Current Options for Treating COVID-19
(as of November 5, 2021 at 9:30 AM PT!)

Rajesh T. Gandhi, MD
Professor of Medicine
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Gandhi has no financial affiliations with ineligible companies. (Updated 10/23/21)

Slide 2

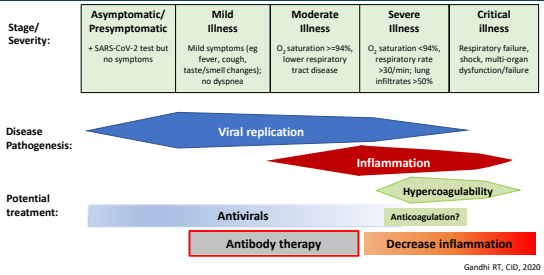
Learning Objectives

After attending this presentation, learners will be able to:

- Describe treatments for nonhospitalized patients with COVID-19
- Summarize use of antibodies to prevent COVID-19
- List therapies for people hospitalized with COVID-19

Slide 3

Treatment Across the COVID-19 Spectrum

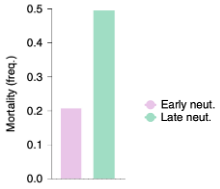


Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Slide 4

Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment: Rationale

- Delayed production of neutralizing antibodies correlates with fatal COVID-19
- Would providing passive immunity through antibody therapy improve clinical outcomes?



Lucas C et al, Nat Med. 2021 May 5. doi: 10.1038/s41591-021-01355-0. PMID: 33953384.

Slide 5

Anti-SARS-CoV-2 Monoclonal Abs for Treatment

- Phase 3 placebo controlled clinical trials in non-hospitalized patients with mild to moderate COVID and with at least one risk factor for severe COVID

Antibody	% Reduction Hospitalization/Death
Bamlanivimab/etesevimab*	70%
Casirivimab/Imdevimab*	70%
Sotrovimab*	85%
BRII-196/BRII-198**	78%
Tixagevimab/Cilgivimab†	50%†
Regdanvimab††	72%††

*Authorized in the US; **Interim analysis; †Reduction in severe COVID-19 or death; ††Approved in South Korea

Dougan M et al, NEJM, 2021; Weinreich et al., NEJM 2021;
Gupta A et al, medRxiv, 2021; https://doi.org/10.1101/2021.05.27.21257256; Evering T et al, IDWeek 2021;
https://www.astrazeneca.com/media-centre/press-releases/2021/vir0947-phiii-trial-positive-in-covid-outpatients.html Ivan MG et al, IDWeek 2021

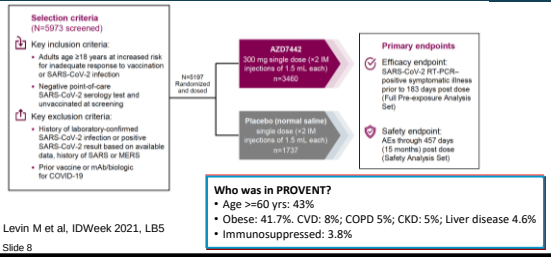
Slide 6

Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention

- Antibodies authorized for **treatment** of non-hospitalized patients with mild to moderate COVID at high risk of progression and within 10 d of symptom onset:
  - Bamlanivimab + Etesevimab (700/1400 mg)
  - Casirivimab + Imdevimab (600/600 mg)
  - Sotrovimab
- Bamlanivimab/etesevimab and casirivimab/imdevimab also authorized for **post-exposure prophylaxis** (in those not fully vaccinated or immunocompromised)
- Tixagevimab/cilgivimab (long-acting anti-spike antibodies) for **pre-exposure prophylaxis** being considered by FDA/EMA (PROVENT trial)

Slide 7

PROVENT: Phase 3 Pre-exposure Prophylaxis Trial
IM Tixagevimab/cilgivimab (AZD7442) vs. Placebo



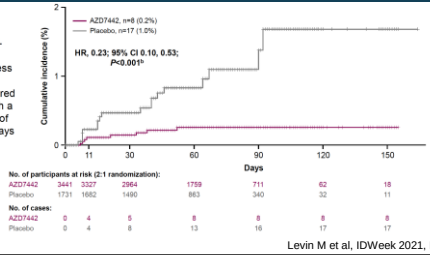
Who was in PROVENT?
- Age >=60 yrs: 43%
- Obese: 41.7%. CVD: 8%; COPD 5%; CKD: 5%; Liver disease 4.6%
- Immunosuppressed: 3.8%

Levin M et al, IDWeek 2021, LB5

Slide 8

Results: 77% Reduction in Symptomatic COVID-19

- Time to first SARS-CoV-2 RT-PCR–positive symptomatic illness was longer for AZD7442 compared with placebo, with a median duration of follow-up of 83 days



Slide 9

Levin M et al, IDWeek 2021, LB5

What about SARS-CoV-2 Variants?

- Alpha (B.1.1.7): expected to be susceptible to authorized antibodies
- Beta (B.1.351), Gamma (P.1)
  - Marked reduction in susceptibility to bam/ete in lab studies
  - Casirivimab/imdevimab, sotrovimab expected to retain activity
- Delta (B.1.617.2)
  - Bamlanivimab/etesevimab, Casirivimab/imdevimab, Sotrovimab expected to have activity

Slide 10

https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

Small Molecule Antiviral for SARS-CoV-2: Molnupiravir

- Oral inhibitor of SARS-CoV-2 replication: viral error catastrophe
- Phase 3 MOVe-OUT Trial
  - Non-hospitalized adults, mild to moderate COVID-19, ≥1 risk factor for severe disease
  - Symptom onset within 5 days of study randomization
- Interim analysis (n=775)

	Hospitalization or death	% Reduction
Molnupiravir	**28/385 (7.3%)**	**48% (p=0.0012)**
Placebo	**53/377 (14%)**	

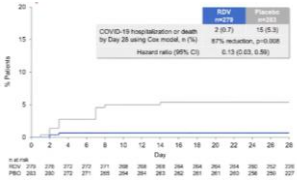
- Appeared to be active against Gamma, Delta and Mu variants

Slide 11

https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/

PINETREE: Remdesivir in Non-Hospitalized Individuals

- Nucleotide prodrug: inhibits viral RNA polymerase: chain terminator
- Randomized trial (n=584):
  - High risk, symptoms <= 7 day
  - RDV IV x 3 days vs. placebo
- RDV: 87% reduction in hospitalization/death
  - No effect on NP SARS CoV-2 level

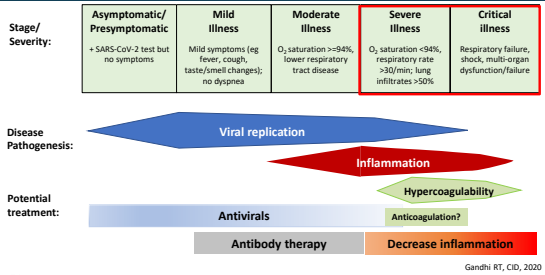


Slide 12

Hospitalized Patients with Severe or Critical COVID-19

Slide 13

Treatment Across the COVID-19 Spectrum



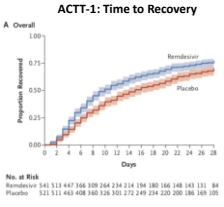
Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Slide 14

Antivirals

Remdesivir (RDV)

- ACTT-1: hospitalized pts, lower respiratory tract infection randomized to RDV or placebo
  - Clinical recovery more rapid with RDV than placebo (10 vs 15 d)
  - Mortality at 29 days: 11.4% RDV, 15.2% placebo (hazard ratio 0.73, 95% CI, 0.52-1.03).
  - Benefit of RDV clearest in those on supplemental oxygen but not intubated



Beigel JH et al, NEJM 2020; Goldman JD et al, NEJM 2020

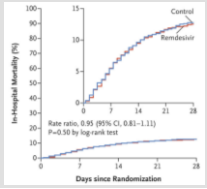
Slide 15

Antivirals

What about SOLIDARITY and DisCoVeRy?

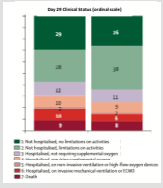
SOLIDARITY (WHO, >30 countries)

- Open label randomized trial
- No effect of RDV on mortality



DisCoVeRY (Europe)

- Open label randomized trial
- >50% of participants also in SOLIDARITY
- Median symptom duration: 9 d
- No effect of RDV on clinical status or mortality



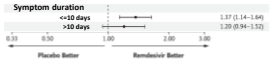
Slide 16

https://www.nejm.org/doi/full/10.1056/NEJMoa2023184; Ader F et al, Lancet, 2021

Antivirals

Where Does that Leave Remdesivir? My Take

- Early therapy more likely to confer benefit than later initiation
  - ACTT-1 Time to Recovery



  - PINETREE: RDV reduced hospitalization/death by 87% in high-risk non-hospitalized patients with symptoms <= 7 days
- RDV may have role in treating COVID-19 but benefit likely greatest if started early; if started when patient requiring increasing amounts of oxygen, combine with immunomodulation

Slide 17

Beigel JH et al, NEJM 2020; Hill J et al, IDWeek, 2021

Decrease inflammation

Dexamethasone

- Open label, randomized trial among patients hospitalized with COVID-19
- Dex 6 mg/day for up to 10 days or until hospital discharge if sooner (n=2104) or usual care (n=4321)

Mortality	Dex	Usual Care	RR mortality
All participants	22.9%	25.7%	**0.83** (0.75 – 0.93)
Mechanical ventilation/ECMO	29.3%	41.4%	**0.64** (0.51 – 0.81)
Oxygen only	23.3%	26.2%	**0.82** (0.72 – 0.94)
No oxygen	17.8%	14%	**1.19** (0.91 – 1.55)

- Dexamethasone: decreased mortality among those requiring oxygen
- No benefit (potential harm) in those not requiring oxygen.

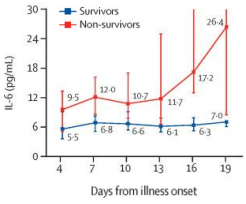
Slide 18

RECOVERY Collaborative Group, NEJM, 2020

Decrease inflammation

Anti-IL-6 Inhibitors

- Elevated interleukin(IL)-6 levels associated with worse clinical outcomes; may be part of dysregulated inflammation that can occur in severe COVID-19
- Early observational studies suggested possible benefit of IL-6 inhibition
- However, early randomized studies (many before dexamethasone era) did not show mortality benefit



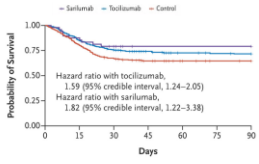
Zhou F et al, Lancet, 2020

Slide 19

IL-6 Blockade in Steroid Era

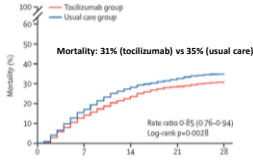
REMAP-CAP

- Adults within 24 hours of starting organ support in ICU (>80% on steroids)
- Improved survival with IL-6 blockade



RECOVERY

- Hospitalized patients with progressive COVID, hypoxemia, CRP >=75 (>80% on steroids)
- Improved survival with tocilizumab



REMAP-CAP, NEJM, 2021; RECOVERY Collaborative Group, Lancet, 2021

Slide 20

Decrease inflammation

Jak Inhibitors: Baricitinib

- Tamp down inflammation: reduce cytokine production
- Baricitinib also proposed to have anti-viral effect
- COV-BARRIER: ~1500 hospitalized patients with COVID pneumonia and elevated inflammatory marker randomized to baricitinib or placebo (about 80% also received steroids)
- 28-day mortality: 8% with baricitinib, 13% with placebo (HR 0.57, p=0.0018)
  - Participants receiving high flow oxygen, non-invasive ventilation had greatest benefit

Marconi V et al, Lancet Resp Med, 2021

Slide 21

Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation

Use one of the following options:
- **Dexamethasone (AI)**
- **Dexamethasone plus remdesivir[h] (BIII)**

For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation:
- Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d]
  - If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** or **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.

Slide 22

Areas of Uncertainty

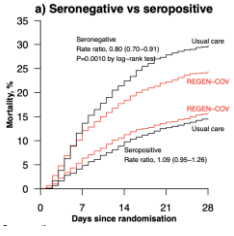
Slide 23

Casirivimab/Imdevimab in Hospitalized Patients

RECOVERY: Hospitalized patients (n=9785) randomized to usual care with casirivimab 4,000 mg + imdevimab 4,000 mg IV or usual care alone

Results

- 28-day mortality: 20% vs. 21% (no difference)
- In those seronegative for anti-spike protein antibody, reduced mortality with casi/imdev: 24% vs. 30% (rate ratio 0.80)

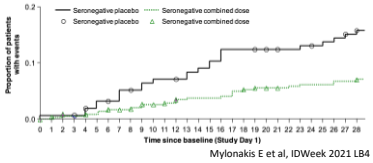


https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf;

Slide 24

Hospitalized Patients on Low Flow or No Oxygen

- Approximately 1100 hospitalized patients on low flow or no oxygen
- Randomized to casirivimab/imdevimab (2.4 or 8 g) or placebo
- In seronegatives: 55.6% reduction in mortality with casirivimab/imdevimab
- In seropositive patients, no reduction in mortality
- **We need rapid and reliable serology test to identify seronegative individuals**



Mylonakis E et al, IDWeek 2021 LB4

Slide 25

Fluvoxamine: TOGETHER trial

- Placebo controlled randomized adaptive platform trial in Brazil
- Participants with risk factors for severe COVID-19 (n≈1500) and within 7 days from symptom onset
- Fluvoxamine 100 mg bid or placebo
- Primary endpoint (composite of hospitalization or ED observation >6 hours): 11% (fluvoxamine) vs. 16% (placebo) (relative risk 0.68)

Intention-to-treat analysis			
	N	n (%)	Relative risk (95% BCI)
Fluvoxamine	741	79 (11%)	0·68 (0·52–0·88)
Placebo	756	119 (16%)	1 (ref)

- No difference in hospitalizations (10% vs. 13%), duration of hospitalization, death (2% vs. 3%), viral clearance
- Most (94%) had not received any vaccine doses

Reis G et al, Lancet Global Health, 2021

Slide 26

Inhaled Steroids: Jury Still Out

- **Inhaled budesonide**
  - STOIC (n=146): open label randomized controlled trial
    Decreased urgent care visits (including ED/hospitalization): 1 vs. 14%
  - PRINCIPLE (n=1856): open label randomized control trial
    Improved time to recovery
    Hospitalization/death: 6.8% vs. 8.8% (OR 0.75, 95% Bayesian CrI 0.55-1.03)
- **Ciclesonide** (30 days) (n=400): placebo controlled randomized clinical trial
  - Days to alleviation of symptoms: 19 days vs. 19 days
  - ED visit/hospitalization: 2/197 (1%) (ciclesonide) vs. 11/203 (5.4%) (placebo) (p=0.03)
  - Hospitalization/death: 3/197 (1.5%) vs. 7/203 (3.4%) (p=0.26, not significant)

Slide 27

COVID-19 Treatment Guidelines: What Not to Use and Areas of Uncertainty

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Not recommended or suggested:

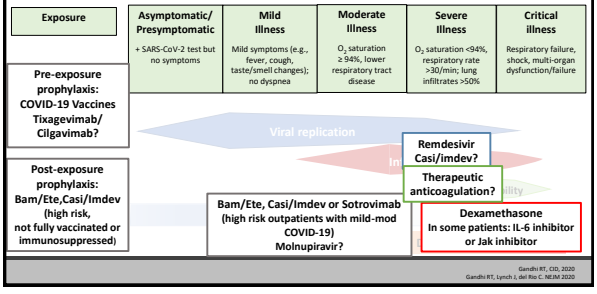
- Hydroxychloroquine
- Azithromycin
- Lopinavir/ritonavir
- Convalescent plasma in hospitalized patients (IDSA)

Insufficient data:

- Ivermectin
- Fluvoxamine
- Inhaled steroids
- Vitamin C, Zinc
- Colchicine

Slide 28

Prophylaxis and Treatment Across the COVID-19 Spectrum



Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

COVID-19 Treatment: Final Thoughts

- Therapy for COVID-19 depends on host and severity of disease: not one-size fits all
- Antiviral therapy (including anti-SARS-CoV-2 monoclonal antibodies): greatest benefit early in disease when viral replication is active and, perhaps, in seronegative hospitalized patients
- Immunomodulators, including dexamethasone (and tocilizumab or baricitinib in select patients): greatest benefit later in course of disease when there is excess inflammation
- New therapies, including oral agents, needed

Slide 30

Lessons from HIV for COVID-19

- Pressure to deploy interventions must be tempered by importance of finding out if a treatment works
- Randomized trials can and must be done during pandemic
- Iterative process
- **Global equity is essential!**

Siedner M, Gandhi RT, Kim AY, JID, 2020

The rapid and simultaneous combination of supportive care and RCTs is the only way to find effective and safe treatments for COVID-19 and any other future outbreak.

Kalil AC, JAMA, 2020

Slide 31

Acknowledgments

- Arthur Y. Kim, MD
- Gregory Eschenauer, PharmD
- Efe Airewele

Slide 32

Question-and-Answer Session