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AUB American University of Beirut

COVID-19 PANDEMIC TREATMENT OPTIONS

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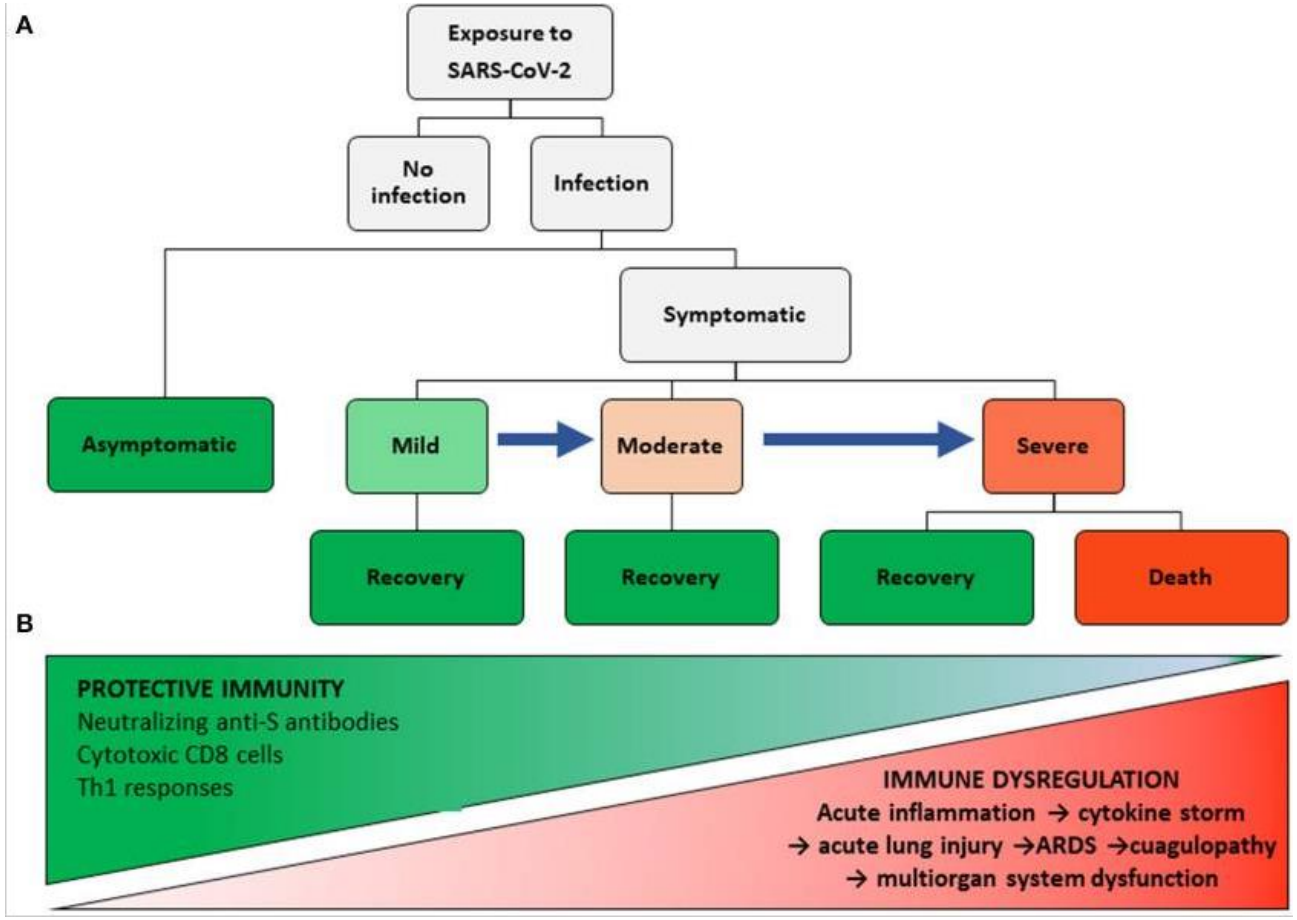
OUTLINE

1. *COVID-19 DISEASE*
   clinical approach
2. *ANTIVIRALS*
3. *STEROIDS AND IMMUNEMODULATORS*
4. *CO-INFECTIONS*

COVID-19 CLINICAL AND IMMUNOLOGICAL SPECTRA



(A) Clinical stages of COVID-19.
(B) Protective immunity and inflammatory spectra.

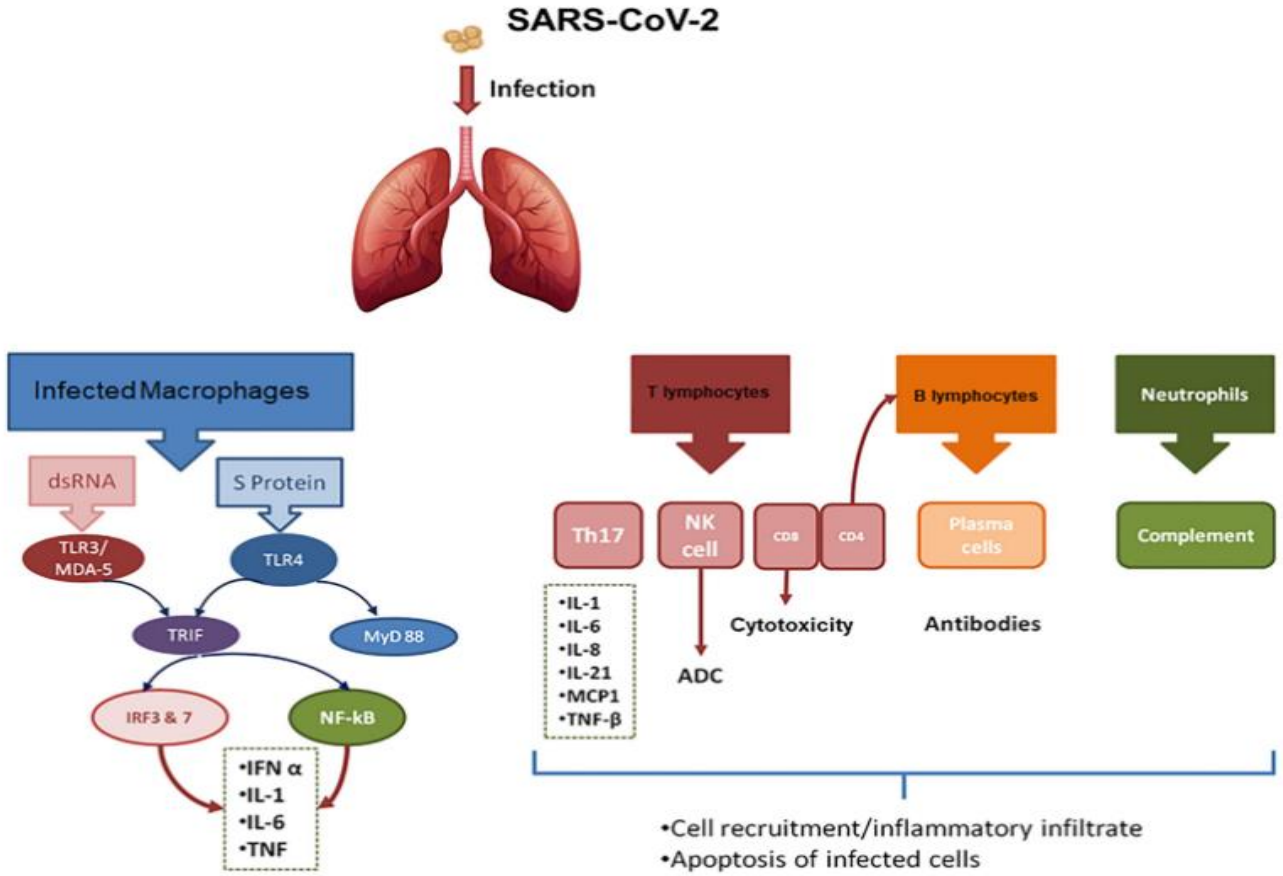
García LF. Front Immunol. 2020;11:1441. Published 2020 Jun 16. doi:10.3389/fimmu.2020.01441

OVERALL DISEASE DISTRIBUTION

- Among individuals with symptomatic coronavirus disease 2019 (COVID-19)
    - Mild to moderate (mild symptoms up to mild pneumonia): 81%
    - Severe (dyspnea, hypoxia, or more than 50% lung involvement on imaging): 14%
    - Critical (respiratory failure, shock, or multiorgan system dysfunction): 5%
- Infection fatality rates are population and age dependent, with very low rates for children and young adults but mortality rates >25% for individuals over age 90.

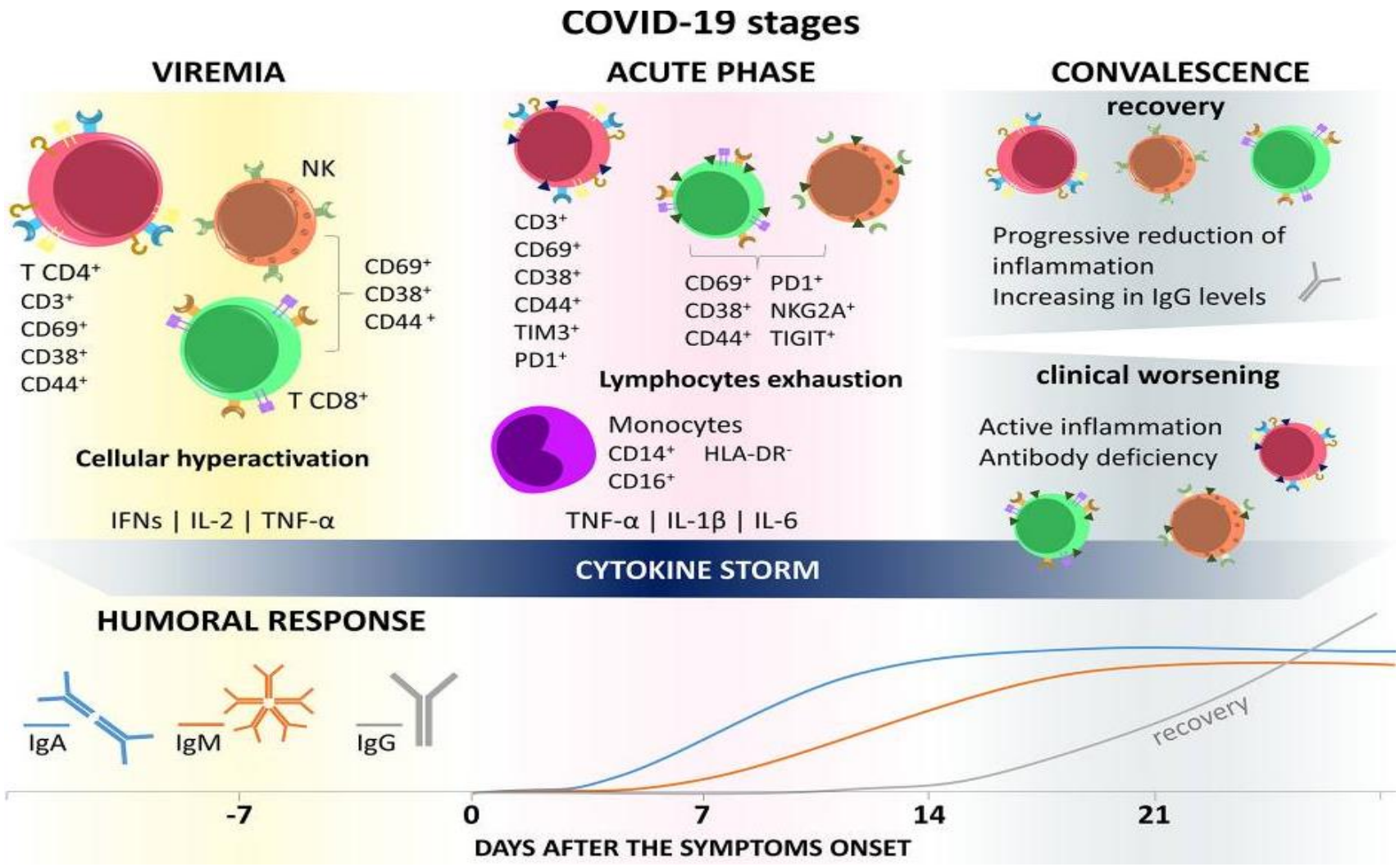
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
WHO. Estimating mortality from COVID-19: Scientific brief, 4 August 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Mortality-2020.

THE IMMUNE RESPONSE TO INFECTION WITH SARS-COV-2



Lauxmann, Martin Alexander, Santucci, Natalia Estefanía, & Autrán-Gómez, Ana María. International braz j urol, 46(Suppl. 1), 6-18. Epub July 27, 2020.https://doi.org/10.1590/s1677-5538.ibju.2020.s10

IMMUNE RESPONSE IN COVID-19 STAGES



Silva TF, Tomiotto-Pellissier F, Sanfelice RA, et al. Front Immunol. 2020;11:562264. Published 2020 Oct 27.

NIH Guidelines: Defining a COVID-19 Severity Spectrum

Stage	Characteristics
Asymptomatic or presymptomatic infection	▪ Positive test for SARS-CoV-2 but no symptoms
Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain) but no shortness of breath, dyspnea, abnormal imaging
Moderate illness	▪ $SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	▪ $SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	▪ Respiratory failure, septic shock, and/or multiorgan dysfunction

ANTIVIRALS

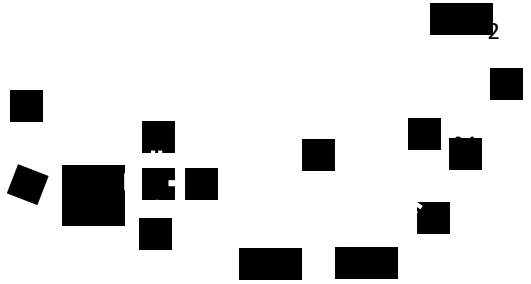
- REMDESIVIR
- No role for Lopinavir/r
- ?other agents
  - Favipiravir

FDA Approval: Remdesivir for Hospitalized Patients

- Remdesivir is a nucleoside analogue of ATP that inhibits SARS-CoV-2 RNA polymerase by competing with ATP for inclusion into nascent RNA→ delayed chain termination during viral RNA replication

FDA Indication

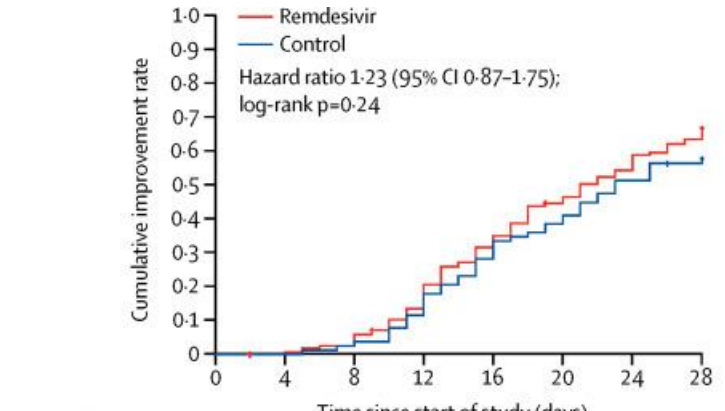
"…indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. [Remdesivir] should only be administered in a hospital or healthcare setting capable of providing acute care comparable to inpatient hospital care."



Remdesivir PI.

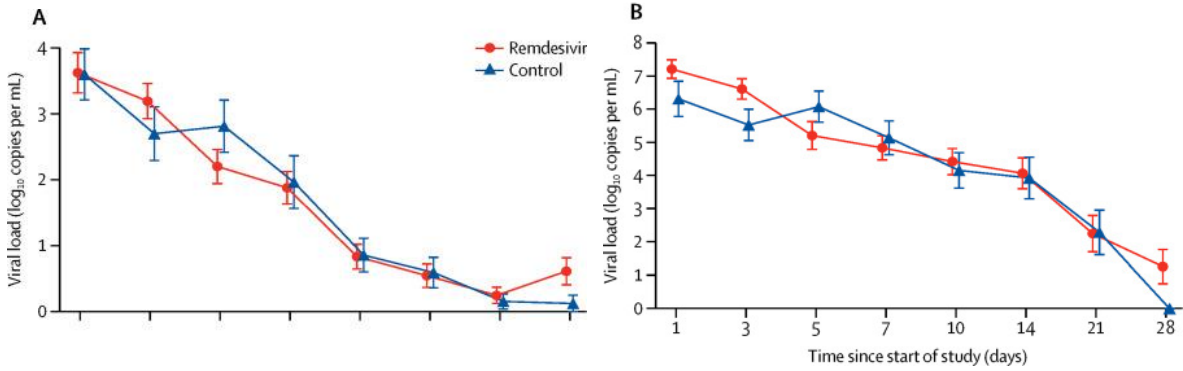
Remdesivir

- **Randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals (Wang et al, 2020)**
  - 237 hospitalized adult COVID-19 patients (158 to remdesivir and 79 to placebo)
  - 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions
  - Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids
  - Primary endpoint was time to clinical improvement up to day 28
  - Remdesivir use was not associated with a difference in time to clinical improvement
  - Patients receiving remdesivir had **a numerically faster time to clinical improvement** than those receiving placebo among patients with symptom duration of 10 days
  - AEs were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients
  - Constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin



URTI

LRTI



REMDESIVIR

- **Adaptive COVID-19 Treatment Trial (ACTT-1; Beigel et al., 2020)**
  - Double-blind, randomized, placebo-controlled trial
  - 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions
  - Patients who received remdesivir had a **31% faster time to recovery than those who received placebo (p<0.001).**
  - Median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo
  - Survival benefit, with a mortality rate of 7.1 % for the group receiving remdesivir versus 11.9% for the placebo group
- **Phase 3 SIMPLE trial evaluating** (Gilead Sciences, Inc.)
  - Patients receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a 5-day treatment course
  - Time to clinical improvement for 50% of patients was 10 days in the 5-day treatment group & 11 days in the 10-day treatment group
  - No new safety signals were identified with remdesivir across either treatment group
  - Early treatment during 1st 10 days of illness was associated with better outcomes (discharge rate 62% vs 49%)

	Overall*	
	Remdesivir (N=538)	Placebo (N=521)
Recovery		
No. of recoveries	334	273
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)
Rate ratio (95% CI)†	1.32 (1.12–1.55 [P<0.001])	
Mortality		
Hazard ratio (95% CI)	0.70 (0.47–1.04)	

FDA grant **remdesivir** emergency use for COVID-19 after ...
Medical News Today - May 7, 2020
According to the researchers, **remdesivir stops** the replication ... 2020, the **NIH**

FDA authorizes experimental drug **remdesivir** for emergency ...
The Verge - May 1, 2020
Under the authorization, the drug can be used to treat patients who are hospitalized with a severe enough case of the disease that they need to ...

Inside the **NIH's** controversial decision to **stop** its big ...
STAT - May 11, 2020
Inside the **NIH's** controversial decision to **stop** its big **remdesivir** study ... as is oft in the case in **clinical** trials — by turns secretive and bureaucratic. ... call on which they **decided** to change the measure that would be used.

REMDESIVIR

- nucleotide analogue that has activity against SARS-CoV-2 in vitro
- *EUA by the FDA for hospitalized children and adults with severe COVID-19 (SpO_2 ≤94 percent on room air, requiring supplemental oxygen, mechanical ventilation, or ECMO)*
- *200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or ECMO)*

  Contra-indications for use:

  elevated LFTs

  renal impairment

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G . Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269. Epub 2020 Feb 4.

Clinical Medicine Publish Ahead of Print, published on August 30, 2020 as doi:10.7861/clinmed.2020-0524

COVID-19 RAPID REPORT Clinical Medicine 2020 Vol 20, No 6 November 2020

REMDESIVIR: SUMMARY

Antiviral treatment for COVID-19: the evidence supporting remdesivir

Authors: Charlotte Richardson,[A] Sanjay Bhagani,[B] and Gabriele Pollara[C]

- *The first randomized clinical trial, involving 237 patients with severe COVID-19 in 10 hospitals in Hubei, China, found no statistically significant clinical benefits to remdesivir.*

- The ACTT-1 study, involving 1063 patients, found that remdesivir was superior to placebo in shortening the time to recovery by 4 days compared with placebo in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection.

- The preliminary results of the Adaptive Covid-19 Treatment Trial (ACTT-1) international randomized controlled trial demonstrated a significant reduction in median time to recovery of 4 days with remdesivir compared to placebo in hospitalized patients requiring supplemental oxygen. No significant effect on mortality was observed.
- An international randomized trial of treatment duration demonstrated no difference in clinical outcomes between 5- and 10-day courses of remdesivir.
- Remdesivir is administered intravenously and has been shown to be well tolerated, with the most common adverse events being anemia, deranged liver function tests, impaired renal function and hyperglycemia.
- Remdesivir received a conditional marketing authorization for use in the EU from the European Medicines Agency on 3 July 2020, applicable in the UK during the post-Brexit transition period. An interim clinical commissioning policy is in place.
- Current limitations include IV formulation and contraindication in renal impairment and patients with liver enzyme elevation >
- Ongoing studies are investigating the combination of remdesivir and various immunomodulatory agents, use of alternative formulations and use in early mild/moderate COVID-19

IMMUNE MODULATORS

- 1- STEROIDS
- 2- IL-6 INHIBITORS

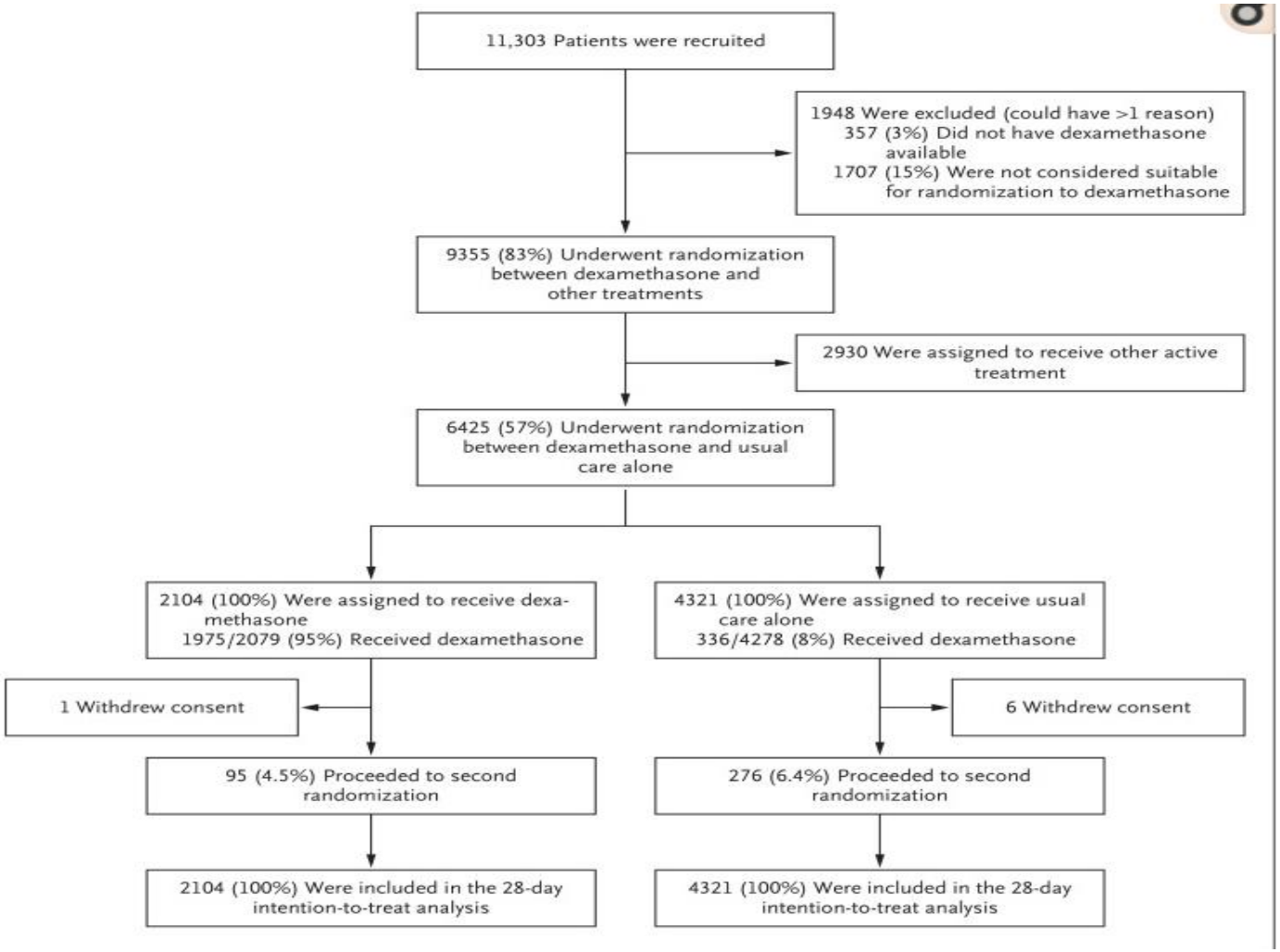
ROLE OF STEROIDS

- DEXAMETHASONE
  - **RECOVERY TRIAL RCT**
    - 2104 patients received DEXA
    - 4321 patients received usual care
  - severely ill patients who are on supplemental oxygen or ventilator support
  - 6mg per day for 10 days
    - 17% reduction in mortality overall
      - Reduction in mortality greater in more severe ill
      - Patients on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at baseline – 36 % RR

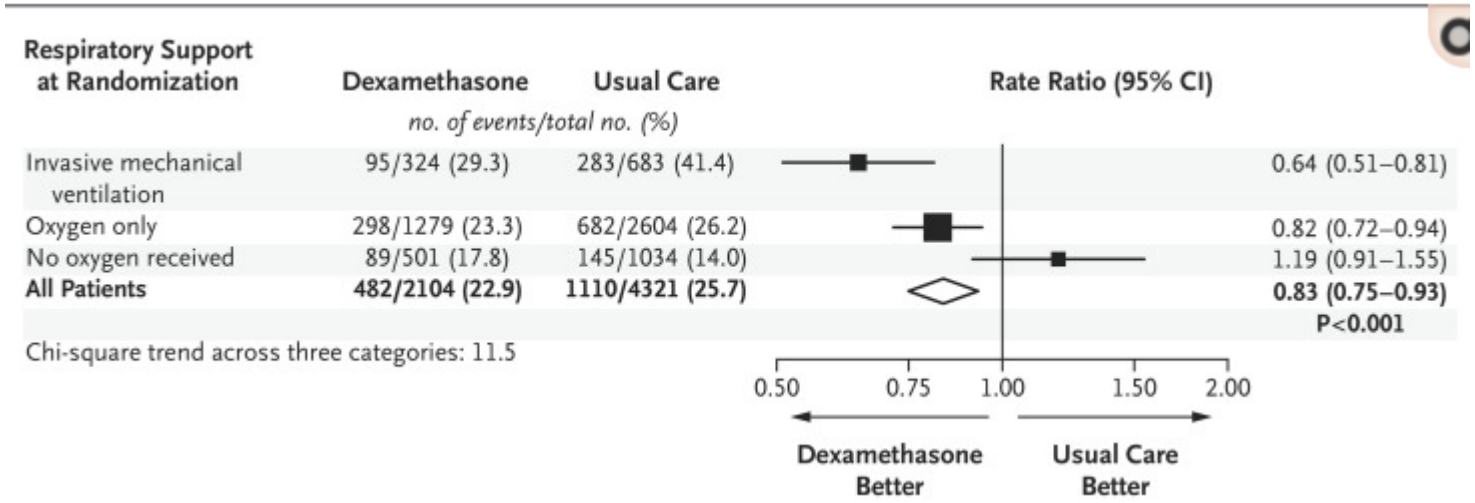
RECOVERY
Randomised Evaluation of COVID-19 Therapy

RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 N Engl J Med. 2020;NEJMoa2021436.

RECOVERY TRIAL



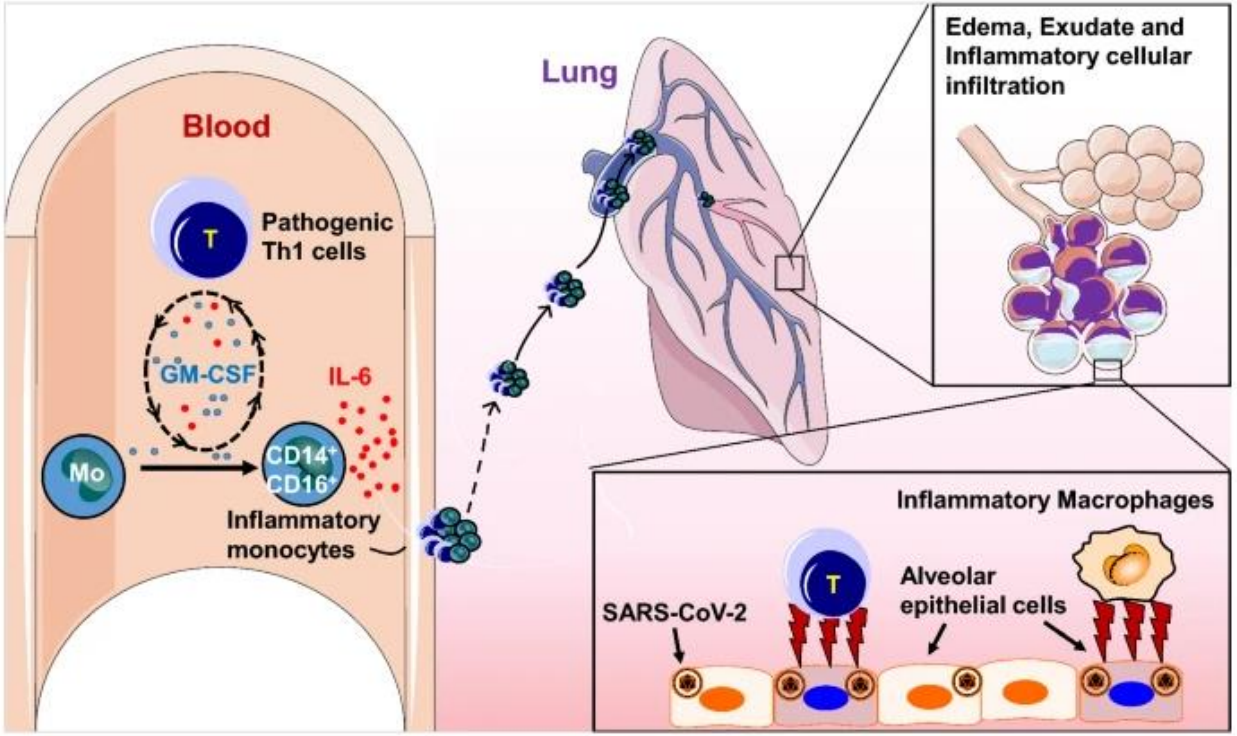
RECOVERY TRIAL RESULTS



Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

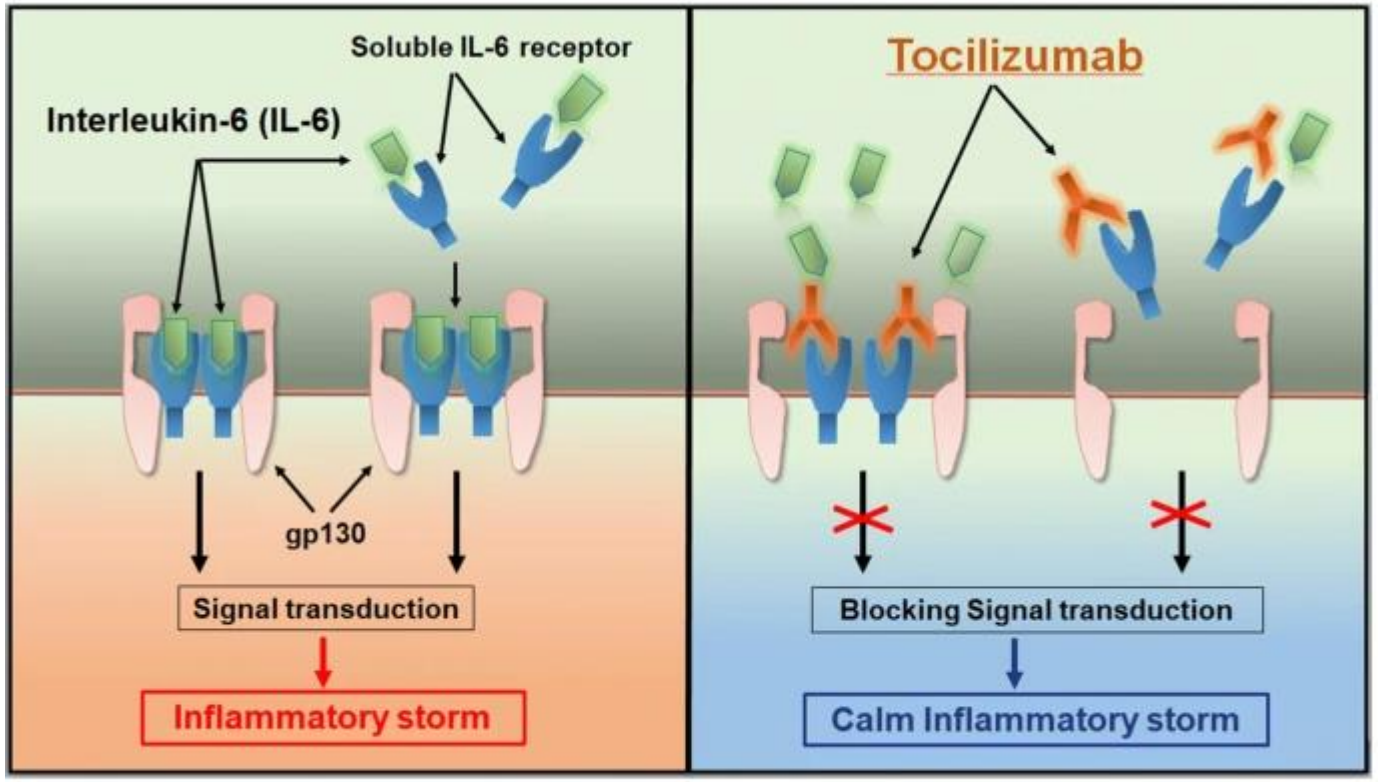
WHY TOCILIZUMAB COULD BE AN EFFECTIVE TREATMENT FOR SEVERE COVID-19?



Pathogenic T cells and inflammatory monocytes with high IL-6 secretion may enter the pulmonary circulation in large numbers,incite the inflammatory storm and lead an immune disorder in severe COVID-19 patients

Fu. J Translational Medicine. 2020;18:164.

ANTI–IL-6 RCEPTORS

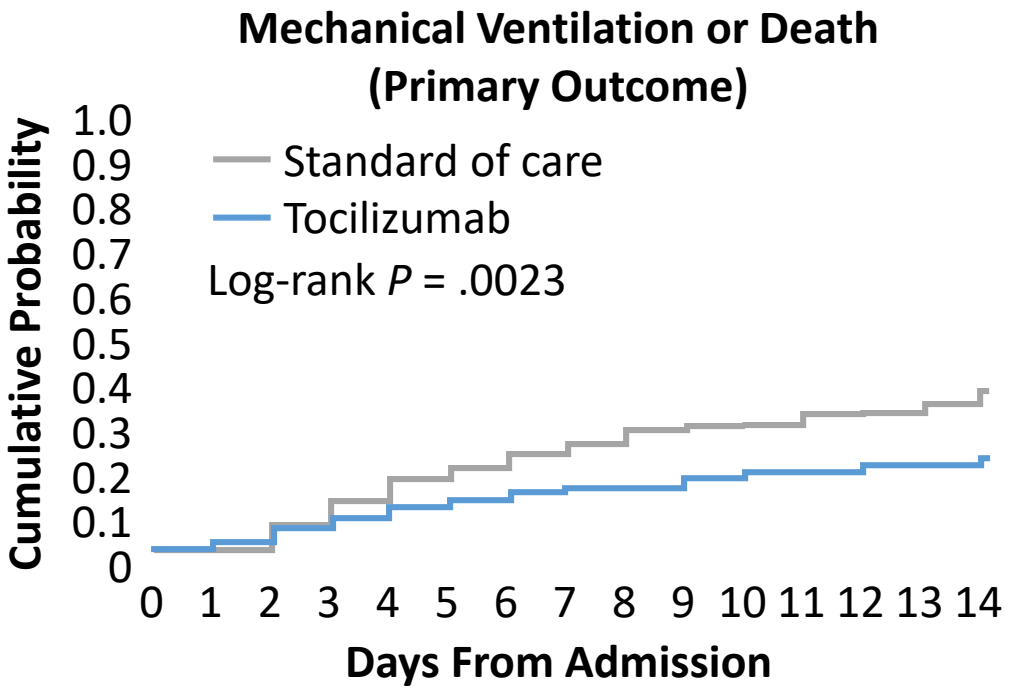


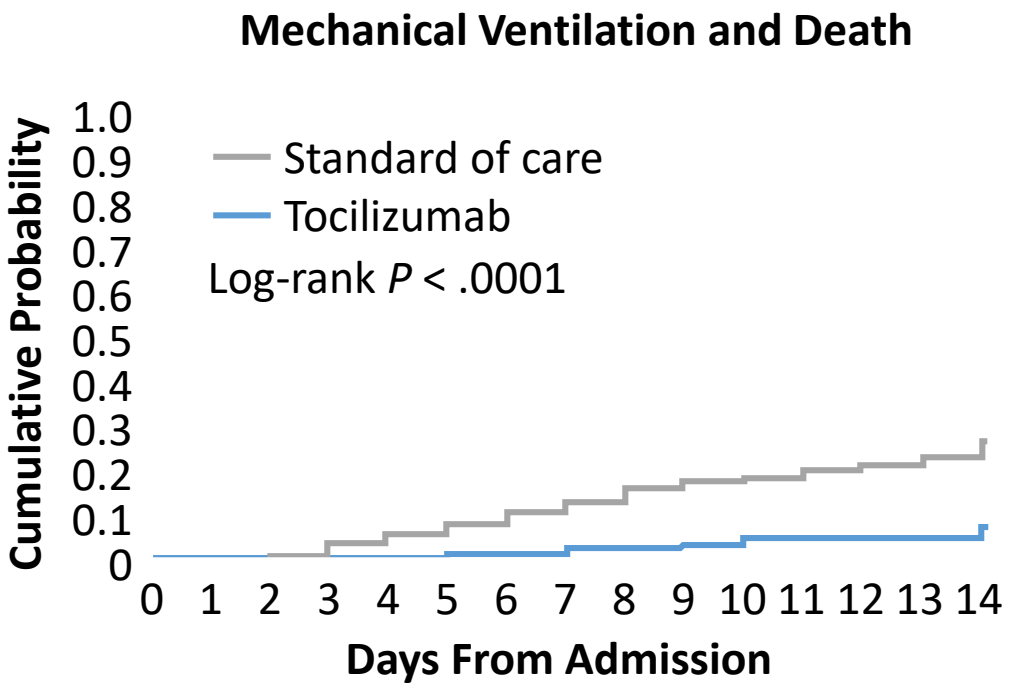
Tocilizumab calms the inflammatory storm through blocking IL-6 receptors

Fu. J Translational Medicine. 2020;18:164.

TESEO Cohort: Tocilizumab to Treat Severe COVID-19 in Italy

- Retrospective, observational, cohort study of adults with severe COVID-19 pneumonia admitted to tertiary care centers in **Italy between February and March 2020** who received tocilizumab plus standard of care (n = 179) vs standard of care alone (n = 365)
  - Tocilizumab: 8 mg/kg via 2 infusions 12 hrs apart or 162 mg SQ in each thigh (324 mg total) when IV formulation unavailable



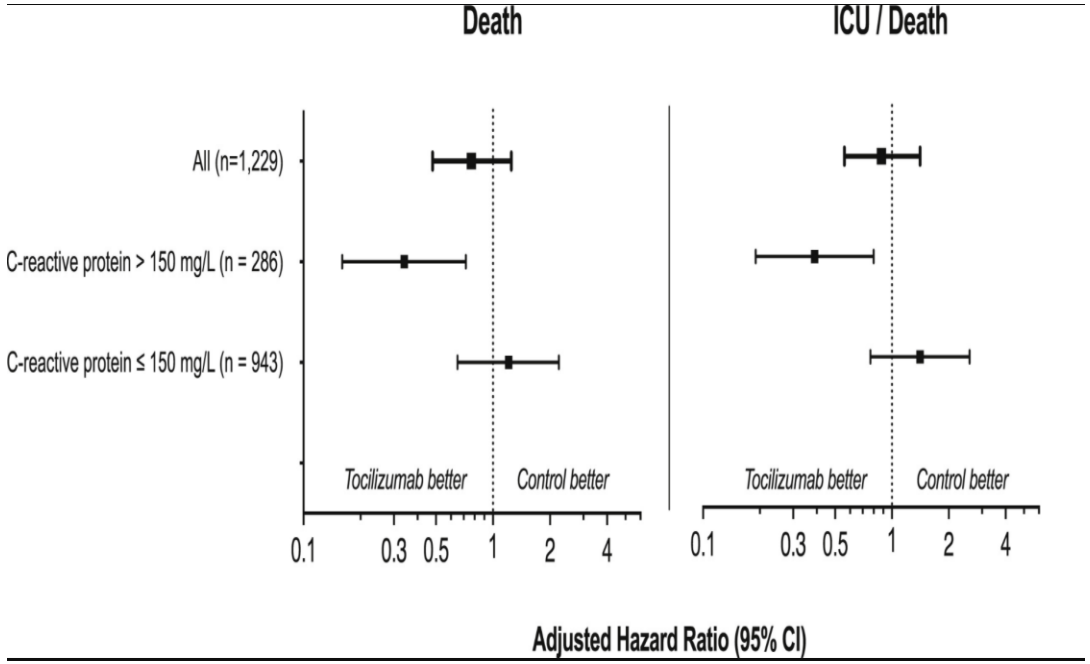


Guarlandi. Lancet Rheumatology. 2020;20:30173.

Slide credit: clinicaloptions.com

Cohort Study of Tocilizumab to Treat Severe COVID-19 in Spain

- Retrospective, observational, cohort study of patients hospitalized with COVID-19 who received tocilizumab (n = 260) vs no tocilizumab (n = 969)
  - Tocilizumab: median total dose of 600 mg
- **Tocilizumab associated with decreased risk of death** (aHR: 0.34; 95% CI: 0.16-0.72; *P* = .005) **and ICU admission or death** (aHR: 0.38; 95% CI: 0.19-0.81; *P* = .011) in patients with baseline CRP > 150 mg/L
  - No association among patients with CRP ≤ 150 mg/L

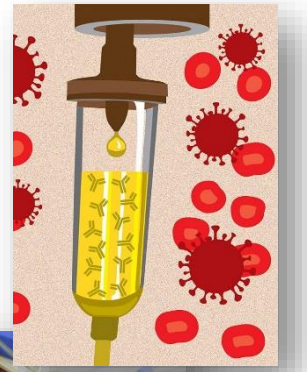


***Adjusted for sex, age, comorbidities (HTN, diabetes, ischemic heart disease, chronic kidney disease, congestive heart failure, lung disease), oxygen use at baseline, oxygen saturation, and time-varying parameters of severity (BP, heart rate, lymphocyte/neutrophil count, LDH, ALT, urea, D-dimer, and CRP.**

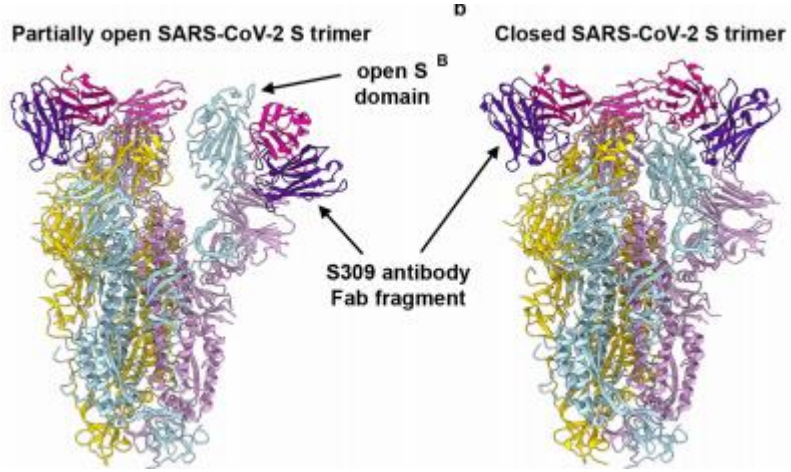
Martínez-Sanz j ET AL. Clinical Microbiology and Infection, 2020, ISSN 1198-743X, https://doi.org/10.1016/j.cmi.2020.09.021.

Slide credit: clinicaloptions.com

Convalescent plasma



- Used in other infectious diseases such as influenza, Ebola, measles, SARS, etc.
- Two small case series reported improvement in oxygenation, sequential organ failure assessment (SOFA) scores, and eventual ventilator weaning in some patients
  - One dose (200 mL) of CP was well tolerated and could significantly increase or maintain the neutralizing antibodies at a high level, leading to disappearance of viremia in 7 d
  - Timelines of improvement varied from days to weeks
- Retrospectively controlled study in Mt Sinai showed improved oxygen requirements at day 14
  - 12.8% of plasma recipients (n=39) and 24.4% of the 1:4 matched control patients had died (not significant)
- S309 mAb recovered from SARS patient cross neutralizes SARS-CoV-2



Shen et al. JAMA 2020; Duan et al. PNAS 2020; Liu et al medRxiv 2020; Pinto et al. Nature 2020;

Original Investigation

June 3, 2020

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19

A Randomized Clinical Trial

Ling Li, MD, PhD[1,2]; Wei Zhang, MD[3,4]; Yu Hu, MD, PhD[5]; et al

Results

Of **103 patients** who were randomized (median age, 70 years; 60 [58.3%] male), 101 (98.1%) completed the trial. Clinical improvement occurred within 28 days in 51.9% (27/52) of the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, −10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; P = .26). Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P = .03); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the convalescent plasma group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; P = .83) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.59 [95% CI, 0.22-1.59]; P = .30) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.95]; P = .12). Convalescent plasma treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; P < .001). Two patients in the convalescent plasma group experienced adverse events within hours after transfusion that improved with supportive care.

Conclusion and Relevance Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference.

ORIGINAL ARTICLE

Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients

Abstract

Objective: To provide an update on key safety metrics after transfusion of convalescent plasma in hospitalized coronavirus 2019 (COVID-19) patients, having previously demonstrated safety in 5000 hospitalized patients.

Patients and Methods: From April 3 to June 2, 2020, the US Food and Drug Administration Expanded Access Program for COVID-19 convalescent plasma transfused a convenience sample of 20,000 hospitalized patients with COVID-19 convalescent plasma.

Results: The incidence of all serious adverse events was low; these included transfusion reactions (n=78; <1%), thromboembolic or thrombotic events (n=113; <1%), and cardiac events (n=677, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=75) and cardiac events (n=597) were judged to be unrelated to the plasma transfusion per se. The 7-day mortality rate was 13.0% (12.5%, 13.4%), and was higher among more critically ill patients relative to less ill counterparts, including patients admitted to the intensive care unit versus those not admitted (15.6 vs 9.3%), mechanically ventilated versus not ventilated (18.3% vs 9.9%), and with septic shock or multiple organ dysfunction/failure versus those without dysfunction/failure (21.7% vs 11.5%).

Conclusion: These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

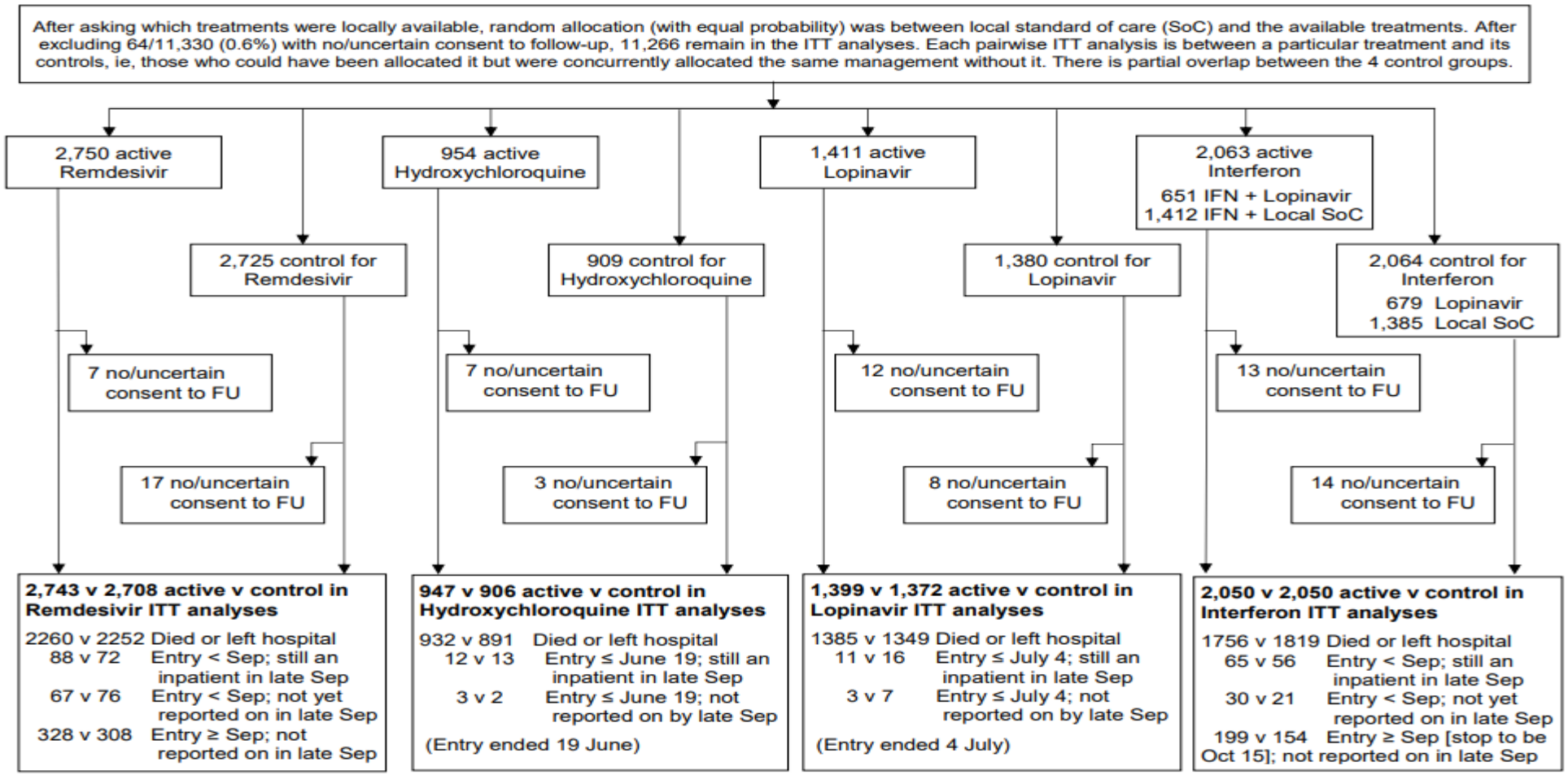
MedRxiv (October 15) version

Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*

*A complete list of SOLIDARITY Trial investigators is provided in the Supplementary Appendix.

Figure 1. WHO Solidarity Trial – information to October 4, 2020 on entry, follow-up (FU) and intent-to-treat (ITT) analyses



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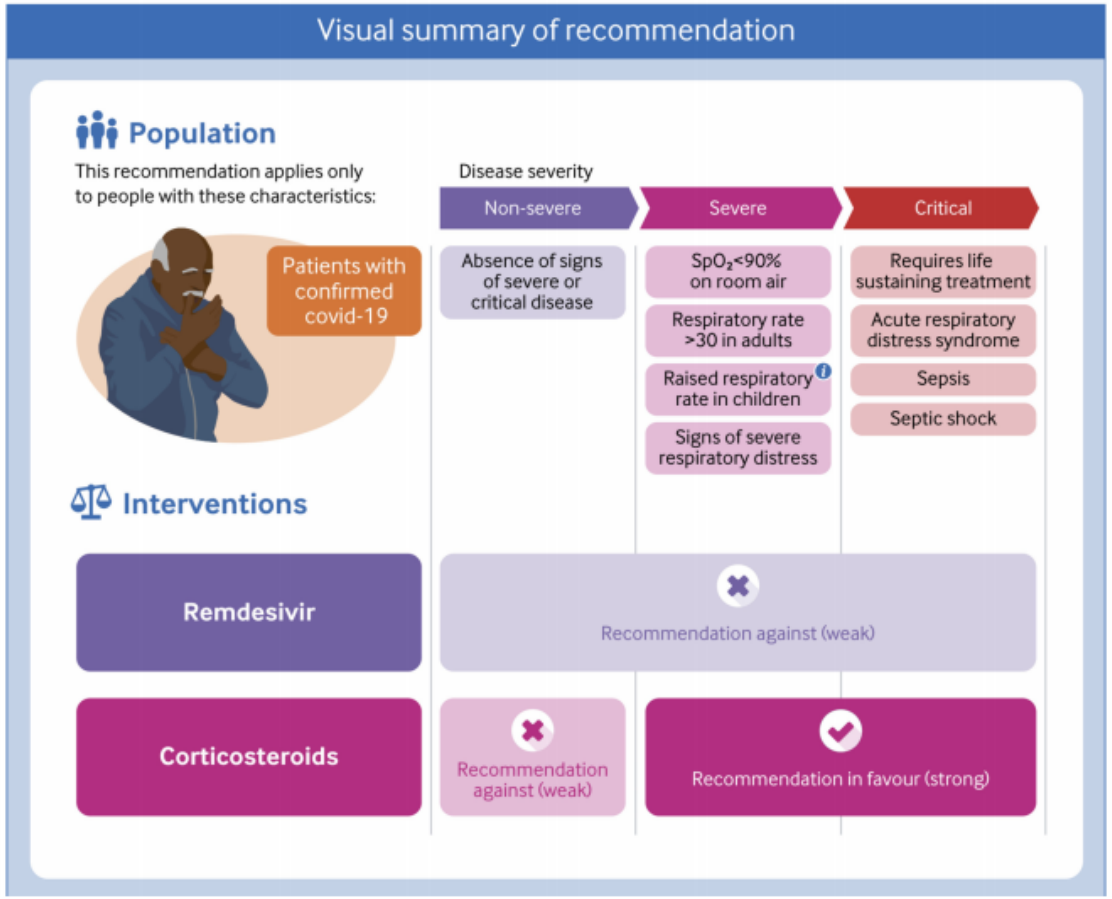
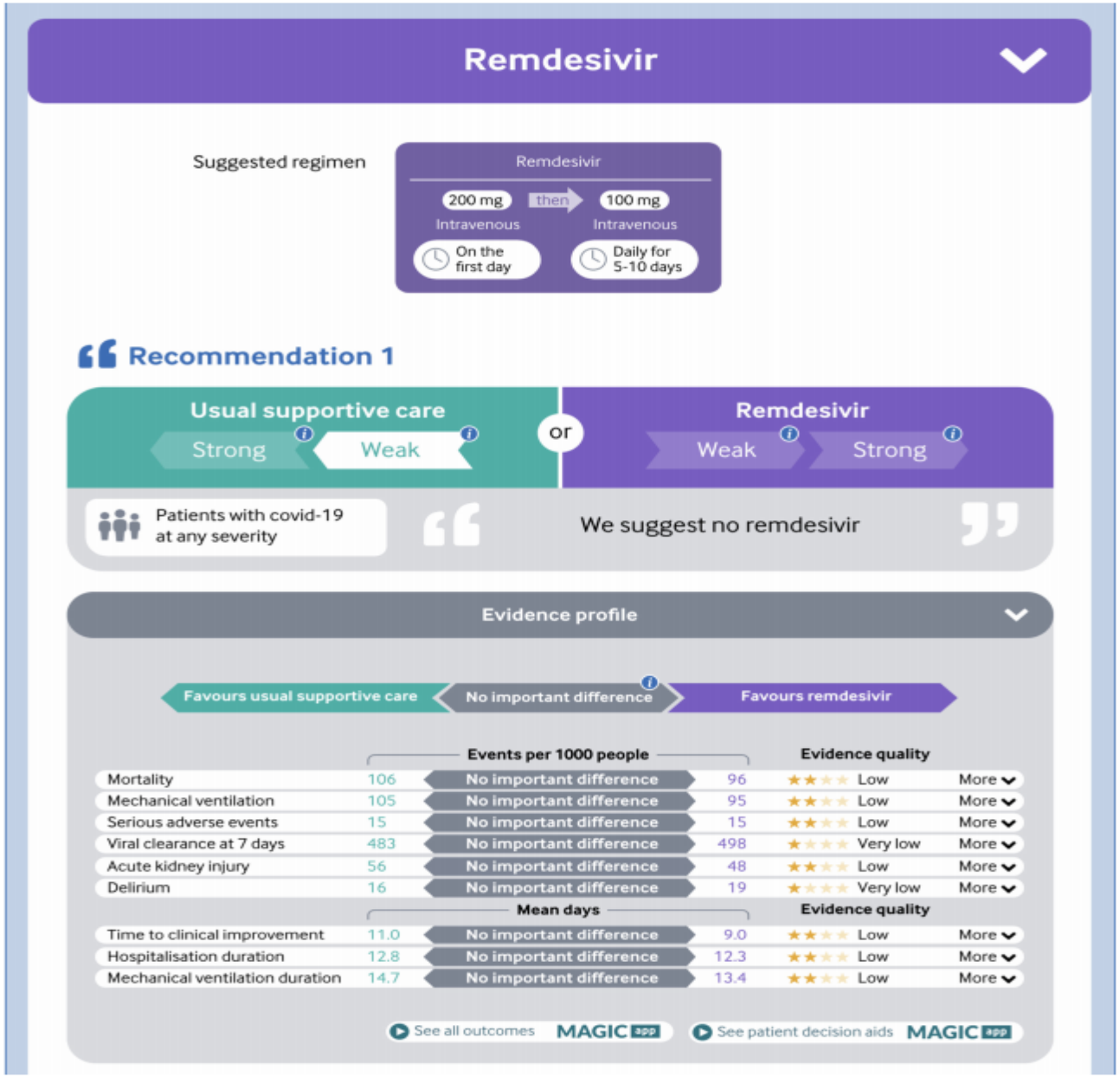
Moderate illness	▪ $SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	▪ $SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	▪ Respiratory failure, septic shock, and/or multiorgan dysfunction

A living WHO guideline on drugs for covid-19

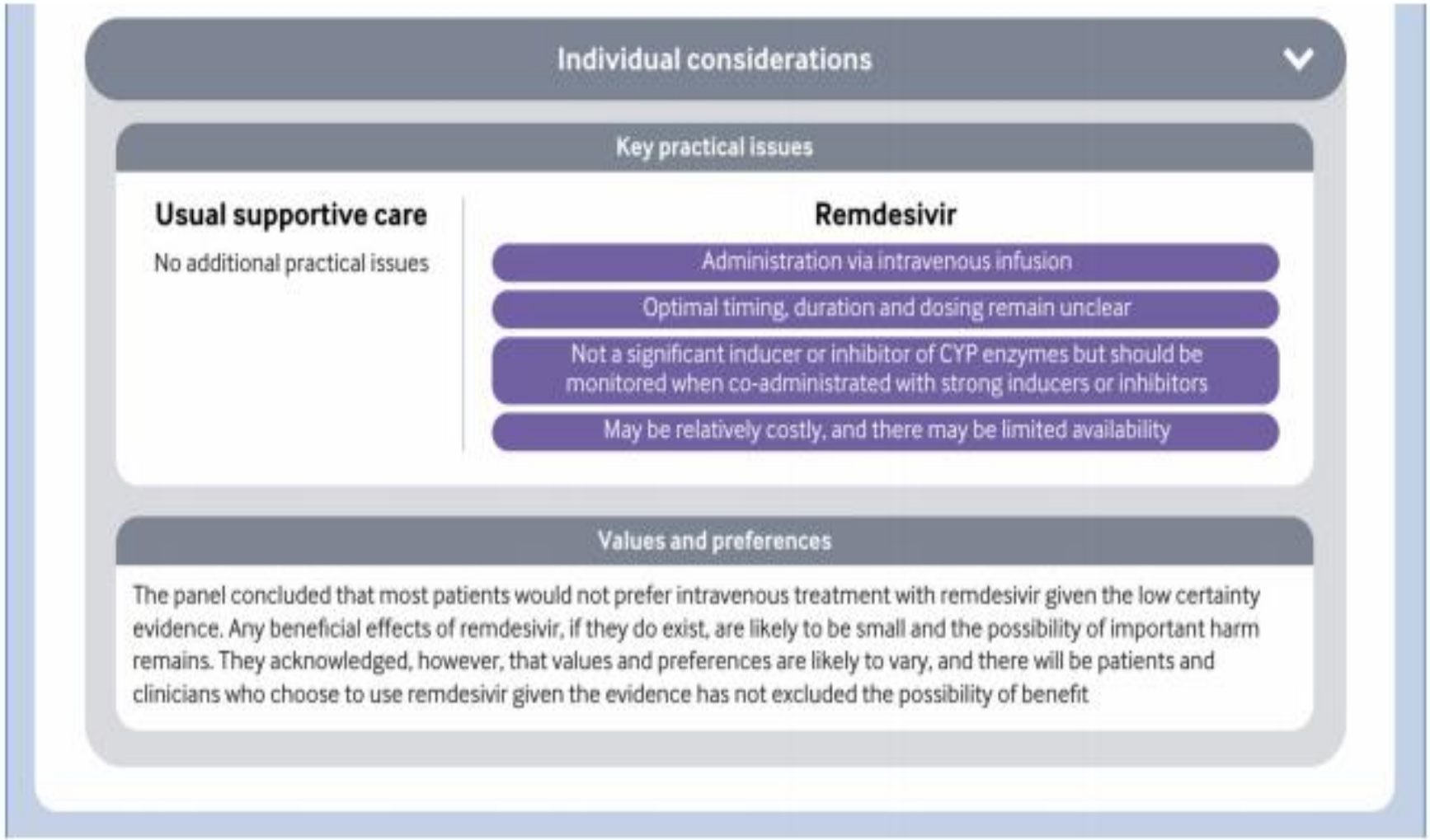
BMJ 2020 ; 370 doi: https://doi.org/10.1136/bmj.m3379 (Published 04 September 2020)
Cite this as: *BMJ* 2020;370:m3379



Rochwerg Bram, Agoritsas Thomas, Lamontagne François, Leo Yee-Sin, Macdonald Helen, Agarwal Arnav et al. A living WHO guideline on drugs for covid-19 BMJ 2020; 370 :m3379



Rochwerg Bram, Agoritsas Thomas, Lamontagne François, Leo Yee-Sin, Macdonald Helen, Agarwal Arnav et al. A living WHO guideline on drugs for covid-19 BMJ 2020; 370 :m3379



Rochwerg Bram, Agoritsas Thomas, Lamontagne François, Leo Yee-Sin, Macdonald Helen, Agarwal Arnav et al. A living WHO guideline on drugs for covid-19 BMJ 2020; 370 :m3379

Corticosteroids

Corticosteroids

Suggested regimen

Acceptable alternative regimens

Dexamethasone	Hydrocortisone	Methylprednisolone	Prednisone
6 mg	50 mg	10 mg	40 mg
Oral or intravenous	Intravenous	Intravenous	Oral
Daily for 7-10 days	Every 8 hours for 7-10 days	Every 6 hours for 7-10 days	Daily for 7-10 days

Recommendation 1

Usual supportive care		or	Corticosteroids	
Strong	Weak		Weak	Strong

Patients with severe and critical covid-19

We recommend corticosteroids

Evidence profile

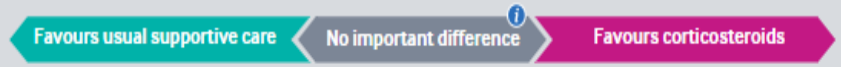
Favours usual supportive care | No important difference | Favours corticosteroids

	Events per 1000 people			Evidence quality	
Mortality with critical illness	415	87 fewer	328	★★★☆ Moderate	More
Mortality with severe illness	334	67 fewer	267	★★★☆ Moderate	More
Gastrointestinal bleeding	48	No important difference	51	★★☆☆ Low	More
Superinfections	186	No important difference	188	★★☆☆ Low	More
Hyperglycaemia	286	46 fewer	332	★★★☆ Moderate	More
Neuromuscular weakness	69	No important difference	75	★★☆☆ Low	More
Neuropsychiatric effects	35	No important difference	28	★★☆☆ Low	More

Critically ill: See all outcomes MAGIC app

Severely ill: See all outcomes MAGIC app

Evidence profile



	Events per 1000 people			Evidence quality	
Mortality with non-severe illness	176	39 fewer	215	★★☆☆ Low	More

Non-severely ill

See all outcomes MAGIC app See patient decision aids MAGIC app

Individual considerations

Key practical issues

Usual supportive care

No additional practical issues

Corticosteroids

In order to help guarantee access to therapy for severe and critical covid-19 patients, it is reasonable to avoid administering corticosteroids to patients who are less likely to derive benefit

Values and preferences

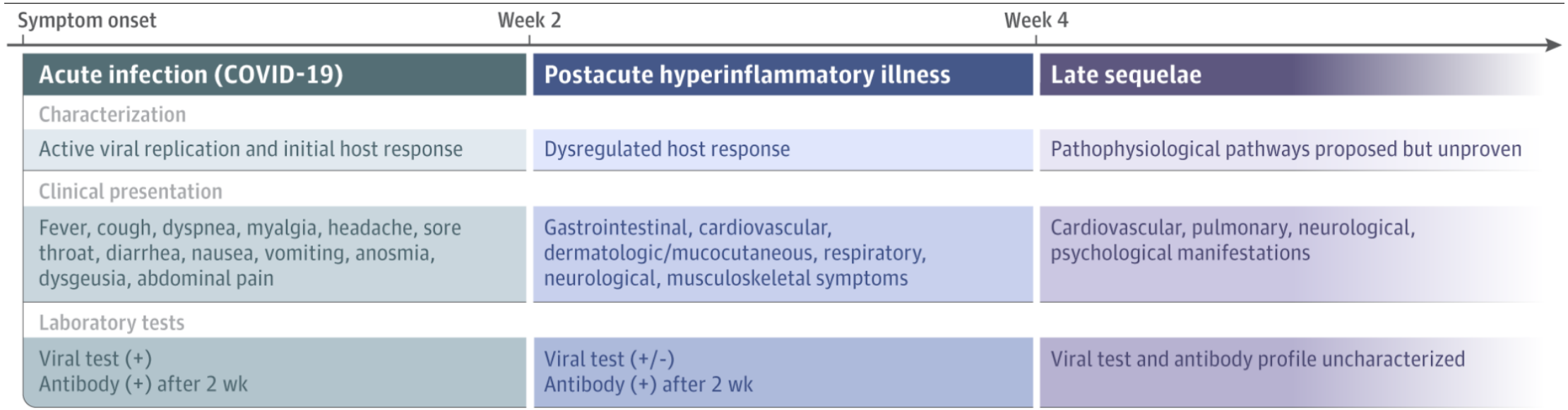
The panel inferred that most fully informed individuals with non-severe illness would not want to receive corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician. When treating patients with non-severe disease, even after 7 days of symptoms, the panel concluded that it was preferable to err on the side of no corticosteroids

November 18, 2020

A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection

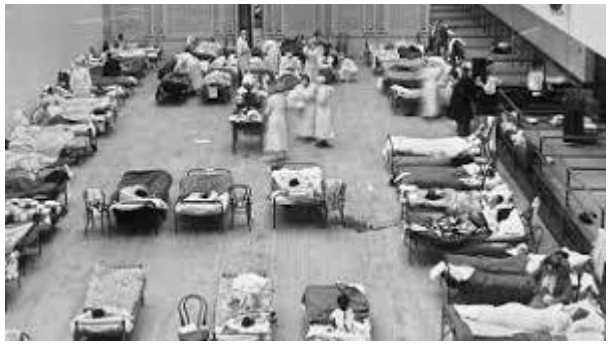
Illness Beyond Acute Infection and Public Health Implications

S. Deblina Datta, MD[1]; Amish Talwar, MD, MPH[1]; James T. Lee, MD, MSc[1,2]



Datta SD, Talwar A, Lee JT. JAMA. Published online November 18, 2020. doi:10.1001/jama.2020.22717

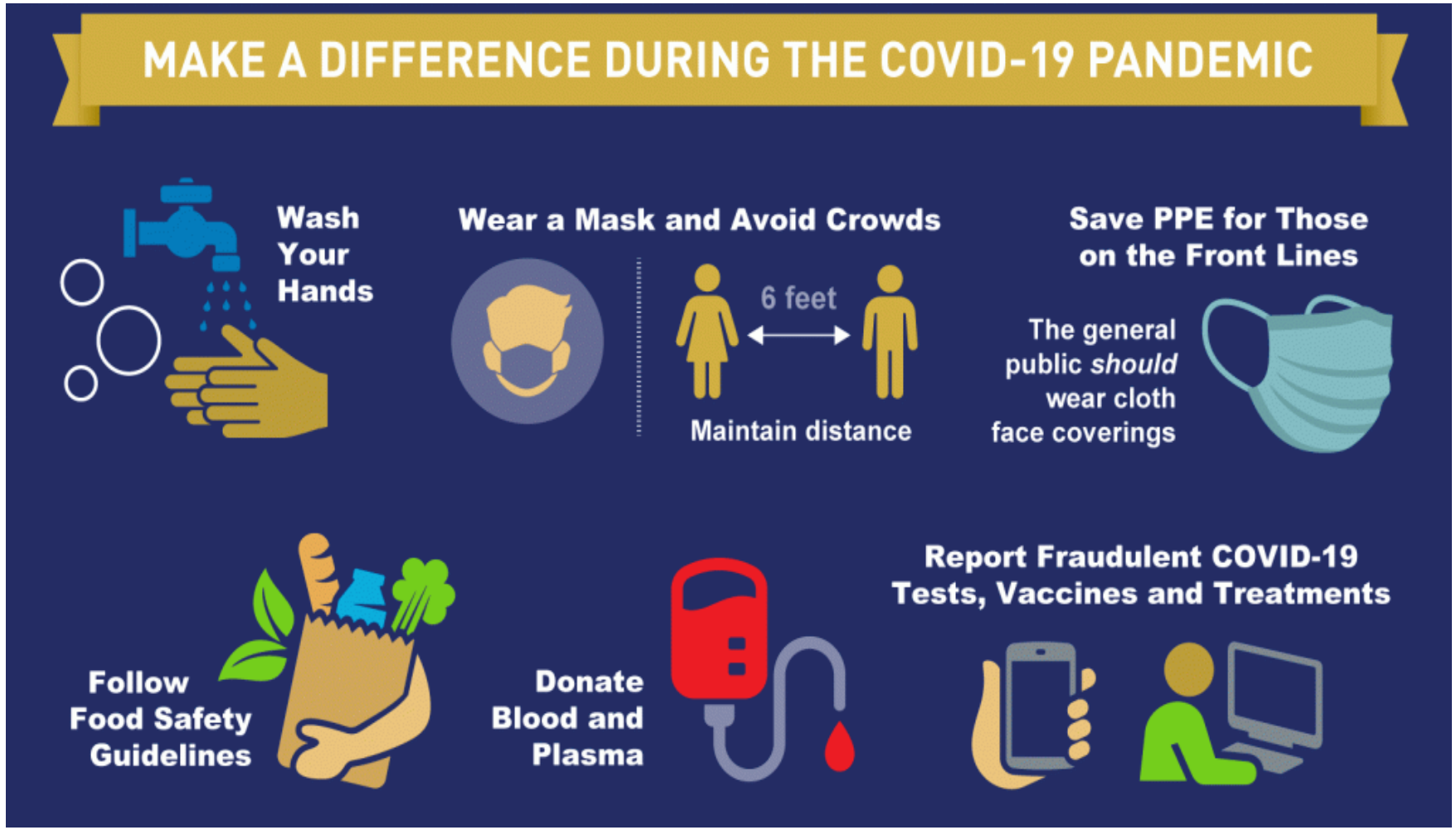
ADDITIONAL CONSIDERATIONS



- LONG COVID-19??
- BURDEN OF CO-INFECTIONS
- DURATION OF IMMUNITY
- RE-INFECTION
- ROLE OF VACCINES

- IS THERE AN END TO THE PANDEMIC?

UNTIL THEN……


MAKE A DIFFERENCE DURING THE COVID-19 PANDEMIC
Wash Your Hands
Wear a Mask and Avoid Crowds
6 feet
Maintain distance
Save PPE for Those on the Front Lines
The general public *should* wear cloth face coverings
Follow Food Safety Guidelines
Donate Blood and Plasma
Report Fraudulent COVID-19 Tests, Vaccines and Treatments

THANK YOU

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