CDC/IDSA COVID-19 Clinician Call

February 6, 2021

Welcome & Introductions

Dana Wollins, DrPH, MGC
Vice President, Clinical Affairs & Guidelines
IDSA

- 53rd in a series of weekly calls, initiated 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/cliniciancalls.

Today's Topics and Featured Experts:

COVID-19 Treatment Updates
and
More Vaccine Q&A

COVID-19 Treatment Updates

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Staff, Department of Infectious Diseases
Cleveland Clinic

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Clinical Professor
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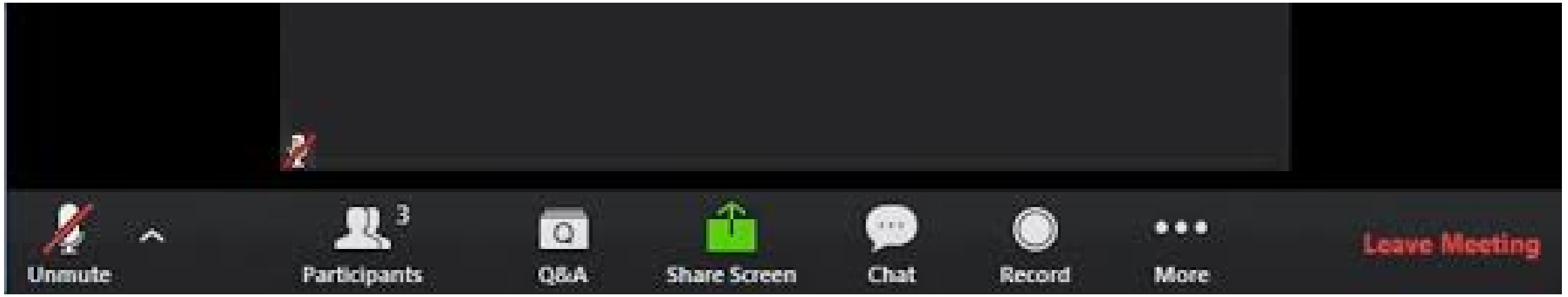
COVID-19 Vaccine Q&A

Sarah Mbaeyi, MD, MPH
Lead, Clinical Guidelines Development
CDC COVID-19 Vaccine Task Force

Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button



COVID-19 Treatment Updates

- **Adarsh Bhimraj, MD, FIDSA**
- **Jason C. Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS**

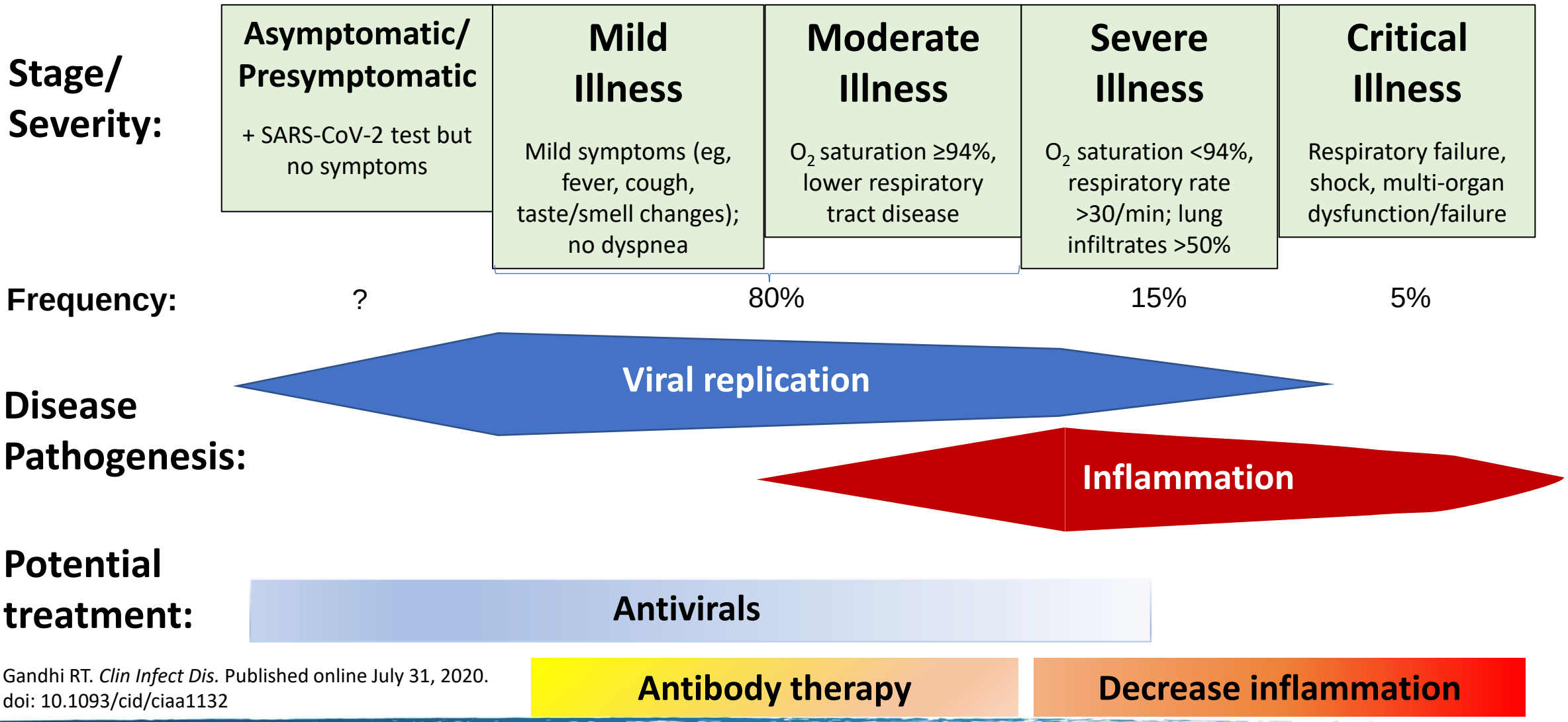
Disclosures

Adarsh Bhimraj has no financial relationships with commercial interests to disclose.

Jason Gallagher has the following relevant financial relationships with commercial interests to disclose:

- Grant/Research Support: Merck
- Consultant: Astellas, Merck, Qpex, scPharmaceuticals, Shionogi, Spero
- Speakers Bureau: Astellas, Merck (both former)

Multidimensional Challenge of Treating COVID-19

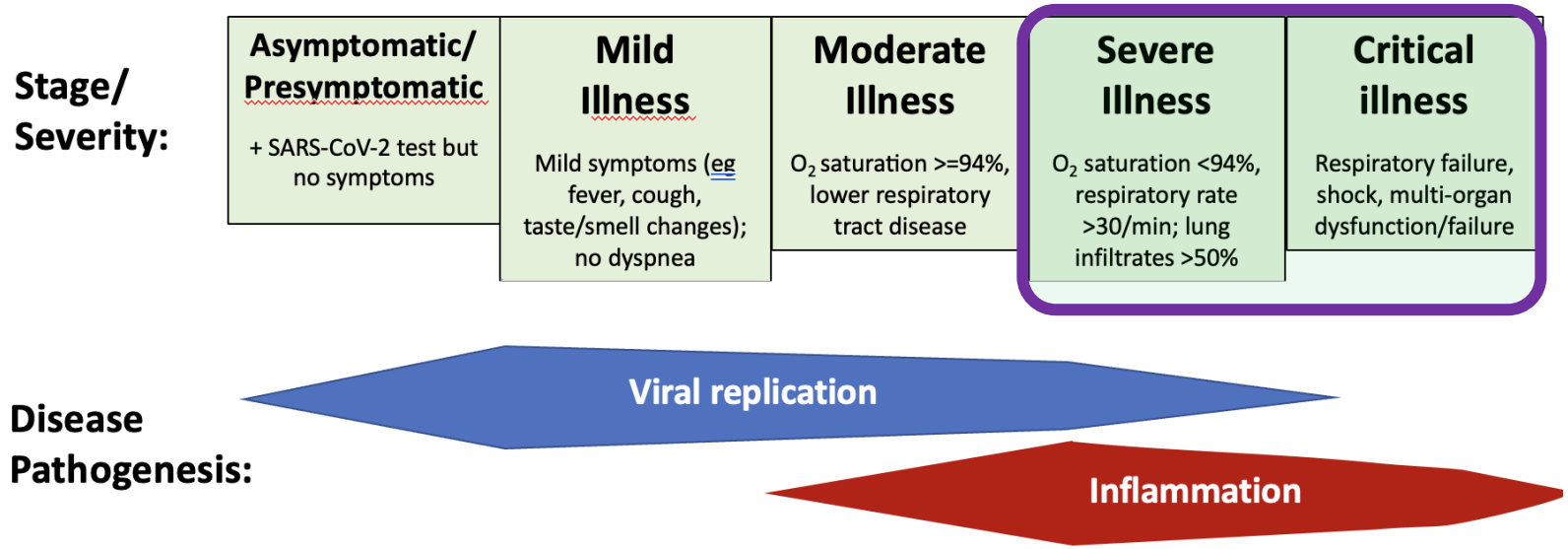


Gandhi RT. *Clin Infect Dis.* Published online July 31, 2020. doi: 10.1093/cid/ciaa1132

Tocilizumab

A tough drug to figure out

- Inhibitor of IL-6 receptors, leading to a reduction of cytokine production
- Used in treatment of RA and cytokine release syndrome
- Given IV, half-life of 13-17 days
- Adverse effects: LFT abnormalities, possible infections



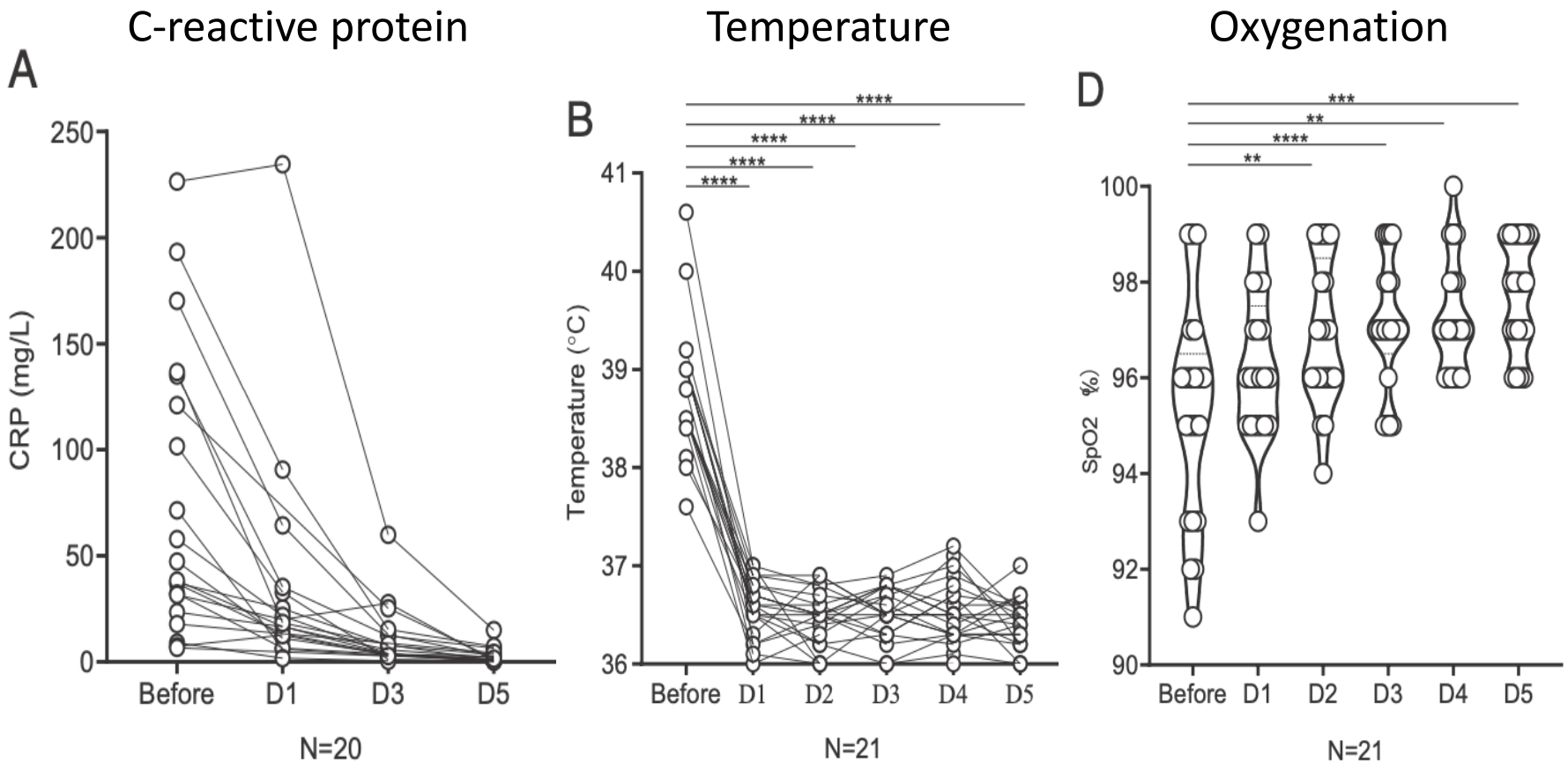
Dose: 8 mg/kg IV x 1-2 doses

RA, rheumatoid arthritis.

Gandhi RT. *Clin Infect Dis.* Published online July 31, 2020. doi: 10.1093/cid/ciaa1132; REMAP-CAP Investigators. medRxiv preprint. https://doi.org/10.1101/2021.01.07.21249390; Rosas I, et al. medRxiv preprint. https://doi.org/10.1101/2020.08.27.20183442.

Tocilizumab: Effects on Surrogate Markers

C-reactive protein, temperature, and SpO_2 in a study of 21 patients with COVID-19 who received tocilizumab



Xu X, et al. *Proc Natl Acad Sci USA*. 2020;117(20)10970-10975.

Tocilizumab: Clinical Trials

Study (n)	Severity	Outcome	Tocilizumab	Control	Comments
REMAP-CAP (747)	>99% critically ill	Hospital mortality	28%*	35.8%	>80% received corticosteroids
COVACTA (452)	70% severe	Clinical status Mortality	ND 19.7%	ND 19.4%	Shorter LOS (20 v 28 d*) and ICU stay (5.8 v 15.5 d*)
Coalition COVID (129)	60% severe 40% HFNC/MV	MV or mortality	28%	20%	Death: 17%* toci, 3* control
EMPACTA (389)	75% moderate	MV or mortality	12.0%*	19.3%	Death: 10.4% toci, 8.6% control
BACC Bay (243)	97% moderate	MV or mortality	18.0%	14.9%	Neutropenia 13.7% toci* vs 1.2%
CORIMUNO-TOCI 1 (131)	Moderate	Clinical status Mortality	ND 11.1%	ND 11.9%	Randomized, not blinded Fewer ICU admissions with toci *$P \leq 0.05$.
RCT-TCZ-COVID-19 (123)	Moderate	ICU or mortality	28.3% 2 deaths	27.0% 1 death	Randomized, not blinded

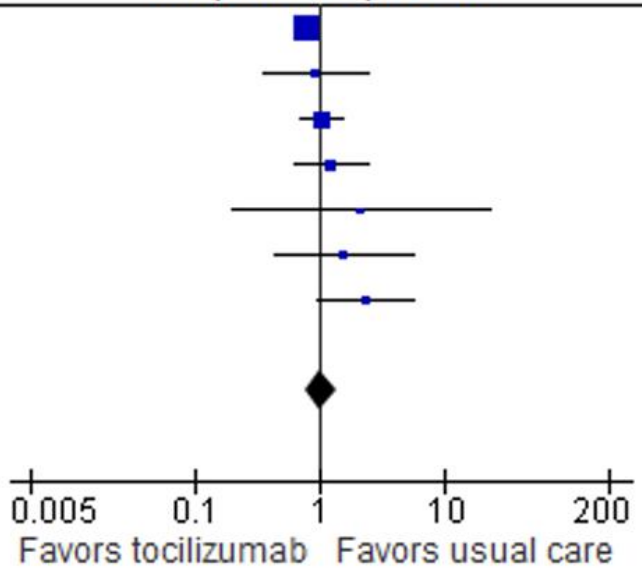
REMAP-CAP. medRxiv preprint. doi.org/10.1101/2021.01.07.21249390; Rosas IO, et al. medRxiv preprint. doi.org/10.1101/2020.08.27.20183442; Salama C, et al. *N Engl J Med*. 2021;384(1):20-30; Salvarani C, et al. *JAMA Intern Med*. 2021;181(1):24-31; Stone JH, et al. *N Engl J Med*. 2020;383(24):2333-2344; Hermine O, et al. *JAMA Intern Med.* 2021;181(1):32-40. Veiga VC et al. *BMJ* 2021;372:n84

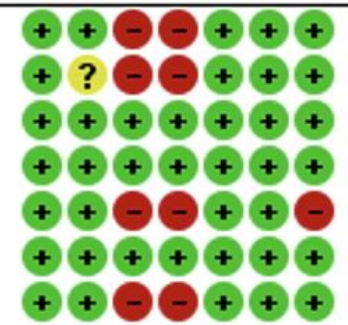
Tocilizumab – Meta-analysis for Mortality

Study or Subgroup	Tocilizumab Events	Tocilizumab Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Gordon 2021 (1)	98	366	142	412	41.3%	0.78 [0.63, 0.96]
Hermine 2020	7	63	8	67	7.2%	0.93 [0.36, 2.42]
Rosas 2020 (2)	58	294	28	144	25.1%	1.01 [0.68, 1.52]
Salama 2020	26	249	11	128	12.8%	1.22 [0.62, 2.38]
Salvarani 2020	2	60	1	63	1.3%	2.10 [0.20, 22.56]
Stone 2020	9	161	3	82	4.2%	1.53 [0.43, 5.49]
Veiga 2021 (3)	14	65	6	64	8.1%	2.30 [0.94, 5.61]
Total (95% CI)		**1258**		**960**	**100.0%**	**1.01 [0.77, 1.33]**
Total events	214		199			

Heterogeneity: Tau² = 0.04; Chi² = 8.39, df = 6 (P = 0.21); I² = 28%

Test for overall effect: Z = 0.10 (P = 0.92)





Footnotes

(1) Gordon allowed for ventilated patients to be included at randomization

(2) Rosas allowed for ventilated patients to be included at randomization

(3) Veiga allowed for ventilated pateints to be included at randomization

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

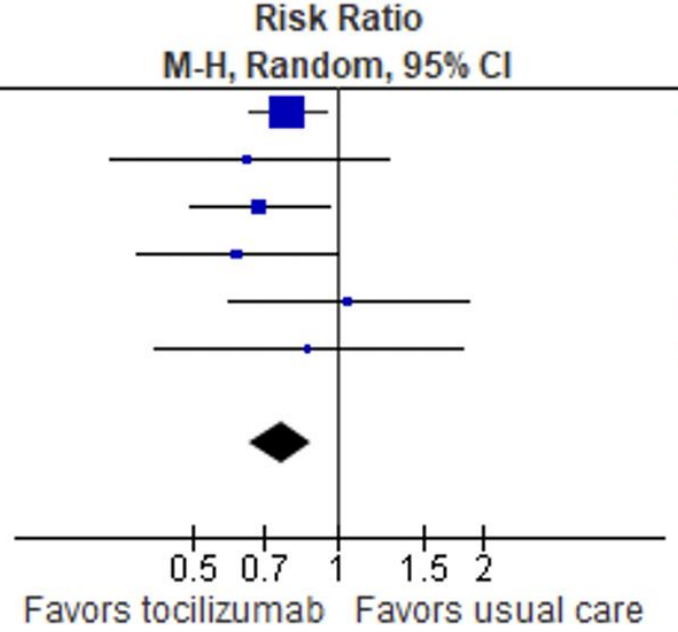
(G) Other bias

Tocilizumab – Meta-analysis for Clinical Deterioration

Study or Subgroup	Tocilizumab Events	Tocilizumab Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Gordon 2021 (1)	100	242	144	273	58.1%	0.78 [0.65, 0.94]
Hermine 2020 (2)	11	63	18	67	4.6%	0.65 [0.33, 1.27]
Rosas 2020 (3)	53	183	38	90	18.6%	0.69 [0.49, 0.96]
Salama 2020 (4)	30	249	25	128	8.6%	0.62 [0.38, 1.00]
Salvarani 2020 (5)	17	60	17	63	6.2%	1.05 [0.59, 1.86]
Stone 2020 (6)	17	161	10	82	3.8%	0.87 [0.42, 1.80]
Total (95% CI)		**958**		**703**	**100.0%**	**0.76 [0.66, 0.88]**
Total events	228		252			

Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 5 (P = 0.74); I² = 0%

Test for overall effect: Z = 3.78 (P = 0.0002)



Footnotes

(1) Need for mechanical ventilation, ECMO, or death; denominator includes those not...
(2) Need for mechanical ventilation or death
(3) Need for mechanical ventilation, death or ICU admission; denominator only includes...
(4) Need for mechanical ventilation or death
(5) Need for mechanical ventilation, death, or PaO2/FiO2 ratio of less than 150mmHg
(6) Need for mechanical ventilation or death

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Tocilizumab: Implications for Practice

- Very difficult to interpret data
- Profound effects on cytokines may hide infection
- Possible mortality benefit for some patients, or prevention of progression to mechanical ventilation
- Await results of RECOVERY trial

Convalescent Plasma – FDA EUA Change

EMERGENCY USE AUTHORIZATION (EUA) OF COVID-19 CONVALESCENT PLASMA FOR TREATMENT OF HOSPITALIZED PATIENTS WITH COVID-19

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product high titer COVID-19 convalescent plasma to treat hospitalized patients with COVID-19. Available evidence suggests potential benefit is associated with transfusion of high titer COVID-19 convalescent plasma early in the course of disease and those hospitalized with impaired humoral immunity. Transfusion of COVID-19 convalescent plasma to hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit.

INTENDED USE

The EUA for COVID-19 convalescent plasma authorizes the use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19.

FDA Convalescent plasma EUA Fact Sheet. https://www.fda.gov/media/141478/download

Convalescent Plasma: RCTs

Study (n)	Outcome	Convalescent plasma	Control	Comments
Libster (160)	Severe COVID	16%	31% (*P*=0.02)	Elderly, early, high titers
Simonovich (228)	Mortality	10.96%	11.43% (*P*=NS)	OR, 0.83 (0.52-1.35) for outcomes
Gharbharan (86)	Mortality	14%	26% (*P*=NS)	No clinical differences
Li (103)	Improvement	51.9%	43.1% (*P*=NS)	More virologic conversion at 72 h
Avendaño-Solà C (81)	MV or death	0%	14% (*P*=NS)	Underpowered
AlQahtani (40)	MV	20%	30% (*P*=NS)	Open-label
Agarwal (464)	Severe or death	19%	18% (*P*=NS)	Open-label
Ray (80)	Mortality	Details not given. No difference between groups.		

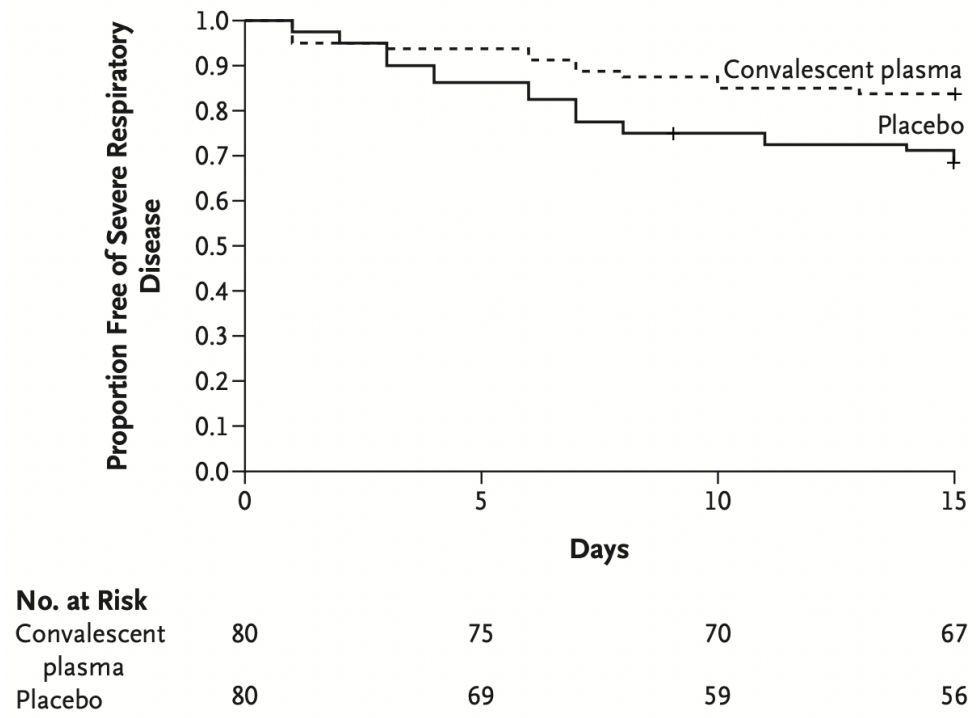
Simonovich VA, et al. *N Engl J Med.* Published online November 24, 2020. doi: 10.1056/NEJMoa2031304; Gharbharan A, et al. medRxiv preprint. doi.org/10.1101/2020.07.01.20139857; Libster R, et al. *N Engl J Med*. Published online. January 6, 2021. doi: 10.1056/NEJMoa2033700; Li L, et al. *JAMA*. 2020;324(5):460-470; Avendaño-Solà C, et al. medRxiv preprint. doi.org/10.1101/2020.08.26.20182444; AlQahtani M, et al. medRxiv preprint. doi.org/10.1101/2020.11.02.20224303; Agarwal A, et al. *BMJ*. 2020;371:m3939; Ray Y, et al. medRxiv preprint. doi.org/10.1101/2020.11.25.20237883

Evidence for High-Titer Convalescent Plasma

30-day mortality in Mayo Expanded-Access Program (subset)

Group	Low	Medium	High
All patients	166/561 (29.6%)	549/2006 (27.4%)	115/515 (22.3%)
Relative risk (95% CI)	Reference	0.92 (0.80–1.07)	0.75 (0.61–0.93)
No ventilator	81/365 (22.2%)	251/1297 (19.4%)	50/352 (14.2%)
Relative risk (95% CI)	Reference	0.87 (0.70-1.09)	0.64 (0.46–0.88)
Ventilator	80/183 (41.6%)	277/666 (41.6%)	64/158 (40.5%)
Relative risk (95% CI)	Reference	0.95 (0.79–1.15)	0.93 (0.72–1.19)

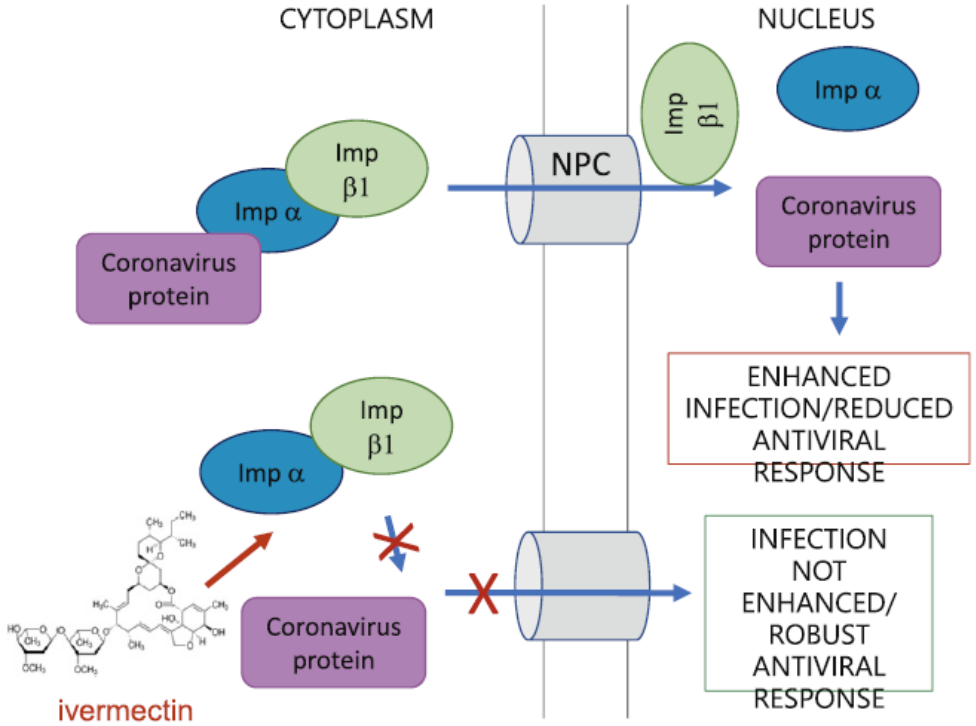
RCT of high-titer CP to prevent severe disease

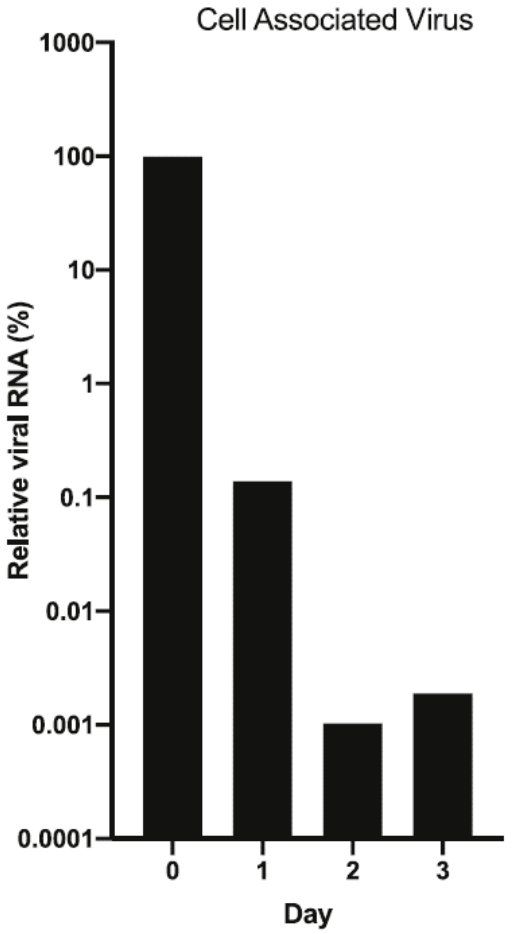


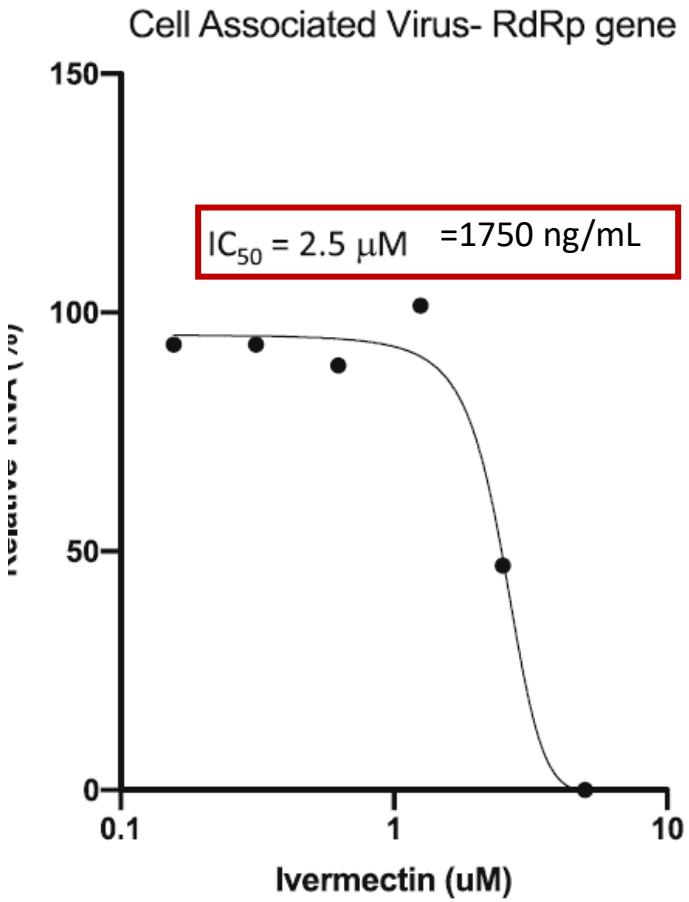
Relative risk, 0.52; 95% CI, 0.29 to 0.94; P=0.03)

Joyner MJ et al. *New Engl J Med.* DOI: 10.1056/NEJMoa2031893. Libster R et al. *New Engl J Med*. DOI: 10.1056/NEJMoa2033700

Ivermectin & SARS CoV2: mechanism & i*n vitro* activity

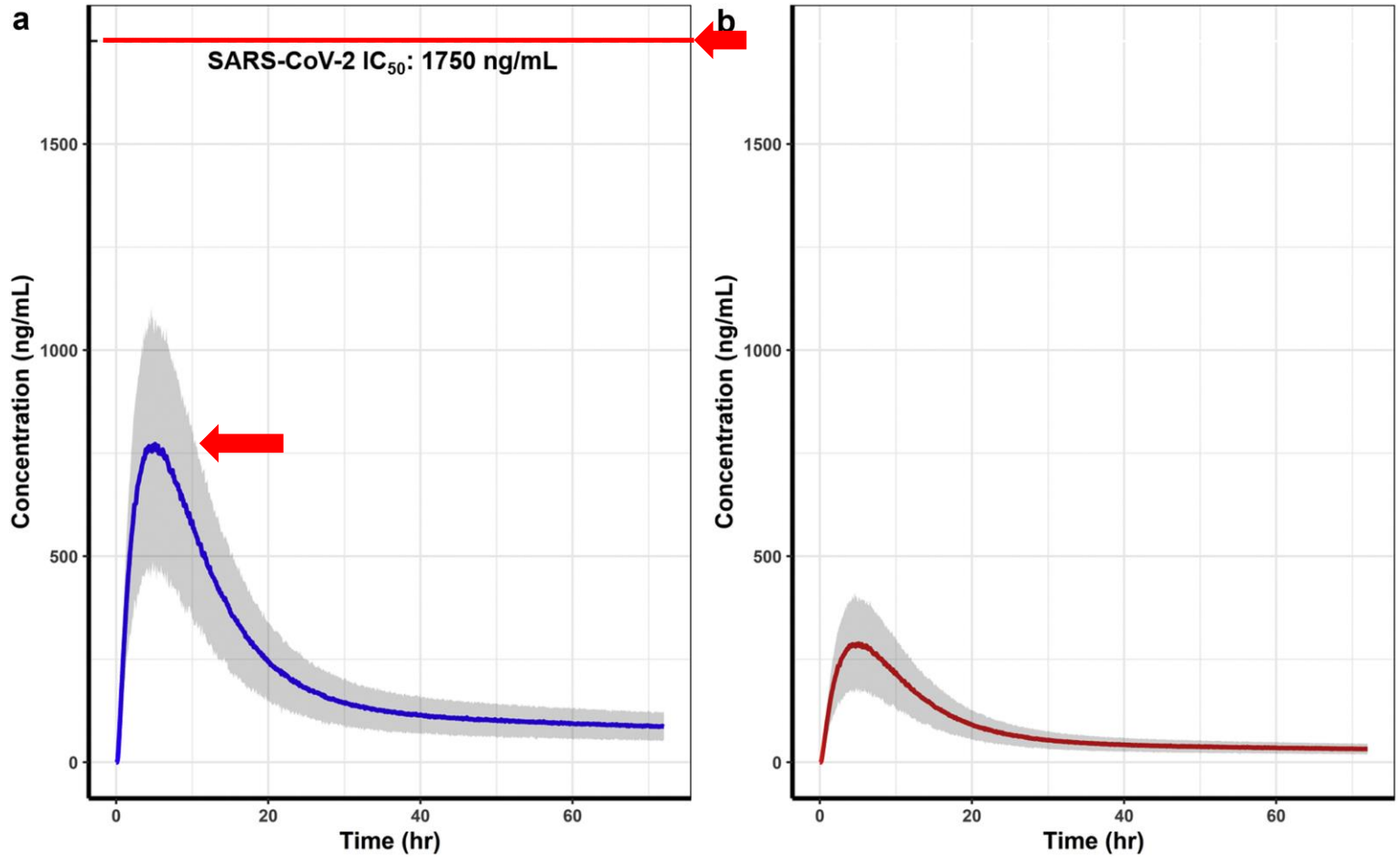






L. Caly, et al. Antiviral Research 178 (2020) 104787

PK model to simulate lung concentrations in humans



Development of a Minimal Physiologically-Based Pharmacokinetic Model to Simulate Lung Exposure in Humans Following Oral Administration of Ivermectin for COVID-19 Drug Repurposing

Jermain B et al. JPharmSci 2020 1093574-3578DOI: (10.1016/j.xphs.2020.08.024

The world this week

News in focus

Peru has been one of the nations hit hardest by the COVID-19 pandemic. Here, patients are cared for in

EMBRACE OF UNPROVEN COVID TREATMENT HINDERS DRUG TRIALS

Unchecked ivermectin use in Latin America is
test how effective the anti-parasite drug is

FDA Letter to Stakeholders: Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans

Español (/animal-veterinary/product-safety-information/carta-de-la-fda-las-partes-interesadas-no-use-ivermectina-destinada-animales-como-tratamiento-para)

April 10, 2020

Democrat & Chronicle

NEWS

Court orders Rochester General to give experimental COVID treatment to patient

Sean Lahman Rochester Democrat and Chronicle

Published 11:58 a.m. ET Jan. 25, 2021 | Updated 2:40 p.m. ET Jan. 25, 2021

https://buffalonews.com/news/local/unapproved-by-fda-ivermectin-useful-as-covid-19-treatment-local-doctors-say/article_8ee56f1a-625d-11eb-b771-b76fa82cbedb.html

Unapproved by FDA, Ivermectin useful as Covid-19 treatment, local doctors say

Dan Herbeck
Feb 2, 2021

Studies considered for the guidelines

- Considered comparative studies reported as RCT's or acceptable risk of bias
- Reported mortality, symptom resolution, viral clearance and adverse events
- Comparator; Ivermectin to inactive comparison (e.g., standard of care with or without placebo)
  - Studies that compared ivermectin to other therapy (e.g., hydroxychloroquine) were excluded, as the presence of an active comparator may bias the effectiveness of ivermectin.
- Hospitalized patients
  - 5 RCTs(Chachar et al., Chaccour et al; Hashim et al; Ahmed et al; Podder et al)
  - 2 non-randomized studies (Gorial et al; Raijter et al)
- Outpatients
  - 2RCTs (Chaccour et al, Hashim et al)

Studies considered

Study/year	Country/Hospital	Study design	N subjects (intervention/comparator)	Outcomes reported
Ahmed/ 2020	Bangladesh	RCT	68: ivermectin alone vs. ivermectin plus doxycycline vs. placebo (22/23/23)	• Length of hospitalization • Incidence of hypoxia • Time to virologic clearance • Biomarker levels • Adverse events
Chaccour/2020	Spain/ Clínica Universidad de Navarra	RCT	24 (12/12)	• Mortality • Viral clearance at day 7 • Progression to severe disease • Viral load at days 4, 7, 14, and 21 • Symptom resolution at days 4, 7, 14, and 21 • Seroconversion day 21
Gorial/ 2020	Iraq/ Al Sharif Hospital	Case control	87 (16/71)	• Mortality • Clinical cure, defined as resolution of symptoms and viral clearance • Length of hospitalization • Adverse events
Hashim/ 2020	Iraq/ Alkarkh and Alforat hospitals	RCT	140 (70/70)	• Mortality • Disease progression after 3 days • Time to recovery
Podder 2020	Bangledesh/ Debidwar Upazila Health Complex	RCT	62 (32/30)	• Viral clearance at day 10 • Duration of symptoms • Time to resolution of symptoms
Rajter JC/2020	Florida, US (4 hospitals)	Retrospective cohort	280 (173/107)	• Mortality • Extubation rates for intubated patients • Length of stay

Risk of Bias

RCTs

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ahmed 2020							
Chaccour 2020							
Hashim 2020							
Podder 2020							

Low | High | Unclear

Non-randomized studies

Study + Overall RoB Judgement	Bias due to confounding	Selection Bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Gorial 2020							
Rajter 2020							

Low | Moderate | Serious | Critical

Ivermectin compared to no ivermectin for patients with COVID-19 hospitalized

Outcome	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty	Importance
Mortality (NRS)	4 [1,2,3,4]	observational studies	serious [a]	not serious	not serious	serious [b]	⨁◯◯◯ VERY LOW	CRITICAL
Symptom Resolution 7 days)	1 [5]	randomized trials	serious [c]	not serious	not serious	very serious [b]	⨁◯◯◯ VERY LOW	CRITICAL
Viral clearance day 7 9RCT)	3 [4,6,7]	randomized trials	serious [d]	not serious	serious [e]	very serious [b]	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events (28d)	1 [4]	randomized trials	not serious	not serious	not serious	very serious [b]	⨁⨁◯◯ LOW	IMPORTANT

Ivermectin compared to no ivermectin for patients with COVID-19 hospitalized

Outcome	№ of studies	Study design	ivermectin	no ivermectin	Relative (95% CI)	Absolute (95% CI)
Mortality (NRS)	4 [1,2,3,4]	observational studies	28/271 (10.3%)	35/260 (13.5%)	**RR 0.57** (0.36 to 0.90)	**58 fewer per 1,000** (from 86 fewer to 13 fewer)
Symptom Resolution 7 days)	1 [5]	randomized trials	16/25 (64.0%)	15/25 (60.0%)	**RR 1.07** (0.69 to 1.65)	**42 more per 1,000** (from 186 fewer to 390 more)
Viral clearance day 7 9RCT)	3 [4,6,7]	randomized trials	29/54 (53.7%)	22/55 (40.0%)	**RR 1.33** (1.00 to 1.78)	**132 more per 1,000** (from 0 fewer to 312 more)
Adverse events (28d)	1 [4]	randomized trials	7/12 (58.3%)	8/12 (66.7%)	**RR 0.88** (0.47 to 1.63)	**80 fewer per 1,000** (from 353 fewer to 420 more)

Ivermectin compared to no ivermectin for patients with COVID-19 NOT hospitalized

Outcome	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty	Importance
Mortality (NRS)	2 [1,2]	randomized trials	serious [a]	not serious	not serious	very serious [b]	⨁◯◯◯ VERY LOW	CRITICAL
Progression to severe disease	2 [1,2]	randomized trials	serious [c]	not serious	not serious	very serious [b]	⨁◯◯◯ VERY LOW	CRITICAL
Viral clearance at d 7	1 [2]	randomized trials	serious [c]	not serious	serious [d]	very serious [b]	⨁◯◯◯ VERY LOW	IMPORTANT
Time to recovery(days)	1 [1]	randomized trials	serious [c]	not serious	not serious [e]	very serious [f]	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events (d28)	1 [2]	randomized trials	serious [c]	not serious	not serious	very serious [b]	⨁◯◯◯ VERY LOW	IMPORTANT

Ivermectin compared to no ivermectin for patients with COVID-19 NOT hospitalized

Outcome	№ of studies	Study design	ivermectin	no ivermectin	Relative (95% CI)	Absolute (95% CI)
Mortality (NRS)	2 [1,2]	randomized trials	0/60 (0.0%)	0/60 (0.0%)	not estimable	
Progression to severe disease	2 [1,2]	randomized trials	0/60 (0.0%)	0/60 (0.0%)	not estimable	
Viral clearance at d 7	1 [2]	randomized trials	0/12 (0.0%)	0/12 (0.0%)	not estimable	
Time to recovery(days)	1 [1]	randomized trials	48	48	-	MD **7.32 days fewer** (9.25 fewer to 5.39 fewer)
Adverse events (d28)	1 [2]	randomized trials	5/12 (41.7%)	5/12 (41.7%)	**RR 1.00** (0.39 to 2.58)	**0 fewer per 1,000** (from 254 fewer to 658 more)

IDSA COVID-19 Guideline recommendations

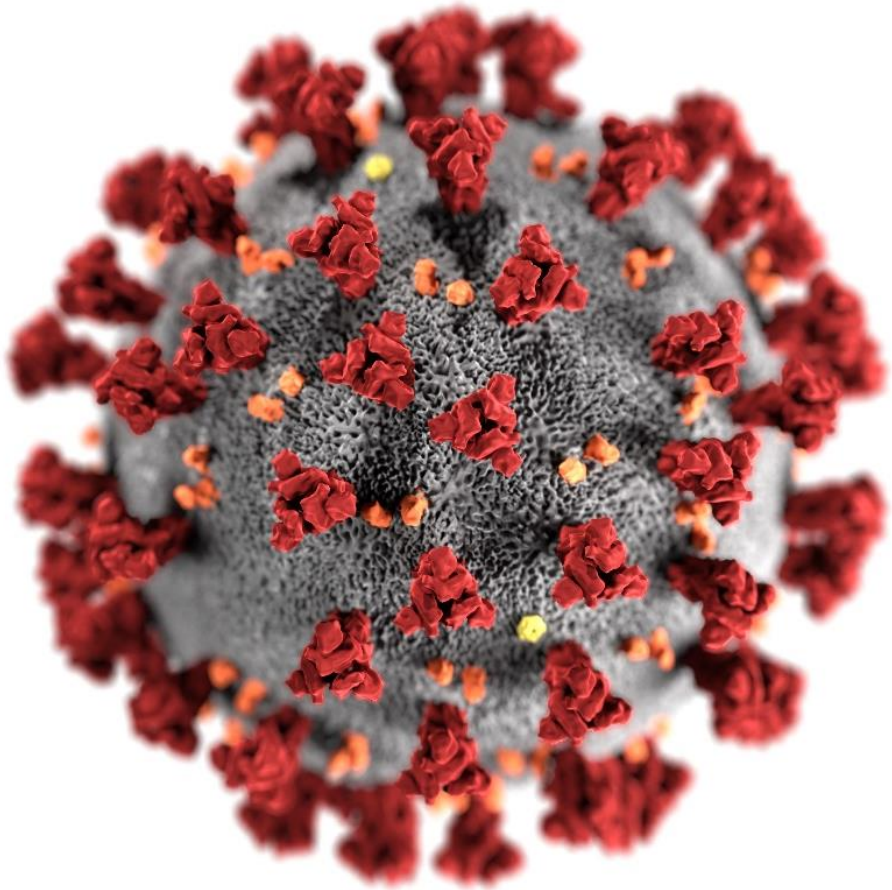
In hospitalized patients with severe COVID-19 , the IDSA panel suggests against ivermectin use outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

In outpatients with COVID-19, the IDSA panel suggests against ivermectin use outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

COVID-19 Treatment Updates Q&A

COVID-19 Vaccine Updates

Sarah Mbaeyi, MD, MPH
Lead, Clinical Guidelines Development
CDC COVID-19 Vaccine Task Force



COVID-19 Vaccine FAQs

Go to www.COVID19LearningNetwork.org and click on “Vaccines FAQ”

Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID19

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

Next Call: **Saturday, February 13th**

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

-- library of all past calls now available --

Contact Us:

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Deirdre Lewis (dlewis@idsociety.org)