Medical University of Graz

COVID-19
Medikamentöse antivirale u. antiinflammatorische Therapie

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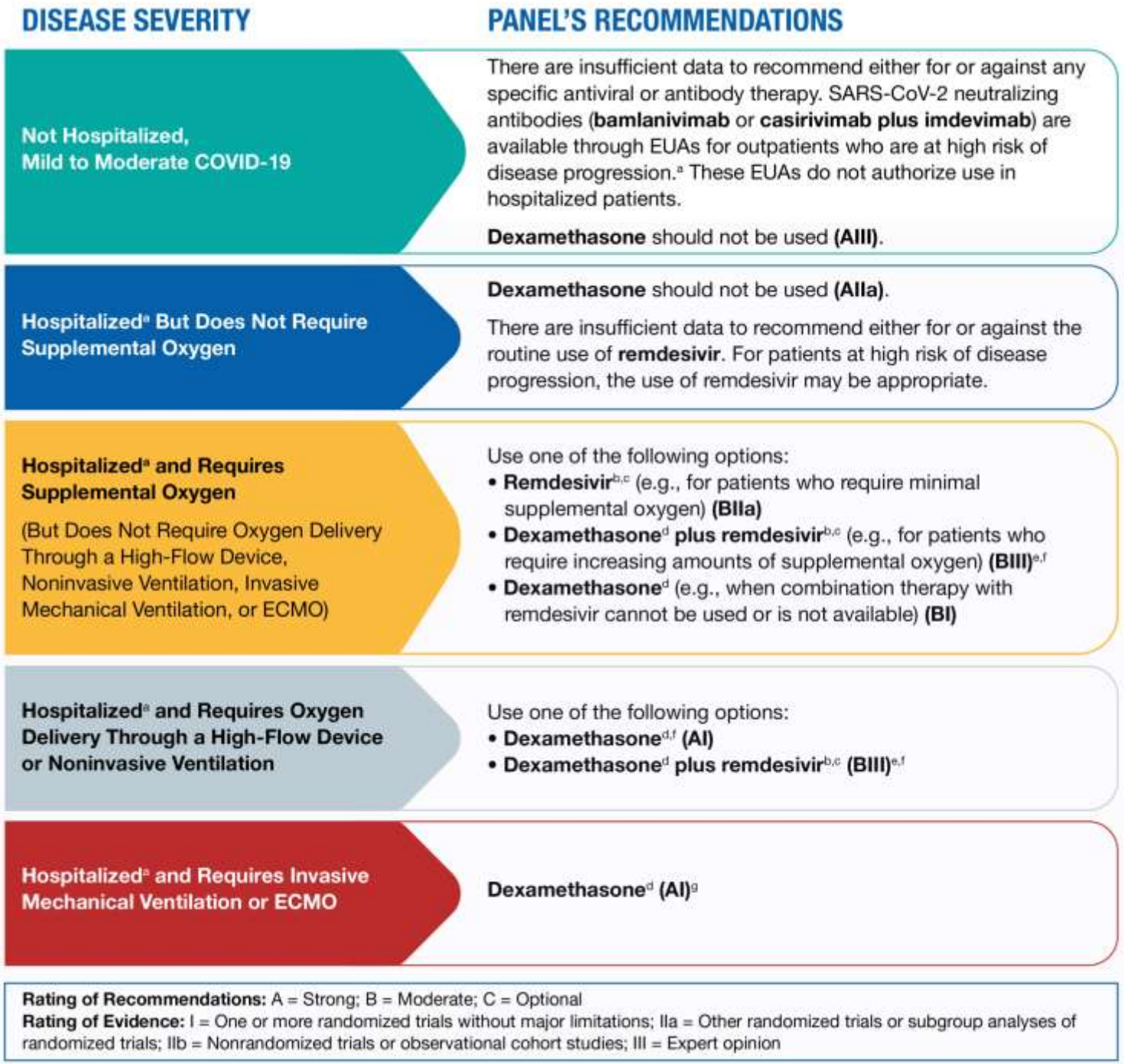
Proposed COVID-19 Treatments

- Hydroxychloroquin
- Azithromycin
- Ivermectin
- Doxycyclin…

- Remdesivir
- Lopinavir/Ritonavir
- Favipiravir

- anti-inflammatory treatment (IL1, IL 6 Inhibitors, Dexamethason…)

- Plasma therapy, Antibodies…



NIH, USA

- Dexamethason
- Remdesivir

https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

Overview of IDSA COVID-19 Treatment Guidelines

Version 3.5.1 – December 2, 2020

		Setting and severity of illness			
		Ambulatory care: *mild-to-moderate disease*	***Hospitalized:*** *mild-to-moderate disease without need for suppl. oxygen*	***Hospitalized:*** *severe but non-critical disease (spO_2 <94% on room air)*	***Hospitalized:*** *critical disease (e.g., in ICU needing MV, or septic shock, ECMO)*
1	*Hydroxy-chloroquine (HCQ)**	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
2	*HCQ* + azithromycin*	NA	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯
3	*Lopinavir + ritonavir*	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
4-6	*Corticosteroids*	NA	**Suggest against use** ⊕◯◯◯	**Suggest use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**	**Recommend use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**
7	*Tocilizumab*	NA	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯
8	*Convalescent plasma*	NA	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)
9-11	*Remdesivir*	NA	**Suggest against routine use** ⊕◯◯◯	**Suggest use** ⊕⊕◯◯ R: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.	**Suggest use** ⊕⊕⊕◯ R: For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.
12	*Famotidine*	NA	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯
13	*Bamlanivimab*	**Suggest against routine use** ⊕◯◯◯ R: In patients at increased risk*** bamlanivimab is a reasonable treatment option if, after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain adverse events.	NA	NA	NA

IDSA, USA

- Corticosteroids
- Remdesivir

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

A living WHO guideline on drugs for covid-19

- We **recommend systemic corticosteroids** rather than no systemic corticosteroids for the treatment of patients with **severe and critical covid-19** (strong recommendation)
- We suggest **not to use corticosteroids** in the treatment of patients with **non-severe covid-19** (weak or conditional recommendation)

- We suggest **against administering remdesivir** in addition to usual care for the treatment of patients hospitalised with covid-19 regardless of disease severity (weak or conditional recommendation).

- We recommend **against using hydroxychloroquine** or chloroquine in addition to usual care for the treatment of patients with covid-19, regardless of disease severity or duration of symptoms (strong recommendation)
- We recommend **against using lopinavir-ritonavir** in addition to usual care for the treatment of patients with covid-19 regardless of disease severity (strong recommendation)

Siemieniuk R, Rochwerg B. BMJ 2020;370:m3379

Medikamentöse Therapie COVID-19

	NIH	IDSA	WHO
Corticosteroids	+	+	+
Remdesivir	+	+	-
Bamlanivimab or others	(+)	(-)	?

Recovery trial – Dexamethason in COVID-19

- Dexamethasone 2104 patients vs. Placebo 4321 patients
  - 8% of usual care (placebo) patients received dexamethasone as part of their clinical care

- Dexamethasone 6mg iv or po 10 days
- Respiratory support
  - 16% invasive mechanical ventilation or extracorporeal membrane oxygenation
  - 60% oxygen only (with or without noninvasive ventilation)
  - 24% no respiratory support

NEJM 2020 DOI: 10.1056/NEJMoa2021436

Recovery trial – Dexamethason in COVID-19

- Dexamethasone vs Placebo
  - **death rate lower** among patients receiving **invasive mechanical ventilation**
    - 29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81)
  - **death rate lower** among patients **receiving oxygen** without invasive mechanical ventilation
    - 23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94
  - **no difference** in patients receiving **no respiratory support** at randomization
    - 17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55

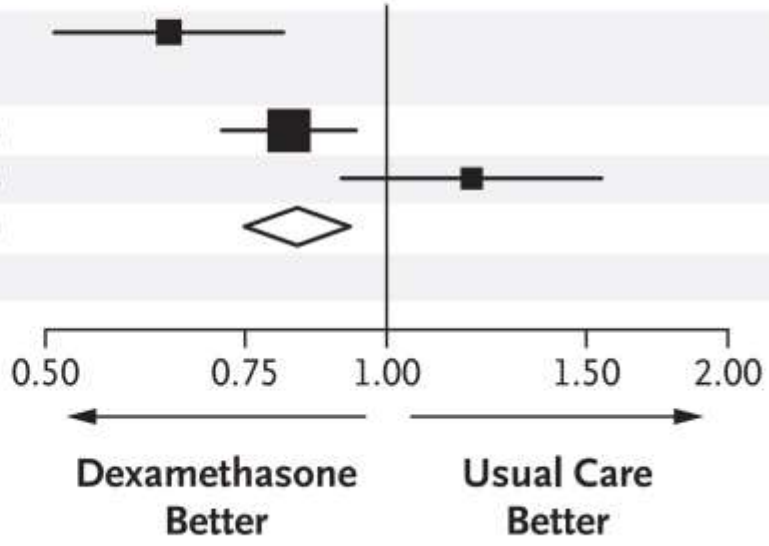
NEJM 2020 DOI: 10.1056/NEJMoa2021436

Recovery trial – Dexamethason in COVID-19

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

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5



NEJM 2020 DOI: 10.1056/NEJMoa2021436

Early Short-Course Corticosteroids in 213 **Hospitalized Patients** With COVID-19 (moderate and severe)

- Corticosteroid use
  - 56.8% in SOC
  - 68.2% in early corticosteroid group (P = .094) (methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days)
- within 48 hours of presentation
  - 12.4% in SOC
  - 41.7% in early corticosteroid group (P < .001)
- median time to initiation
  - 5 days (IQR: 3–7, range 1–9) in SOC
  - 2 days (IQR: 1–3, range 0–8) in early corticosteroid group
- endpoint (clinical deterioration) early corticosteroid group compared to the SOC group
  - 54.3% in SOC
  - 34.9% early corticosteroid group (P = .005)

Fadel.CID 2020;71(16):2114-20

Remdesivir ACTT study

- Adaptive Covid-19 Treatment Trial (ACTT-1)
- Pt inclusion February 21, 2020, until April 19, 2020
- United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1)

- Remdesivir 1x200mg d1, 1x100mg d2-10; or Placebo

- severe disease
  - mechanical ventilation
  - supplemental oxygen required
  - Spo2 ≤94% (room air)
  - tachpnoea ≥24 breaths per minute

Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study

- **primary outcome** was the time to recovery
- defined as the first day, during the 28 days after enrollment, on which a patient met the criteria for category 1, 2, or 3
  - =discharge or hospitalization for infection-control purposes only

Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study

- **primary outcome** was the time to recovery
- defined as the first day, during the 28 days after enrollment, on which a patient met the criteria for category 1, 2, or 3 (=discharge or hospitalization for infection-control purposes only)

- 1, not hospitalized and no limitations of activities
- 2, not hospitalized, with limitation of activities, home oxygen requirement, or both
- 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons)

- 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions)
- 5, hospitalized, requiring any supplemental oxygen
- 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices
- 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- 8, death

Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study

- several **secondary outcomes**
- clinical status at day 15
  - initially this was the primary outcome
  - changed to secondary outcome in April 2020

Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study

- 1062 pts
- 36% female, 64% male
  - 541 remdesivir
  - 521 placebo group
- 159 (15.0%) mild-to-moderate disease
- 903 (85.0%) severe disease

- median number of days between symptom onset and randomization was 9 (interquartile range, 6 to 12)

Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study

Overall

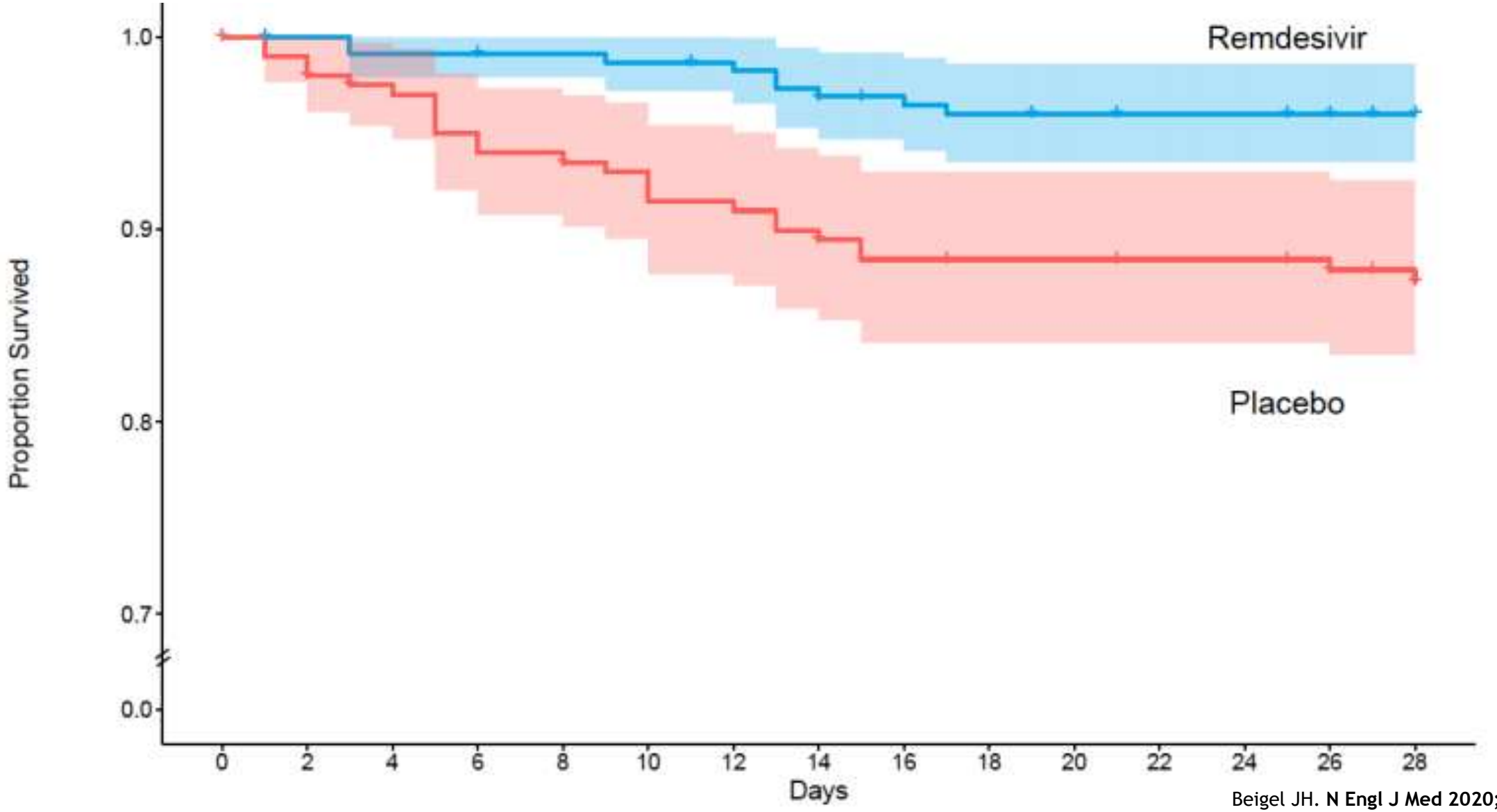
	Remdesivir (N=541)	Placebo (N=521)
Recovery		
No. of recoveries	399	352
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])	
Mortality through day 14‡		
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)	
No. of deaths by day 15	35	61
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)
Mortality over entire study period‡		
Hazard ratio (95% CI)	0.73 (0.52–1.03)	
No. of deaths by day 29	59	77
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)

10 days vs 15 days

Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study, survival

Baseline score 5 → hospitalized, requiring any supplemental oxygen



Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study

- Kaplan–Meier estimates of mortality
  - by day 15 were 6.7% (remdesivir) and 11.9% (placebo)
    - hazard ratio, 0.55; 95% CI, 0.36 to 0.83
  - by day 29 were 11.4% (remdesivir) and 15.2% (placebo)
    - hazard ratio, 0.73; 95% CI, 0.52 to 1.03

- largest difference seen among patients with a baseline ordinal score of 5 (hazard ratio, 0.30; 95% CI, 0.14 to 0.64).

Beigel JH. **N Engl J Med 2020;383:1813-26**

Remdesivir ACTT study

- Remdesivir
  - Fewer subsequent days of **oxygen need** (median, 13 days vs. 21 days)
  - lower incidence of new **oxygen use** (36% [95% CI, 26 to 47] vs. 44% [95% CI, 33 to 57])
  - equal subsequent duration of noninvasive ventilation or high-flow oxygen (6 days)
  - lower incidence of **new noninvasive ventilation or high-flow oxygen** (17% [95% CI, 13 to 22] vs. 24% [95% CI, 19 to 30])
  - Fewer **subsequent duration of mechanical ventilation or ECMO** (median, 17 days vs. 20 days)
  - lower incidence of **new mechanical ventilation or ECMO use** (13% [95% CI, 10 to 17] vs. 23% [95% CI, 19 to 27])
  - acute kidney injury 3.9 vs 4.1 (placebo)

Beigel JH. **N Engl J Med 2020;383:1813-26**

WHO solidarity trial

- mortality trials of four repurposed antiviral drugs
  - Remdesivir
  - Hydroxychloroquine
  - Lopinavir
  - interferon beta-1a
  - Versus standard of care without drugs above
- in patients hospitalized with coronavirus disease 2019 (Covid-19)

2.12.2020. WHO consortium. DOI: 10.1056/NEJMoa2023184

WHO solidarity trial, interim results 2.12.2020

- 405 hospitals in 30 countries
- March 22 to October 4, 2020

- “definite COVID-19” (?)

- 11 330 adults
  - 2750 remdesivir
  - 954 hydroxychloroquine
  - 1411 to lopinavir
  - 2063 to interferon (including 651 to interferon plus lopinavir)
  - 4088 no trial drug

2.12.2020. WHO consortium. DOI: 10.1056/NEJMoa2023184

WHO solidarity trial

- 11 330 adults

- 1253 **deaths** (median day of death, day 8; interquartile range, 4 to 14)
- 28-day mortality 11.8%
  - 39.0% in pts receiving ventilation at randomization
  - 9.5% otherwise

  - **Death** in 301 of 2743 (11%) pts receiving remdesivir
  - in 303 of 2708 (11%) pts receiving its control (P=0.50)

  - 104 of 947 (11%) pts receiving hydroxychloroquine
  - 84 of 906 (9%) pts receiving its control

  - 148 of 1399 (11%) pts receiving lopinavir
  - 146 of 1372 (11%) pts receiving its control

  - 243 of 2050 (12%) pts receiving interferon
  - 216 of 2050 (11%) pts. receiving its control

2.12.2020. WHO consortium. DOI: 10.1056/NEJMoa2023184

WHO solidarity trial

- **No drug** definitely **reduced mortality**, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration.

2.12.2020. WHO consortium. DOI: 10.1056/NEJMoa2023184

Solidarity trial

- unclear
  - time to medication related to symptom onset
  - exact time of hospitalization related to initiation of study drug

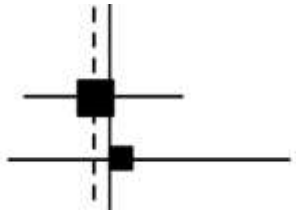
  - broad range of deaths in control group
    - 28.7% deaths in mechanically ventilated controls (in lopinavir arm)
    - 37.8% deaths in mechanically ventilated controls (in remdesivir arm)

    - 19.3% deaths in mechanically ventilated controls (in ACTT trial)

Solidarity trial

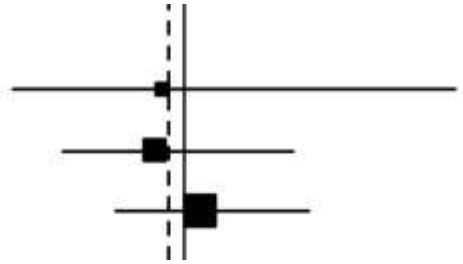
- unclear
  - cortocosteroids harmful (in Remdesivir vs control arm)?

	Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%)				
	Remdesivir	Control			
Corticosteroids at entry or later (ignoring any biases*)					
Yes	210/1310 (16.6)	225/1288 (17.9)	-5.6	106.8	0.95 [0.74-1.22]
No	91/1433 (8.0)	78/1420 (6.9)	1.2	41.1	1.03 [0.69-1.54]



  - Latin America harmful? (compared to other locations? in Remdesivir vs control arm)

Geographic location‡					
Europe or Canada	33/715 (5.2)	27/698 (5.1)	-1.1	14.5	0.93 [0.47-1.82]
Latin America	82/470 (20.6)	115/514 (23.8)	-4.4	46.2	0.91 [0.62-1.33]
Asia and Africa	186/1558 (13.3)	161/1496 (12.0)	3.4	84.1	1.04 [0.79-1.38]



NEJM editorial zu WHO solidarity trial 2.12.2020

- Even without a reduction in in-hospital mortality, **reducing** the **time to recovery and hospital discharge** among patients who survive is important, both for patients and for stressed health care systems, and was the basis for the recent approval of remdesivir by the Food and Drug Administration.

Harrington DP. NEJM 2.12.2020 **DOI: 10.1056/NEJMe2034294**

IL-6 inhibitor Tocilizumab and COVID 19

- COVACTA Roche, July 2020
- EMPACTA Roche, Sept 2020

- Stone NEJM, 10.12.2020
  - In this randomized, double-blind, placebo controlled trial, we **did not find** any **efficacy** of interleukin-6 receptor blockade for the treatment of hospitalized patients with Covid-19
- Salama NEJM, 17.12.2020
  - In hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, **tocilizumab reduced the likelihood of progression** to the composite outcome of mechanical ventilation or death, but it did not improve survival.

COVACTA trial, Tocilizumab (IL-6 inhibitor) vs. Placebo in COVID-19 with pneumonia and respiratory failure

- no difference in **28d mortality**
  - Tocilizumab vs placebo 19.7% vs. 19.4%; difference, 0.3%; 95% CI, -7.6% to 8.2%; *P*=0.9410
- no difference in median number of **ventilator-free days**
  - Tocilizumab vs placebo 22 days vs. 16.5 days; difference, 5.5 days; 95% CI, -2.8 to 13.0 days; *P*=0.3202
- no difference in **28d infection rates**
  - Tocilizumab vs placebo 38.3% vs. 40.6%
  - serious infection rates 21.0% vs. 25.9%

https://www.roche.com/dam/jcr:6d8de90d-2e31-43c8-b4e1-0a24a2675015/en/29072020-mr-covacta.pdf

EMPACTA trial, Tocilizumab (IL-6 inhibitor) vs. Placebo in COVID-19 with pneumonia and respiratory failure

- patients with COVID-19 associated pneumonia who received Actemra/RoActemra plus standard of care were **44% less likely to progress** to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97])
- The cumulative proportion of patients who **progressed to mechanical ventilation** or death by day 28 was 12.2% in the Actemra/RoActemra arm versus 19.3% in the placebo arm.
- **No difference** in death rate, hospital discharge, time to improvement

https://www.roche.com/dam/jcr:6d8de90d-2e31-43c8-b4e1-0a24a2675015/en/29072020-mr-covacta.pdf

EMPACTA trial, Tocilizumab (IL-6 inhibitor) vs. Placebo in COVID-19 with pneumonia and respiratory failure

Table S5. Proportion of patients who received systemic corticosteroids and antivirals within 7 days prior to first dose of study drug or during the study (modified intent-to-treat population)

Drug, no. (%)	Tocilizumab N=249	Placebo N=128	All Patients N=377
Systemic corticosteroid	200 (80.3)	112 (87.5)	312 (82.8)
Antiviral	196 (78.7)	101 (78.9)	297 (78.8)

Table S6. Proportion of patients who received dexamethasone and remdesivir within 7 days prior to first dose of study drug or during the study (modified intent-to-treat population)

Drug, no. (%)	Tocilizumab N=249	Placebo N=128	All Patients N=377
Dexamethasone	138 (55.4)	86 (67.2)	224 (59.4)
Remdesivir	131 (52.6)	75 (58.6)	206 (54.6)

Corticosteroids within 7 days **prior to or during study?**
Drugs?
Dose?
Duration?

ıe.com/dam/jcr:6d8de90d-2e31-43c8-
l5/en/29072020-mr-covacta.pdf

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19 (ACTT2)

- **Baricitinib plus remdesivir was superior** to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation.
- Patients receiving baricitinib had a median time to recovery of **7 days** (95% confidence interval [CI], 6 to 8), as compared with **8 days** (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03)
- and a **30% higher odds of improvement in clinical status at day 15** (odds ratio, 1.3; 95% CI, 1.0 to 1.6).

Kalil. NEJM 11.12.2020
DOI:10.1056/NEJMoa2031994

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

- Glucocorticoids permitted only for standard indications such as adrenal insufficiency, asthma exacerbation, laryngeal edema, septic shock, and acute respiratory distress syndrome.

Kalil. NEJM 11.12.2020
DOI:10.1056/NEJMoa2031994

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

- Baricitinib, an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2, was predicted with the use of artificial intelligence algorithms to be a potential therapeutic against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

- **NIH**
  - There are **insufficient data** for the Panel to **recommend either for or against** the **use of baricitinib** in combination with remdesivir for the treatment of COVID-19 in hospitalized patients in cases where corticosteroids can be used instead

Kalil. NEJM 11.12.2020
DOI:10.1056/NEJMoa2031994
https://www.covid19treatmentguidelines.nih.gov/statement-on-baricitinib-eua/

COVID-19 Treatments

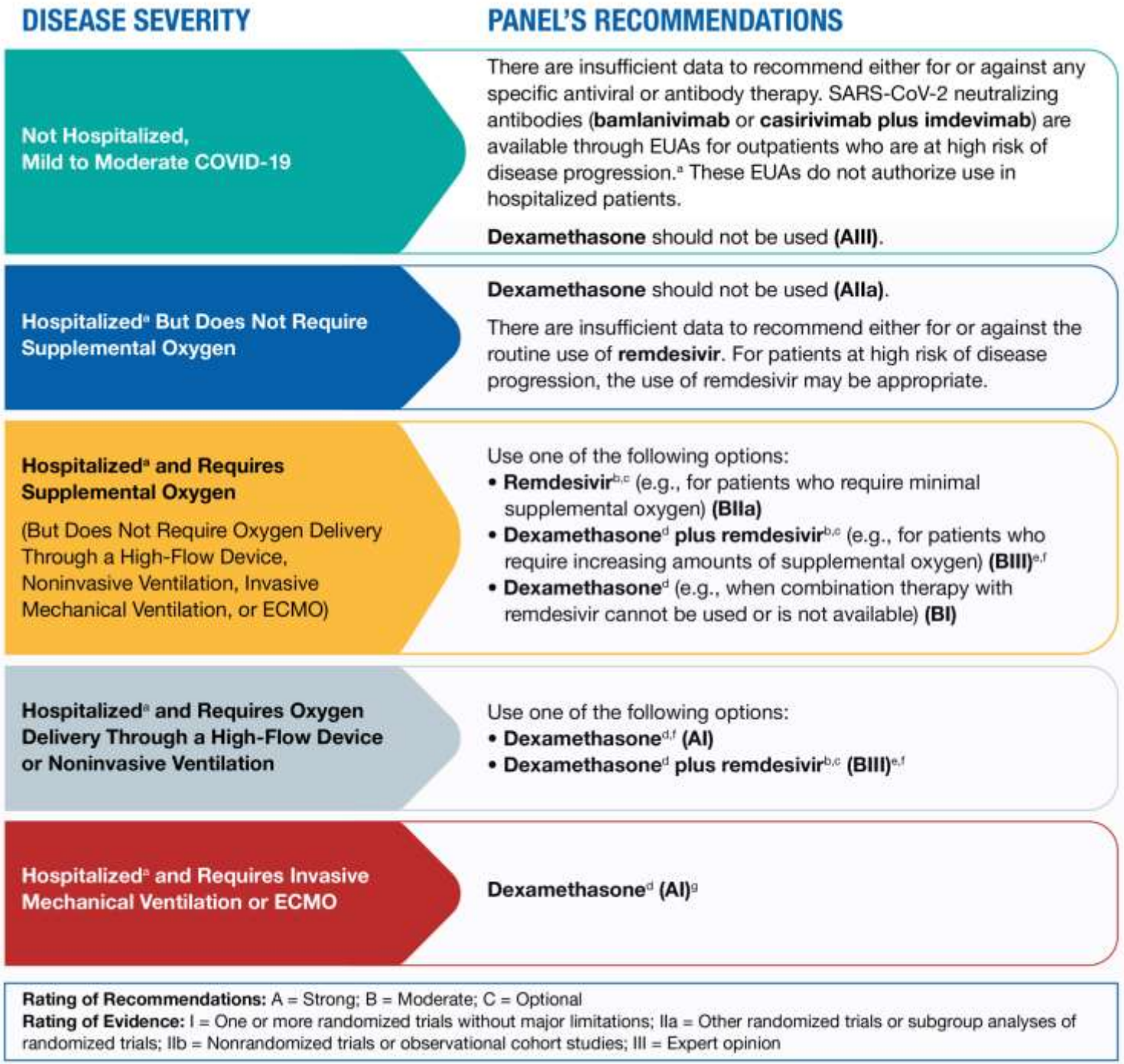
- ~~Hydroxychloroquin~~
- ~~Azithromycin~~

- Remdesivir
- ~~Lopinavir/Ritonavir~~
- Favipiravir ?

- anti-inflammatory treatment (~~IL 6 Inhibitors~~, Dexamethason)

- Plasma therapy
  - Emergency use authorization FDA 23.8.2020
    - no difference in mortality (14.5% plasma vs. 13.5% no plasma; 10.96% plasma vs. 11.43%)
- ~~Antibodies~~

Agarwal. MedRxiv. **doi:** https://doi.org/10.1101/2020.09.03.20187252
Simonovic A. NEJM 10.1056/NEJMoa20313042020



NIH, USA

- Dexamethason
- Remdesivir

https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/