# CDC/IDSA COVID-19 Clinician Call

November 14, 2020

## Welcome & Introductions

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Vice President, Clinical Affairs & Guidelines
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- 44th in a series of weekly calls, initiated in January by CDC as a forum for information sharing among frontline clinicians caring for patients with COVID-19
- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.
- This webinar is being recorded and can be found online at www.idsociety.org/podcasts.

# Ask the Experts: Q&A with IDSA's Treatment & Management Guideline Panel

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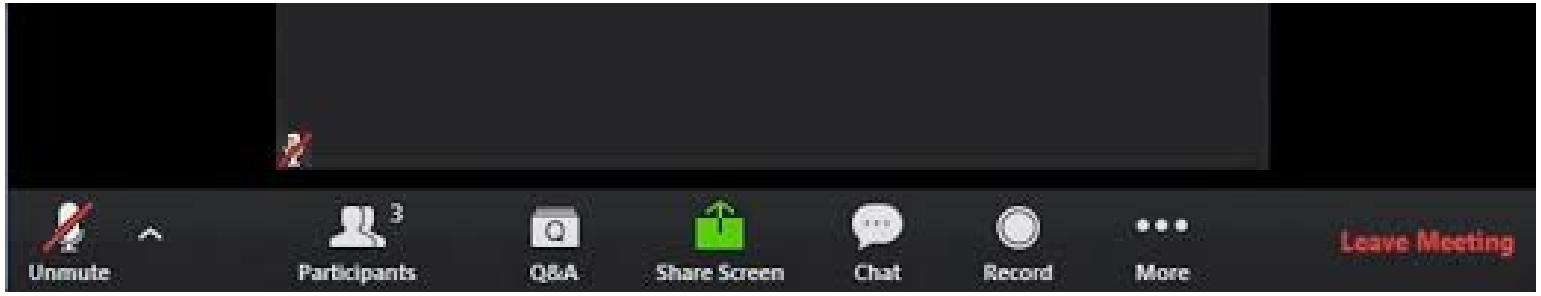
# Disclosures

- Adarsh Bhimraj- nothing to disclose
- Jason Gallagher- advisory role for Astellas, Shionogi, Spero and Qpex; receives research funding from Merk
- Rajesh Gandhi- nothing to disclose
- John O'Horo- nothing to disclose
- Amy Hirsch Shumaker- nothing to disclose

# To Ask a Question:
# Use the “Q&A” Button

Like a Question?
**Upvote** in the Q&A box

Phone Participants:
Text Your Question to
415-559-1736

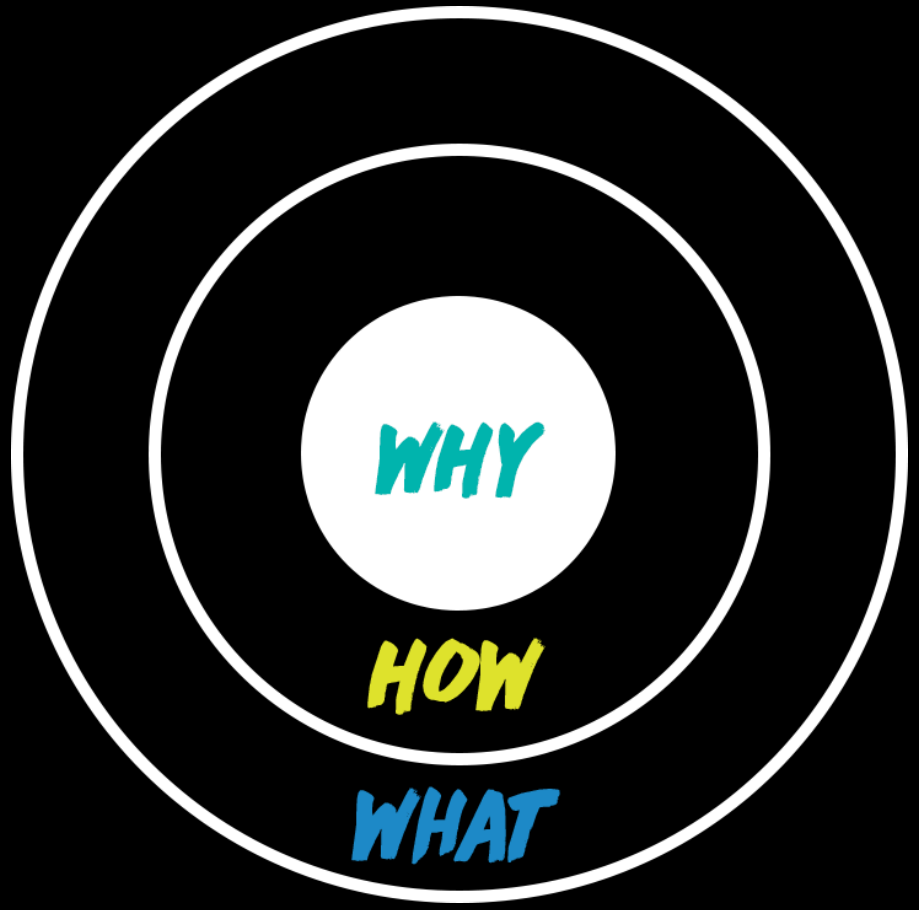



Comment?
Use the “Chat” Button

# What should I do?...

## Should I use Rx "X" for my COVID-19 patient?

The what and the how matter not if the WHY is not right …



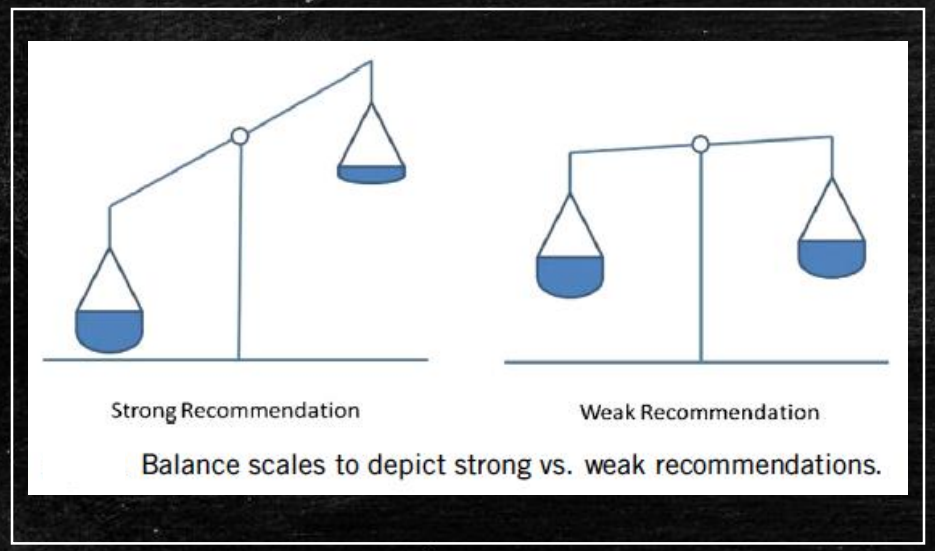

- WHY?: Evidence for the choice
- "Trustworthy" guidelines should
  - Appraise and synthesize evidence (why)
  - Recommend actions based on evidence (What & How)

# GRADE RECOMMENDATION "language"

## "Recommend" FOR (STRONG)

Guideline panel is confident…

- Desirable effects of an intervention outweigh undesirable effects
- Most or all individuals will be best served by the recommended course of action



Balance scales to depict strong vs. weak recommendations.

## "Suggest" FOR (weak or conditional or qualified)

Guideline panel after discussion concludes…

Desirable effects probably outweigh undesirable effects, but appreciable uncertainty exists

Not all individuals will be best served by the recommended course of action

Need to consider more carefully than usual the individual patient's circumstances, preferences, and values

Caregivers need to allocate more time to shared decision making, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.

# Outcomes: Patient important outcomes

## "What ultimately maters to patients"

| rating scale: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **least** importance | | | | | | | | **most** importance |
| limited importance for making a decision (not included in evidence profile) | | | **IMPORTANT,** but not critical for making a decision (included in evidence profile) | | | **CRITICAL** for making a decision (included in evidence profile) | | |

### Patient important outcomes ("CRITICAL")

Death (mortality)
Disability
Discomfort ( clinical symptom improvement)

### Disease/ dysfunction-oriented outcomes (IMPORTANT)

Viral clearance
CRP or IL 6 levels
O2 sats

Minimize use of surrogate end points/ disease-oriented outcomes like viral clearance or lab data as they are causally INDIRECT

# How to read an Evidence Profile:
# e.g. Corticosteroids in critically ill patients

Clinical outcomes

**Table 4.** GRADE evidence profile, Recommendation 4

**Question**: Glucocorticoids compared to no glucocorticoids for critically ill patients with COVID-19

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Glucocorticoids | corticosteroids | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow up: 28 days)** | | | | | | | | | | | | |
| 7 [1] | randomized trials | not serious | not serious | not serious | not serious | none | 280/749 (37.4%) | 485/1095 (44.3%) | **OR 0.66** (0.54 to 0.82) | **99 fewer per 1,000** (from 143 fewer to 48 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **Hospital discharge (follow up: 28 days)** | | | | | | | | | | | | |
| 1 [2] | randomized trials | not serious [a] | not serious | serious [b] | not serious | none | 1360/2104 (64.6%) | 2639/4321 (61.1%) | **RR 1.11** (1.04 to 1.19) | **67 more per 1,000** (from 24 more to 116 more) | ⨁⨁⨁◯ MODERATE | IMPORTANT |
| **Serious adverse events** | | | | | | | | | | | | |
| 6 [1] | randomized trials | not serious | not serious | not serious | serious [c] | none | 6 trials reported 64 events among 354 patients randomized to corticosteroids and 80 events among 342 patients randomized to standard care (Stern 2020). | | | | ⨁⨁⨁◯ MODERATE | CRITICAL |

| Quality of Evidence | Symbol |
|---|---|
| High | ⨁⨁⨁⨁ |
| Moderate | ⨁⨁⨁◯ |
| Low | ⨁⨁◯◯ |
| Very low | ⨁◯◯◯ |

**CI:** Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

**Explanations**

a. Analysis adjusted for baseline age.
b. Indirectness due to different health care system (allocation of intensive care resources in an unblinded study). Indirectness to other corticosteroids.
c. The 95% CI includes the potential for both harm as well as benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

**References**


1. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA **2020**.
2. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv **2020**: 2020.06.22.20137273

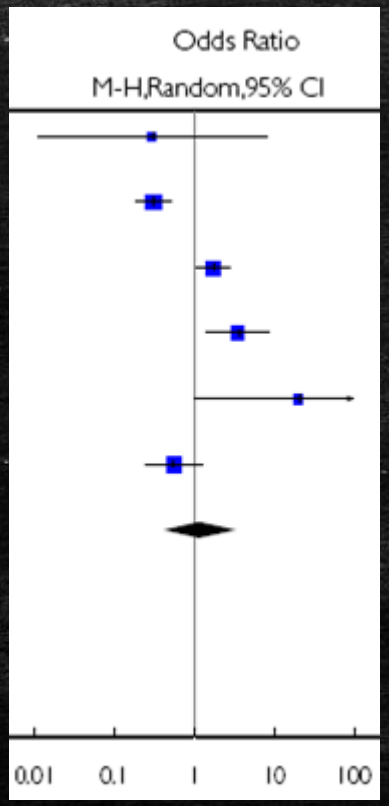
# Quality of evidence/ Confidence in evidence

Criteria to evaluate clinical studies in COVID 19

| Methodological/study limitations | Inconsistency of results | Indirectness of evidence | Imprecision of results | Publication bias |
|---|---|---|---|---|

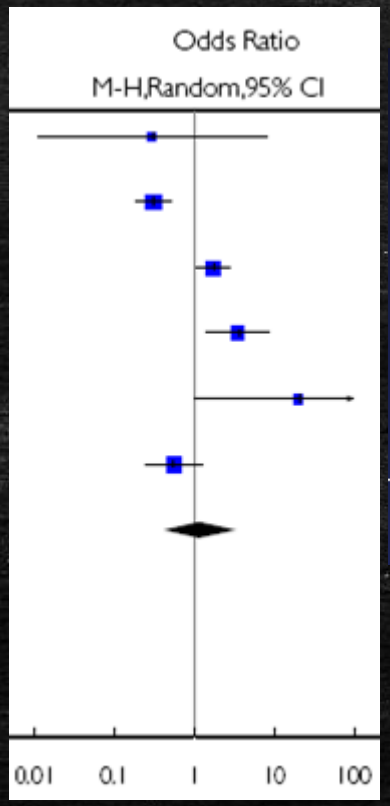
Risk of bias:
(systematic error)

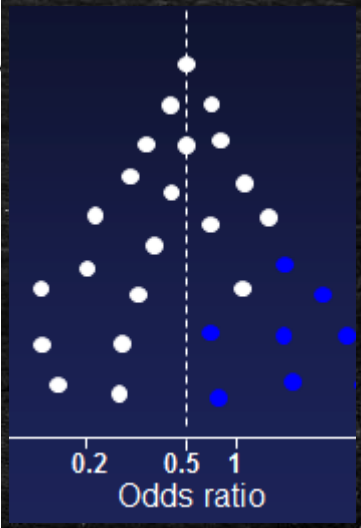
- Allocation concealment
- Blinding
- Intention-to-treat
- Follow-up
- Stopped early




Sources of indirectness:
Indirect comparisons-

- Patients
- Interventions
- Comparators
- Outcomes




Modified slides from Dr. Yngve Falck-Ytter

# What after apprising the evidence?
# …From evidence to recommendations

1. Quality of evidence (systematic error and random error)
2. Balance between Benefits, harms & cost
3. Variability & uncertainties in patient values and preferences
4. Resource considerations

# Corticosteroids Recommendation "LANGUAGE"

- **Recommendation 4: Among hospitalized critically ill patients with COVID-19, the IDSA guideline panel RECOMMENDS dexamethasone rather than no dexamethasone. (Strong recommendation, Moderate certainty of evidence)**

**Remark**: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used. Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

- **Recommendation 5: Among hospitalized patients with severe, but non-critical, COVID-19 the IDSA guideline panel SUGGESTS dexamethasone rather than no dexamethasone. (Conditional recommendation, Moderate certainty of evidence)**

**Remark**: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

- **Recommendation 6: Among hospitalized patients with non-severe COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel SUGGESTS AGAINST the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)**

-

# 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 |
| **Frequency:** | ? | 80% | | 15% | 5% |

**Disease Pathogenesis:**

Viral replication

Inflammation

**Potential treatment:**

Antivirals

Antibody therapy

Decrease inflammation

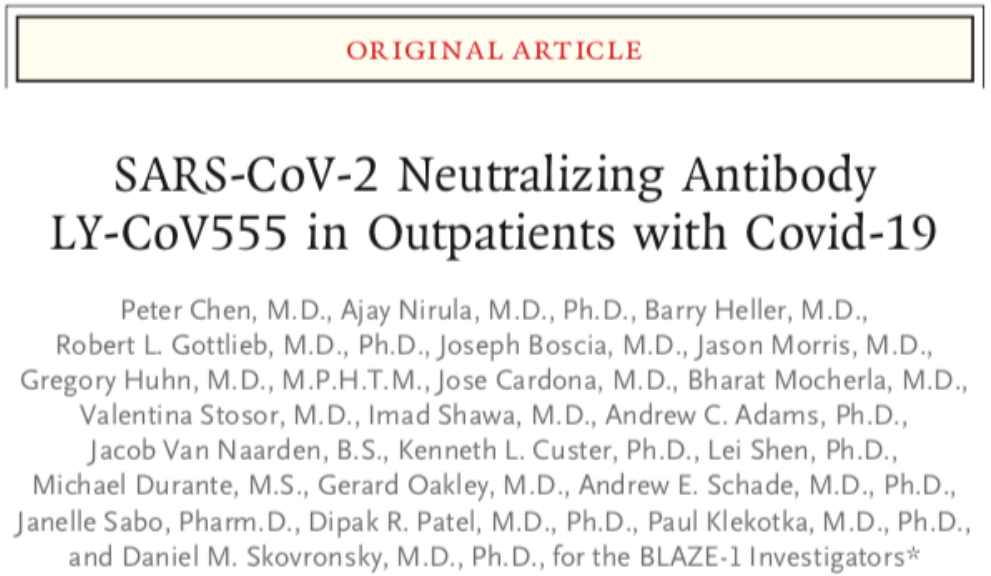


Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

## Monoclonal Antibodies

Monoclonal antibodies against SARS-CoV-2 being studied for treatment and prevention

In outpatients with mild to moderate disease (n=452), participants randomized to received iv infusion of placebo or one of three doses of a neutralizing antibody directed against SARS-CoV-2 spike protein (LY-CoV555)



ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*



Chen P et al, NEJM,

# LY-CoV555 (Bamlanivimab)

- At day 11, 2800 mg dose of antibody appeared to accelerate decline in viral load as compared to placebo
  - 3.4-fold lower in 2800 mg group than in the placebo group
  - Viral load decline did not differ significantly between other antibody doses and placebo
- In all 3 dose groups, there appeared to be a separation in virus level decay as compared to placebo

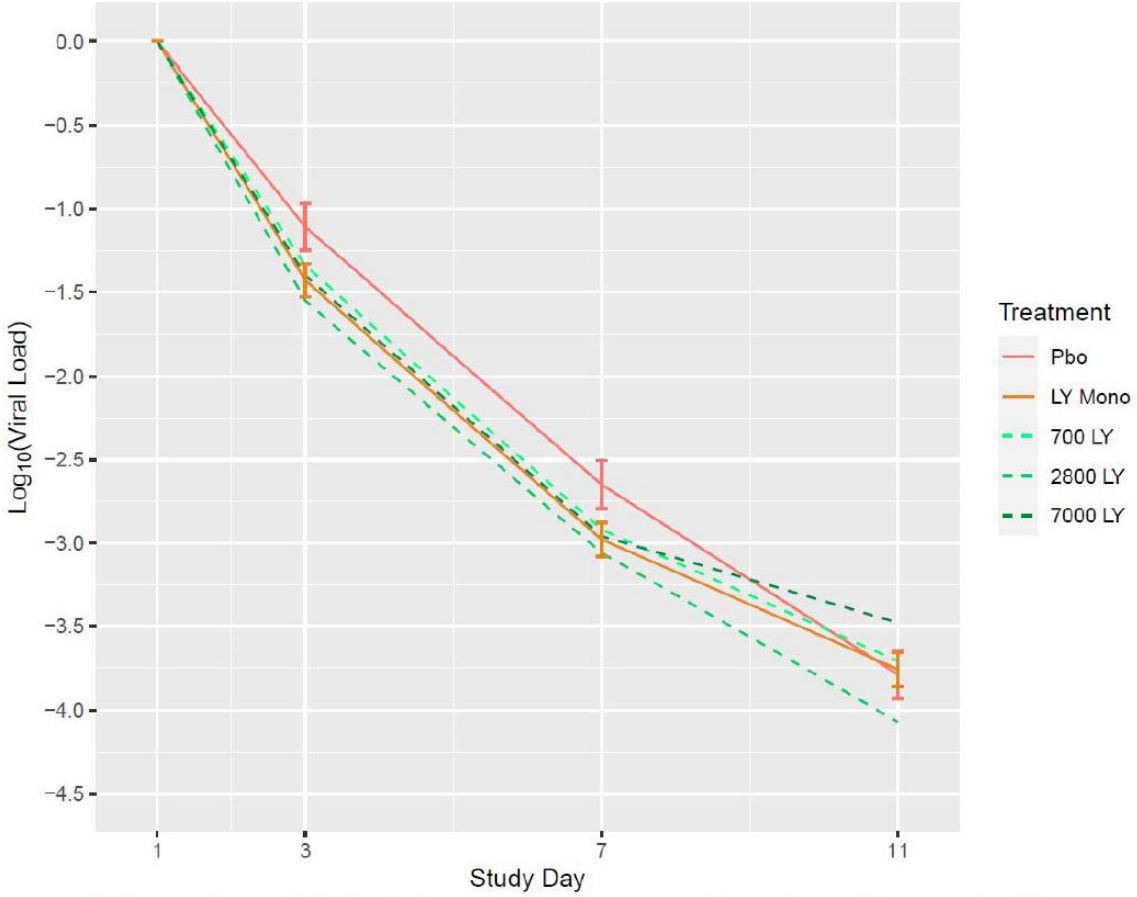



**Figure 1: SARS-CoV-2 viral load change from baseline by visit.**



Chen P et al, NEJM, 2020; https://www.fda.gov/media/143602/download

# LY-CoV555 (Bamlanivimab)

- ED visit or hospitalization:
  - 1.6% in antibody group, 6.3% in placebo group
  - >65 year old, BMI >35: 4% in antibody group, 15% in placebo group

Median time to symptom improvement: 6 days for participants who received bamlanivimab and 8 days for those who received placebo.

Safety profile of bamlanivimab and placebo similar

| Hospitalization/ED Visit: All Participants | | | |
|---|---|---|---|
| **Treatment** | **N** | **Events** | **Proportion** |
| **Placebo** | 156 | 9 | 6% |
| **700 mg** | 101 | 1 | 1% |
| **2800 mg** | 107 | 2 | 2% |
| **7000 mg** | 101 | 2 | 2% |
| **Pooled antibody** | 309 | 5 | 2% |

| Hospitalization/ED Visit: Participants at Higher Risk of Hospitalization | | | |
|---|---|---|---|
| **Treatment** | **N** | **Events** | **Proportion** |
| **Placebo** | 69 | 7 | 10% |
| **700 mg** | 46 | 1 | 2% |
| **2800 mg** | 46 | 1 | 2% |
| **7000 mg** | 44 | 2 | 5% |
| **Pooled antibody** | 136 | 4 | 3% |



Chen P et al, NEJM, 2020; https://www.fda.gov/media/143602/download

# Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression - 1

Body mass index (BMI) ≥35

Chronic kidney disease

Diabetes

Immunosuppressive disease or receiving immunosuppressive treatment

≥65 years of age

≥55 years of age AND have
- cardiovascular disease, OR
- hypertension, OR
- chronic obstructive pulmonary disease/other chronic respiratory disease

Criteria also listed for those who are 12 – 17 years of age

https://www.fda.gov/media/143602/download

# Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression - 2

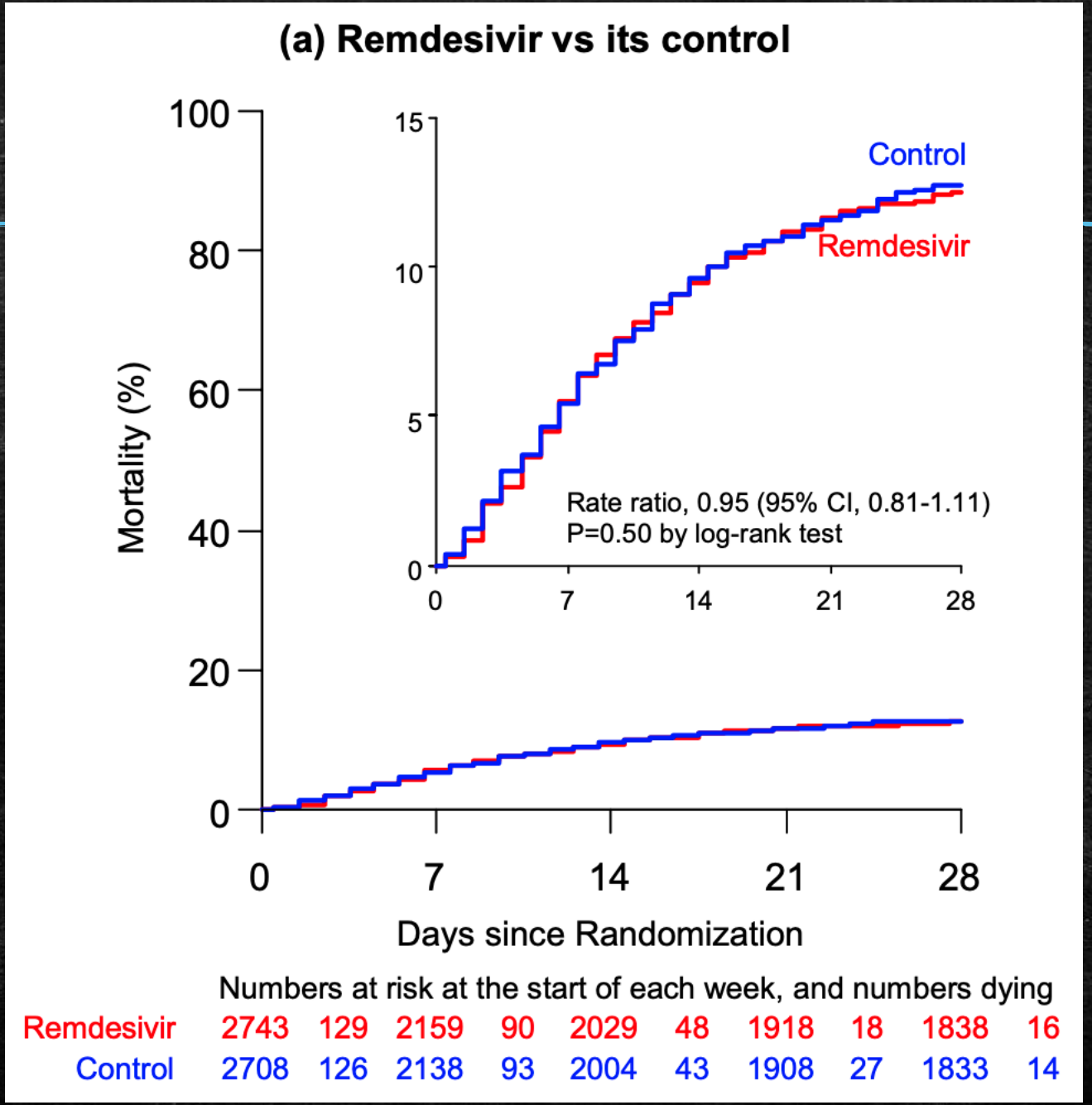
12 – 17 years of age

- BMI 85$^{th}$ percentile for their age and gender
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders, eg cerebral palsy
- Medical related technological dependence, for example tracheostomy, gastrostomy or positive pressure ventilation
- Asthma, reactive airway or other chronic respiratory disease that requires daily medicine

# LY-CoV555 in Hospitalized Patients

- LY-CoV555 sub-study of ACTIV-3 trial closed after data suggested a lack of clinical benefit for LY-CoV555 in a hospitalized population

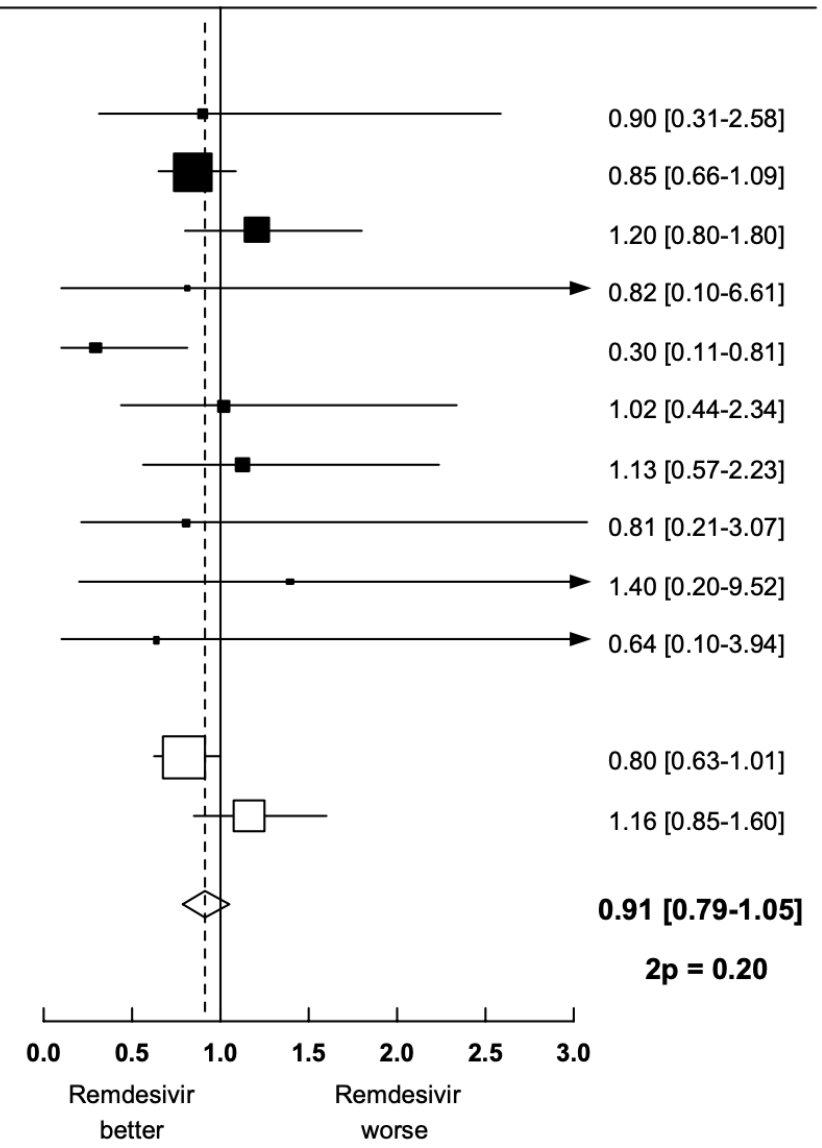
# Remdesivir and SOLIDARITY




https://doi.org/10.1101/2020.10.15.20209817.

# Remdesivir and SOLIDARITY

| Trial name, and initial respiratory support | Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%) | | Remdesivir deaths: Observed-Expected | | Ratio of death rates (RR), & 99% CI (or 95% CI, for total) |
|---|---|---|---|---|---|
| | Remdesivir | Control | (O-E)* | Var (O-E) | Remdesivir : Control |
| Solidarity: no $O_2$ | 11/661 (2.0) | 13/664 (2.1) | -0.6 | 6.0 | 0.90 [0.31-2.58] |
| Solidarity: low/hi-flow $O_2$ | 192/1828 (12.2) | 219/1811 (13.8) | -16.9 | 101.8 | 0.85 [0.66-1.09] |
| Solidarity ventilation | 98/254 (43.0) | 71/233 (37.8) | 7.6 | 40.8 | 1.20 [0.80-1.80] |
| ACTT: no $O_2$ | 3/75 (4.1) | 3/63 (4.8) | -0.3 | 1.5 | 0.82 [0.10-6.61] |
| ACTT: low-flow $O_2$ | 9/232 (4.0) | 25/203 (12.7) | -8.0 | 6.7 | 0.30 [0.11-0.81] |
| ACTT: hi-flow $O_2$ or non-invasive ventilation | 19/95 (21.2) | 20/98 (20.4) | 0.2 | 9.6 | 1.02 [0.44-2.34] |
| ACTT: invasive ventilation | 28/131 (21.9) | 29/154 (19.3) | 1.7 | 14.3 | 1.13 [0.57-2.23] |
| Wuhan: low-flow $O_2$ | 11/129 (8.5) | (7/68) x2† (10.3) | -0.8 | 3.7 | 0.81 [0.21-3.07] |
| Wuhan: hi-flow O2 or ventilation | 11/29 (37.9) | (3/10) x2† (30.0) | 0.6 | 1.8 | 1.40 [0.20-9.52] |
| SIMPLE: no $O_2$ | 5/384 (1.3) | (4/200) x2† (2.0) | -0.9 | 2.0 | 0.64 [0.10-3.94] |
| **Subtotals** | | | | | |
| Lower risk groups (with no ventilation) | 231/3309 (7.0) | 282/3277 (8.6) | -27.6 | 121.6 | 0.80 [0.63-1.01] |
| Higher risk groups | 156/509 (30.6) | 126/505 (25.0) | 10.1 | 66.5 | 1.16 [0.85-1.60] |
| **Total** | **387/3818 (10.1)** | **408/3782 (10.8)** | **-17.5** | **188.2** | **0.91 [0.79-1.05]** |
| | | | | | **2p = 0.20** |




■/□ 99% or ◇ 95% confidence interval (CI), K-M Kaplan-Meier.

* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.log$_e$HR for ACTT strata (with the weight w being the inverse of the variance of log$_e$HR, which is got from the HR's CI). RR is got by taking log$_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the log$_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

https://doi.org/10.1101/2020.10.15.20209817.

# Convalescent Plasma

**Recommendation 8: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap)**

**Table 8.** GRADE evidence profile, Recommendation 8

**Question**: Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | convalescent plasma | no convalescent plasma | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (RCT) (follow up: range 15 days to 60 days)** | | | | | | | | | | | | |
| 2 [1,2] | randomized trials | serious [a,b] | not serious | not serious | very serious [c] | none | 14/95 (14.7%) | 23/94 (24.5%) | **RR 0.60** (0.33 to 1.10) | **98 fewer per 1,000** (from 164 fewer to 24 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Mortality at 30 days (NRS)** | | | | | | | | | | | | |
| 1 [3] | observational studies | serious [d,e] | not serious | not serious [e] | not serious | none [f] | 115/515 (22.3%) [g] | 166/561 (29.6%) | **RR 0.75** (0.61 to 0.93) [e,h] | **74 fewer per 1,000** (from 115 fewer to 21 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Mortality at 7 days (NRS)** | | | | | | | | | | | | |
| 1 [3] | observational studies | serious [d,e] | not serious | not serious [e] | not serious | none [f] | 46/515 (8.9%) [g] | 77/561 (13.7%) | **RR 0.65** (0.46 to 0.92) [e,i] | **48 fewer per 1,000** (from 74 fewer to11 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |

Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID

We want to hear from you! Please complete the post-call survey.

Next Call: Saturday, November 21st on Monoclonal Antibodies

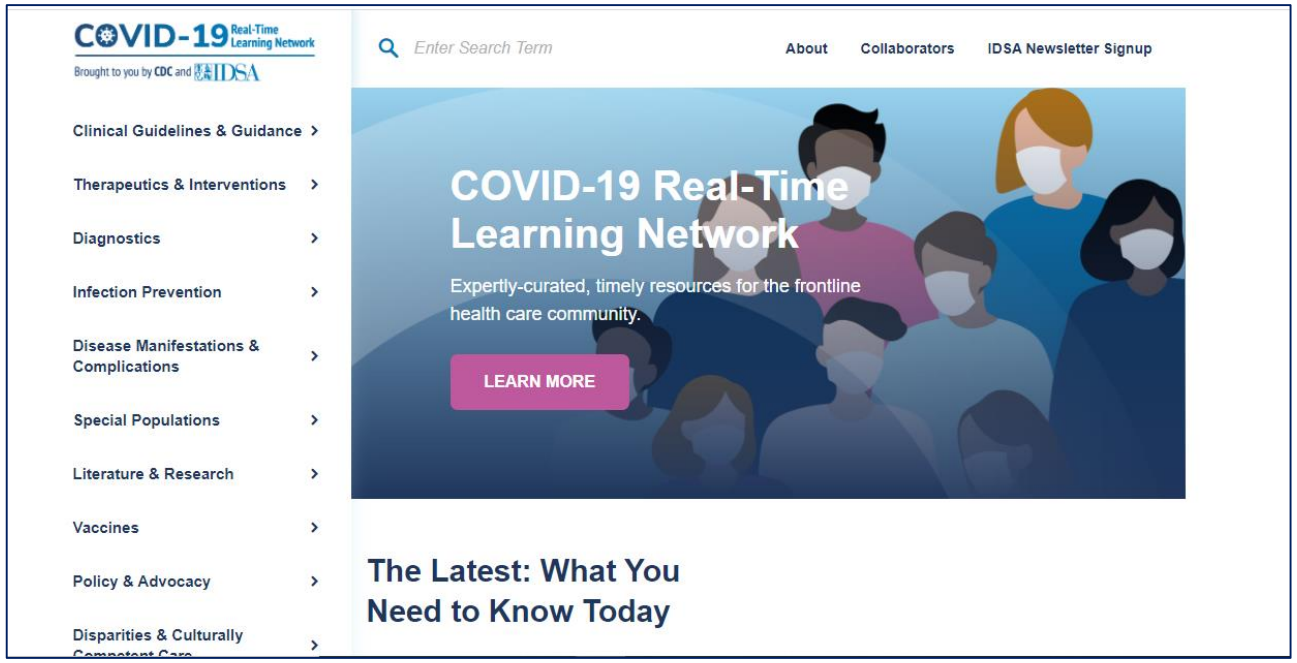
A recording of this call will be posted on Monday at www.idsociety.org/cliniciancalls

*-- library of all past calls now available --*

**Contact Us:**

Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)

# COVID-19 Real-Time Learning Network




With funding from the Centers for Disease Control and Prevention, IDSA has launched the COVID-19 Real Time Learning Network, an online community that brings together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.

**Specialty Society Collaborators:**

- American Academy of Family Physicians
- American Academy of Pediatrics
- American College of Emergency Physicians
- American College of Physicians
- American Geriatrics Society
- American Thoracic Society
- Pediatric Infectious Diseases Society
- Society for Critical Care Medicine
- Society for Healthcare Epidemiology of America
- Society of Hospital Medicine
- Society of Infectious Diseases Pharmacists

www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID

# CDC-IDSA Partnership: Clinical Management Call Support

*Announcing a new service for clinicians:*

**FOR WHOM?**

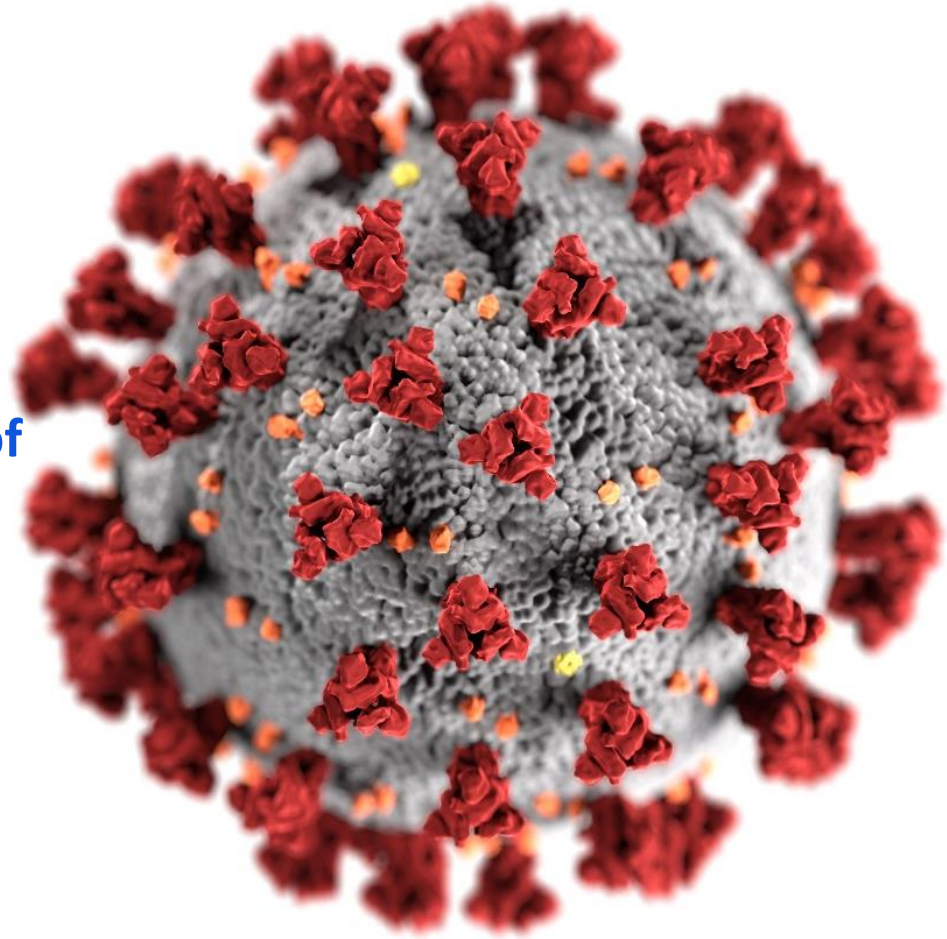
- Clinicians who have questions about the clinical management of COVID-19

**WHAT?**

- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

**HOW?**

- Clinicians may call the main CDC information line at 800-CDC-INFO (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form



IDSA
Infectious Diseases Society of America

cdc.gov/coronavirus