COVID-19:
Focus on Inpatient Treatment

Paul E. Sax, M.D.
Clinical Director, Division of Infectious Diseases
Brigham and Women's Hospital
Professor of Medicine, Harvard Medical School
psax@bwh.harvard.edu
@PaulSaxMD

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S
Department of Medicine

HARVARD
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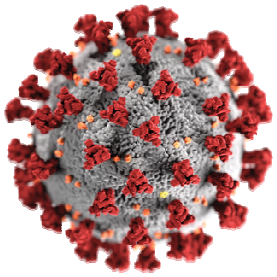
TEACHING AFFILIATE

Disclosures

- None

COVID-19: Outline

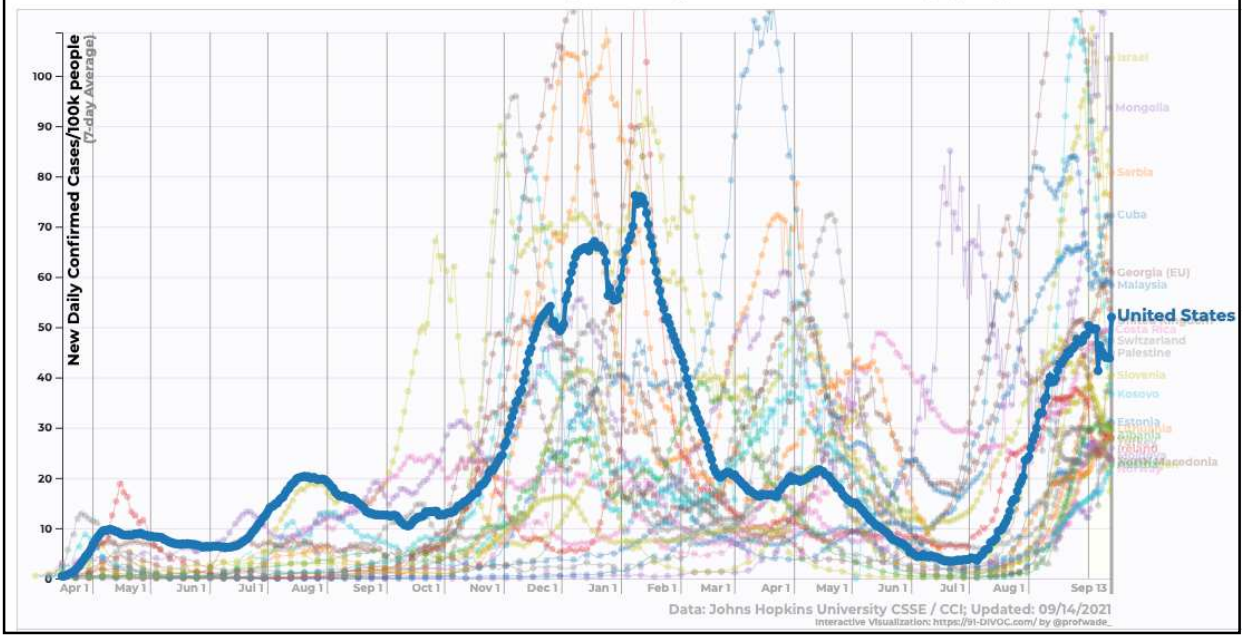
- **What happened since last year's course?**
- Clinical presentation and diagnosis
- Treatment



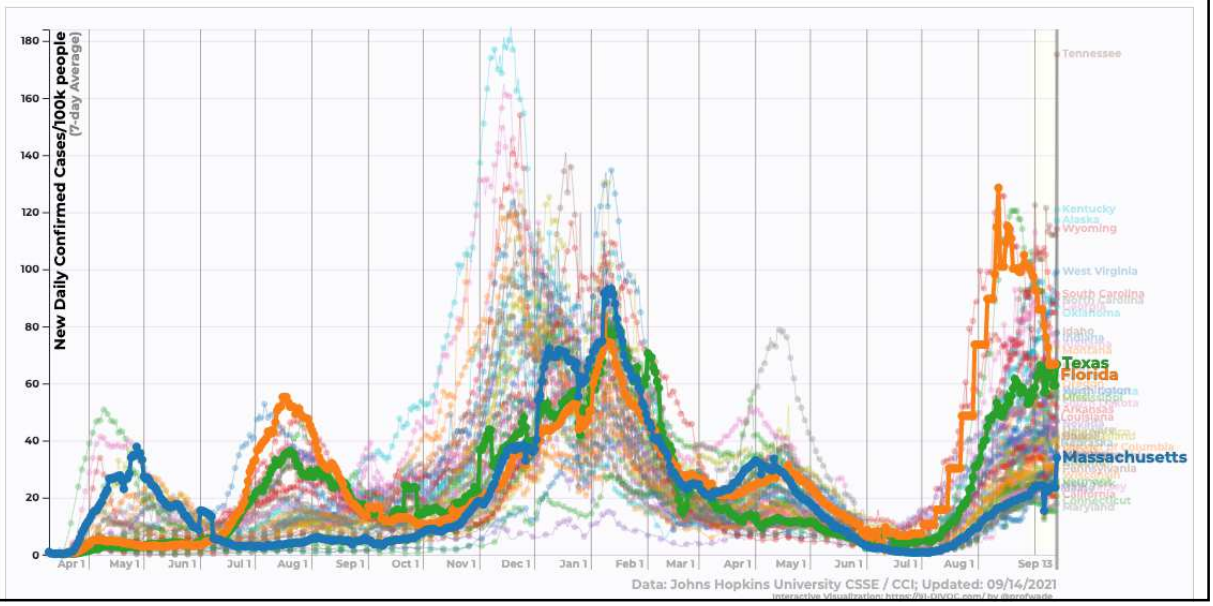
What happened since October 2020, the last hospital medicine update?

- Fading of summertime surge of cases in South and Midwest USA
- Synchronous massive increase in USA December-January 2021, followed by huge rise in some countries – notably India, Brazil, South Africa
- Greater understanding of the science of SARS-CoV-2 transmission
- Widespread utilization of remdesivir and dexamethasone, +/- tocilizumab, for inpatient treatment
- Emergency use authorization of 3 highly effective vaccines and monoclonal antibodies for outpatient treatment
- Recognition of more transmissible and (possibly) more severe and vaccine-evasive variants, leading to the current domination of delta
- Ongoing debates regarding masks, schools, vaccination policies

New Confirmed COVID-19 Cases per Day, normalized by population

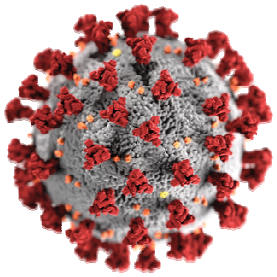


New Confirmed COVID-19 Cases per Day by States/Territories, normalized by population



COVID-19: Outline

- What happened since last year's course?
- **Clinical presentation and diagnosis**
- Treatment

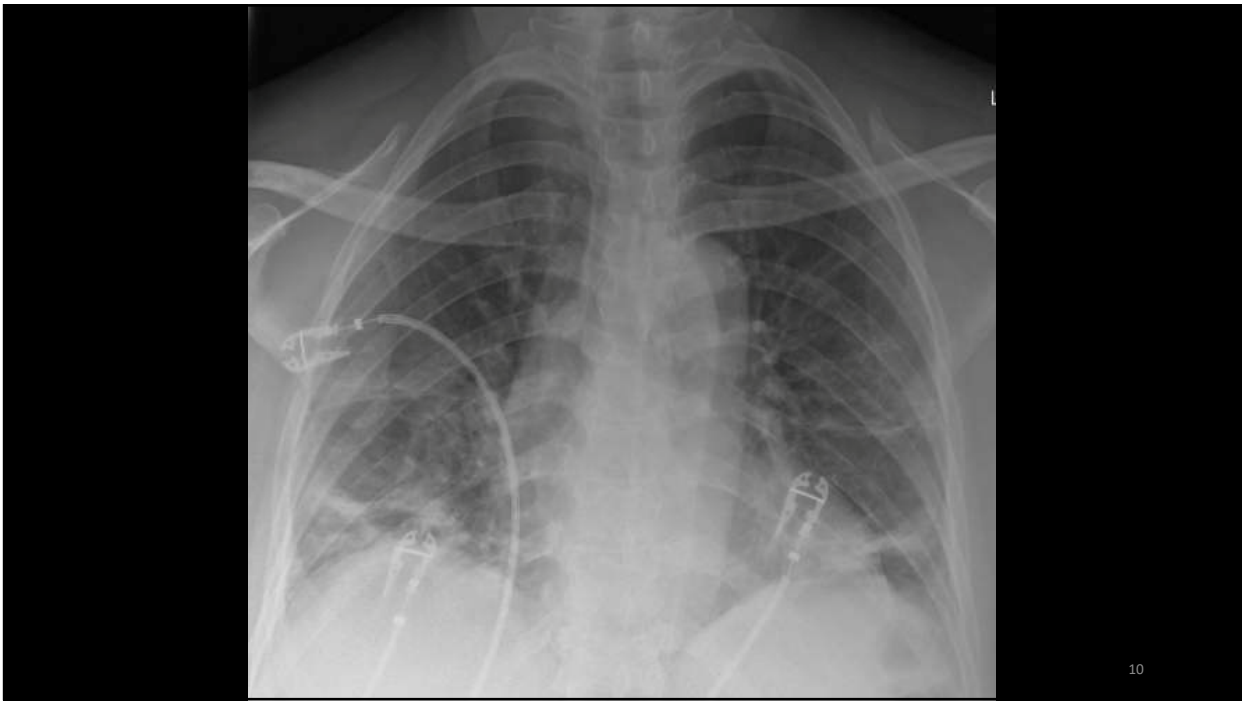


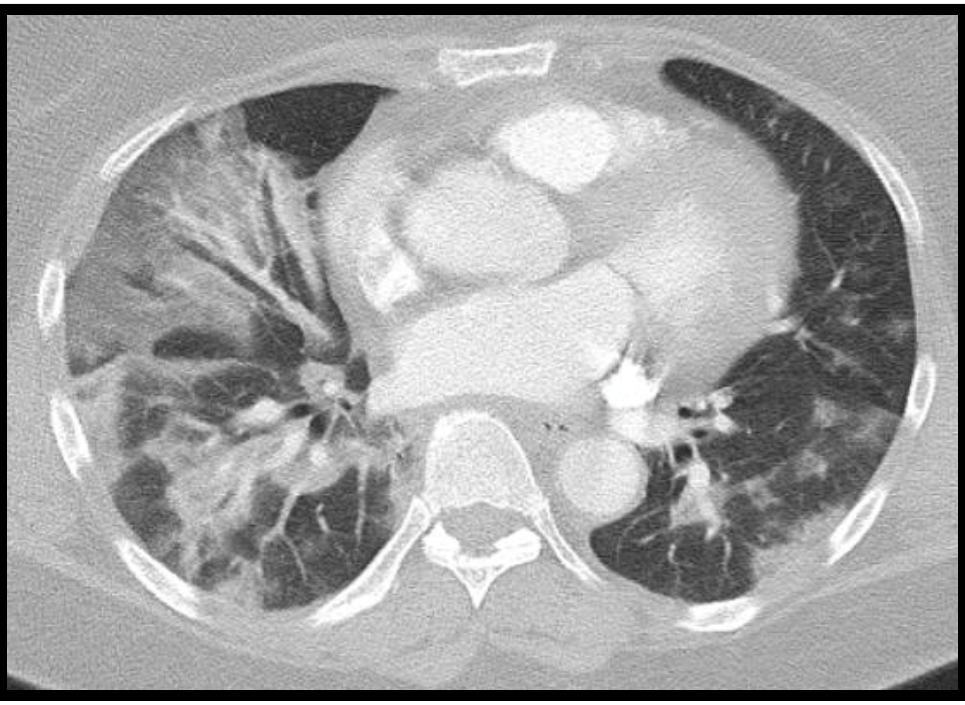
Case presentation: History

- 55-year-old woman with cough, shortness of breath, and fever
- Chose not to be vaccinated – "I have my reasons"
- Onset of malaise, headache, sore throat, and chills 7 days prior to admission
- Home COVID-19 antigen test positive the next day
- Last 24 hours before admission – escalating cough and shortness of breath
- PMHx: obesity (BMI 41), diabetes, hypertension, chronic renal disease
- Daughter insisted she go to the hospital when she couldn't complete sentences over the phone
- Exam: T 101.4, HR 110, BP 170/110, RR 20, RA O2 sat 91%

Case Presentation: Laboratory and radiographic evaluation

COVID Labs			
WBC		3.14	3.40
ANC		2.04	2.62
Lymph#		0.79	0.37
Procalcitonin			0.46
AST (SGOT)		82	72
ALT (SGPT) (U/L)		119	102
LDH			RESU...
D-Dimer (ng/mL)			1,960
CRP (mg/L)			18.5
Ferritin			2,638
CK			33
Troponin T-hs Gen5		15	15
NT-proBNP		248	447
IL-6			8.4
Creatinine		1.95	1.88
GFR (estimated)		28	30
QTC Interval		446	

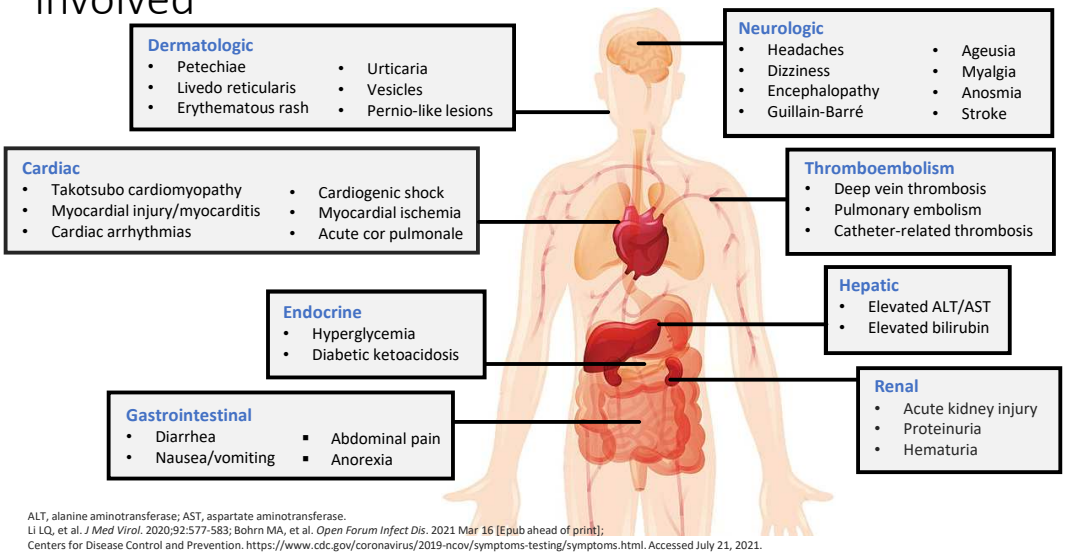




Questions to consider

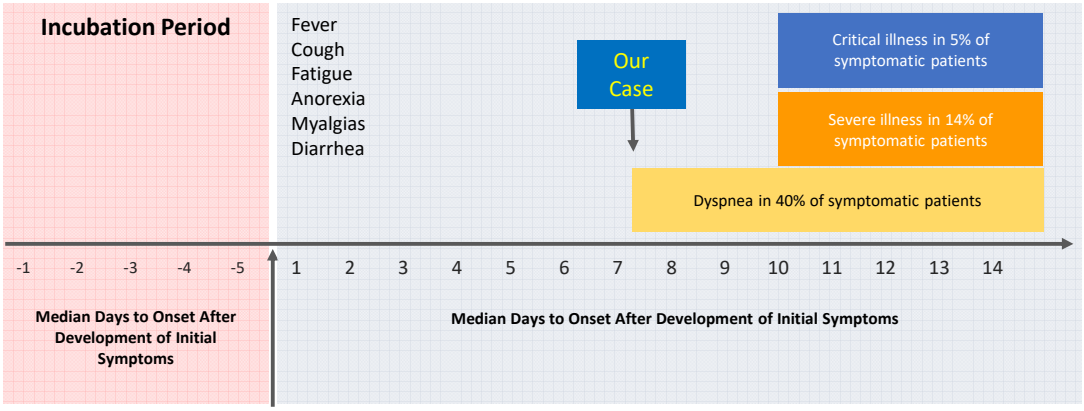
- Where is she in her clinical course?
- What is the preferred diagnostic test?
- What treatment should she receive?
  - Antibiotics?
  - Monoclonal antibodies?
  - Remdesivir?
  - Dexamethasone?
  - Tocilizumab?
  - Baracitinib?
  - (Ivermectin?)
- What is the status of outpatient therapy?

Clinical manifestations: Nearly every organ system involved



ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Li LQ, et al. *J Med Virol*. 2020;92:577-583; Bohrn MA, et al. *Open Forum Infect Dis*. 2021 Mar 16 [Epub ahead of print];
Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed July 21, 2021.

Clinical course of symptoms



Profound **and prolonged post-illness fatigue – very common**

Li LQ, et al. *J Med Virol*. 2020;92:577-583; Arentz M, et al. *JAMA.* 2020;323:1612-1614;
Chen N, et al. *Lancet.* 2020;395:507-513; Guan W, et al. *N Engl J Med.* 2020;382:1708-1720; Li W, et al. *N Engl J Med.* 2020;382:1708-1720.

Risk factors predictive of disease severity

- Obesity
- Hypertension
- Diabetes
- Chronic renal disease
- Coronary artery disease
- COPD
- Congestive heart failure
- Pregnancy
- Immunosuppression, esp B-cell depleting therapies
- HIV

- ***Every* study – older age, males**
  - Teens and young adults – highest incidence
  - Why are infants and children largely protected from severe disease?
- Uncertain
  - "Healthy" HIV – no comorbidities
  - Asthma

Garg S. Hospitalization rates and characteristics of patients hospitalized with COVID-19—COVID-NET, 14 states, March 1–30, 2020. *MMWR* 2020 April 8
Goyal P. Clinical Characteristics of Covid-19 in New York City. *NEJM* 2020 Apr 17.
Richardson S. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020 April 22.

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Our Case

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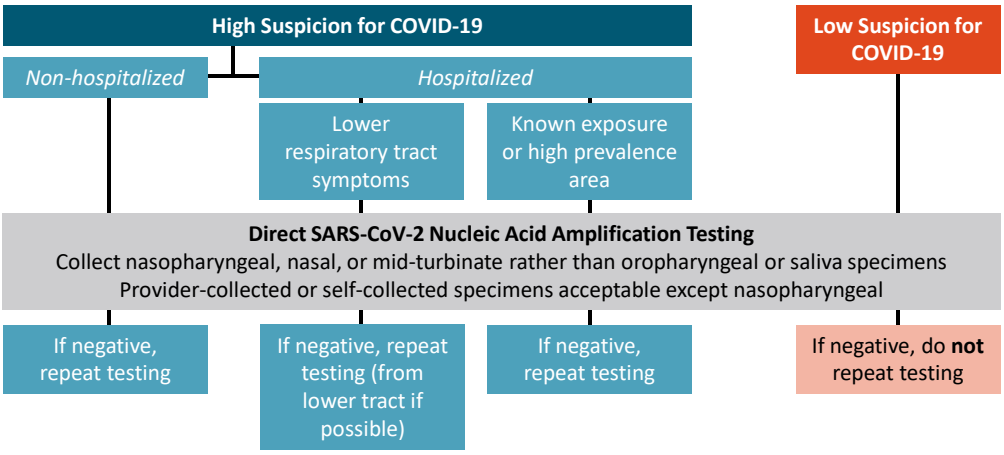
IDSA: SARS-CoV-2 nucleic acid amplification (NAAT) testing of symptomatic individuals



IDSA. COVID-19 Guideline, Part 3: Diagnostics. Version 1.0.1.

Estimated sensitivity and specificity based on clinical sample collection – sensitivity *not* 100%

Test, % (95% CI)		Sensitivity	Specificity
Sample location (3 studies)	▪ Upper respiratory tract	76 (51-100)	100 (99-100)
	▪ Lower respiratory tract	89 (84-94)	100 (99-100)
Upper respiratory tract samples (11 studies)*	▪ Oral	56 (35-77)	99 (99-100)
	▪ Nasal	76 (59-94)	100 (99-100)
	▪ Nasopharyngeal	97 (92-100)	100 (99-100)
	▪ Nasal (vs nasopharyngeal)	95 (87-100)	100 (99-100)
	▪ Saliva	85 (69-94)	100 (99-100)
	▪ Mid-turbinate	100 (93-100)	100 (99-100)
Repeat testing via nasopharyngeal swab (3 studies)	▪ Single test	71 (65-77)	100 (99-100)
	▪ Repeat test	88 (80-96)	100 (99-100)

*Not head-to-head comparisons. Not all specimens were collected from the same patients at the same time point, the time of collection from symptom onset was not provided in all studies, and the studies used various approaches for establishing SARS-CoV-2 positivity to define positive results.

IDSA. COVID-19 Guideline, Part 3: Diagnostics. Version 1.0.1.

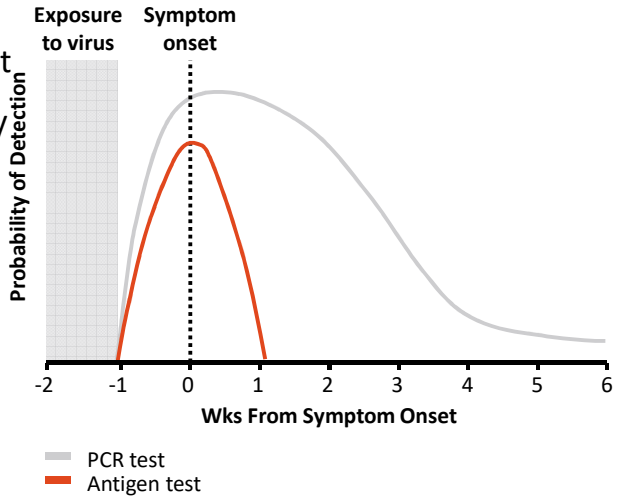
Common COVID-19 diagnostic methods: PCR and antigen testing compared

Characteristic	Nucleic Acid Amplification Test (NAAT/PCR)	Antigen Test
Intended use	▪ Detect current infection	▪ Detect current infection
Analyte detected	▪ Viral RNA	▪ Viral antigens
Specimen types	▪ Nasal, nasopharyngeal, sputum, saliva	▪ Nasal, nasopharyngeal
Sensitivity	▪ Varies by test, but generally high	▪ Moderate
Specificity	▪ High	▪ High
Test complexity	▪ Varies by test	▪ Relatively easy to use
Authorized for POC	▪ Most are not, some are	▪ Most are, some are not
Turnaround time	▪ 15 min to > 2 days	▪ 15-30 min
Cost	▪ Moderate (~ $100/test)	▪ Low (~ $1 to $50/test)
Considerations	▪ Primary method for COVID-19 diagnosis in hospital setting ▪ Duration of positive tests highly variable	▪ Reduced sensitivity vs PCR may result in false negatives ▪ May be necessary to confirm with NAAT ▪ At-home tests authorized by FDA

Udugama. ACS Nano. 2020;14:3822. Lee. Front Immunol. 2020;11:879.
CDC. Interim guidance for antigen testing for SARS-CoV-2. Last updated December 16, 2020.

Timing of PCR and antigen test positivity

- Both RNA and antigen are detectable before symptom onset
- Antigen positivity declines quickly after symptom onset, but RNA may be detectable for weeks
- Some argue antigen tests are more accurate for detecting "infectiousness" – data are supportive, not definitive



https://www.nature.com/articles/d41586-020-02661-2

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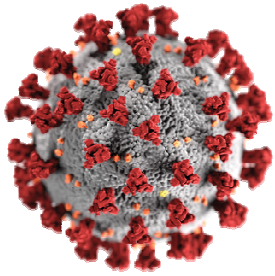
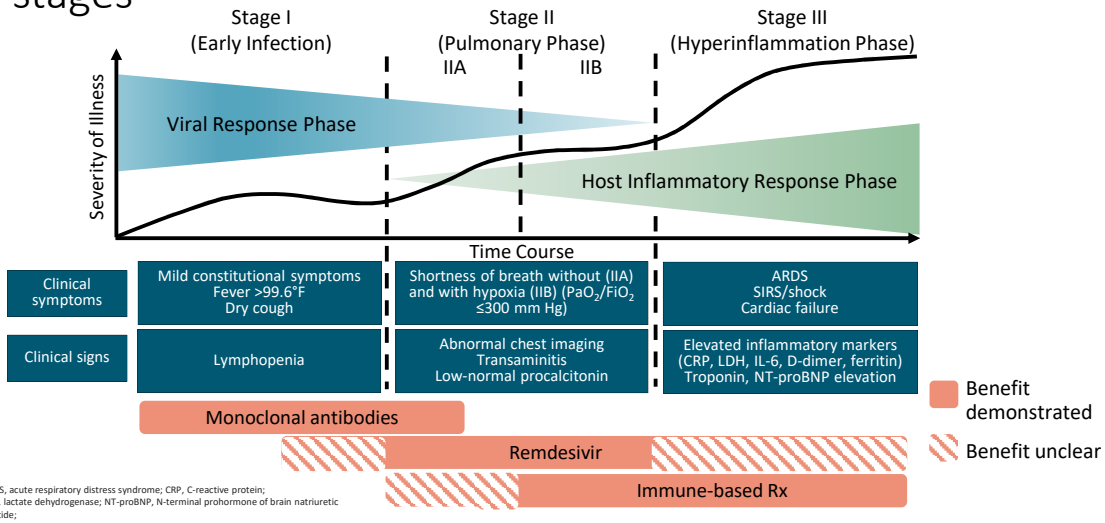


Selected Therapies for COVID-19

- Inpatient
  - **Antivirals**
    - **Monoclonal antibodies**
    - **Remdesivir**
  - Immunomodulators
    - Dexamethasone
    - Tocilizumab
    - Baricitinib
- Outpatient
  - Monoclonal antibodies
  - Fluvoxamine
  - Budesonide, ciclesonide
  - Molnupiravir
  - Colchicine
  - Metformin
  - Vitamin D
  - Ivermectin

COVID-19 therapies provide benefit at different stages



ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; LDH, lactate dehydrogenase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide;
SIRS, systemic inflammatory response syndrome;
PaO_2/FiO_2, arterial oxygen partial pressure/fractional inspired oxygen.
Siddiqi HK, Mehra MR. *J Heart Lung Transplant*. 2020;39:405.

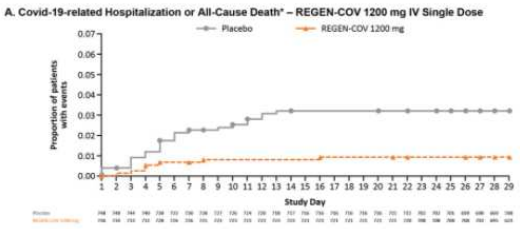
Monoclonal antibody therapy for patients with mild-to-moderate COVID-19

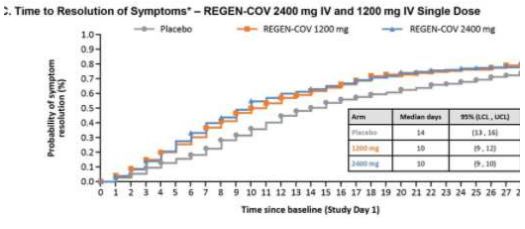
	Casirivimab / Imdevimab (Combination mAb)	**Bamlanivimab / Etesevimab** (Combination mAb)	**Sotrovimab** (Single mAb)
EUA Issued	November 21, 2020 (updated June 3, 2021)	February 9, 2021 ***Distribution paused, then resumed Aug 27, 2021***	May 26, 2021
Ages	Adults and Children aged ≥12 years	Adults and Children aged ≥12 years	Adults and Children aged ≥12 years
Administration	**Single dose (600 mg each)** IV infusion over 1 hour *May give as SC injection if IV infusion is not feasible or would lead to treatment delay.	**Single dose** 700 mg bamlanivimab and 1,400 mg of etesevimab	**Single dose (500 mg)** IV infusion over 30 min

EUA, Emergency Use Authorization; IV, intravenous; mAb, monoclonal antibody; SC, subcutaneous.
National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management. Accessed July 21, 2021;
US Food and Drug Administration. Fact Sheet for Healthcare Providers: EUA of Casirivimab / Imdevimab (updated June 2021). https://www.fda.gov/media/145611/download. Accessed July 21, 2021;
US Food and Drug Administration. Fact Sheet for Healthcare Providers: EUA of Sotrovimab. https://www.fda.gov/media/149534/download. Accessed July 21, 2021; US Department of Health & Human Services, Public Health Emergency. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/bamlanivimab-etesevimab-distribution-pause.aspx. Accessed July 21, 2021.

Casirivimab + Imdevimab for mild-to-moderate COVID-19: Results from phase 3 randomized controlled trial

- Phase 3 randomized, placebo-controlled trial of 4,057 Covid-19 **outpatients** with one or more risk factors for severe disease
- *70% reduction in COVID-19–related hospitalization or all-cause death* compared to placebo (p = .0024)
- Treatment also led to faster time to resolution of symptoms and decline in viral load





Weinreich DM, et al. MedRxiv May 21, 2021. doi.org/10.1101/2021.05.19.21257469

Monoclonal antibody treatments as of September 2021

- Casirivimab plus imdevimab, or sotrovimab, (or bamlanivimab plus etesevimab for susceptible variants) reduce risk of disease progression in high-risk outpatients
- Start as soon as possible – preferably < 10 days after onset of symptoms
  - Can also can be given as post-exposure prophylaxis -- even to inpatients
- Prior vaccination should not influence treatment decisions
- ***Inpatient use for COVID-19 disease is not covered under the current EUA***

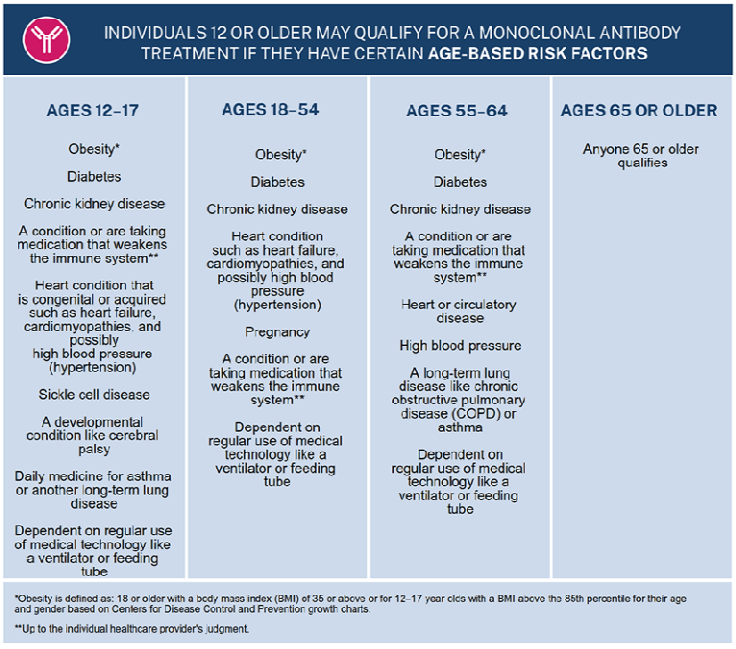
  "They may be available through expanded access programs for patients who have not developed an antibody response or who are not expected to mount an effective immune response to SARS-CoV-2 infection"

www.covid19treatmentguidelines.nih.gov

NIH COVID-19 Treatment Guidelines

Eligibility criteria for treatment

- Confirmed COVID-19 by PCR or Ag testing
- Mild-moderate symptoms (not asymptomatic)
- Do NOT require oxygen (or increase from baseline O2)
- Not hospitalized
- Infusion must be completed within 10 days of symptom onset
- Have at least 1 risk factors for progression to severe disease (see table)
- Vaccination not exclusionary



www.covid19treatmentguidelines.nih.gov

Monoclonal antibody treatment challenges

Opinion

We Have a Lifesaving Treatment for Covid-19. Why Is It So Hard to Get?

Doctors like me want monoclonal antibodies for our high-risk patients, but the medicine is difficult to come by.

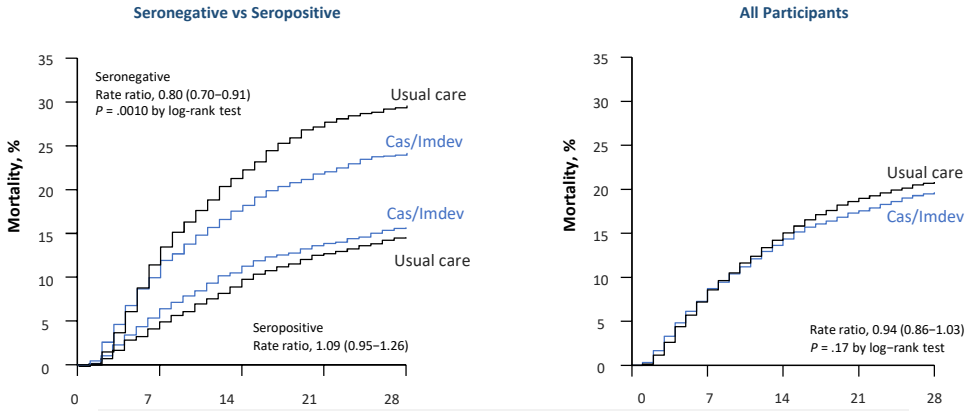
By Perry Cook
Dr. Cook is a hematologist and oncologist at NewYork-Presbyterian Brooklyn Methodist and Weill Cornell hospitals in New York City.

March 31, 2021

- Optimally given soon after onset of symptoms – or even before for high risk patients
- IV access required in most cases
- Treatment/observation takes 1 hour or longer
- Paperwork complex
- EUA means no ready supply in community
- Patients maximally infectious during early disease – where should they be safely treated, and how do they travel?
- Infusion centers often serve many immunocompromised patients
- Primary purpose of EDs is patient triage and stabilization, not treatment

The New York Times. https://www.nytimes.com/2021/03/31/opinion/covid-monoclonal-antibodies-treatment.html.

RECOVERY: Casirivimab/imdevimab for **inpatients** with COVID-19 improved survival for seronegatives



Among seronegative patients, casirivimab/imdevimab monoclonal antibody therapy reduced deaths by 20% (*P* = .001)

UK, United Kingdom. RECOVERY Collaborative Group, et al. *medRxiv* [Preprint]. 2021.06.15.21258542.

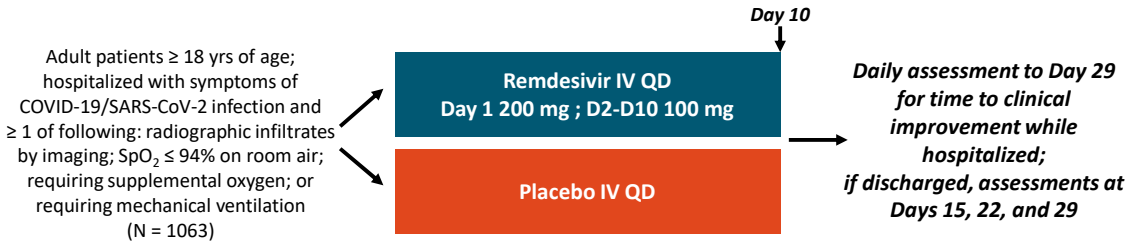
Inpatient monoclonal antibody treatment: Not yet, but soon

- Despite benefits seen in seronegative participants in RECOVERY trial, inpatient therapy not yet available
- Dose higher than outpatient trials – uncertain what recommended inpatient dose might be
- Possible signal of harm for seropositives
- To implement:
  - Change in emergency use authorization EUA
  - On-site anti-spike antibody testing with rapid turnaround
  - Wider distribution to inpatient pharmacies

Slide adapted from A Kim.

Remdesivir COVID-19 treatment trial (NIAID ACTT-1): Study design

- Multicenter, adaptive, randomized, double-blind, placebo-controlled phase III trial



- Primary endpoint: time to recovery* by Day 29 according to ordinal scale
- Secondary endpoints: treatment-related improvements in 8-point ordinal scale at Day 15

*Day of recovery is first day patient satisfies 1 of these categories from ordinal scale: 1) hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care; 2) not hospitalized, limitation on activities and/or requiring home oxygen; or 3) not hospitalized, no limitations on activities.

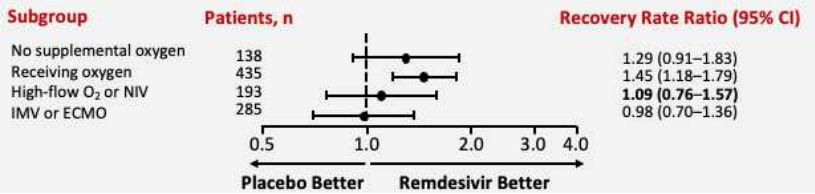
Beigel. NEJM. 2020;[Epub]. NCT04280705.

NIAID ACTT-1: Efficacy and safety of remdesivir in a double-blind trial

- Preliminary results from 1059 patients with data available after randomization

Outcome	Remdesivir (n = 538)	Placebo (n = 521)	HR (95% CI)	*P* Value
Median recovery time, days	11	15	1.32 (1.12-1.55)	< .001
Mortality by 14 days, %	7.1	11.9	0.70 (0.47-1.04)	NS

- ***Benefit greatest for those treated earliest after symptom onset***
- Serious AEs: 21.1% (114/541) with remdesivir and 27.0% (141/522) with placebo



Beigel. NEJM. 2020.

Remdesivir: Miscellaneous issues and controversies

- Three randomized clinical trials showed no benefit
  - Study in China underpowered
  - WHO SOLIDARITY and DISCOVER: No benefit – but time from onset of symptoms generally 7 days or longer
- Should all patient complete 5 days of treatment?
- Should it be given to patients
  - Who do not require O2? (My opinion – *yes)*
  - Who require mechanical ventilation and or ECMO?
  - Who have > 7 days of symptoms?
- Should treatment be extended in certain immunocompromised hosts?
- Should it be given to outpatients?
- *If decision is made to treat, start ASAP*

Wang Y, et al. Lancet 2020; WHO SOLIDARITY NEJM 2021; Ader F, et al. Lancet 2021.

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  - **Immunomodulators**
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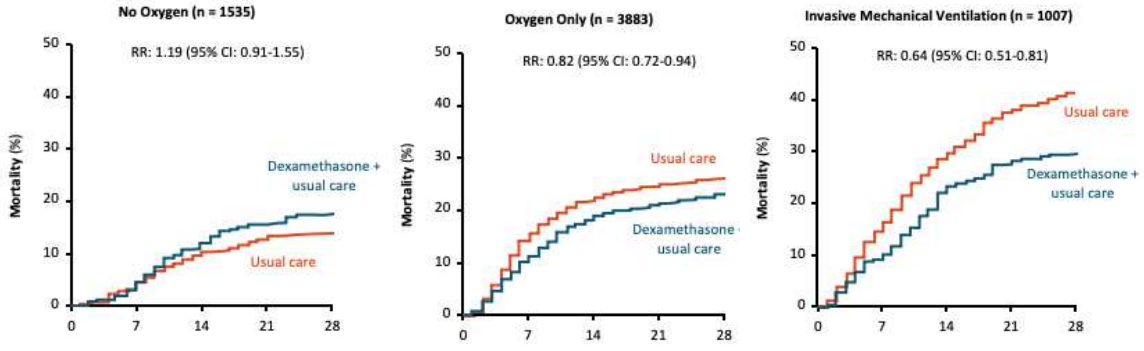
  - Metformin
  - Vitamin D
  - Ivermectin

RECOVERY: Benefits of dexamethasone depend on disease severity at baseline

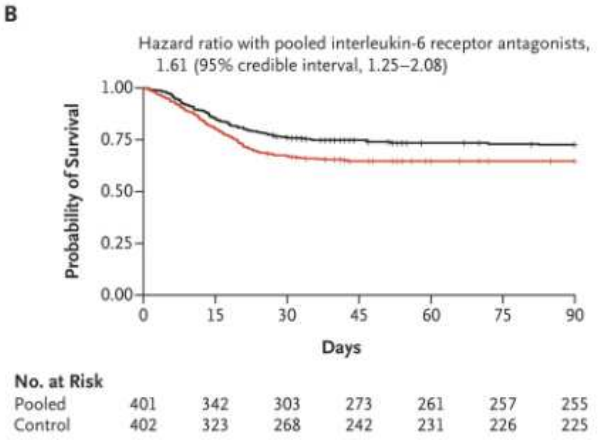


- Survival benefit seen in patients with O2 requirement and greater severity
- In those not requiring O2, suggestion that dexamethasone worsens outcomes

RECOVERY Collaborative Group. NEJM. 2020;[Epub].

REMAP-CAP: IL-6 inhibitors improve survival in critical illness

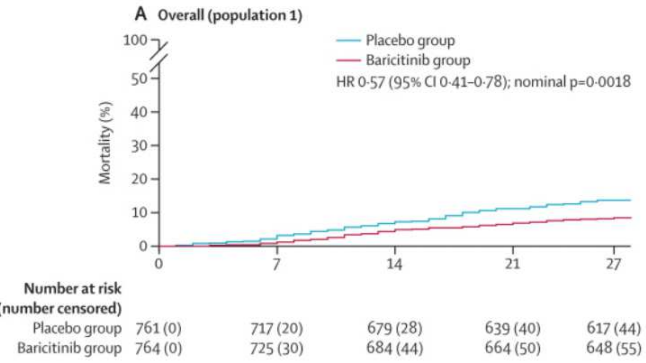
- Adult patients within 24 hours of requiring organ support in ICU randomized to IL-6 inhibitor (tocilizumab or sarilumab) or standard care
- Outcomes of organ-support free days and overall survival favored intervention arm



N Engl J Med 2021; 384:1491-1502

COV-BARRIER: Baricitinib for inpatients with COVID-19

- Eligible: Non-intubated COVID-19 pneumonia with at least one elevated inflammatory marker (C reactive protein, D-dimer, lactate dehydrogenase, ferritin)
- Primary endpoint: Disease progression
- Secondary endpoint: Mortality
- Study participants could receive remdesivir (18%) and/or dexamethasone (79%)
- Baracitinib treatment significantly reduced 28-day mortality



Marconi V, et al. Lancet 2021.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.

NIH | COVID-19 Treatment Guidelines

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Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**

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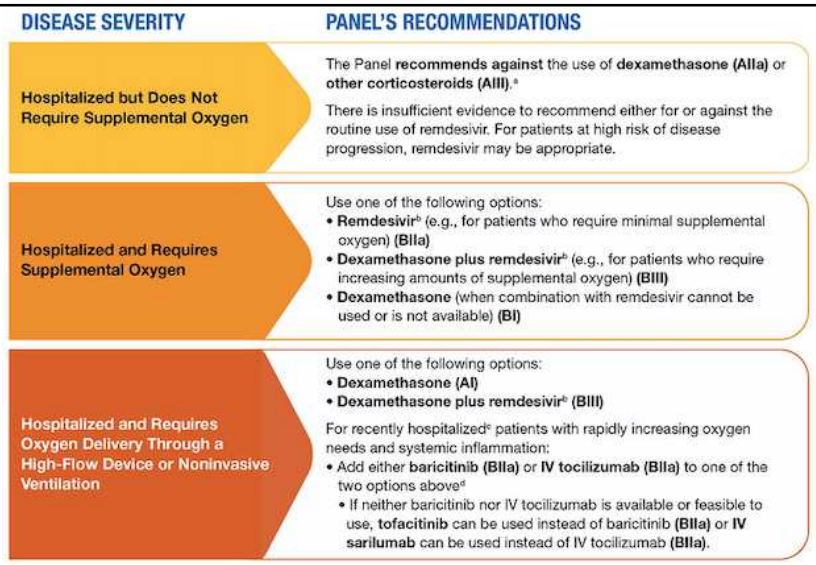
NIH COVID-19 Treatment Guidelines

covid19treatmentguidelines.nih.gov



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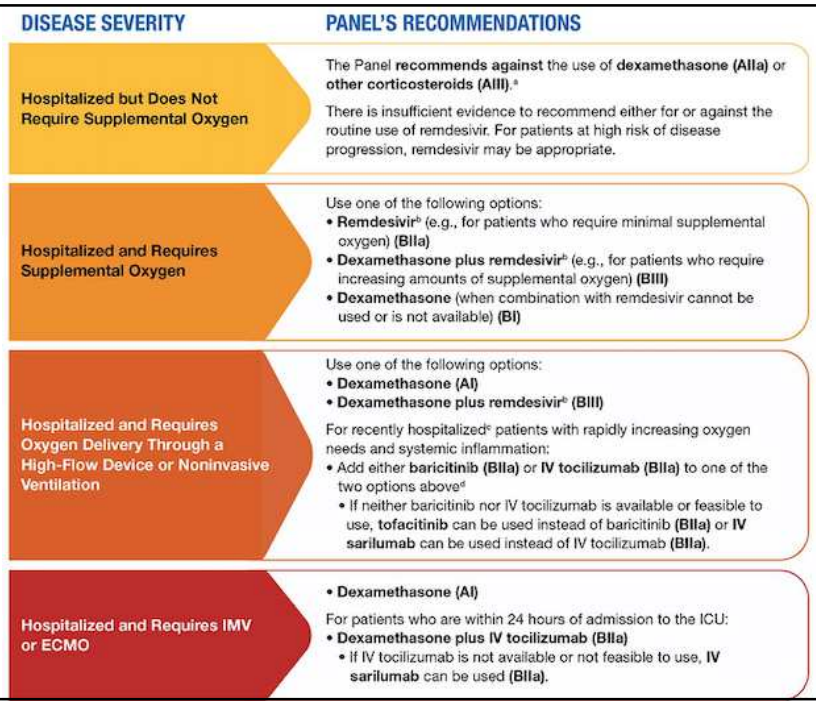


- Review of 154 studies involving 30,623 people with COVID-19
- Antibiotics prescribed in 75%, more common with critical illness
- Bacterial co-infection identified in 8.6%
- IDSA guidelines: *"There are inadequate data regarding the use of empiric antibacterial agents in patients with mild or moderate COVID-19. Most guidelines recommend against use of empiric antimicrobials in patients admitted to the hospital with non-severe COVID-19."*

Langford BJ, et al. CMI 2021. opencriticalcare.org/covid-dashboard

Questions to consider – Now with answers

- Where is she in her clinical course? **Start of inflammatory stage**
- What is the preferred diagnostic test? **PCR**
- What treatment should she receive?
  - Antibiotics **Usually not indicated – stop early if cultures negative**
  - Monoclonal antibodies? **No – but if antibody *negative*, likely soon**
  - Remdesivir? **Yes**
  - Dexamethasone? **Yes**
  - Tocilizumab? **Not unless headed to ICU**
  - Baracitinib? **Same as tocilizumab, or alternative to dexamethasone**
  - Ivermectin? **No**
- How will outpatient therapy potentially change in the future?

Ivermectin

- Antiparasitic agent with marginal in vitro activity against SARS-CoV-2
- Some (not all) observational studies and unpublished RCTs show benefit in prevention and treatment
- Not recommended in NIH or IDSA guidelines except in clinical trials
- Extensive off-label prescribing in certain regions
- Several well-designed clinical trials ongoing

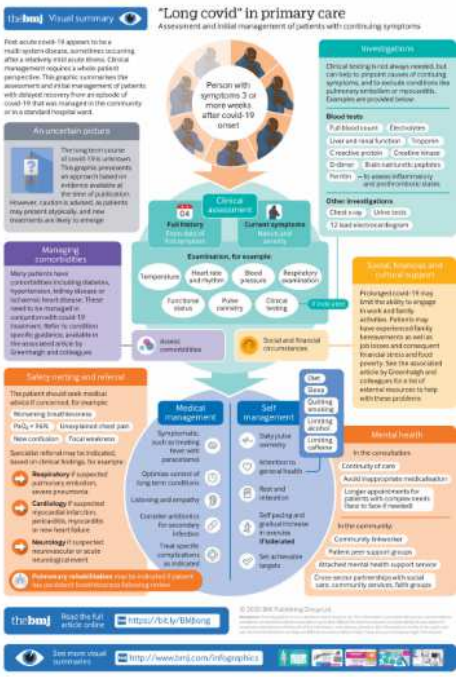
Selected Therapies for COVID-19

- Inpatient
  - Antivirals
    - Monoclonal antibodies
    - Remdesivir
  - Immunomodulators
    - Dexamethasone
    - Tocilizumab
    - Baricitinib
- Outpatient
  - **Monoclonal antibodies**
  - **Fluvoxamine**
  - **Budesonide, ciclesonide**
  - **Molnupiravir**
  - **Colchicine**
  - Metformin
  - Vitamin D
  - Ivermectin

Case outcome

- Received remdesivir loading dose and dexamethasone in the emergency room
  - Baseline nucleocapsid antibody: positive
- Also received ceftriaxone and azithromycin – stopped after 2 days
- Treated 5 days of remdesivir then discharged home; dexamethasone stopped at discharge
- Advised to seek immunization after complete recovery

NY Times, Jan 21, 2021



Management of "Long COVID"/PASC

- Post-Acute Sequelae of SARS-CoV-2 infection – PASC
- Pathophysiology not clear
- Must distinguish between non-specific symptoms (e.g. SOB, fatigue, neurocognitive "brain fog") and serious complications (e.g. VTE, heart failure, pulmonary fibrosis)
- For fatigue: graded exercise program based on degree of symptomatology with cardiology clearance if known cardiac sequelae
- Mental health support

Greenhalgh et al. BMJ 2020. 370

Question regarding post-COVID-19 syndromes

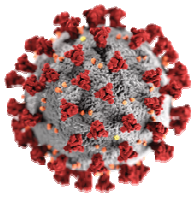
- How common are post-COVID symptoms?
- How should we evaluate such patients?
- What tests should we order?
- How should they be managed?

February 23, 2021

NIH launches new initiative to study "Long COVID"

Take-home points: Inpatient management of COVID-19

- All symptomatic patients:
  - Remdesivir, started as soon as possible
  - No need to give full 5-day course if recovery is rapid
  - No benefit if started "too late"
  - (Coming soon – monoclonal Abs if antibody negative on admission)
- Patients requiring oxygen:
  - Dexamethasone added to remdesivir
  - Baricitinib if dexamethasone contraindicated
- Patients about to require, or soon after requiring, ICU care:
  - Add tocilizumab or baricitinib
  - (Sarilumab may be used if tocilizumab is unavailable; tofacitinib if baricitinib unavailable)



Acknowledgments

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