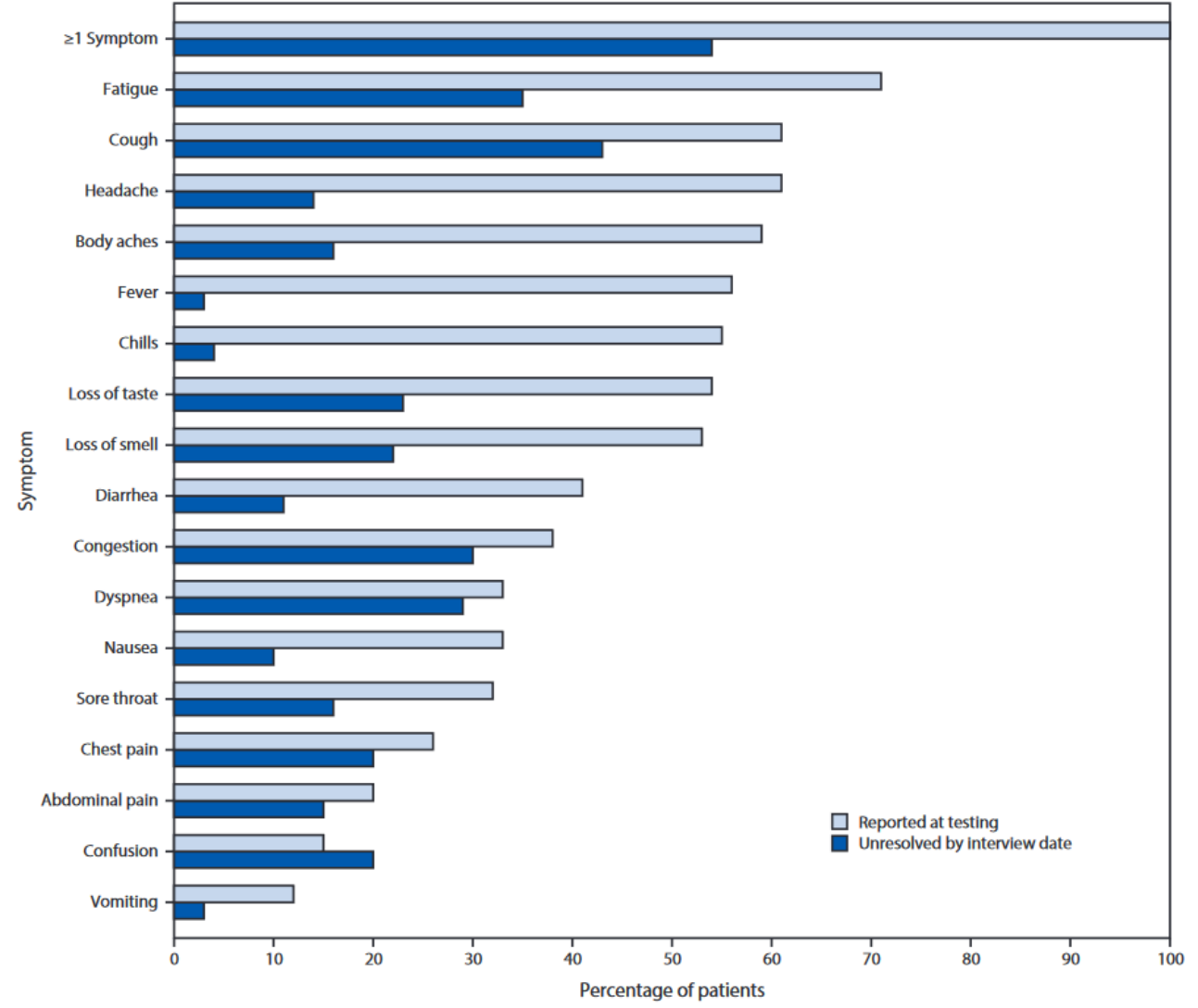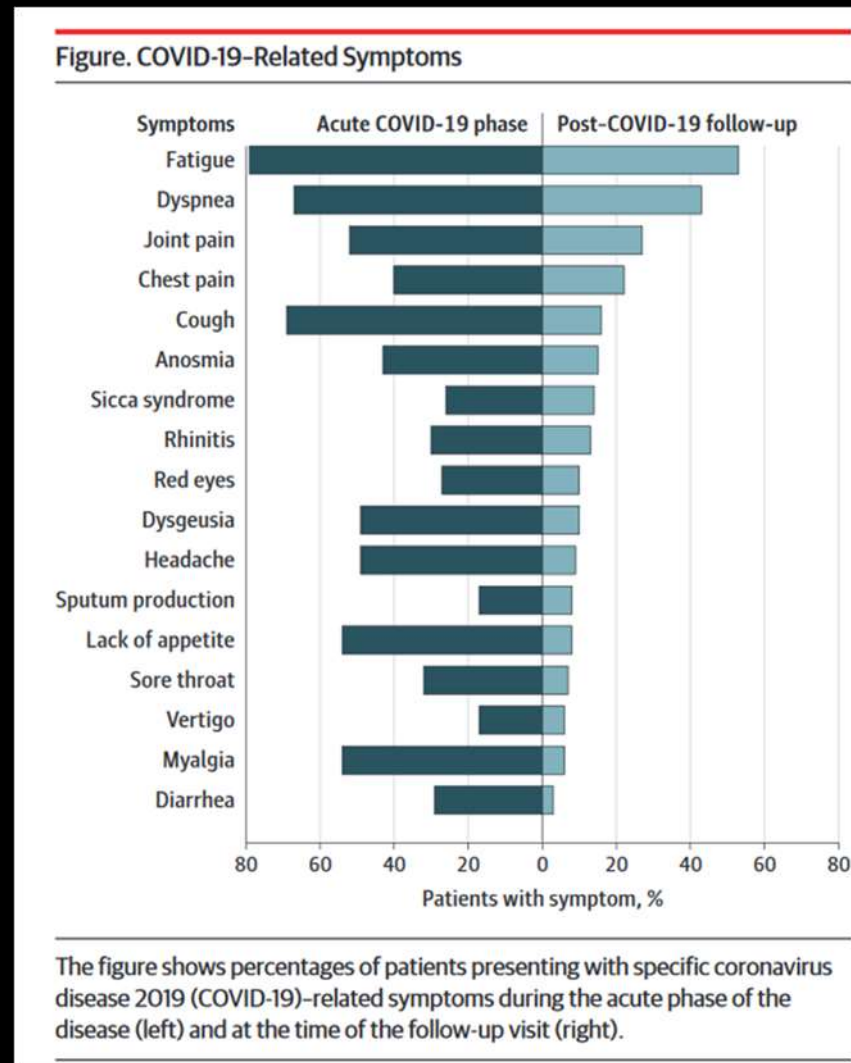
Persistent symptoms after COVID-19

- Post-care assessment of symptoms in patients with COVID-19 in Rome
- April–May 2020; post-acute outpatient service for discharged patients; 2 negative RT-PCR tests
- Results:
  - N = 143
  - Mean age 56.6, 37% female
  - During hospitalization: 72.7% evidence of interstitial pneumonia; mean length of hospital stay 13.5 days; 15% non-invasive ventilation; 5% mechanical ventilation
  - Mean time at assessment: **60.3 days from first symptom**
  - 87.4% reported persistence of at least one COVID-related symptom
  - 55% had 3+ symptoms; no fever or acute signs of illness
  - Common symptoms: fatigue 53.1%, dyspnea 43.4%, joint pain 27.3%, chest pain 21.7%
  - Worsened quality of life 44.1%

Persistent symptoms in patients after acute COVID-19
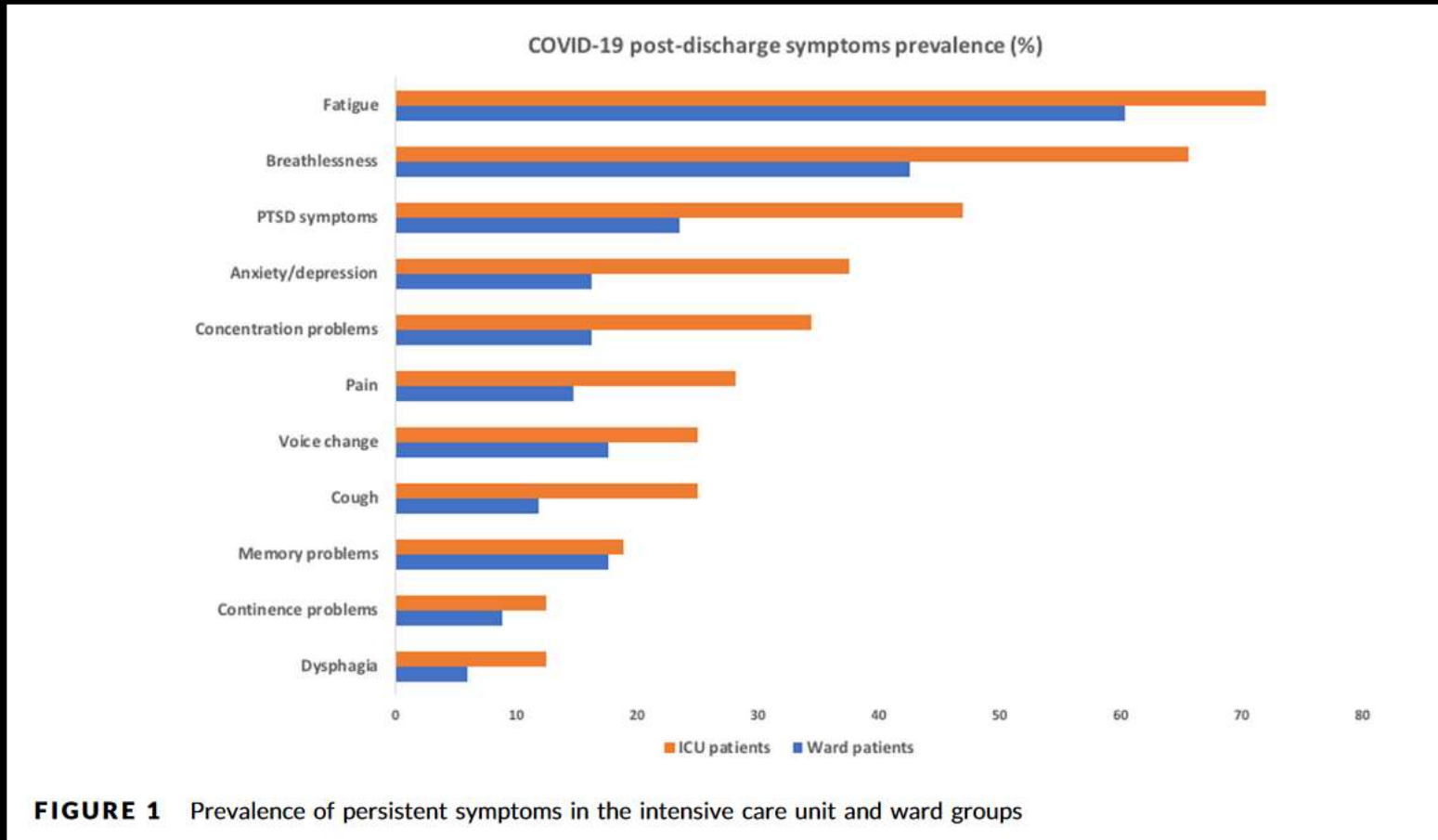
Figure. COVID-19–Related Symptoms

The figure shows percentages of patients presenting with specific coronavirus disease 2019 (COVID-19)–related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

Post-discharge symptoms and rehab needs in survivors of COVID-19

- Assess the nature & prevalence of post-COVID symptoms after discharge
- Purposive sample 100 survivors, >18 yrs old, discharged from a University hospital (UK), assessed **4-8 weeks after discharge**, telephone screening tool
- Results:
  - **48 days post-discharge** (29-71 days)
  - 32 treated in ICU (mean age 58.5, 40.6% women), 68 on wards (mean age 70.5, 48.5% women)
  - New fatigue most common symptom (72% ICU group, 60.3% ward group)
  - Breathlessness (65.6% ICU group, 42.6% ward group)
  - Psychological distress (46.9% ICU group, 23.5 ward group)
  - Drop EQ5D (68.8% ICU group, 45.6% ward group)—assessed mobility, personal care, usual activities, pain, anxiety/depression

Halpin SJ, et al. J Med Virol. 2020;1-10.

Post-discharge symptoms and rehab needs in survivors of COVID-19

COVID-19 post-discharge symptoms prevalence (%)

FIGURE 1 Prevalence of persistent symptoms in the intensive care unit and ward groups

Halpin SJ, et al. J Med Virol. 2020;1-10.

Post-discharge persistent symptoms

- Assess post-discharge symptoms, quality of life
- Single-center study (Paris); data obtained via phone questionnaire; 279 hospitalized March-April 2020 (excluded: unreachable, non-French speaking, dementia, declined)
- Results: N=120, mean **110.9 days since admission**
- Fatigue 55%, dyspnea 42%, loss of memory 34%, sleep disorders 30.8%, concentration 28%, loss of hair 20% (20 women, 4 men)
  - No statistical differences between ICU vs. ward patients
- Of pre-COVID active workers (46.7% of total): 69.1% had returned to work; 71.8% had returned to regular sports activities but at a lower level

Follow-up adults with non-critical COVID-19 60 days after symptom onset

- Describe clinical evolution & predictors of symptom persistence at D30 and D60 in patients with initial non-critical COVID-19 confirmed by RT-PCR

- University Hospital, Tours, France; N=150, March-June 2020; D30 & D60 follow-up by EHR and phone call

- 68% with at least one symptom (D30), 66% (D60)
  - Anosmia/ageusia: 59% at onset, 28% (D30), 23% (D60)
  - Dyspnea: 36.7% (D30), 30% (D60)
  - Asthenia: 50% (D30), 40% (D60)

- Persistent symptoms D30: severe COVID-19, dyspnea at symptom onset

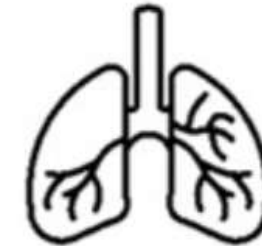- Persistent symptoms D60: age 40-60 years, hospital admission, abnormal auscultation at symptom onset

Carvalho-Schneider C, et al. Clin Micro Infect. doi.org/10.1016/j.cmi.2020.09.052

23

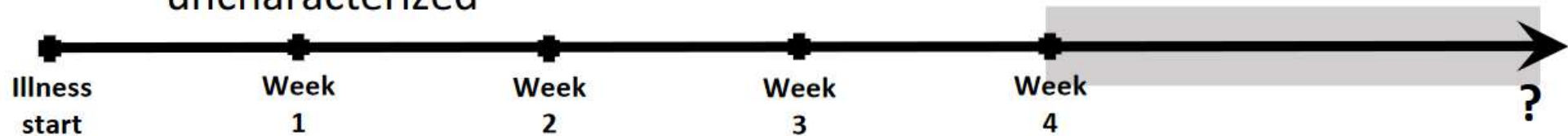|	Tenforde	Carfi	Garrigues	Halpin	Carvalho-Schneider
Patients	Ambulatory	Hospitalized	Hospitalized	Hospitalized	Non-critical
Time since dx	14-28 d	60d post onset	110d post DC	4-8 wks post DC	30d, 60d post onset
Not returned to baseline	35%				68% D30, 66% D60
No COVID sx		12.6%			
Cough	42%		16.7%	Ward ~12%, ICU ~25%	
Fatigue	35%	53.1%	55%	Ward ~60%, ICU ~72%	36% D30, 21% D60
Dyspnea	29%	43.4%	42%	Ward ~43%, ICU ~66%	11% D30, 8% D60
Fever		none			
Joint pain		27.3%			10% D30, 16% D60
Anosmia		13%	13.3%		28% D30, 23% D60
Memory loss			34%	Ward 16%, ICU 18%	
Worse mental health			yes	yes	
Worse physical health			yes	yes	

LATE SEQUELAE

Commonly see cardiovascular, pulmonary, and central nervous system manifestations[7–12]

Pathophysiological pathways are proposed, but *unproven*

Laboratory tests:
Viral test, Antibody profile uncharacterized

Illness start — Week 1 — Week 2 — Week 3 — Week 4 — ?

S. Deblina Datta, MD, FIDSA, Clinical Team Lead CDC COVID 19 Response, 23 October 2020

"…honoring the story of the patient…"

Greenhalgh T, et al. *BMJ* 2020;370:m3026

COVID-19 Real-Time Learning Network

Stay up to date on COVID-19 disease manifestations and complications.

Multimedia

Management of post-COVID Symptoms: Experiences from the Center for Post-COVID Care in NYC

An American Thoracic Society COVID-19 Critical Care Training Forum discussion with physicians who helped organize Mt. Sinai's Center for Post-COVID Care about the most common and uncommon symptoms they have encountered.
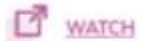
WATCH   15 Sep

Podcast - Managing Patients Post-COVID-19: From Symptoms to Lasting Complications

Drs. Robin Trotman of Cox Health and Inessa Gendlina of Montefiore Medical Center discuss the long-term effects of COVID-19 and how to manage recovered patients.

Listen Now   01 Sep

COVID-19 Podcast: Survivors of COVID-19 (June 13, 2020)

"There was no sense of what was coming next." Drs. Buddy Creech & Anna Person of Vanderbilt University & Michael Saag of the University of Alabama share their experiences as physicians infected with COVID-19.

Listen Here   13 Jun

Post-Acute COVID-19 Syndrome

https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/post-covid-syndrome/

27

What about the heart?

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

Valentina O. Puntmann, MD, PhD; M. Ludovica Carerj, MD; Imke Wieters, MD; Masia Fahim; Christophe Arendt, MD; Jedrzej Hoffmann, MD; Anastasia Shchendrygina, MD, PhD; Felicitas Escher, MD; Mariuca Vasa-Nicotera, MD; Andreas M. Zeiher, MD; Maria Vehreschild, MD; Eike Nagel, MD

➕ Editorial
➕ Supplemental content

IMPORTANCE Coronavirus disease 2019 (COVID-19) continues to cause considerable morbidity and mortality worldwide. Case reports of hospitalized patients suggest that COVID-19 prominently affects the cardiovascular system, but the overall impact remains unknown.

OBJECTIVE To evaluate the presence of myocardial injury in unselected patients recently recovered from COVID-19 illness.

DESIGN, SETTING, AND PARTICIPANTS In this prospective observational cohort study, 100 patients recently recovered from COVID-19 illness were identified from the University Hospital Frankfurt COVID-19 Registry between April and June 2020.

EXPOSURE Recent recovery from severe acute respiratory syndrome coronavirus 2 infection, as determined by reverse transcription–polymerase chain reaction on swab test of the upper respiratory tract.

MAIN OUTCOMES AND MEASURES Demographic characteristics, cardiac blood markers, and cardiovascular magnetic resonance (CMR) imaging were obtained. Comparisons were made with age-matched and sex-matched control groups of healthy volunteers (n = 50) and risk factor–matched patients (n = 57).

RESULTS Of the 100 included patients, 53 (53%) were male, and the mean (SD) age was 49 (14) years. The median (IQR) time interval between COVID-19 diagnosis and CMR was 71 (64-92) days. Of the 100 patients recently recovered from COVID-19, 67 (67%) recovered at

- Frankfurt, 100 patients
- Age-matched & sex-matched control groups healthy volunteers plus risk factor-matched patients; 1/3 hospitalized
- Cardiac blood markers, cardiovascular magnetic resonance (CMR) imaging

- 53% male, mean age 49 yrs
- Median time from diagnosis to CMR: 71 days

- hsTnT >3 pg/mL in 71%, >13.9 in 5%
- **78 abnormal CMR**:
    - Raised myocardial native T1 71%
    - Raised native T2 60%
    - Late gadolinium enhancement 32%
    - Pericardial enhancement 22%
- Endomyocardial biopsy in severe findings: active lymphocytic infiltration

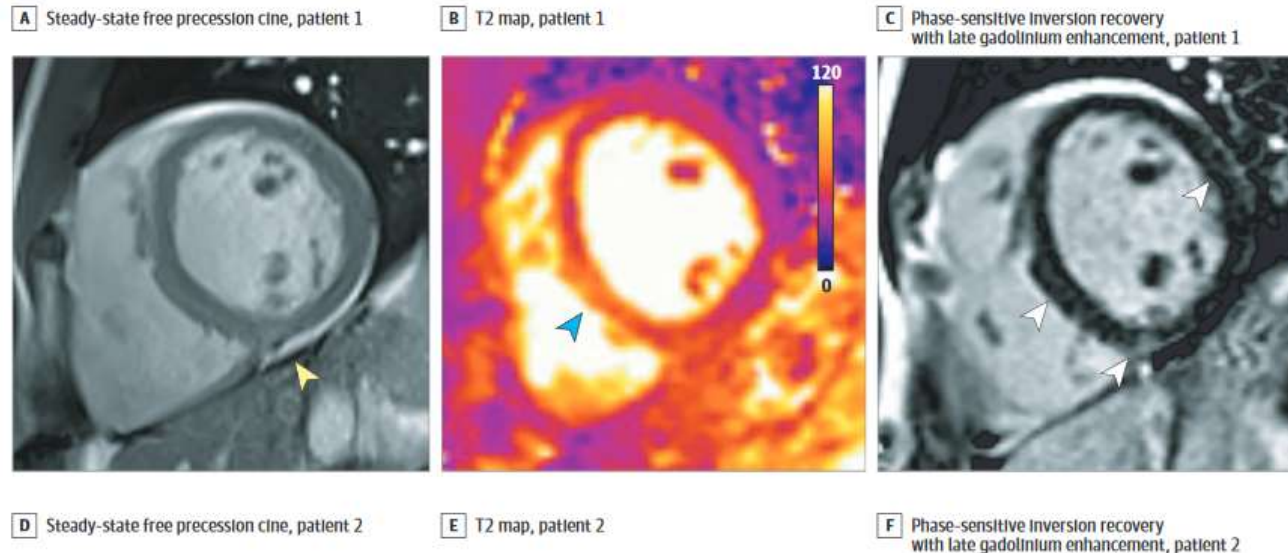- Native T1 and T2: best discriminators to detect COVID-19-related pathology

Puntmann V, et al. JAMA Cardiology July 27, 2020

- Ohio State, 26 athletes, 57% male
- Football, basketball, soccer, lacrosse, track
- All outpatient; 12 mild symptoms only

- Evaluated 11-53 days after quarantine

- EKG: without ST/T changes
- Troponin I: normal
- TTE & CMR: ventricular volumes & fxn WNL

- 4: signs of myocarditis on CMR (elevated T2 signal + late gadolinium enhancement)
  - 2 with mild symptoms only

- 8 with LGE but without T2 → prior myocardial injury

Rajpal S, et al. JAMA Cardiology, Sept. 11, 2020

10/26/2020

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

Figure 2. Proposed Coronavirus Disease 2019 (COVID-19) Return-to-Play Algorithm for Recreational Masters Athletes
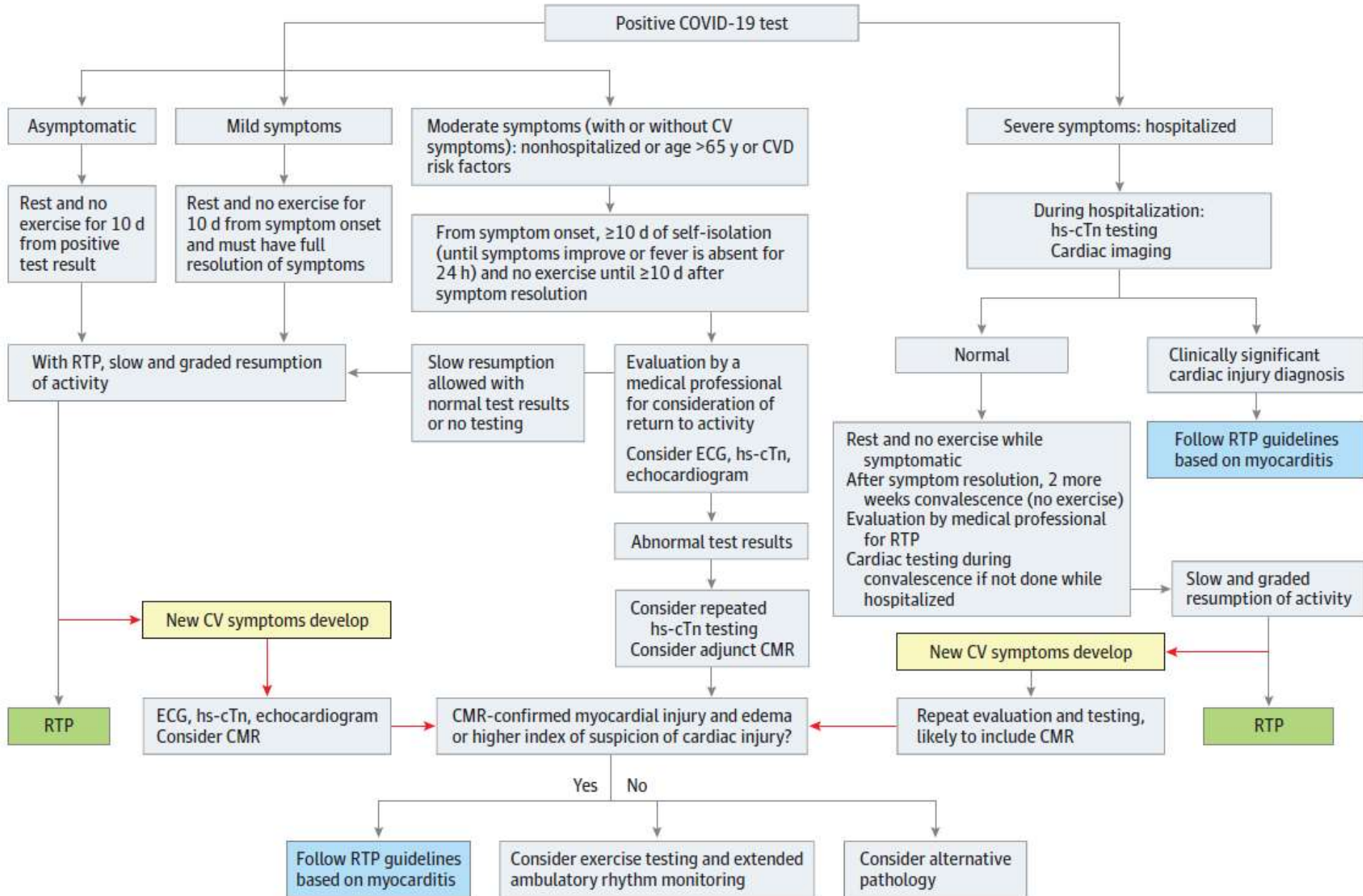
EDITORIAL

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

As the coronavirus disease 2019 (COVID-19) pandemic began to evolve, case reports suggested that a clinical syndrome con- of athletes with positive COVID-19 test results on collegiate or professional teams or athletes with high profiles who have posi-

Patient advocacy

For example…Body Politic COVID-19 Support Group

- COVID-19 patients created, analyzed a survey targeted at patients experiencing symptoms for over two weeks
  - 640 responses; April 21 and May 2, 2020
- "While we acknowledge that this analysis pertains to a ***biased sample of patients with higher recovery times than typically reported***, we hope the report will inform public health professionals, inspire future research, and give family, friends, employers, and the general public deeper insight into the range of experiences of people living with COVID-19."

https://bit.ly/bp-covid-survey-analysis

https://www.wearebodypolitic.com/bodytype/2020/8/16/covid-19-support-group-long-haul

https://www.theatlantic.com/health/archive/2020/08/long-haulers-covid-19-recognition-support-groups-symptoms/615382/

From Body Politic: survey results

- Women more commonly affected than men (bias: more likely to participate in Body Politic and the survey)
- Symptomatic/more severely ill patients: more likely to develop prolonged symptoms
- Even those not hospitalized may experience prolonged symptoms
- Many symptoms suggestive of **dysautonomia**
  - Perturbations of the autonomic nervous system; damage from virus or an overactive immune system?
  - Post-exertional malaise: e.g., walking up a flight of stairs and then confined to bed for 2 days
    - Likened to myalgic encephalomyelitis (i.e., Chronic Fatigue Syndrome)
    - Managing fatigue "*becomes a full-time job*"

https://www.theatlantic.com/health/archive/2020/08/long-haulers-covid-19-recognition-support-groups-symptoms/615382/
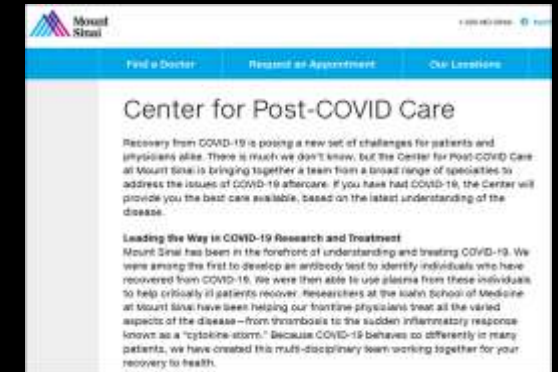
Body Politic— patient quotes

- *"Feel terrible for a week then have 2 good days then back to feeling terrible. And when I say 2 good days that just means I can walk to the kitchen without feeling like I need a break in between. I feel as if I have more of a disability now [than] just some virus bug."*

- *"I am 20 years old and very active. I see a lot of my friends not taking social distancing seriously because they don't think it will affect someone of their demographic. Yet here I am, super sick for a month now."*

- *"I can't do any [exercise] my HR goes up very quickly and I get shortness of breath."*

Healthcare and "Post-covid" patients

- Often require care from multiple specialists: pulmonologists, cardiologists, neurologists, rheumatologists, psychiatrists, physical medicine/rehabilitation
  - Not necessarily infectious disease physicians
- New York, Chicago, LA, and other area health systems: launched COVID-19 rehabilitation and recovery programs, to serve as a _medical home_ for patients with myriad complications who require coordinated care

COVID Recovery & Rehabilitation

Center for Post-COVID Care

Hackensack Meridian _Health's_ COVID Recovery Center

New Jersey's first center dedicated to assisting COVID-19 patients after their recovery.

- Pulse oximeter, BP cuff at home
- Orthostatic vital signs
- Patients not the same as at admission
- Neurologic/psychiatric changes
- Residual pulmonary symptoms

Screening for post-covid syndrome?

- No data yet, hopefully soon
- Yes, athletes, strenuous exercise: do screen these people with exam, cardiac eval, forced rest period, then re-eval; _watch evolving data_
- Anxiety/depression screens, especially in older persons, perhaps those in ICU: not unreasonable to screen them
  - More subtle deficiencies in concentration—needs to be studied
- Setting up a clinic: consider the goal. Address patients' concerns; also valuable research opportunities
- Patients want someone to listen and to be validated

Late sequelae: pathogenesis hypotheses

- Organ damage from acute infection
  - Pulmonary fibrosis?
  - Cardiac scarring?
- Manifestations of long-term hyperinflammatory state
- Persistent virus in protected reservoir (like Ebola) with ongoing viral activity
- Post- ICU syndrome?
  - Slow resolution of symptoms, PTSD, memory/concentration

ddatta@cdc.gov

Open questions

- What is the burden of disease?
- Who are the vulnerable individuals?
- What are the risk factors for prolonged complications/sequelae?
- What is the underlying pathophysiology?
- What are the best approaches for management?
- What is the duration of illness?
- How should "recovery" be defined?
- What is the long-term prognosis?
- What are the long-term effects after pediatric infection?

Concluding comments

Listen

Patients will tell us what is wrong

<u>Do not ever underestimate</u> the potential of the pandemic

Always <u>must</u> do ethically sound research during the outbreak

<u>Be flexible and humble enough to change</u> guidelines and policies as the data evolves

Make a commitment to <u>address the social determinants health</u>

Anthony Fauci, MD, MACP | 10 September 2020

Conclusions

- Persistence of symptoms is common after symptomatic COVID-19
  - More common in hospitalized, severely ill, older, those with co-morbidities
- Most common: fatigue, dyspnea, cough
  - Long term fevers uncommon
- Pressing need for ongoing investigation of the long-term cardiovascular consequences of COVID-19
  - Do screen high-performance athletes
- Healthcare systems should consider developing multi-specialty clinics to provide post-COVID-19 care
- High-quality research is necessary, especially in a pandemic

Thank you

47