Therapeutic Options to Prevent Severe COVID-19 in Immunocompromised People

Clinician Outreach and Communication Activity (COCA) Webinar

Thursday, August 12, 2021

Free Continuing Education

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- Planners have reviewed content to ensure there is no bias.

- The presentation will not include any discussion of the unlabeled use of a product or a product under investigational use except parts of the presentation will focus on monoclonal antibodies that are not FDA approved but are FDA authorized under Emergency Use Authorization (EUA) and there will be mention of COVID-19 serology tests that have FDA EUA and have been used for post-vaccine serology determinations for clinical trials and research studies (as noted in published or pre-print articles).

- CDC did not accept commercial support for this continuing education activity.

Objectives

At the conclusion of today's session, the participant will be able to accomplish the following—

1. Describe FDA's role in issuing EUA for Casirivimab/Imdevimab.
2. Outline the process for ordering and distributing Casirivimab/Imdevimab.
3. Discuss findings of studies on mAbs for COVID-19 (published or in unpublished pre-print).
4. Describe the National Institutes of Health (NIH) COVID-19 Treatment Guidelines' Panel's recommendations on using monoclonal antibodies to treat non-hospitalized patients with mild-to-moderate COVID-19.
5. List options for post-exposure prophylaxis use of Casirivimab/Imdevimab.

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov.

Today's Presenters

- **Elliot Raizes, MD**
  Task Force Lead
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  COVID-19 Response
  Centers for Disease Control and Prevention

- **Adi V. Gundlapalli, MD, PhD**
  Co-Lead, Serology and Correlates of Protection Tiger Team, COVID-19 Response
  Chief Public Health Informatics Officer
  Center for Surveillance, Epidemiology, and Laboratory Services
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- **John Farley, MD, MPH**
  Director, Office of Infectious Diseases
  Center for Drug Evaluation and Research
  Office of New Drugs
  U.S. Food and Drug Administration

- **Colin Shepard, MD**
  CDC Liaison to the Assistant Secretary for Preparedness and Response (ASPR)
  Center for Preparedness and Response
  Centers for Disease Control and Prevention

- **Rajesh Gandhi, MD**
  Director, HIV Clinical Services and Education, Massachusetts General Hospital
  Professor of Medicine, Harvard Medical School

Resources: NIH COVID-19 Treatment Guidelines

- Anti-SARS-CoV-2 Monoclonal Antibodies
  - Visit https://bit.ly/3lRDyKX
- Therapeutic Management of Nonhospitalized Adults With COVID-19
  - Visit https://bit.ly/3gdjJdJ
- Therapeutic Management of Hospitalized Adults With COVID-19
  - Visit https://bit.ly/3sgC7qQ

Serological Testing

Adi V. Gundlapalli, MD, PhD
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Center for Surveillance, Epidemiology, and Laboratory Services
Centers for Disease Control and Prevention

August 12, 2021
Clinician Outreach and Communication Activity Call

SARS-CoV-2 Serology

- **SARS-CoV-2 binding antibody assays**
  - Currently 87 individual emergency use authorizations (EUA) from FDA
  - Most are qualitative assays; 12 are semi-quantitative; one is quantitative
  - Most measure IgG antibodies to SARS-CoV-2; some measure IgM and IgG
  - These tests assess antibodies to viral nucleocapsid protein (N), spike protein (S), or receptor binding domain protein (RBD)

- **The current indication for these serology tests as stated in the EUA letter**
  - "For use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection"

https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-serology-and-other-adaptive-immune-response-tests-sars-cov-2#individual-serological

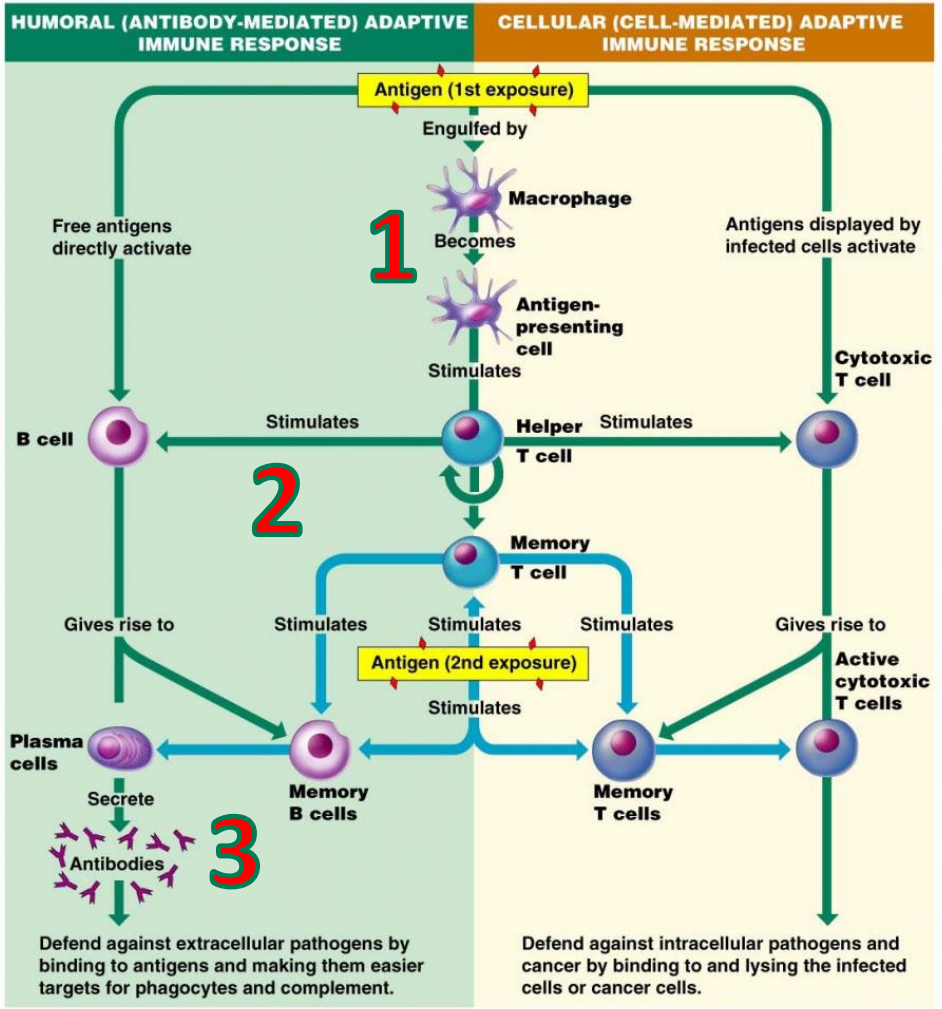
Overview of the Adaptive Humoral Immune Response

1. Antigen ingestion and processing by antigen presenting cells; presentation to and stimulation of T helper cells

2. T helper cells stimulate B cells; direct activation of B cells also occurs

3. B cells mature into plasma cells; memory B cells are also generated

4. Antibodies are produced; IgM, then switch to IgG Binding antibodies, subset are neutralizing



Immune Response to SARS-CoV-2

- **Antigen-specific antibodies**
  - Detection acknowledges a significant and measurable end-product of the complex machinery of the adaptive immune system (in commercial assays)
    - False positives may occur
  - Knowledge of absence of antibodies is informative
    - Disruption in the adaptive immune response cascade can occur
    - False negatives may occur due to antibody decay or assay performance
- **None of the commercially available serology assays are FDA-approved nor recommended for assessing protective immunity**
  - Established or accepted serologic correlates of protection are pending at this time
  - Only one quantitative IgG assay approved for results that are traceable to an international standard (to quantify and to compare results across labs and assays)
- **Host response includes innate and cellular immune responses**

https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#laboratory-testing
Open Forum Infect Dis. Jan 2021;8(1):ofaa555. doi:10.1093/ofid/ofaa555

Immune responses to COVID-19 vaccinations in immunocompromised people

- **Underlying immune compromise or therapies** disrupt the adaptive immune response
- **Post-vaccine serological testing** has been performed as part of clinical trials or research studies
  - The clinical utility of post-vaccination serological testing has not been established
- **Evidence of decreased production of binding and neutralizing antibodies to COVID-19 vaccination** (small N in individual studies)
  - Dialysis patients
  - Chronic liver disease
  - Hematology-Oncology patients
  - Immunosuppressive therapies
  - Transplant patients
    - Solid organ
    - Hematopoietic stem cell transplant patients
  - **Variability noted based on severity of underlying immunocompromise and therapy**
- **Cellular immune responses are also impaired**

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#laboratory-testing
Reviewed in https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/07-COVID-Oliver-508.pdf
J Hepatol. Apr 2021;74(4):944-951. doi:10.1016/j.jhep.2021.01.032

Serological correlates of protection or risk for breakthrough infections

- **What we know**
  - From publications on serology, vaccine effectiveness, and breakthrough infections (small N in individual studies)
  - Consistent relationship between quantitative binding antibody and neutralizing antibody levels
  - Neutralizing and binding antibody levels correlate with protection or risk of breakthrough infection after vaccination in cohorts of individuals
  - Need for higher levels of neutralizing antibodies for variants of concern
  - Binding antibodies may be a practical solution as neutralizing antibody assays are not readily available

- **Not yet known**
  - Threshold levels or ranges such as "% protection above a certain level or in this range of antibodies" are not yet available
  - Impact of variants on estimating and setting levels of antibodies for protection or risk
  - Heterogeneity by age, race/ethnicity, immunocompromise status

- **Limitation:** Availability of approved quantitative binding assays with results that are traceable to certified WHO international standard reference materials is limited

Nat Med. Jul 2021;27(7):1205-1211. doi:10.1038/s41591-021-01377-8
N Engl J Med. Jul 28 2021;doi:10.1056/NEJMoa2109072
Vaccine. Jul 22 2021;39(32):4423-4428. doi:10.1016/j.vaccine.2021.05.063
Nature. Jul 8 2021;doi:10.1038/s41586-021-03777-9
medRxiv. 2021:2021.06.21.21258528. doi:10.1101/2021.06.21.21258528
medRxiv. 2021:2021.08.09.21261290. doi:10.1101/2021.08.09.21261290

Summary

- **Currently available commercial serology assays for SARS-CoV-2 are not authorized nor recommended for assessing protective immunity in natural infections or after vaccination**
  - If ordering or reviewing serology test results, please note that a positive test for spike protein could indicate prior infection and/or vaccination
  - To evaluate for evidence of prior infection in an individual with a history of COVID-19 vaccination, an assay that specifically evaluates antibody to the nucleocapsid protein should be used

- **Binding and neutralization antibody results after COVID-19 vaccinations have been reported from clinical trials and research studies**
  - Adaptive immune responses to COVID-19 vaccination are sub-optimal in immunocompromised people
  - Variability noted based on severity of underlying immunocompromise and therapy

- **Data on serological correlates of protection are now being reported**
  - Population thresholds pending for binding and neutralizing antibodies
  - Interpretation and extrapolation to immunocompromised people will be challenging

Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Disclaimer

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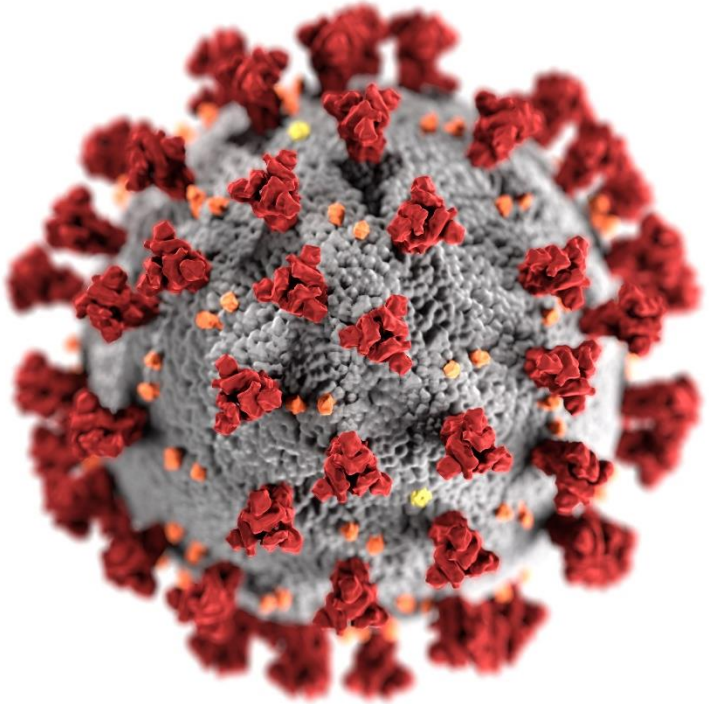

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FDA Emergency Use Authorization of REGEN-COV
(casirivimab and imdevimab)
for Treatment and Post-Exposure Prophylaxis of COVID-19

CDC Clinician Outreach Call – August 12, 2021

John Farley, MD, MPH

Director, Office of Infectious Diseases, Office of New Drugs, CDER

Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

Treatment Authorization (Nov. 21, 2020)

…for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitation of Authorized Use

- REGEN-COV (casirivimab and imdevimab) is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Treatment Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset

- For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

Link to current FDA Fact Sheets and Reviews: https://bit.ly/2VNLFx3

Post-Exposure Prophylaxis Authorization

(July 30, 2021)

…in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- Not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact* criteria per Centers for Disease Control and Prevention (CDC)

    or
  - who are at high-risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Post-Exposure Prophylaxis Authorization (Cont.)

(July 30, 2021)

Limitations of Authorized Use

- Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19.
- REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

*Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example.

Post-Exposure Prophylaxis Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible following exposure to SARS-CoV-2.

- For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for **longer than 4 weeks and who are not expected** to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is:
  - 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

Data Supporting the Post-Exposure Prophylaxis Authorization

- **COV-2069 trial (NCT04452318):** This is a randomized, double-blind, placebo-controlled Phase 3 clinical trial studying REGEN-COV (casirivimab and imdevimab) for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2 (index case).

- **COV-2093 trial**: This is a randomized, double-blind, placebo-controlled Phase 1 trial evaluating the safety, pharmacokinetics, and immunogenicity of repeated doses of 600 mg of casirivimab and 600 mg of imdevimab administered subcutaneously in healthy adult subjects.

Uses Not Presently Authorized

- **There are a number of uncertainties regarding pre-exposure prophylaxis.**
  - Which patients are unlikely to mount an adequate immune response to complete SARS-CoV-2 vaccination?
  - What is/are the most appropriate intervention(s) for which patients?
- **Ongoing and completed clinical trials may be informative.**
  - NCT04625725: Phase 3 double-blind, placebo-controlled study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adults (PROVENT) has a listed actual primary completion date of May 5, 2021.
- **Some physicians are requesting uses of REGEN-COV under expanded access that are not presently authorized under EUA.**
  - Expanded access criteria under 21CFR 312.305 and 312.310 must be met. (See CFR Title 21: https://bit.ly/3AvkwhM)
  - Sponsor must agree to provide drug. (See compassionate use policy: https://bit.ly/3yCIffn)

EUA Requirements

- **EUA Declaration:** Before FDA may issue an EUA, the HHS Secretary must declare that circumstances exist justifying the authorization (usually a public health emergency).

- **Criteria for Issuance:**
  - Agent referred to in the Secretary's declaration can cause a serious or life-threatening disease or condition.
  - Based on the totality of scientific information available, including data from adequate and well-controlled trials if available, it is reasonable to believe that the product "may be effective" to prevent, diagnose, or treat serious or life-threatening diseases or conditions caused by the threat agent.
  - Known and potential benefits of the product, when used to diagnose, prevent, or treat the disease or condition, outweigh the known and potential risks of the product.

Expanded Access Requirements

21 CFR Sec. 312.305 (for all expanded access uses):

FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

21 CFR Sec. 312.310 (additional requirements for individual patient use):

(1) The physician must determine that the probable risk to the person from the investigational new drug (IND) is not greater than the probable risk from the disease or condition; and

(2) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

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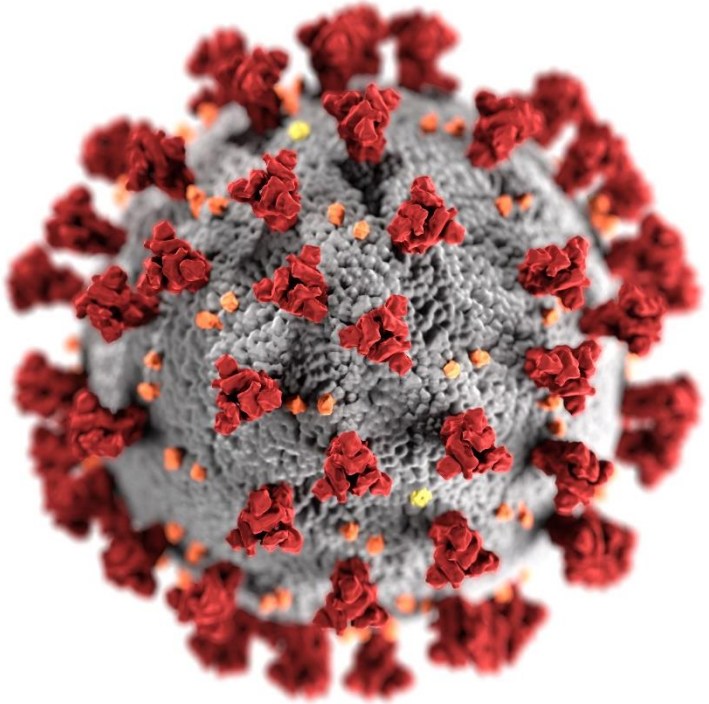

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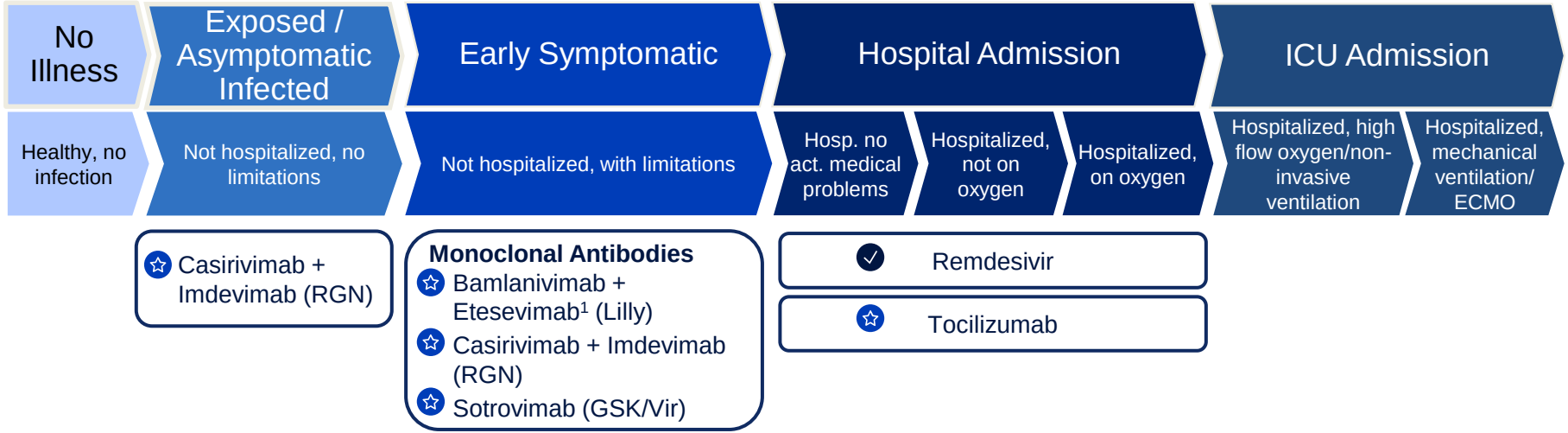
ASPR's Role in Distribution and Administration of Monoclonal Antibodies

Colin Shepard, MD

U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response

August 12, 2021

Summary of COVID-19 Therapeutics



1. National shipment pause on bamlanivimab + etesevimab due to variants, as of 06/25/2021

Key: ✓ FDA approved ☆ EUA issued

U.S. government (USG) role in distribution of COVID-19 Monoclonal Antibodies (mAbs)

Our goal: Facilitate the effective use of monoclonal antibody therapeutics to reduce COVID-19 hospitalizations

Three outpatient mAbs have been granted EUA for the treatment of COVID-19 based on their potential to reduce progression to severe disease and hospitalization in patients at high risk:

- Post-exposure prophylaxis
  - REGEN-COV (casirivimab and imdevimab)

- Active COVID-19 infection in patients at higher risk for severe COVID-19 with mild to moderate symptoms
  - REGEN-COV (casirivimab and imdevimab)
  - Bamlanivimab/Etesevimab (currently paused[1])
  - Sotrovimab (commercially available)

HHS/ASPR has oversight responsibility for the fair and transparent allocation and distribution of REGEN-COV and bamlanivimab/etesevimab

1. National shipment pause of bamlanivimab/etesevimab and etesevimab alone due to variants, as of 06/25/2021

USG-procured therapies are provided at no-cost

- Healthcare providers can order product directly through the distributor AmerisourceBergen at no cost; information on ordering available at www.phe.gov
- CMS reimbursement rates have recently been increased to $450 for most outpatient settings; and $750 when administered in a patient's home
- Additional information on reimbursement can be found at https://go.cms.gov/3fQKOmq
- Treatment options for uninsured available from Health Resources & Services Administration https://bit.ly/3CFcJ2S

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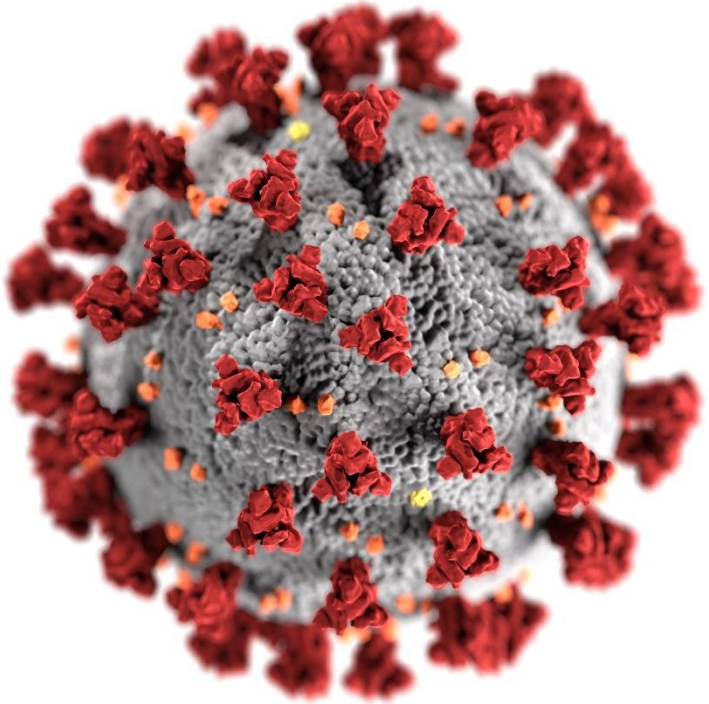


cdc.gov/coronavirus

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

Rajesh T. Gandhi, MD

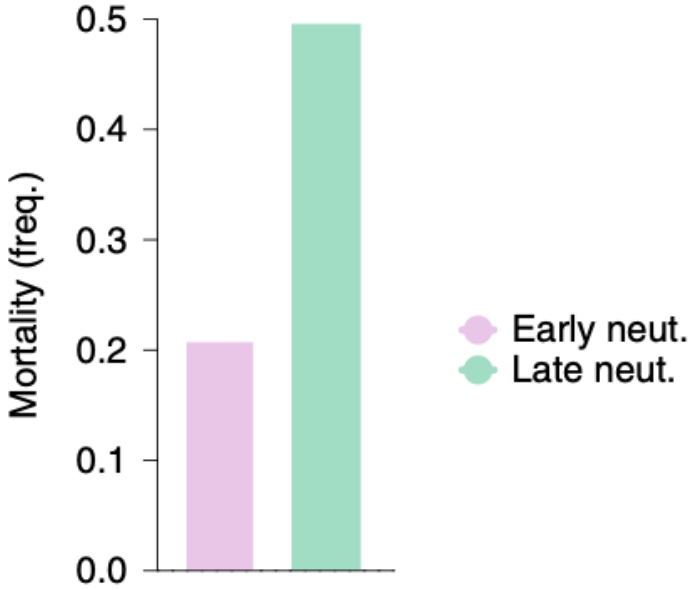
Massachusetts General Hospital

Harvard University Center for AIDS Research

Disclosures (for past year): none
Member of the NIH and Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels
Acknowledgments: Dr. Arthur Kim. Efe Airewele

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

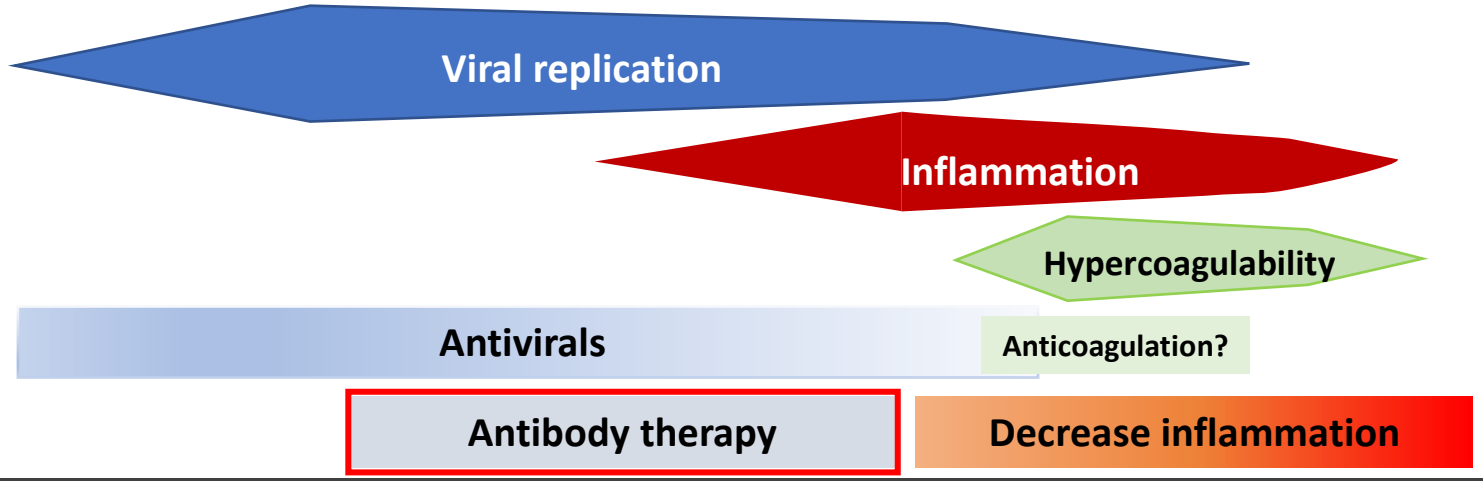
- Delayed production of neutralizing antibodies correlates with fatal COVID-19
- Would providing passive immunity through antibody therapy improve clinical outcomes?



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

Outpatient Treatment Across the COVID-19 Spectrum

Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea	O_2 saturation ≥ 94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



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

Anti-SARS CoV-2 Monoclonal Antibodies for Treatment

- Emergency Use Authorizations (EUAs) for treatment of ambulatory patients with mild to moderate COVID-19 at high risk of progression and within 10 days of symptom onset:
  - Casirivimab + Imdevimab (600/600 mg) (IV administration preferred)
  - Bamlanivimab + Etesevimab (700/1400 mg) (distribution paused)
  - Sotrovimab

Anti-SARS CoV-2 Monoclonal Antibodies for Post-Exposure Prophylaxis

- Casirivimab/imdevimab (subcutaneous or intravenous) for post-exposure prophylaxis in individuals who are at high risk for progression to severe COVID-19 and are:
  - Not fully vaccinated or not expected to mount adequate immune response to COVID-19 vaccination (e.g., immunosuppressed individuals) AND
    - Have been exposed* to an individual with COVID-19

      or
    - At high risk of exposure because of occurrence of COVID-19 in same institutional setting (e.g., nursing homes, prisons)

*Within 6 feet for ≥15 min, providing care at home, direct contact, exposed to respiratory droplets of infected person

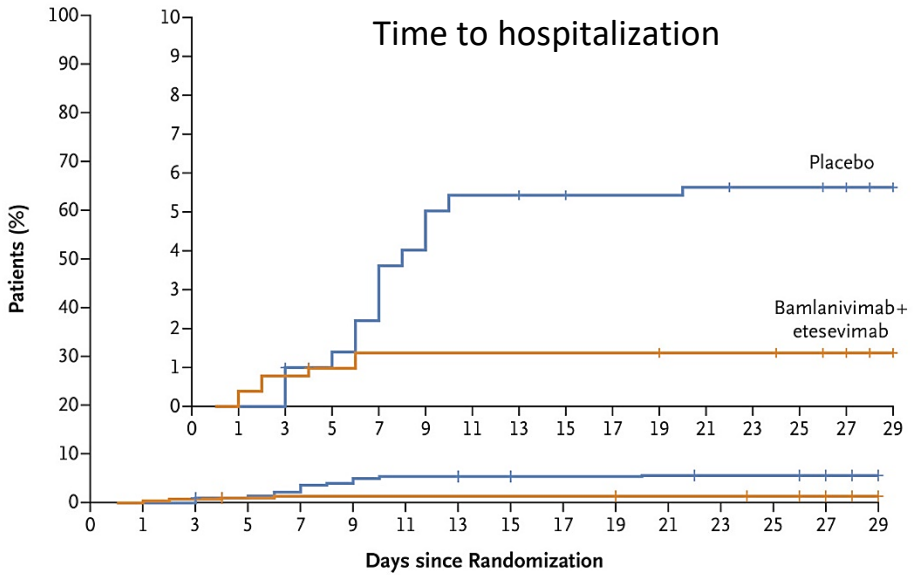
What are the Data for Use of Anti-SARS CoV-2 Antibodies for Treatment?

Bamlanivimab/Etesevimab: Outpatient Treatment

- Outpatients with mild to moderate COVID-19 within 3 days of first positive test; 1 or more risk factors for developing severe COVID-19 (n=1035)
- IV bamlanivimab 2800 mg/ etesevimab 2800 mg or placebo

Results:

- 70% reduction in COVID-19 hospitalization or any cause of death by day 29 (P<0.001)
- Similar results with bamlanivimab/etesevimab 700/1400 mg (authorized dose)



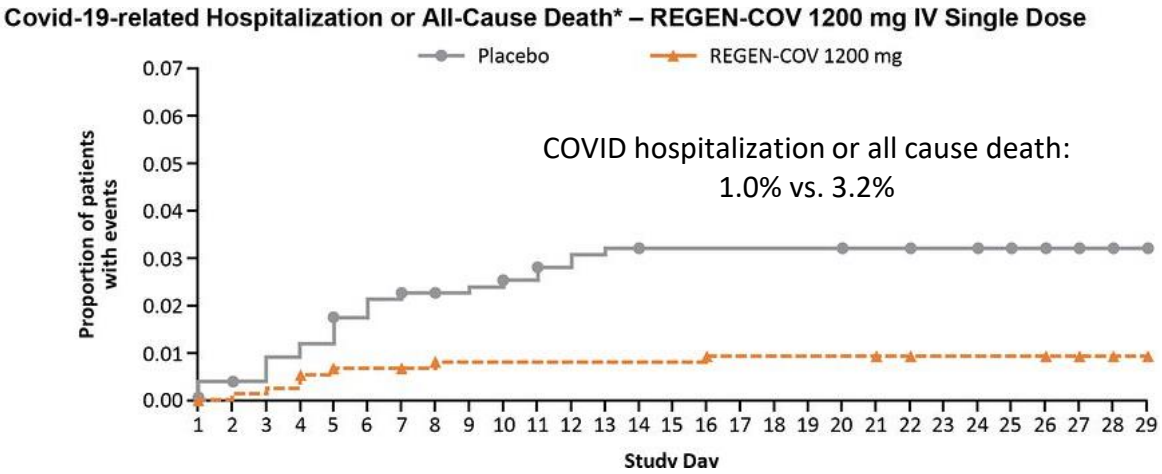
Dougan M et al, NEjM, 2021; https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced

Casirivimab/Imdevimab: Outpatient Treatment

- Outpatients (n=4057) with mild to moderate COVID-19: placebo or intravenous casirivimab/imdevimab (various doses)
- Modified full analysis set: +PCR; ≥1 risk factor for severe COVID-19

Results:

- In 600/600 mg group, 70% reduction in COVID-19 hospitalizations or death
- More rapid resolution in symptoms in the antibodies group: 10 vs. 14 days



Weinreich et al., REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients, https://doi.org/10.1101/2021.05.19.21257469

Sotrovimab: Outpatient Treatment

- Outpatients with mild to moderate COVID-19 at high risk of hospitalization (n=583)
- Randomized to receive sotrovimab or placebo

Result:

- 85% reduction in hospitalization or death

	N	Hospitalized/ death	Percent Reduction
Sotrovimab	**291**	**3 (1%)**	**85% (p=0.002)**
Placebo	**292**	**21 (7%)**	**85% (p=0.002)**

Gupta A et al, medRxiv preprint, 2021; https://doi.org/10.1101/2021.05.27.21257096

What about SARS-CoV-2 Variants?

Variants and Anti-SARS-CoV-2 Antibodies: In Vitro Studies

- Alpha (B.1.1.7): susceptible to the authorized antibodies
- Beta (B.1.351), Gamma (P.1)
  - Marked reduction in susceptibility to bam/ete (distribution paused in US)
  - Casirivimab/imdevimab, sotrovimab expected to retain activity
- Delta (B.1.617.2)
  - Marked reduction in susceptibility to bam; modest reduction in susceptibility to bam/ete
  - Casirivimab/imdevimab, sotrovimab expected to have activity

Clinical impact of in vitro susceptibilities unknown

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

NIH COVID-19 Treatment Guidelines

Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: July 8, 2021

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the proportion of potentially resistant variants **(AIII)**.[a] See text for details. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]

What about people who develop COVID-19 after vaccination?

- *For people who develop COVID-19 after receiving COVID-19 vaccination, prior vaccination should not affect treatment decisions, including use of and timing of treatment with monoclonal antibodies.*

What are the Data for Use of anti-SARS CoV-2 Antibodies for Post-exposure Prophylaxis?

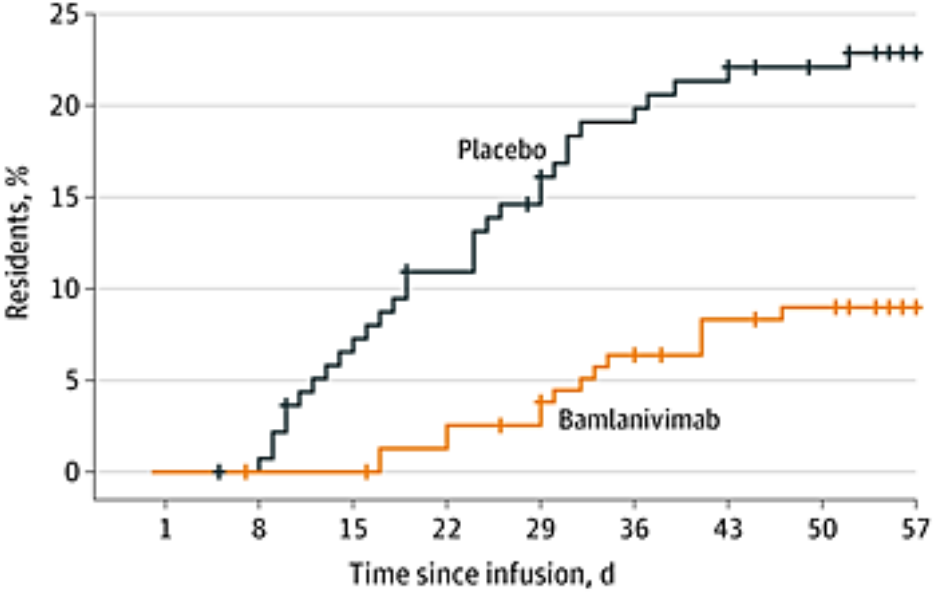
Bamlanivimab: Post-exposure prophylaxis—Long-term care facilities

- Phase 3 randomized trial among residents and staff of long-term care facilities with at least 1 COVID-19 case (n=1175)
- Randomized to receive IV bamlanivimab or placebo

Results

- Among residents in the prevention population, incidence of mild or worse COVID-19 was 80% lower in bamlanivimab group (P<0.001)
- Residents who became infected more likely to have low viral loads and to clear virus more quickly

Time from infusion to development of mild or worse COVID-19 in Residents



Casirivimab/Imdevimab: Post-exposure prophylaxis

- Phase 3 placebo-controlled trial among household contacts of person with positive SARS CoV-2 test within past 96 hours
- Casi/imdev (600/600 mg) or placebo given subcutaneously

Symptomatic SARS CoV-2 Infection in Participants who were PCR and antibody negative at baseline

	N	Events	Proportion	Risk Reduction
Placebo	752	59	7.8%	81% (p<0.0001)
Antibodies	753	11	1.5%	81% (p<0.0001)

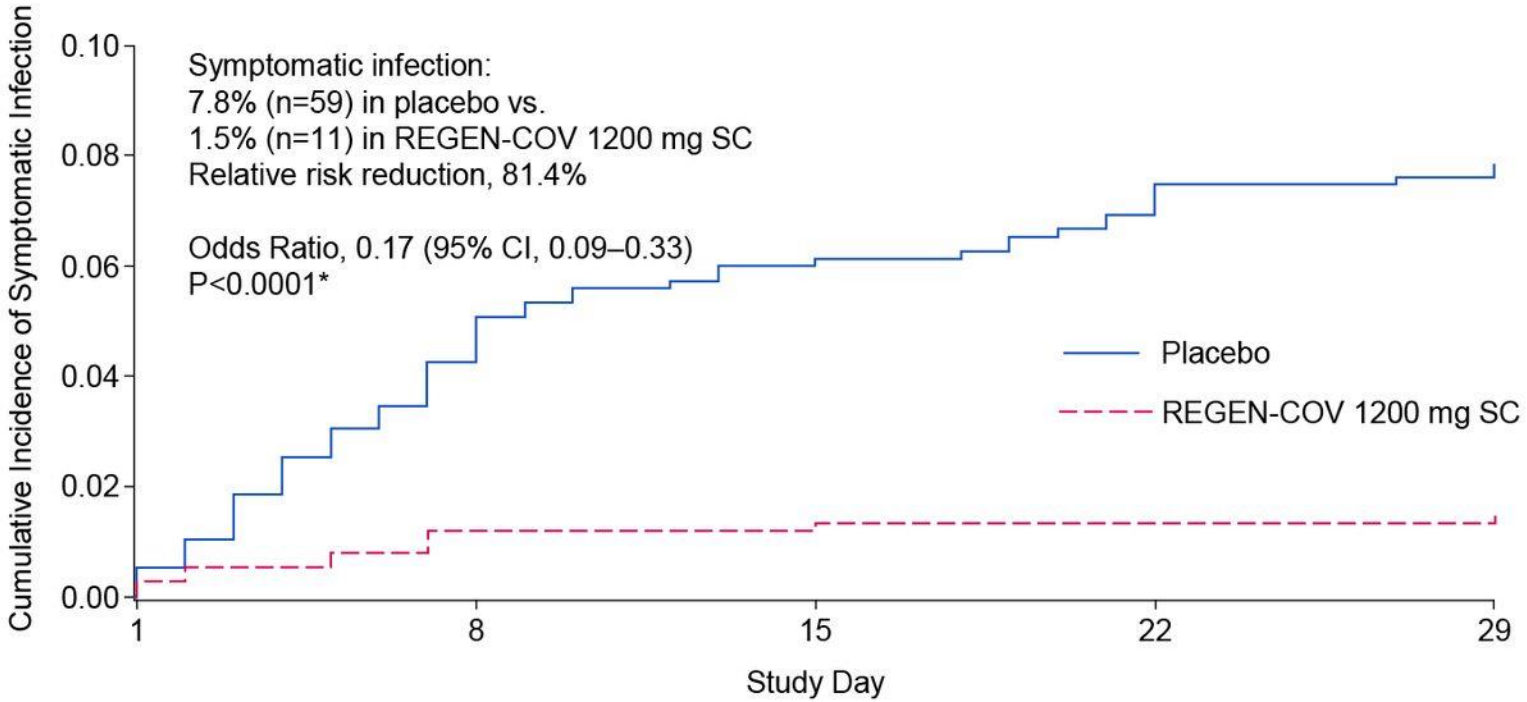
Results:

- Among participants who were PCR-negative and seronegative at baseline (n=1505), 81% reduction in symptomatic SARS CoV-2 infection in casirivimab/imdevimab group (P<0.0001)
- Among infected participants, antibody group had shorter duration of symptoms (1.2 vs. 3.2 weeks) and shorter duration of high viral loads (0.4 vs 1.3 weeks)

O'Brien M et al, NEJM 2021

Casirivimab/Imdevimab: Post-exposure prophylaxis (Cont.)

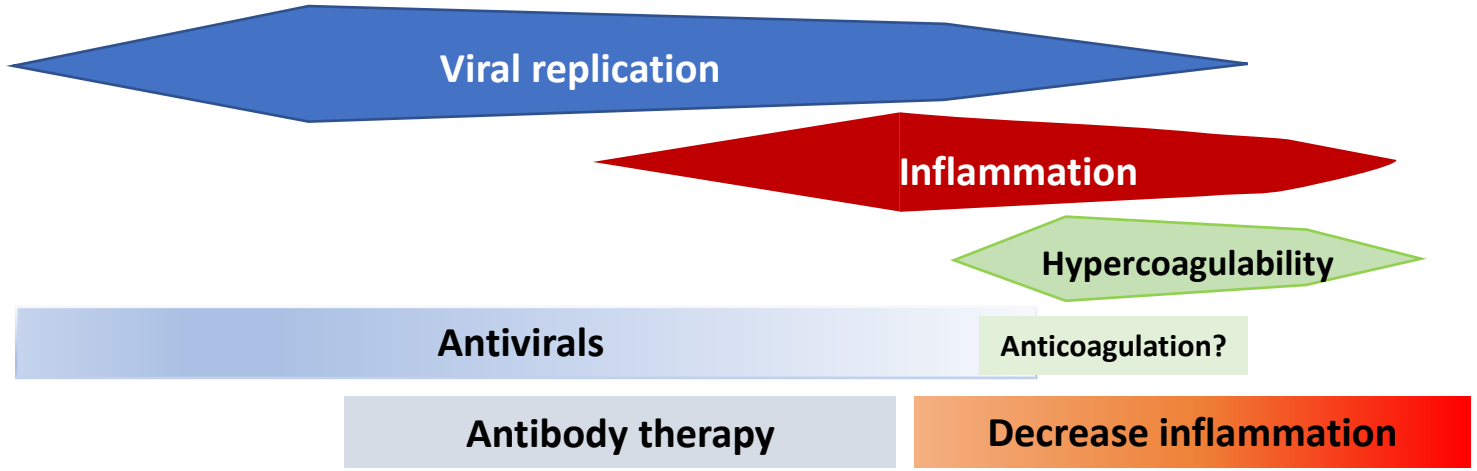
A. Cumulative Incidence of Symptomatic Infection Following Administration of REGEN-COV or Placebo



What about Patients Hospitalized Due to COVID-19?

Inpatient Treatment Across the COVID-19 Spectrum

Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O_2 saturation ≥ 94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



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

Do Monoclonal Antibodies Have Role in Hospitalized Patients?

- Bamlanivimab monotherapy did not show benefit in hospitalized patients with COVID-19 (ACTIV-3)
  - Subset without neutralizing Abs and with elevated viral levels appeared to benefit
- Trial of casirivimab/imdevimab in hospitalized patients on high flow oxygen/mechanical ventilation stopped
- Therapies stopped due to futility (ACTIV-3): Sotrovimab; BRII-196 and BRII-198
- AZD7442: participants continue to be enrolled (ACTIV-3)

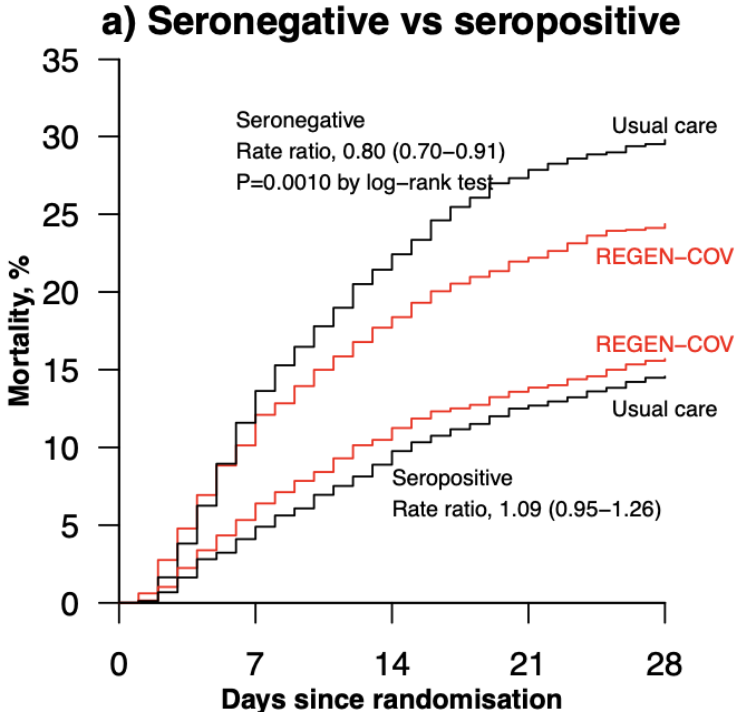
ACTIV-3/TICO LY-CoV555 Study Group, NEJM 2020. https://www.medrxiv.org/content/10.1101/2021.07.19.21260559v1. https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies. https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends.

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 all-cause mortality: 20% vs. 21% (no difference)
- In those seronegative for anti-spike protein antibody, reduction in mortality with casi/imdev: 24% vs. 30% (rate ratio 0.80; 95% CI, 0.70–0.91; P = 0.001)



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

Casirivimab/Imdevimab in Hospitalized Patients

- Casirivimab/imdevimab not yet authorized for treatment of hospitalized patients
- We need rapid and reliable serology test to identify seronegative individuals
- Casirivimab/imdevimab only available through expanded access program for hospitalized patients who are not on high flow oxygen or mechanically ventilated

Rapidly evolving information with more to come ….

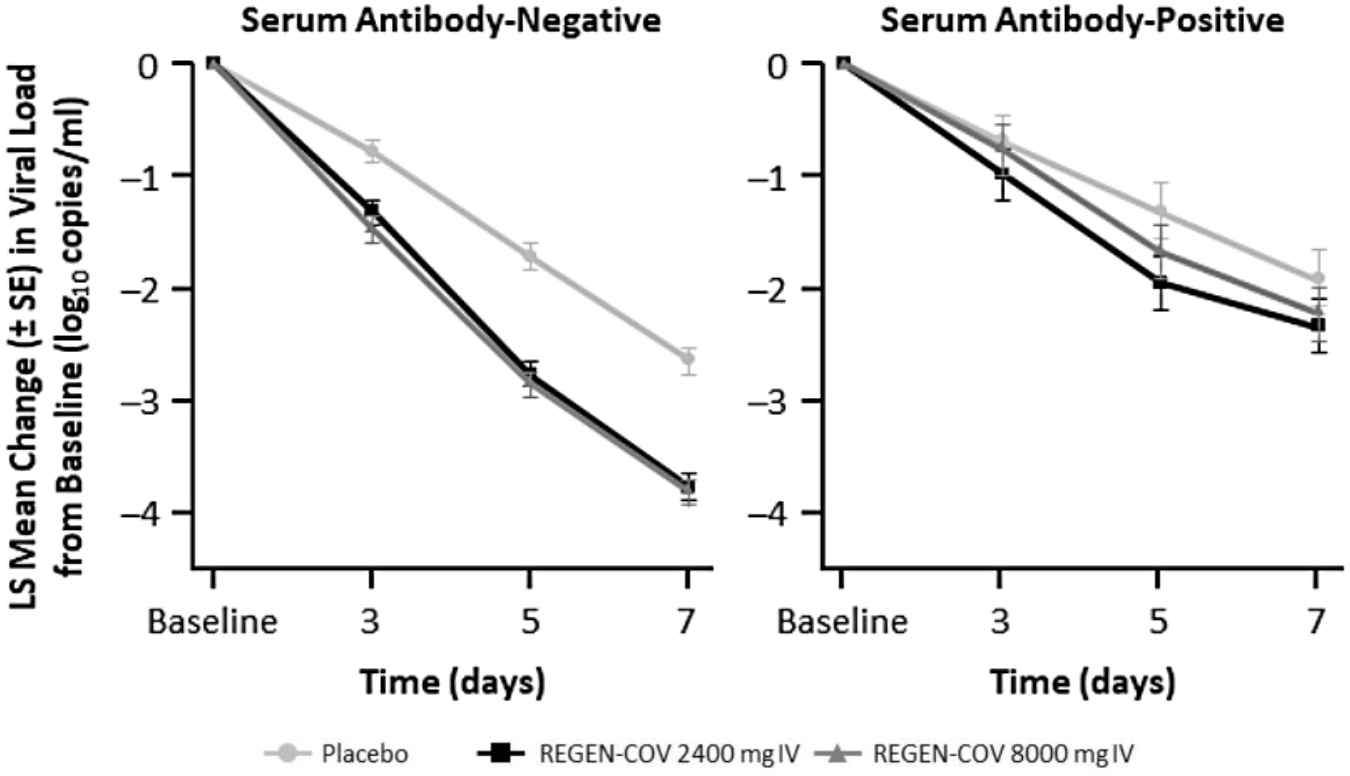
Anti-SARS CoV-2 Monoclonal Antibodies in Immunocompromised Patients

Anti-SARS CoV-2 Monoclonal Antibodies in Immunocompromised Patients

- Only small proportion of participants in trials were immunocompromised:
  - Bamlanivimab/etesevimab phase 3 treatment trial: 6.5%
  - Casirivimab/imdevimab phase 3 treatment trials: 3%
  - Bamlanivimab post-exposure prophylaxis study: 19% of prevention cohort
- Immunocompromised patients, who may not mount an endogenous antibody response, may have protracted viral replication
- Anti-SARS CoV-2 monoclonal antibodies may be particularly effective in reducing viral load in patients who don't mount their own antibody response

Dougan M et al, NEJM, 2021; Weinreich et al., REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients, https://doi.org/10.1101/2021.05.19.21257469
Cohen M et al, JAMA 2021; Choi B et al, NEJM, 2020; Haidar G and Mellors JW, CID, 2021

SARS CoV-2 Viral Load Changes by Baseline Serum Antibody Status



Weinreich et al., REGEN-COV Antibody Cocktail in Outpatients with Covid-19, https://doi.org/10.1101/2021.06.09.21257915, 2021

Anti-SARS CoV-2 Monoclonal Antibodies: Summary

Treatment:

- mAbs authorized to treat high-risk outpatients with mild-moderate COVID-19
  - Because of variants: casirivimab/imdevimab or sotrovimab
  - Not authorized for use in people hospitalized due to COVID-19; may be used in people hospitalized for reasons other than COVID-19 (see FDA FAQ)
  - In the future, mAbs may have role in seronegative hospitalized patients but need rapid and reliable serologic test

Post-exposure prophylaxis:

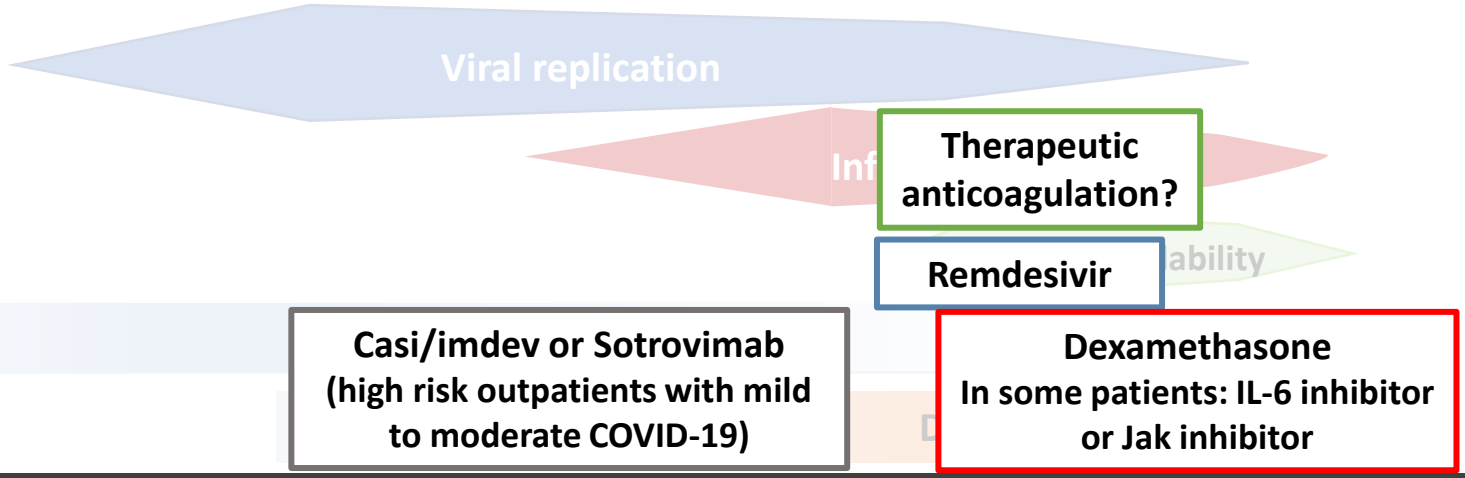
- Casirivimab/imdevimab authorized for post-exposure prophylaxis for people who are at higher risk for severe COVID-19 who are not fully vaccinated or who are not expected to mount an immune response (e.g., immunocompromised hosts)

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions

Post-Exposure Prophylaxis and Treatment Across the COVID-19 Spectrum

Exposure

Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
+ SARS-CoV-2 test but no symptoms	Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea	O_2 saturation ≥ 94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



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

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As-needed messages that provide specific, immediate action clinicians should take. Contains comprehensive CDC guidance so clinicians can easily follow recommended actions.

COCA Products & Services

Monthly newsletter providing updates on emergency preparedness and response topics, emerging public health threat literature, resources for health professionals, and additional information important during public health emergencies and disasters.

Informs clinicians of new CDC resources and guidance related to emergency preparedness and response. This email is sent as soon as possible after CDC publishes new content.

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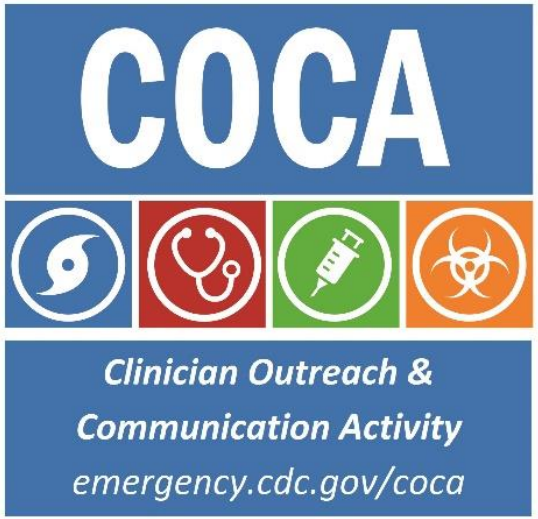

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