UWTASP

tele-antimicrobial stewardship program

- Didactic: COVID-19 Therapeutics
- Case discussions

10/6/2020

UWTASP

tele-antimicrobial stewardship program

COVID-19 Therapeutics, updates as of 10/6/2020

Rupali Jain, PharmD

UW Medicine

rupali@uw.edu

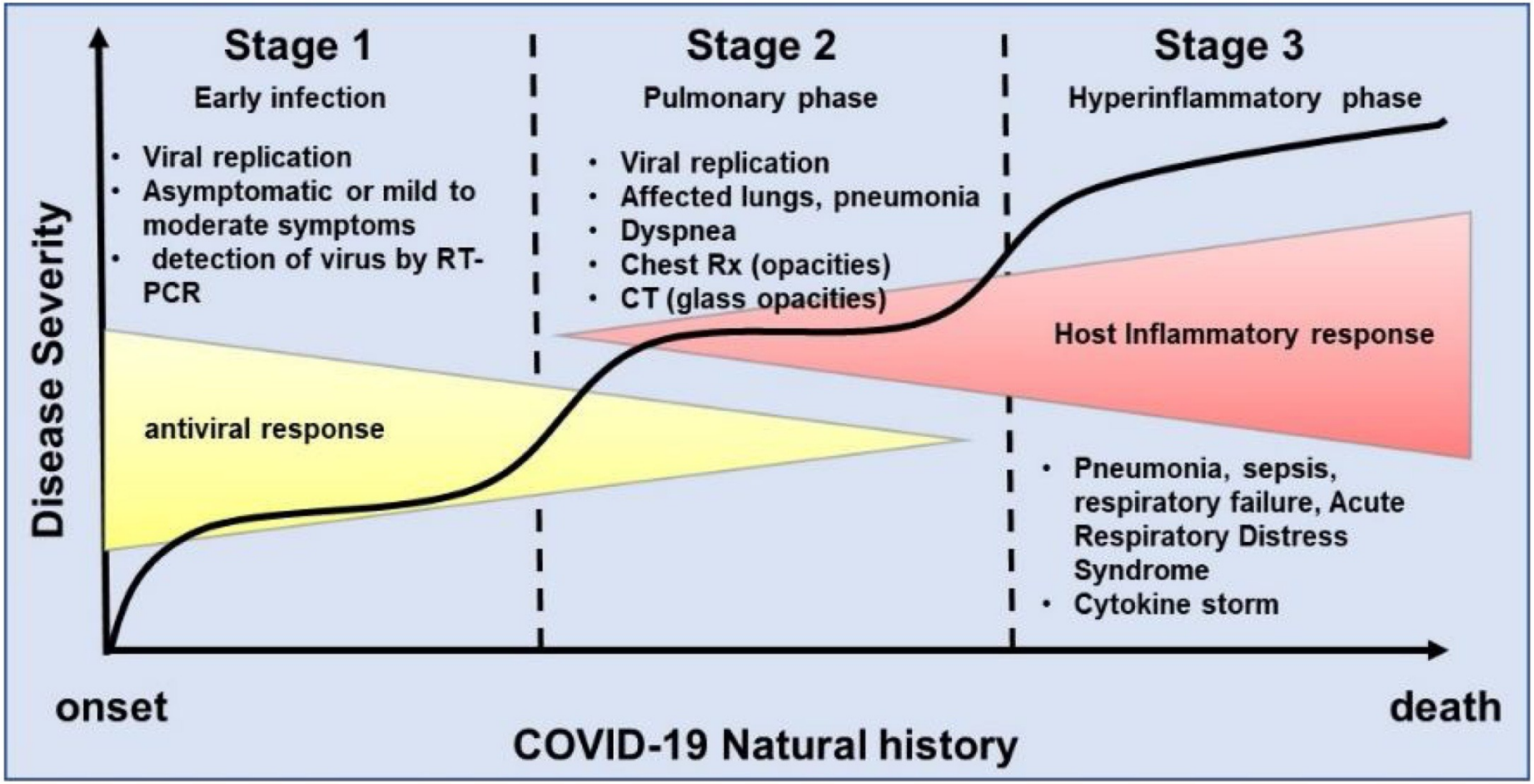
Objectives

- Review key data for the treatment of COVID-19
- Summarize National Institutes of Health and Infectious Diseases Society of America guidelines

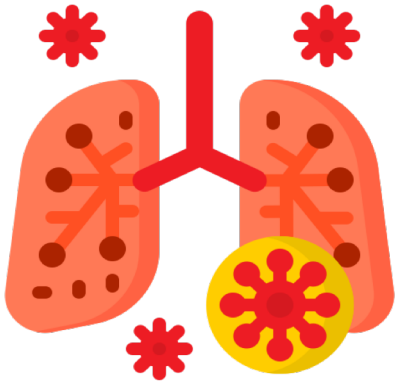
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5

https://www.covid19treatmentguidelines.nih.gov/

COVID-19 Natural History



Manifestations: mild/moderate to severe disease

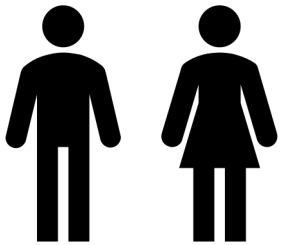


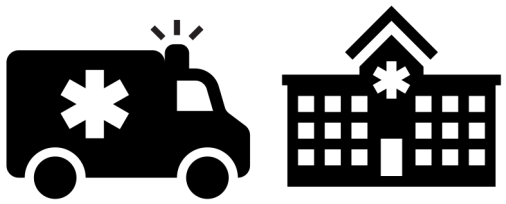
81%
mild/moderate
disease

14% severe disease

5% critical disease

Risk Factors:
Age >65
CV disease
DM
Chronic Lung Disease
Cancer
CKD
Obesity
Smoking





JAMA. 2020;323(13):1239-1242.
N Engl J Med 2020. DOI: 10.1056/NEJMcp2009249
Lancet 2020; 395:497

Therapeutics landscape

ASYMPTOMATIC: TEST POSITIVE; BUT NO SYMPTOMS

MILD: SIGNS/SYMPTOMS (FEVER, COUGH, SORE THROAT, MALAISE, HEADACHE, MUSCLE PAIN) BUT NO SHORTNESS OF BREATH, DYSPNEA, OR ABNORMAL CHEST IMAGING

MODERATE: LOWER RESPIRATORY DISEASE

CHEST IMAGING **OR** SATURATION OF O2 (SpO2) ≥94% ON ROOM AIR

SEVERE ILLNESS: RESP FREQUENCY > 30 BREATHS/MIN, SpO2 <94% on ROOM AIR, RATIO OF ARTERIAL PARTIAL PRESSURE OF OXYGEN TO FRACTION OF INSPIRED OXYGEN (PaO_2/FiO_2) <300 MMHG, OR LUNG INFILTRATES >50%

CRITICAL ILLNESS: RESPIRATORY FAILURE, SEPTIC SHOCK AND/OF MULTIPLE ORGAN DYSFUNCTION

Therapeutics landscape

HOME: ASYMPTOMATIC/ MILD DISEASE

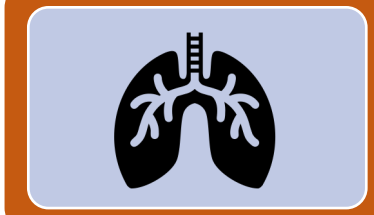
Treatment: NO TREATMENT

CLINICAL TRIALS

MODERATE:

IV REMDESIVIR?

NO DEXAEMETHASONE



SEVERE:

- IV REMEDESIVIR
- DEXAMETHASONE
- CONVALSCENT PLASMA -?

CRITICAL ILLNESS

- IV REMDESIVIR
- DEXAMETHASONE

Prevention- Hydroxychloroquine

Did not prevent symptomatic disease in patients with moderate or high risk exposures (HCQ vs placebo, 11.8% vs 14.3% p =0.35) [1]

- HCQ group had more side effects: diarrhea, nausea, abdominal discomfort
- 66% were HCW

Did not prevent infections among HCW exposed to patients with COVID-19 (HCQ vs placebo, 6.3% vs 6.6% P >0.99) [2]

- Ended early for futility

1.Boulware, et al N Engl J Med 2020; 383:517-525
2. Abella BS. *JAMA Intern Med.* Published online September 30, 2020.

Asymptomatic

- no additional laboratory testing and
- no specific treatment for persons with suspected or confirmed asymptomatic or presymptomatic SARS-CoV-2 infection (AIII).

Active area of research:

- Monoclonal Ab

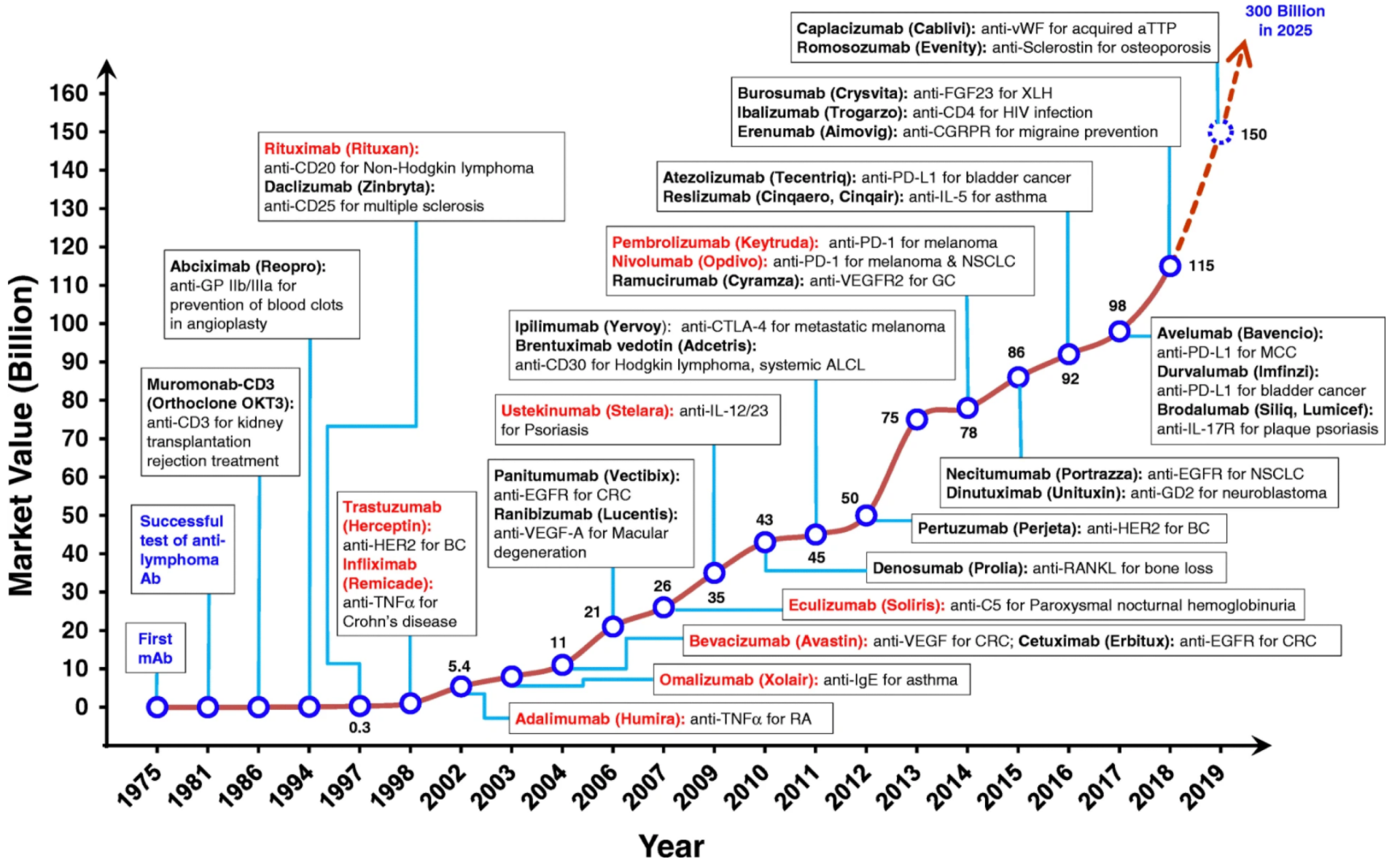
Mild illness

- Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or remote visits.
- All patients with symptomatic COVID-19 and risk factors for severe disease should be closely monitored.
- In some patients, the clinical course may rapidly progress.

Active area of research:

- Monoclonal Ab
- IV Remdesivir

Monoclonal Antibodies



What are they?

- Monoclonal antibodies (mAbs) are produced by B cells and specifically target antigens
- protein made in the lab that bind to specific receptors or cells in the body

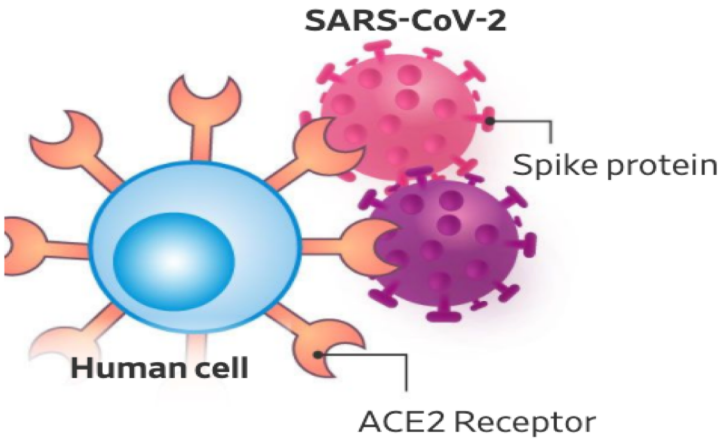
- A monoclonal antibody is made so that it binds to only one substance.
- They can be used alone or to carry drugs, toxins, or radioactive substances directly to cancer cells.

National Cancer Institute.

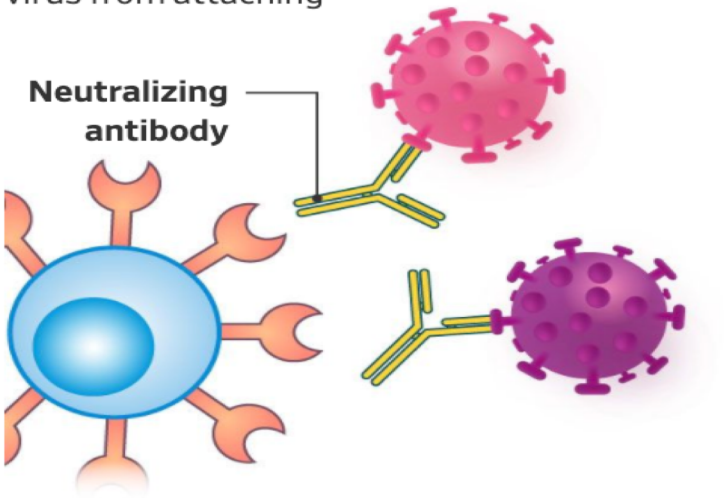
Protection With mAbs

Monoclonal antibody therapies are drugs that could provide a 'bridge' of immunity until vaccines are ready.

Without any antibodies, the coronavirus will bind to the ACE2 receptor on a human cell



The antibody acts as a blocker, preventing the virus from attaching



How do they help?

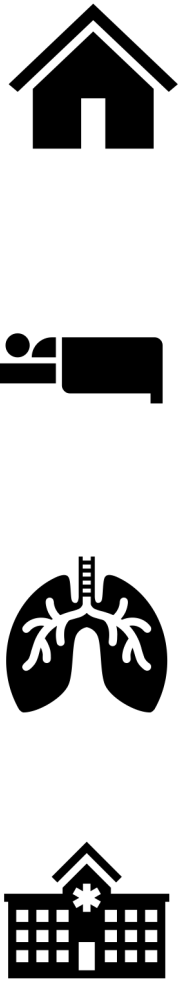
- have the potential to be used for both prevention and treatment of infection.
- Several products being evaluated
- Lilly product (LYCoV555)
  - Press report: viral load reduction and decreased rate of hospitalization and ER visits
- Regeneron (REGN 10933 and REGN10987)
  - REGN-COV2 rapidly reduced viral load through Day 7 in seronegative patients

Limitations:

- unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs

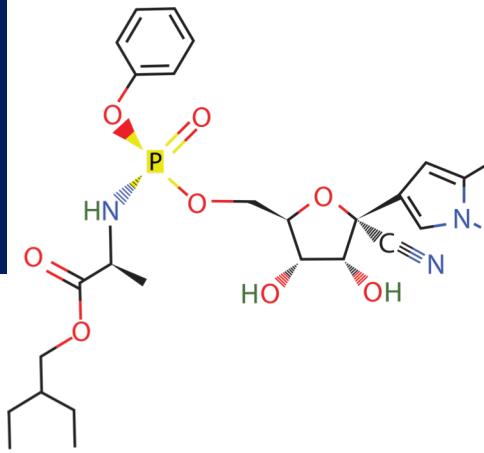
https://investor.lilly.com/news-releases/news-release-details/lilly-announces-proof-concept-data-neutralizing-antibody-ly
JAMA. 2020;324(2):131-132.
https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and

Therapeutics landscape



MODERATE: LOWER RESPIRATORY DISEASE (CHEST IMAGING OR SATURATION OF O2 (SpO2) ≥94% ON ROOM AIR)

Remdesivir (GS-5734)



- Adenosine nucleotide analogue prodrug
- Broad-spectrum against several RNA viruses
- Requires phosphorylation for activation triphosphate form
- Competes for incorporation with adenosine triphosphate (ATP)

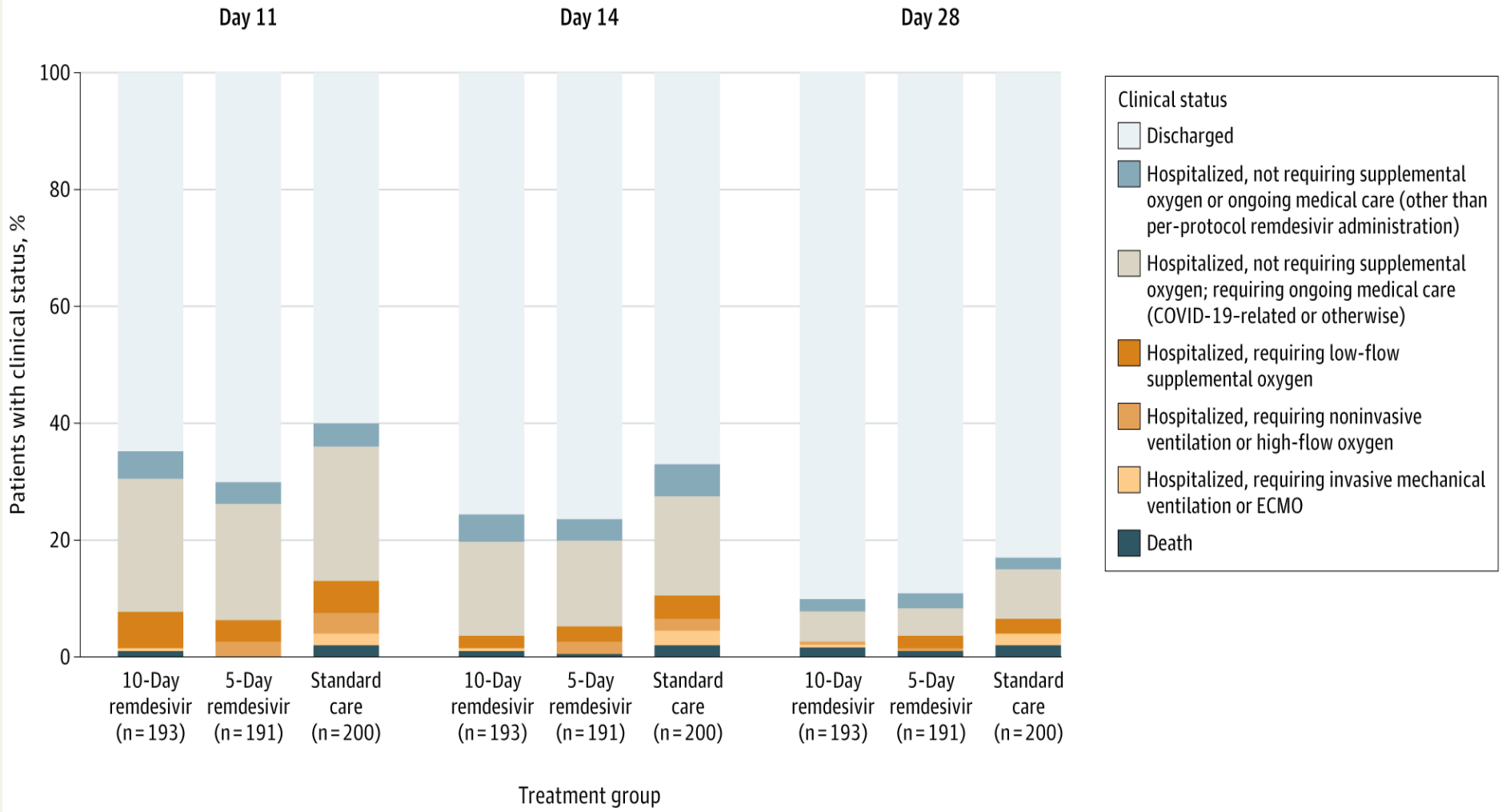
- Selectivity of ATP versus Remdesivir
  - Ebola RNA-dependent RNA polymerase ~ 4:1
  - RSV RNA-dependent RNA polymerase ~ 3:1
  - Human mitochondrial RNA polymerase ~ 500:1

Tchesnokov EP, et al. Viruses 2019;11(4). pii: E326

UNIVERSITY of WASHINGTON

IDEA INFECTIOUS DISEASES EDUCATION & ASSESSMENT

IV Remdesivir -MODERATE



Is there Consensus?

IDSA:

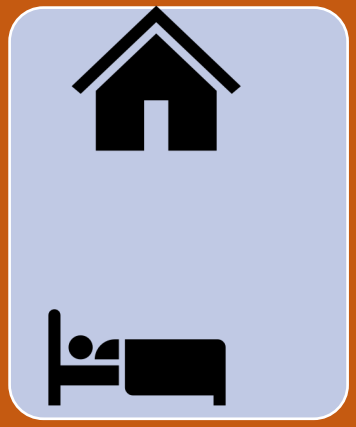
In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, IDSA suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)

NIH:

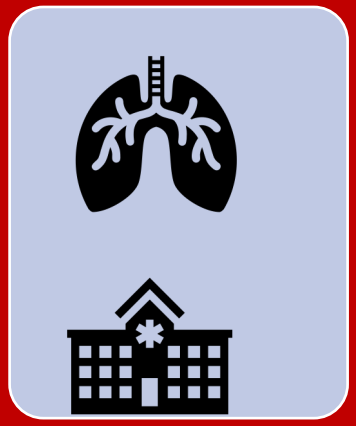
Recommendation for Patients With Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of **remdesivir** in patients with mild or moderate COVID-19.

Therapeutics landscape



SEVERE ILLNESS: RESP FREQUENCY > 30 BREATHS/MIN, SpO2 <94% on ROOM AIR, RATIO OF ARTERIAL PARTIAL PRESSURE OF OXYGEN TO FRACTION OF INSPIRED OXYGEN (PaO_2/FiO_2) <300 MMHG, OR LUNG INFILTRATES >50%



CRITICAL ILLNESS: RESPIRATORY FAILURE, SEPTIC SHOCK AND/OF MULTIPLE ORGAN DYSFUNCTION

Concept of Using Convalescent Plasma to Treat COVID-19

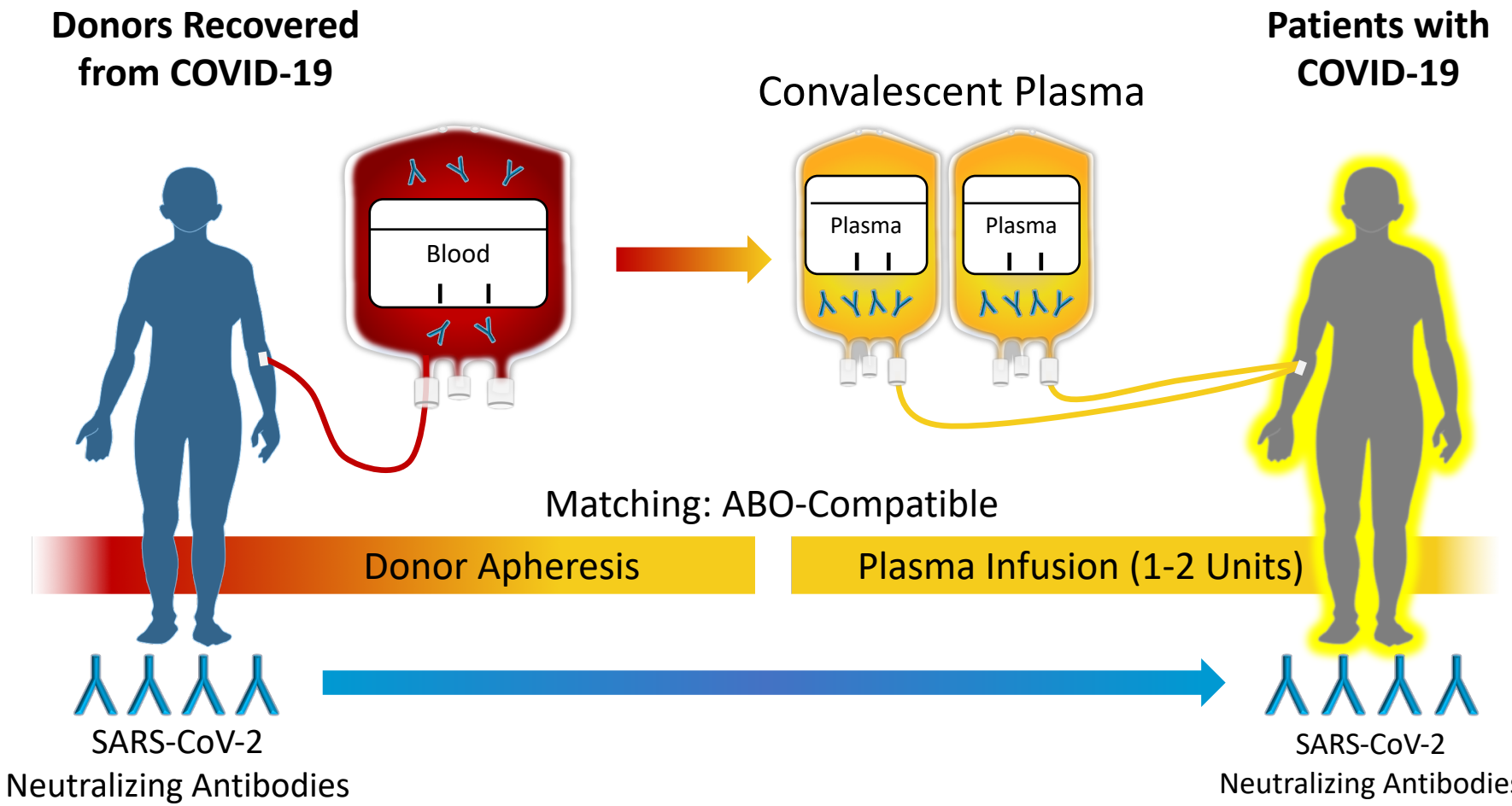
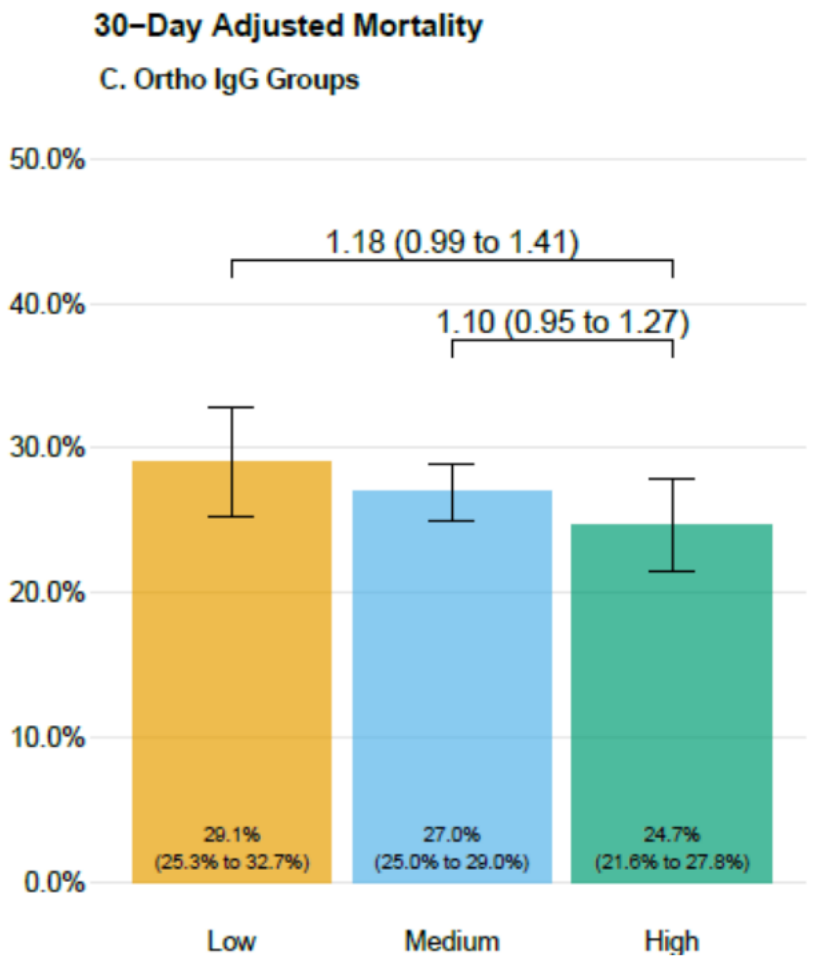


Illustration: David H. Spach, MD

Convalescent Plasma Through a National Expanded Access Program

- 20,000 patients enrolled nationwide
- Adults with severe, life-threatening disease
- No placebo arm
- Main outcomes were safety including data, SAEs at 4 hour and 7 days after transfusion
- The overall mortality rate was 8.6% at 7 days.
- therapy was associated with a low incidence (<1%) of serious transfusion-related events.

There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of **COVID-19 convalescent plasma** for the treatment of COVID-19.



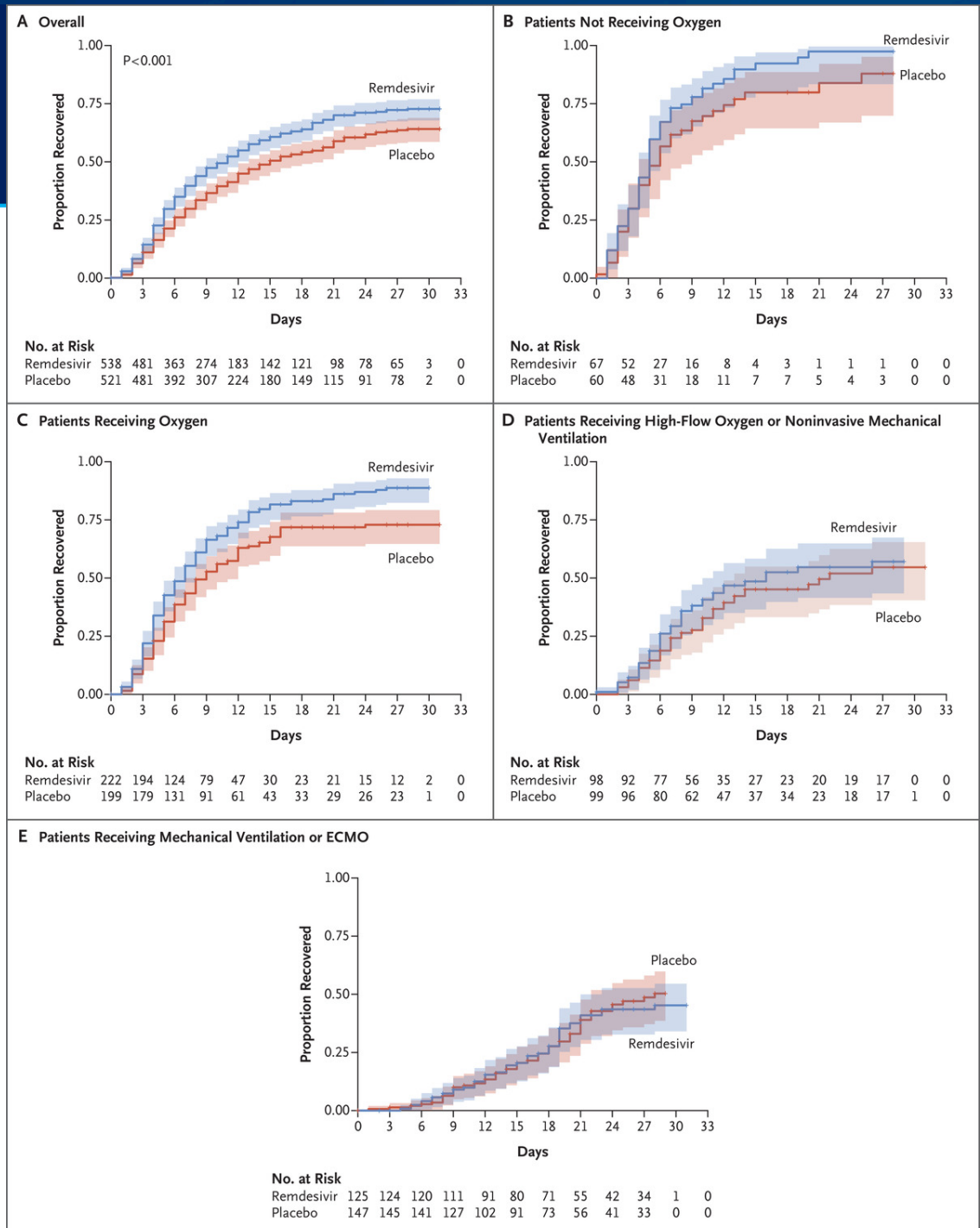
https://doi.org/10.1101/2020.08.12.20169359; NIH guidelines

ACTT-1, preliminary

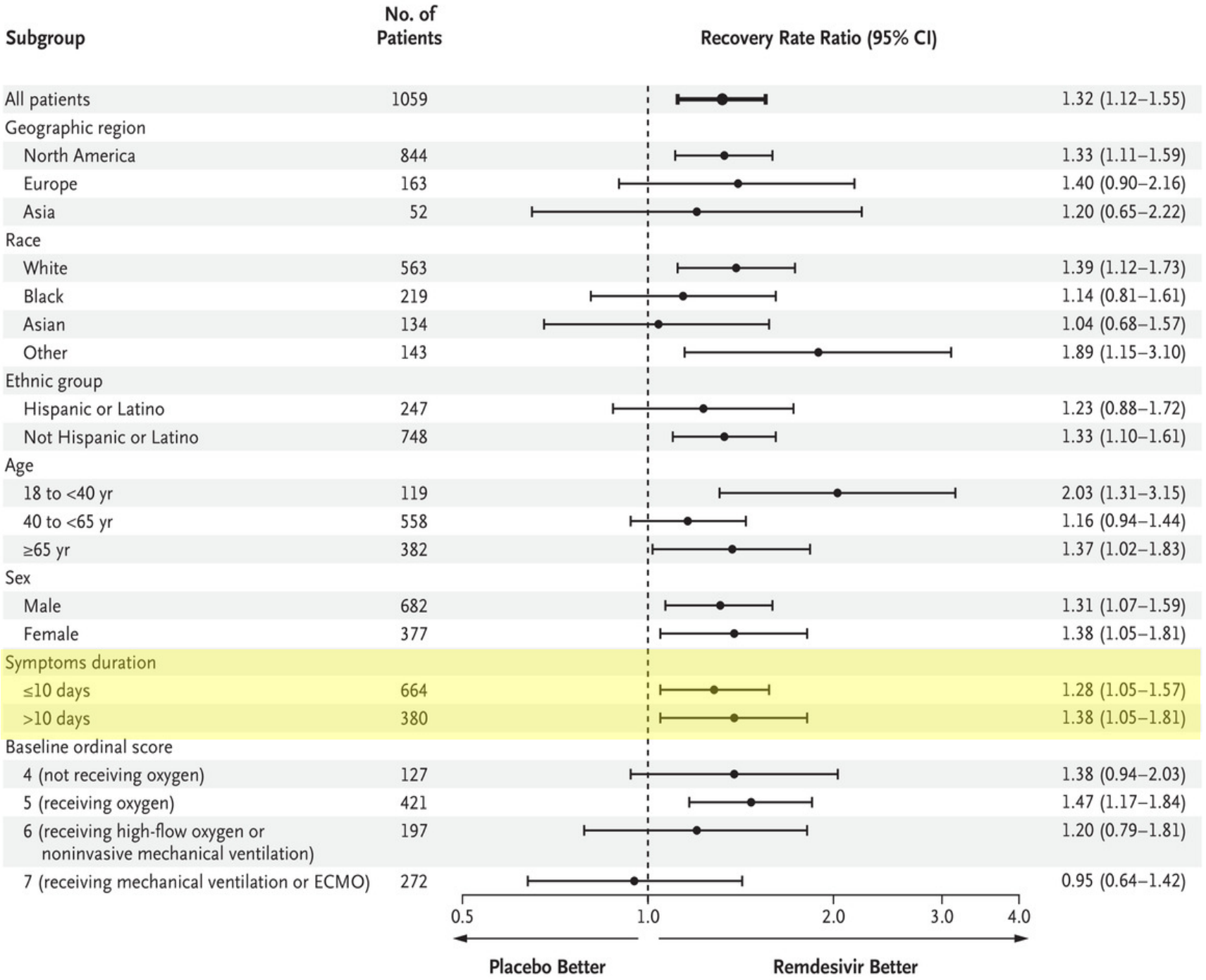
Randomized controlled trial
IV Remdesivir x 10 days, any hospitalized pt with COVID-19

The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

Majority of patients included were on supplmental oxygen



DOI: 10.1056/NEJMoa2007764


Subgroup
No. of Patients
Recovery Rate Ratio (95% CI)
All patients 1059 1.32 (1.12–1.55)
Geographic region
North America 844 1.33 (1.11–1.59)
Europe 163 1.40 (0.90–2.16)
Asia 52 1.20 (0.65–2.22)
Race
White 563 1.39 (1.12–1.73)
Black 219 1.14 (0.81–1.61)
Asian 134 1.04 (0.68–1.57)
Other 143 1.89 (1.15–3.10)
Ethnic group
Hispanic or Latino 247 1.23 (0.88–1.72)
Not Hispanic or Latino 748 1.33 (1.10–1.61)
Age
18 to <40 yr 119 2.03 (1.31–3.15)
40 to <65 yr 558 1.16 (0.94–1.44)
≥65 yr 382 1.37 (1.02–1.83)
Sex
Male 682 1.31 (1.07–1.59)
Female 377 1.38 (1.05–1.81)
Symptoms duration
≤10 days 664 1.28 (1.05–1.57)
>10 days 380 1.38 (1.05–1.81)
Baseline ordinal score
4 (not receiving oxygen) 127 1.38 (0.94–2.03)
5 (receiving oxygen) 421 1.47 (1.17–1.84)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation) 197 1.20 (0.79–1.81)
7 (receiving mechanical ventilation or ECMO) 272 0.95 (0.64–1.42)
0.5
1.0
2.0
3.0
4.0
Placebo Better
Remdesivir Better

Duration of therapy

IDSA: In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)

- **Remark:** In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.

NIH: Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

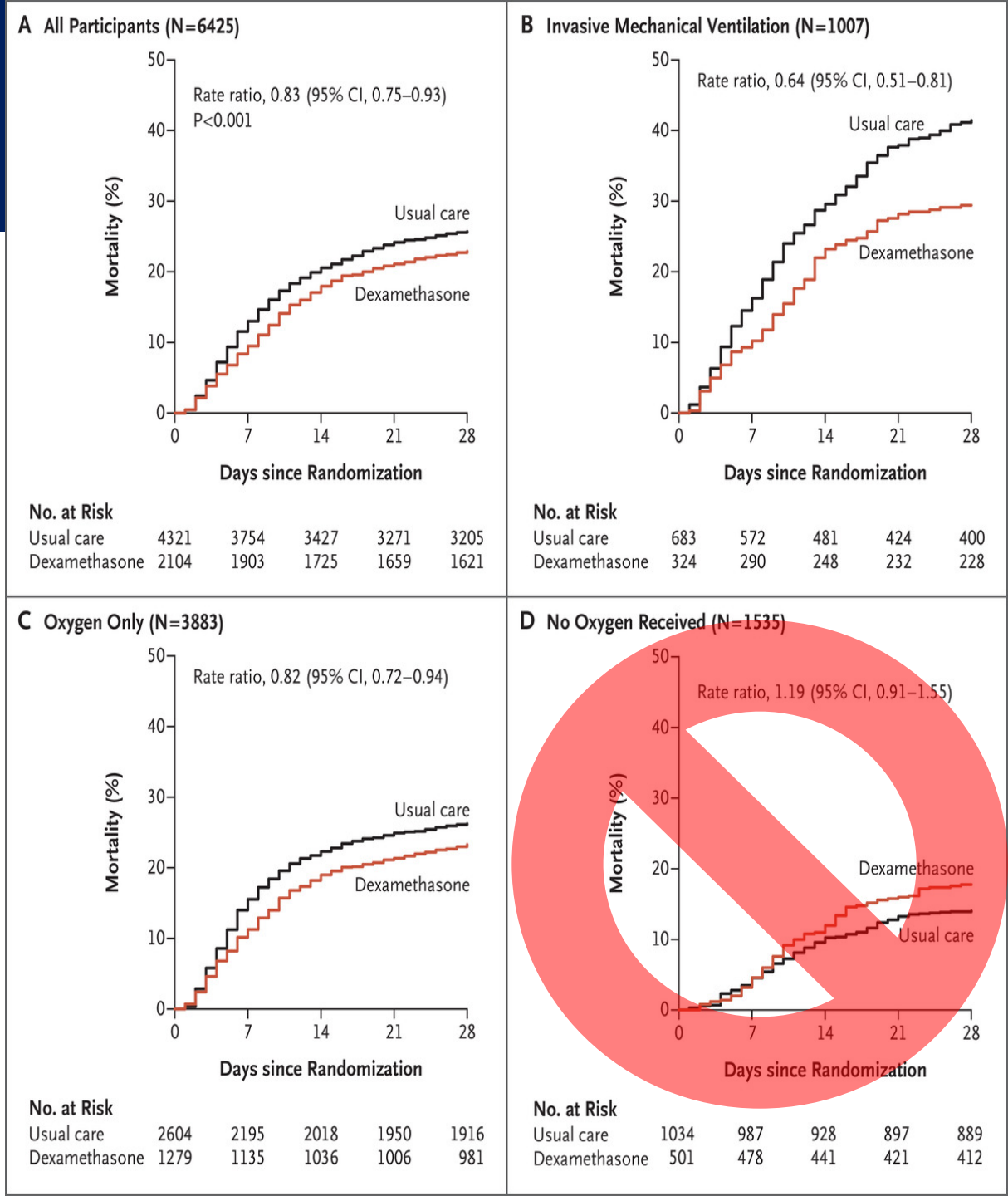
- There are insufficient data on the optimal duration of **remdesivir** therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Recommendations for Patients with COVID-19 Who Require Supplemental Oxygen

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir ***progresses*** to requiring delivery of oxygen through a high-flow device, noninvasive ventilation, or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

Dex

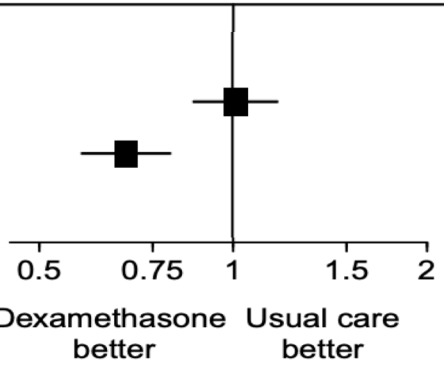
- Open-label trial who were hospitalized with COVID-19
- Randomized to IV/PO dexamethasone 6mg/day or usual care
- Primary outcome death at 28 days



Symptoms >7 days did better with Dexamethasone

Figure S1: Effect of allocation to dexamethasone on 28−day mortality by other pre−specified baseline characteristics

Subgroup	Dexamethasone	Usual care	RR (95% CI)	Het/trend
Days since symptom onset				
≤7	269/916 (29.4%)	500/1801 (27.8%)	1.01 (0.87−1.17)	χ^2_1=12.3
>7	212/1184 (17.9%)	604/2507 (24.1%)	0.69 (0.59−0.80)	



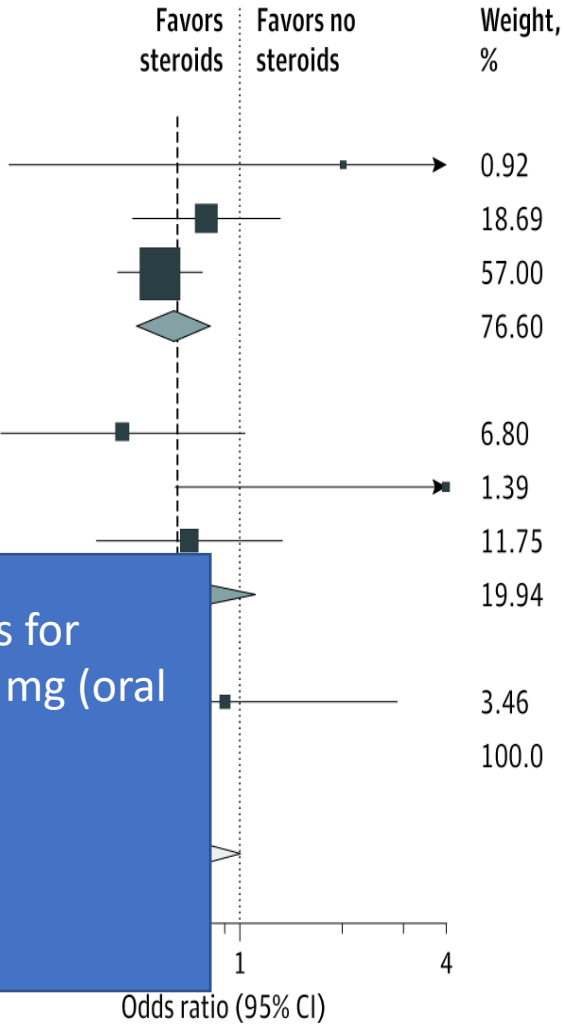
- The Panel recommends using **dexamethasone** 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated **(AI)** and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**.

•The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**.

•If **dexamethasone** is not available, the Panel recommends using alternative glucocorticoids

Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect						19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every				3.46
Overall (fixed effect)						100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])						



The total daily dose equivalencies for these drugs to dexamethasone 6 mg (oral or intravenous [IV]) are:

- Prednisone 40 mg
- Methylprednisolone 32 mg
- Hydrocortisone 160 mg

JAMA. Published online September 2, 2020. doi:10.1001/jama.2020.17023

Warnings

- Monitor pts for hyperglycemia, secondary infections, psychiatric effects, avascular necrosis
- Steroids and influenza: not a great combination
  - Increased risk for prolonged viral shedding and worse outcomes
- Steroids may increase risk of reactivation of infections (Hepatitis B, herpes, strongyloidiasis, tuberculosis)

Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26950335.

Therapeutics landscape

HOME: ASYMPTOMATIC/ MILD DISEASE

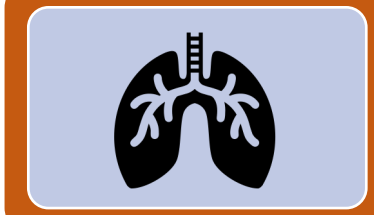
Treatment: NO TREATMENT

CLINICAL TRIALS

MODERATE:

IV REMDESIVIR?

NO DEXAEMETHASONE



HOSPITALIZED WITH O2 REQUIREMENT

- IV REMEDESIVIR
- DEXAMETHASONE
- CONVALSCENT PLASMA -?

CRITICAL ILLNESS

- IV REMDESIVIR
- DEXAMETHASONE

Summary

- Emerging therapy for monoclonal Antibodies
- More definitive data for Steroids
- IV Remdesivir remains mainstay antiviral for hospitalized patient requiring O_2
- Convalescent Plasma is no longer routinely recommended

FAQs

Anticoagulation

- **What is the recommended VTE prophylaxis in patients with COVID-19?**
- All hospitalized adults with COVID-19 should receive pharmacologic thromboprophylaxis.

https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation
https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/

Vitamins

Vitamin C:

- Data are insufficient to recommend for or against the use

Vitamin D:

- Data are insufficient to recommend for or against the use