MA/REGION 1 PARTNERSHIP *for*
Regional Disaster Health Response

Update on the Current Treatment Options for COVID-19: A Review for Planners and Others

November 6, 2020

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

FEMA

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- The speakers have no affiliation or financial interests/relationships to disclose.

Speakers

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- Gary J. Kleinman
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- Russell Webster
  Regional Administrator, FEMA Region 1
  Region 1 Federal Coordinating Officer for COVID-19
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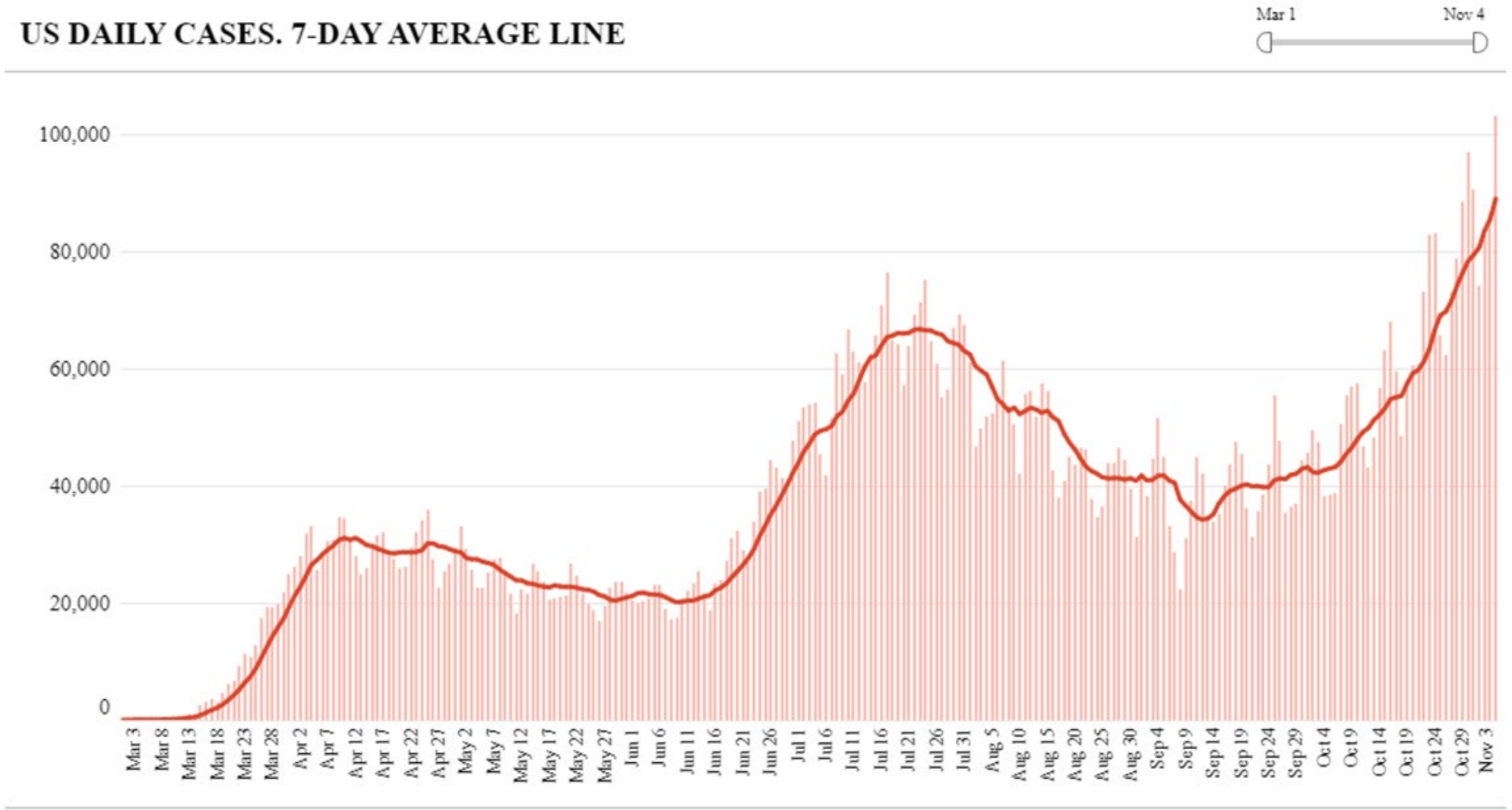
Agenda

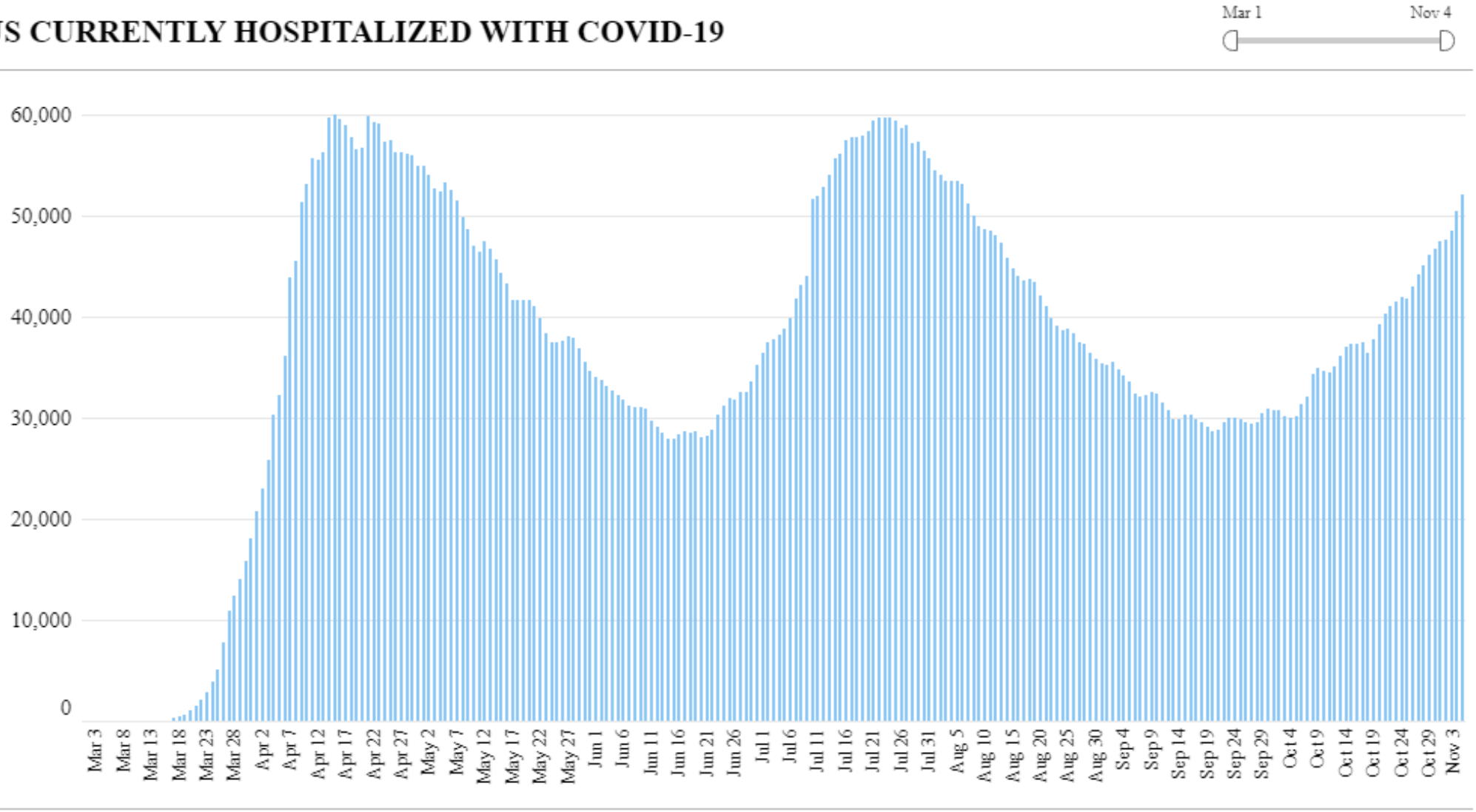
- Review data regarding the current case rates and changing demographics of infection
- Identify how clinical care is changing and may be affecting outcomes with COVID-19
- Discuss currently available and anticipated pharmacological interventions and their impact on COVID-19

US DAILY CASES. 7-DAY AVERAGE LINE



The COVID Tracking Project

US CURRENTLY HOSPITALIZED WITH COVID-19

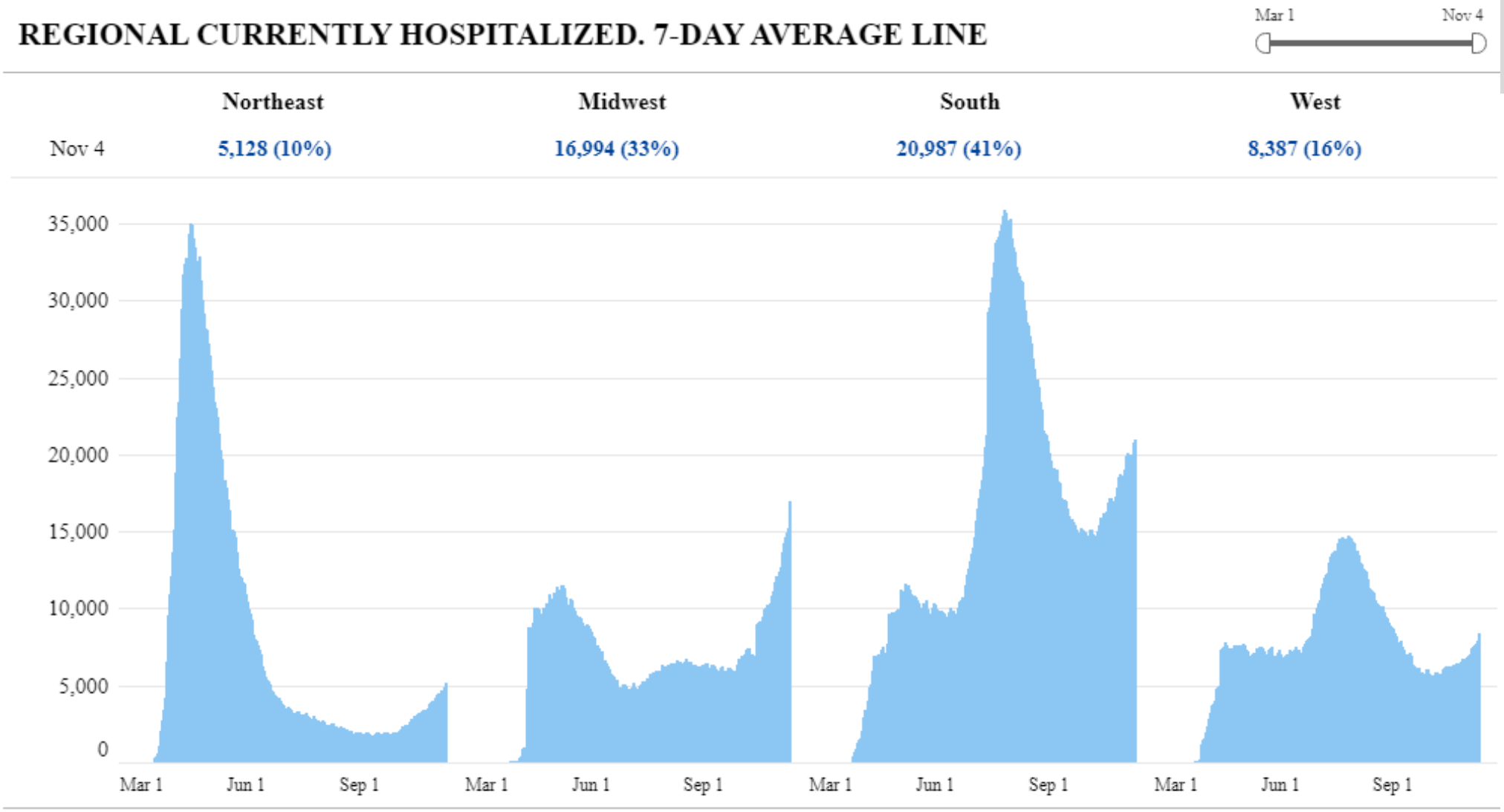


The COVID Tracking Project

Note: Florida began reporting this figure on July 10.

MA/REGION 1 PARTNERSHIP for Regional Disaster Health Response

REGIONAL CURRENTLY HOSPITALIZED. 7-DAY AVERAGE LINE

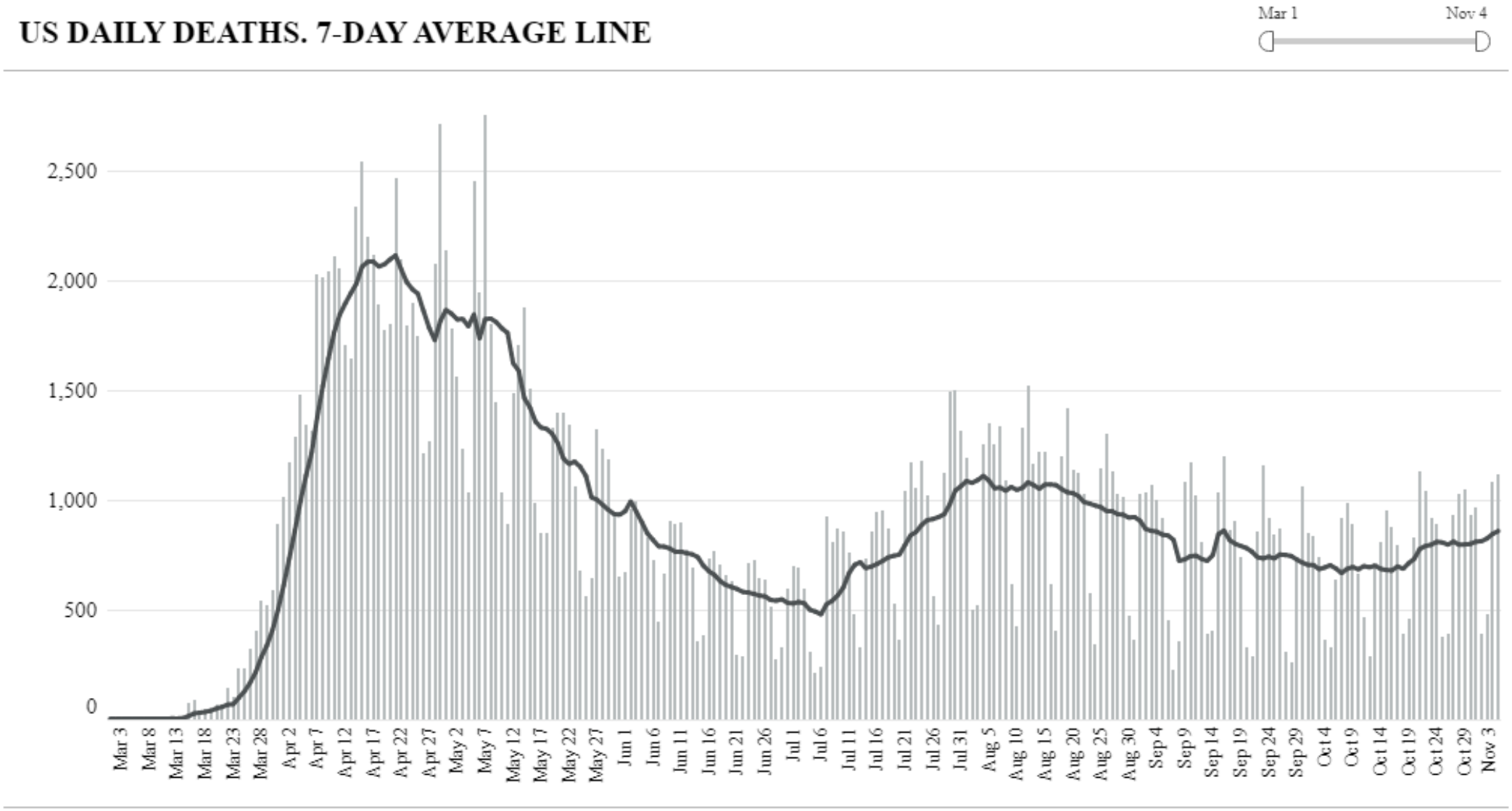


The COVID Tracking Project

Regions displayed in our charts are defined by the US Census

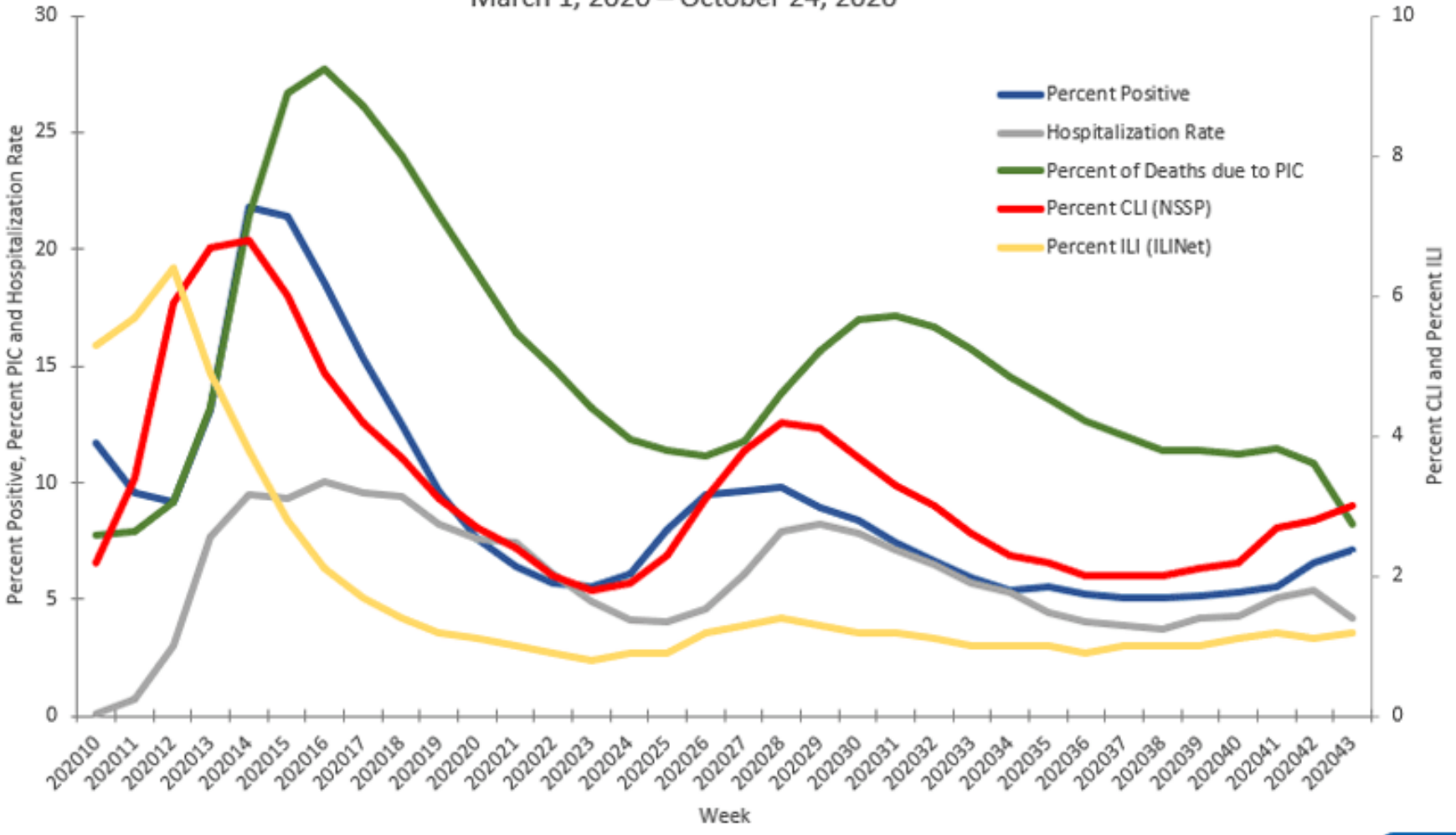
MA/REGION 1 PARTNERSHIP for Regional Disaster Health Response

US DAILY DEATHS. 7-DAY AVERAGE LINE



The COVID Tracking Project

National COVID-19 Activity Indicators:
Laboratory, Outpatient/Emergency Department, Hospitalization and Mortality Data
March 1, 2020 – October 24, 2020*

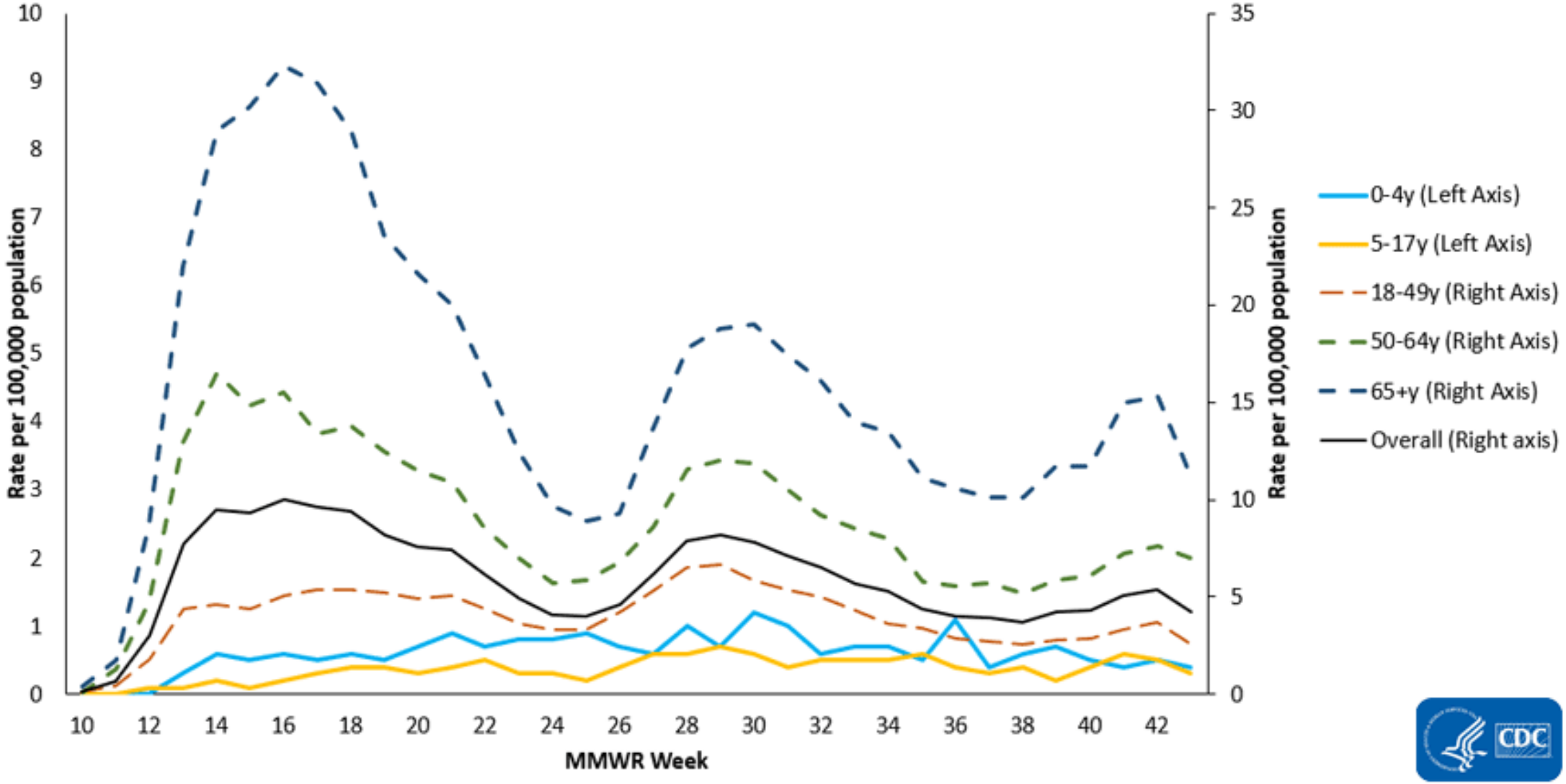


*Data are preliminary and may change as more reports are received.

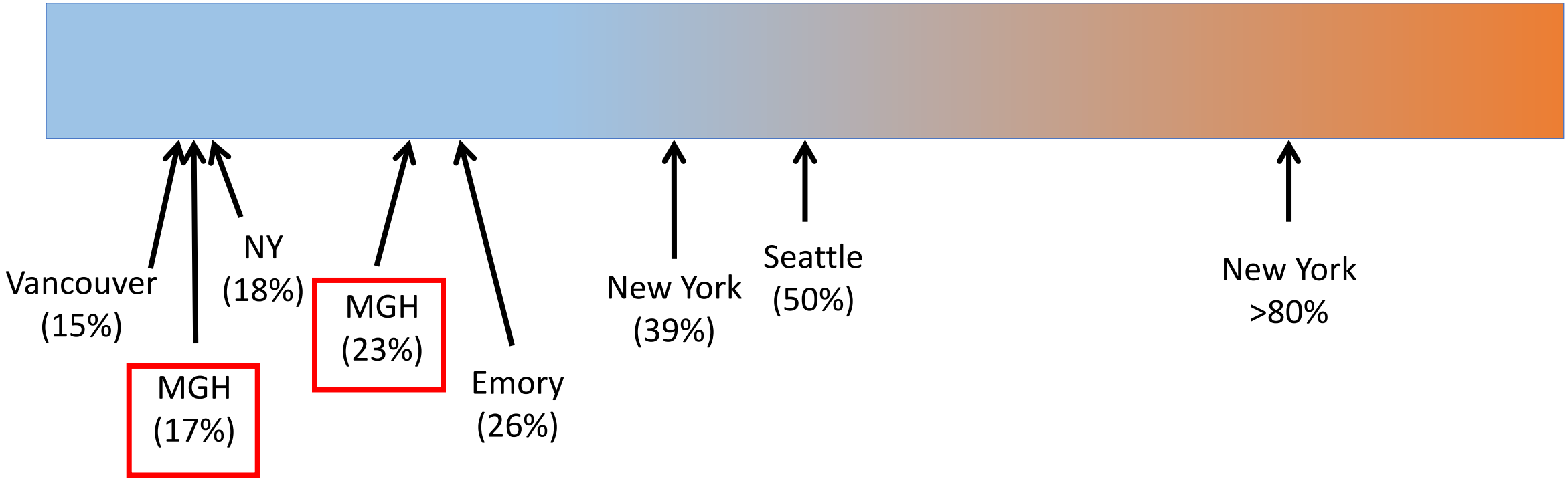
Hospitalization rates per 100,000 population by age and race and ethnicity — COVID-NET, March 1, 2020–October 24, 2020

Age Category	Non-Hispanic American Indian or Alaska Native		Non-Hispanic Black		Hispanic or Latino		Non-Hispanic Asian or Pacific Islander		Non-Hispanic White	
	Rate[1]	Rate Ratio[2,3]	Rate[1]	Rate Ratio[2,3]	Rate[1]	Rate Ratio[2,3]	Rate[1]	Rate Ratio[2,3]	Rate[1]	Rate Ratio[2,3]
0—17 years	13.6	3.3	20.9	5.1	28.6	**7.0**	8.4	2.0	4.1	1
18—49 years	307.3	7.6	215.1	5.3	311.8	**7.7**	64.6	1.6	40.5	1
50—64 years	704.5	**5.6**	593.4	4.7	680.4	5.4	189.7	1.5	126.0	1
65+ years	828.5	2.4	1168.2	**3.4**	904.8	2.6	368.5	1.1	347.3	1
Overall rate[4] (age-adjusted)	398.8	4.3	389.8	4.2	407.8	**4.4**	120.8	1.3	93.5	1

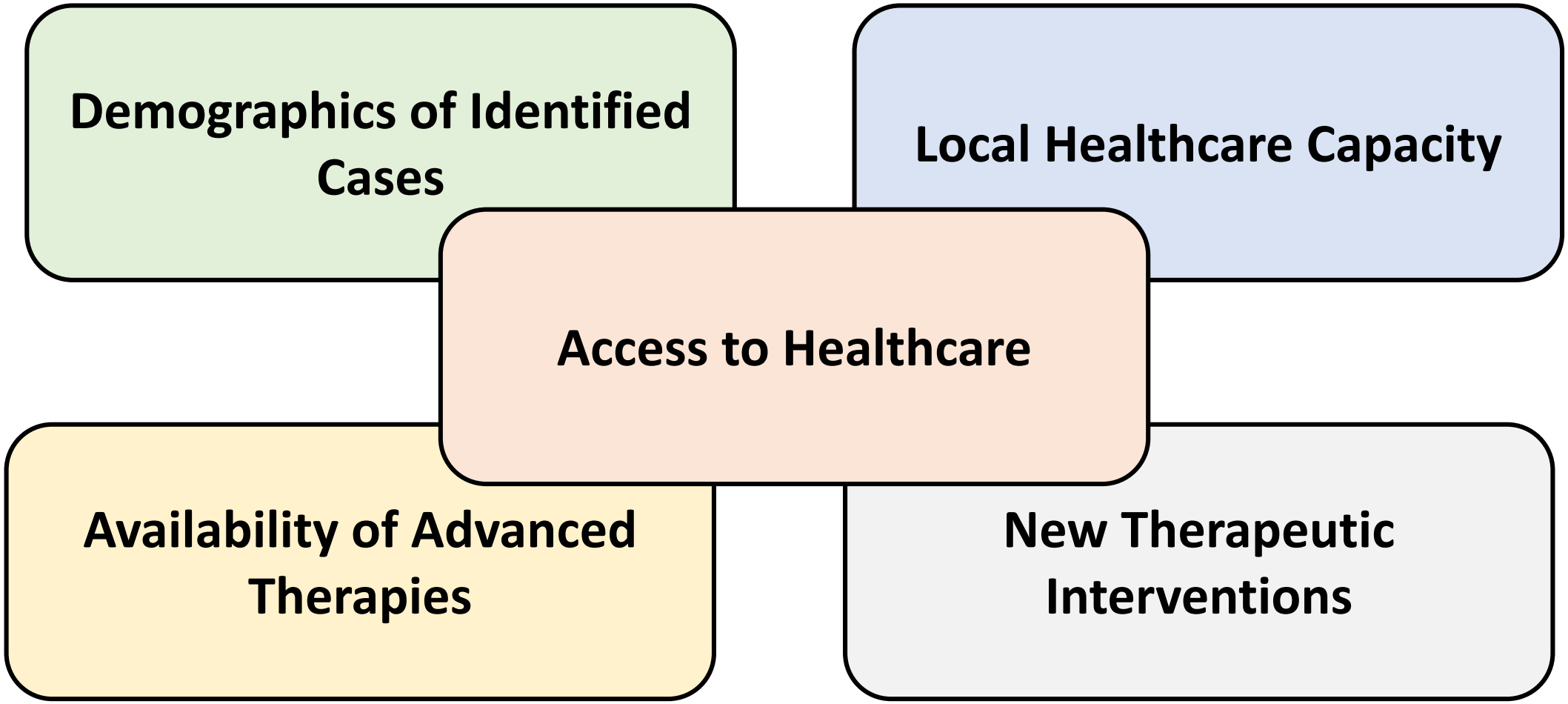
Weekly COVID-19-associated hospitalization rates by age group — COVID-NET, March 1–October 24, 2020



Are Outcomes Changing?



What Determines Outcomes?

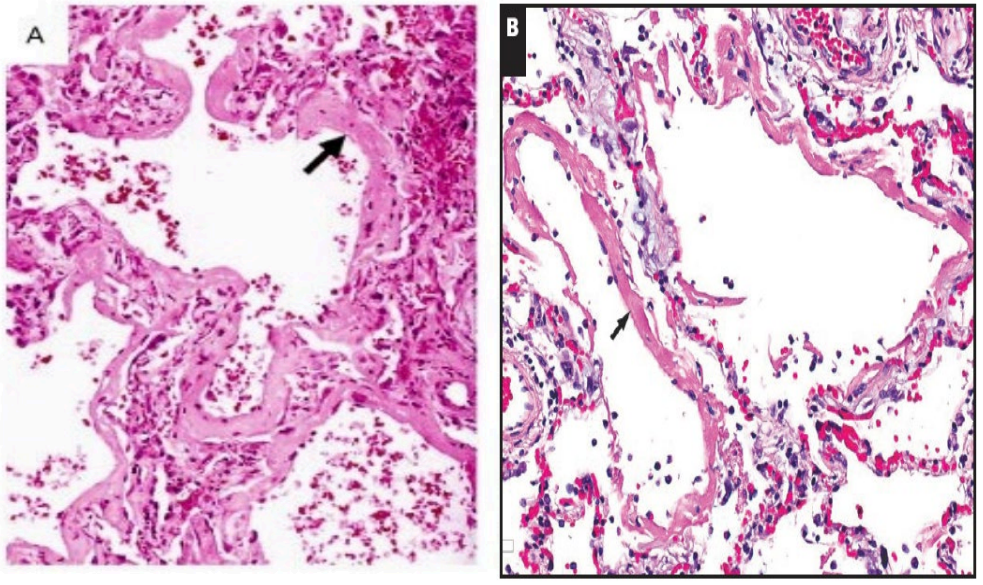


Critical Care Interventions

In the absence of an extremely effective pharmacologic intervention, what is the standard of care for critically ill COVID-19 patients? Does it improve outcomes?

COVID-19 Respiratory Failure is ARDS

Timing	Within 1 week of known clinical insult or new/worsening symptoms		
Chest Imaging	Bilateral opacities (not fully explained by effusions, lobar/lung collapse, nodules		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Oxygenation	Mild	Moderate	Severe
	200 < PaO2/FiO2 ≤ 300	100 < PaO2/FiO2 ≤ 200	PaO2/FiO2 ≤ 100



- Patients almost universally meet Berlin definition
- Majority of pathology samples have diffuse alveolar damage
- Reported mechanics and gas exchange similar to prior ARDS cohorts

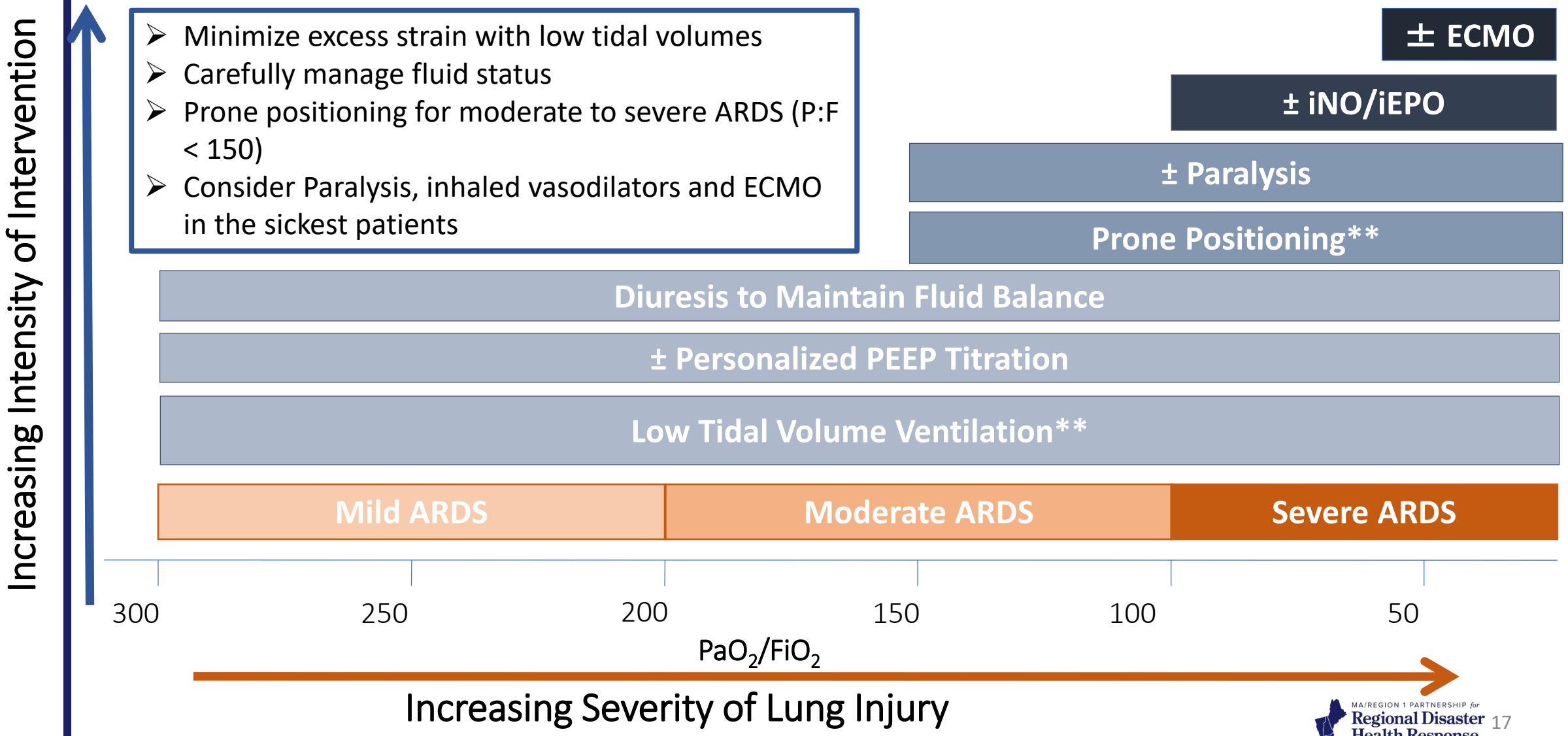
Ware & Matthay. NEJM 2000
Barton, et al. Am J Clin Path 2020
JAMA, 2012

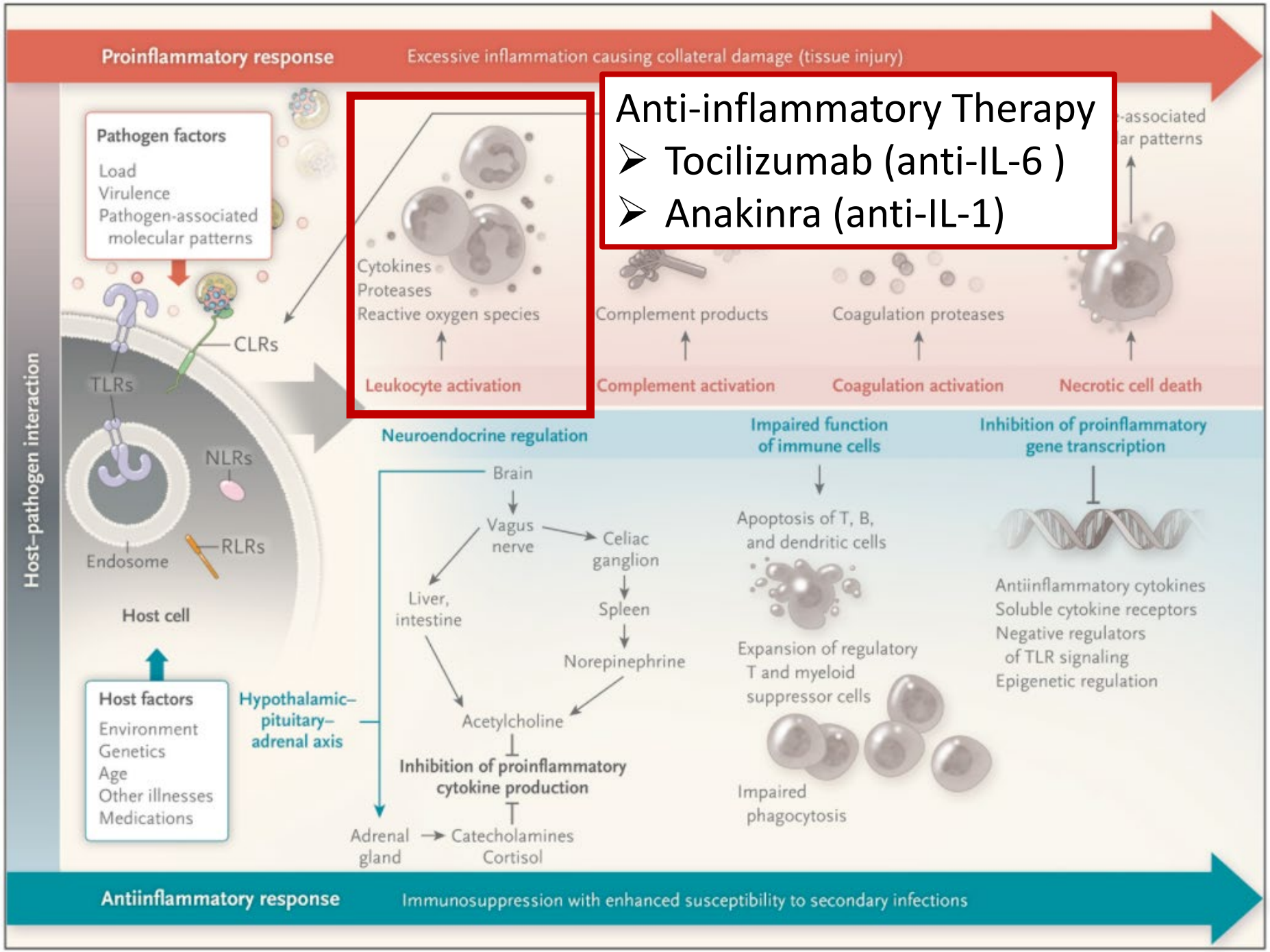
Critical Care Interventions

	PaO2/FiO2 Ratio (mean)	Compliance (mean, ml/cmH2O)
Guerin C , et al. NEJM, 2013	100	35
Bellani F, et al. JAMA, 2016	161	n/a
Graselli, et al. JAMA, 2020	160	n/a
Bhatraju, et al. NEJM, 2020	142	29
Ziehr et al AJRCCM, 2020	182	35

- Cohorts of COVID-19 ARDS patients fall into the range of other cohorts of ARDS
- Reported mortality rates, though incomplete, are also consistent with prior ARDS cohorts (16-40%)

Critical Care Interventions





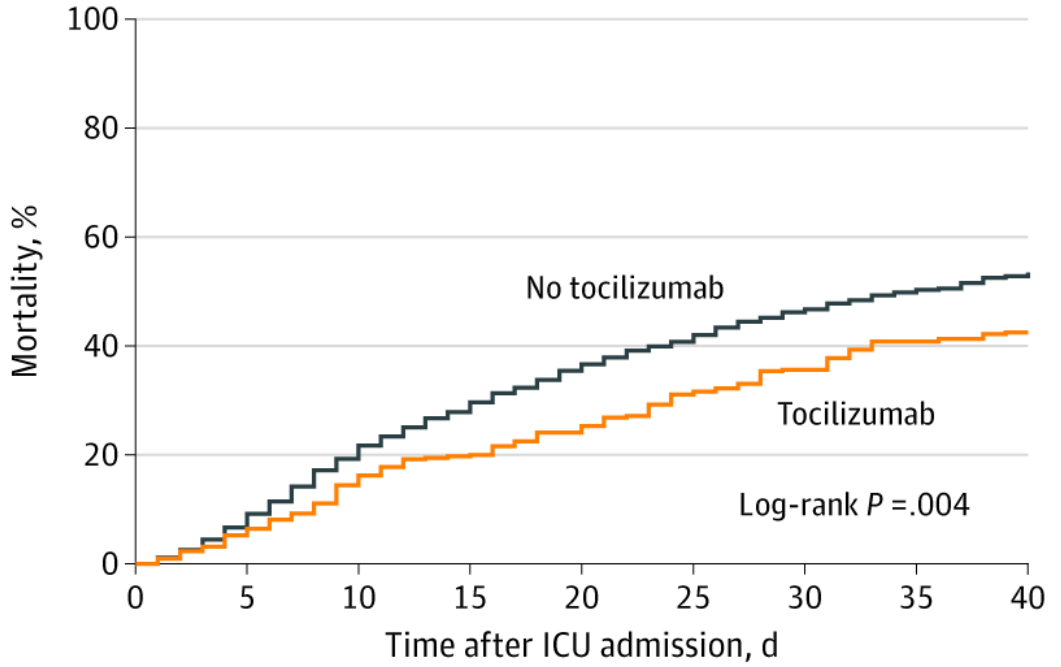
Anti-inflammatory Therapy

- Tocilizumab (anti-IL-6)
- Anakinra (anti-IL-1)

Angus D, NEJM, 2013

Tocilizumab

- Observational cohort of trial of 126 patients with COVID-19
- *Possible* association between tocilizumab and decreased mortality, concern that results may be confounded



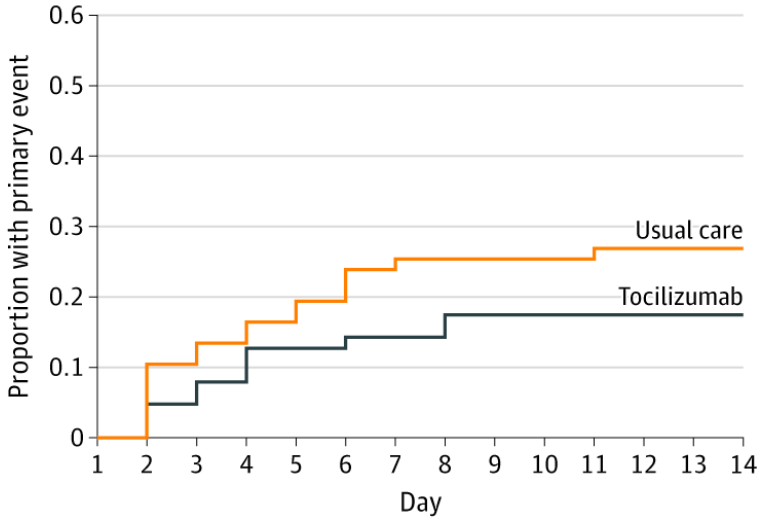
No. at risk					
Tocilizumab	419	311	190	110	50
No tocilizumab	3492	2460	1433	789	369

Gupta S, JAMA, 2020

Tocilizumab

- Randomized trial of 126 patients with COVID-19
- *May* reduce need for mechanical ventilation, no impact on survival

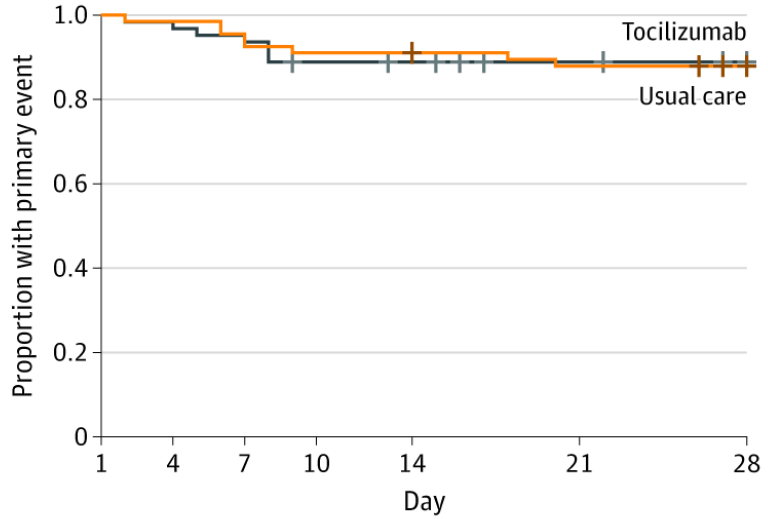
B Probability of death or MV at day 14



No. at risk

Tocilizumab	63	63	60	58	55	55	54	54	52	52	52	52	52	52
Usual care	67	67	60	58	56	54	51	50	50	50	50	49	49	49

C Probability of overall survival at day 28



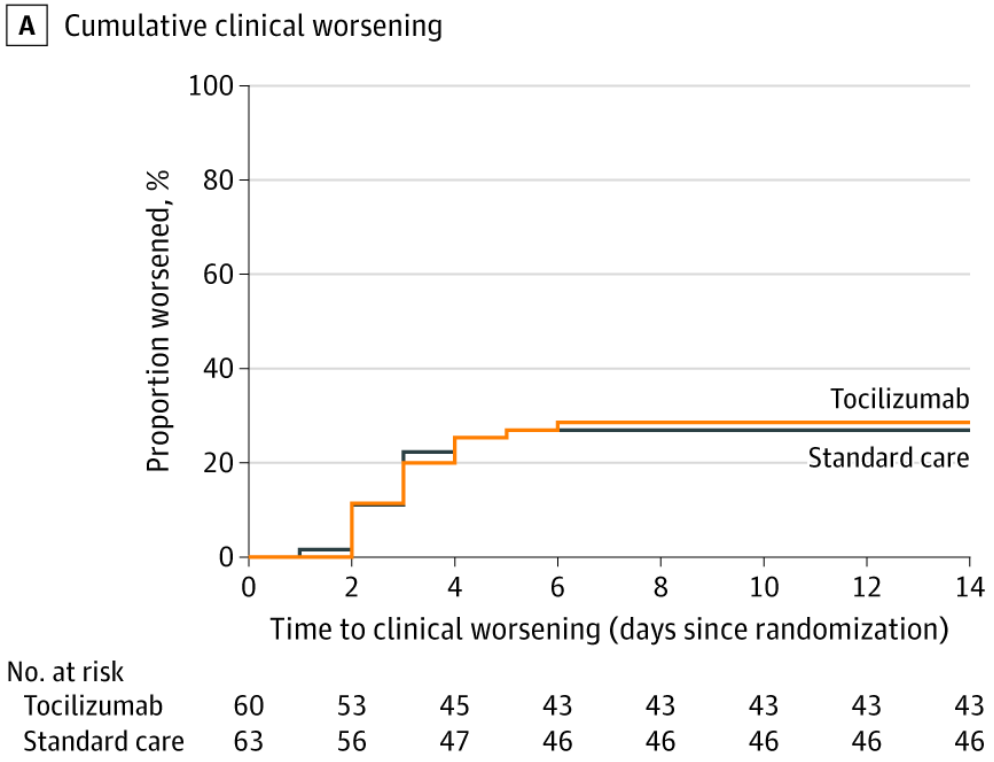
No. at risk

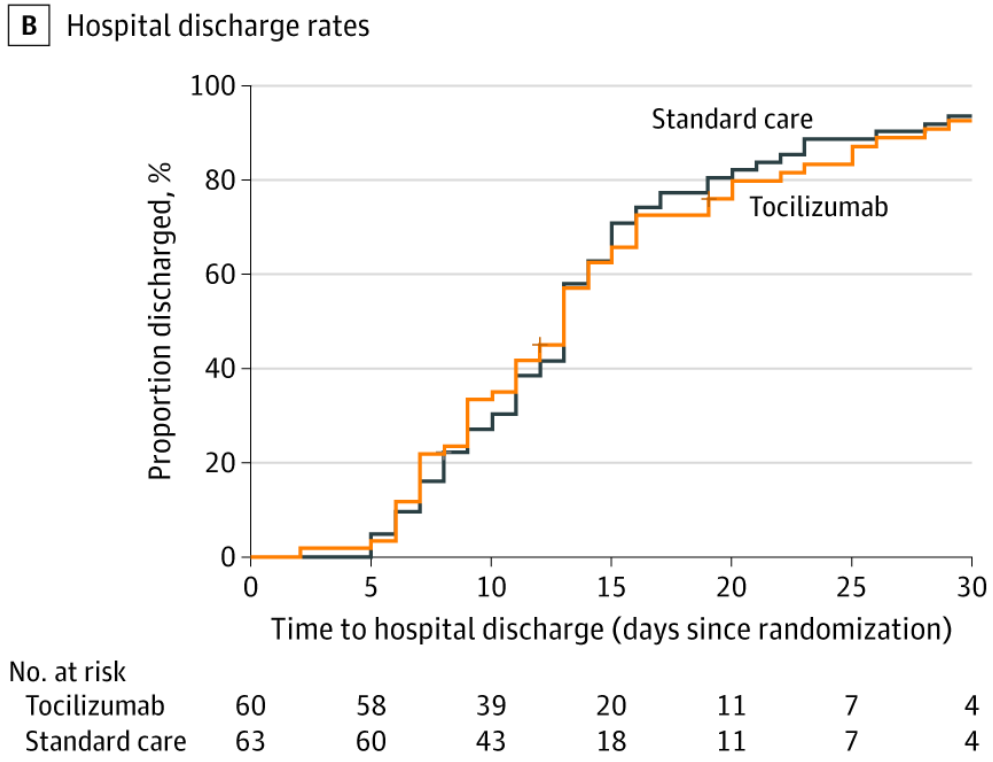
Tocilizumab	63	62	60	55	54	50	46
Usual care	67	66	64	61	61	56	50

Hermine O, JAMA, 2020

Tocilizumab

- Randomized trial of 126 patients with severe COVID-19 pneumonia
- No benefit observed

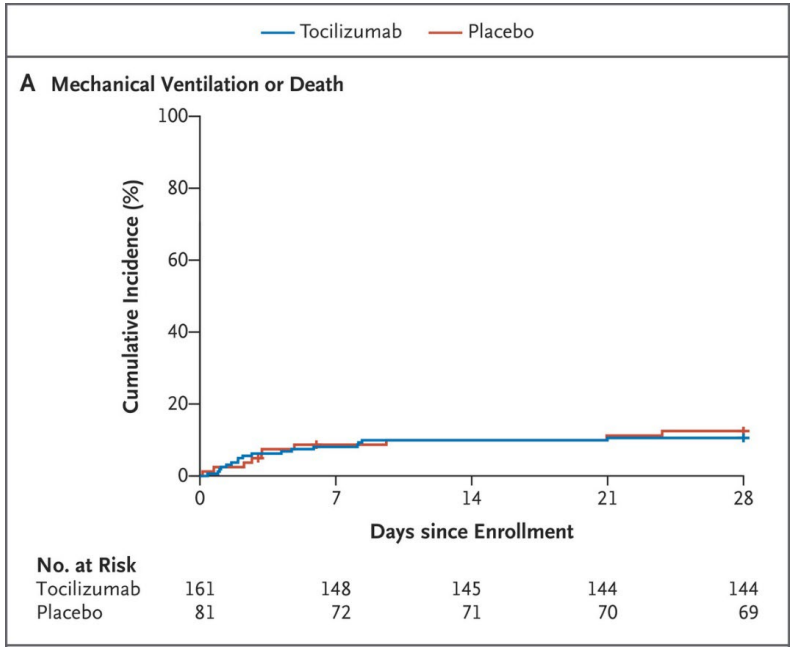


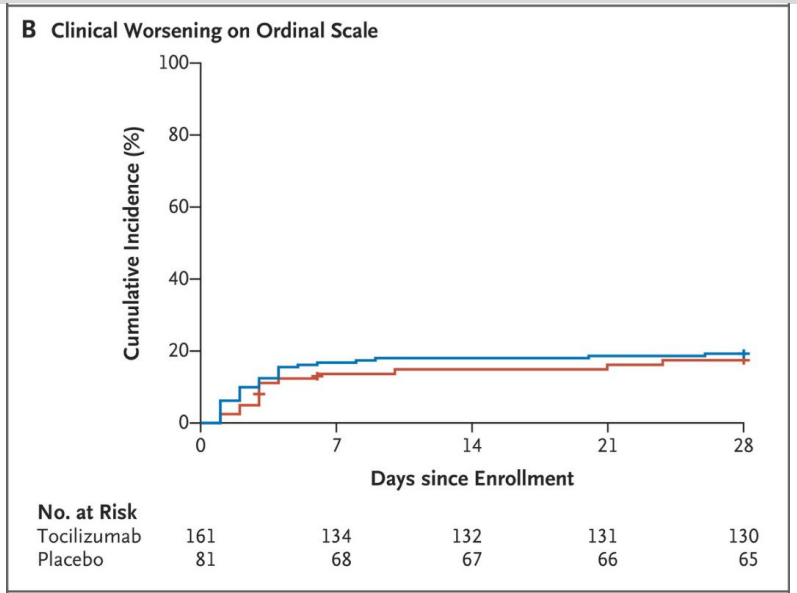


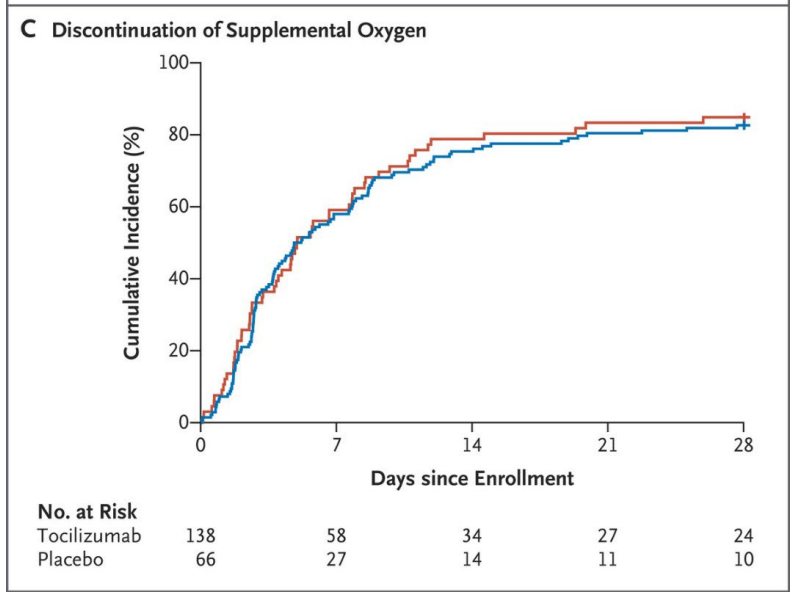
Salvarani C, JAMA, 2020

Tocilizumab

- Randomized trial of 243 patients with COVID-19 pneumonia
- No benefit observed







Stone JH, NEJM, 2020

Tocilizumab

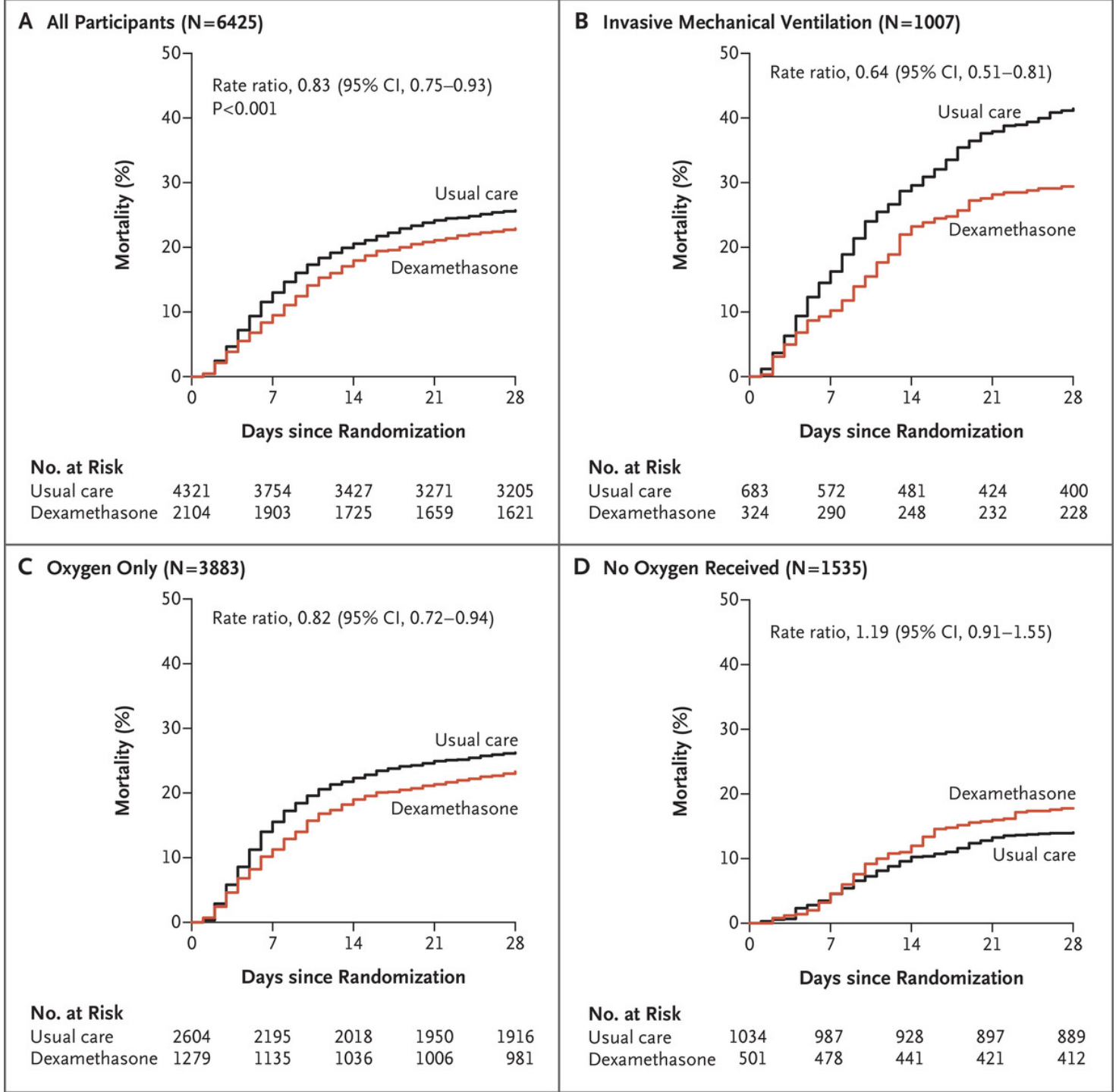
The Bottom Line

- The immune response to COVID-19 is complex and not all inflammation is bad
- Trial data available to date do not support the use of tocilizumab for patients with COVID-19 except in the context of a clinical trial
- There may be subgroups of patients who will benefit, but tocilizumab (or, similarly, anakinra) are unlikely to be a “magic bullet”

Dexamethasone

- Many studies over decades of steroids in non-COVID-19 respiratory failure and septic shock → decidedly mixed results
- Steroids are pleiotropic and in addition to non-specific immunosuppression and provide some adrenal support
- The mechanism of their action in critically ill patients, and of their potential benefit, remains poorly understood
- Many large studies of dexamethasone have demonstrated safety in patients with severe respiratory failure and shock

RECOVERY Group, NEJM, 2020



RECOVERY Trial

- Large, pragmatic trial that assigned > 6400 pts in 1:2 ratio to dexamethasone or usual care
- Overall, decreased mortality in the treatment group
- Benefit *<u>focused in patients requiring oxygen</u>* with possible harm signal in patients who did not receive oxygen

RECOVERY Group, NEJM, 2020

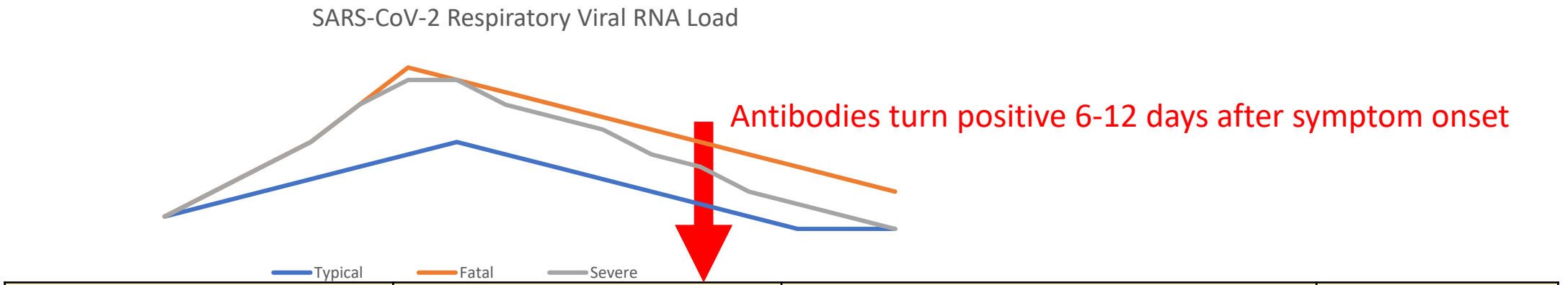
Dexamethasone

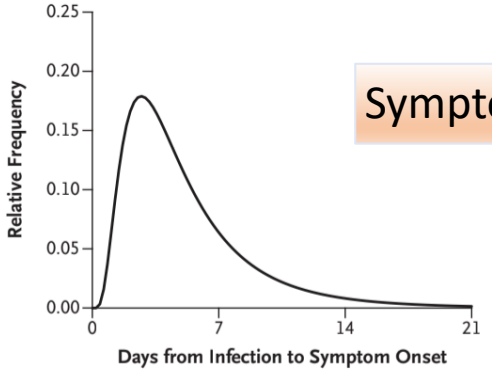
The Bottom Line

- Likely benefits patients who with COVID-19 who require supplemental oxygen and/or mechanical ventilation
- Substantial prior experience in critical illness is reassuring for safety, generic and cheap drug
- Unclear if there is a subgroup of patients who are *harmed* by steroids, and what the interaction may be with other therapeutic interventions
- No large, blinded study (gold standard), but may not be feasible to accomplish at this point

RECOVERY Group, NEJM, 2020

COVID-19 Disease Course





Symptom onset

Hallmarks: dyspnea, tachypnea, hypoxemia

* Acute Mild Phase: nonspecific symptoms. Most commonly fevers, cough, myalgias, fatigue. Nausea, diarrhea reported <50% of the time

Pan Lancet ID 2020 https://doi.org/10.1016/S1473-3099(20)30113-4
Zou NEJM 2020 DOI: 10.1056/NEJMc2001737
Zhou Lancet 2020 https://doi.org/10.1016/S0140-6736(20)30566-3
Li NEJM 2020 DOI: 10.1056/NEJMoa2001316
Wang JAMA 2020 doi:10.1001/jama.2020.1585
Siddiqi JHLT 2020 doi:10.1016/j.healun.2020.03.012
Wolfel Nature doi:10.1038/s41586-020-2196-x

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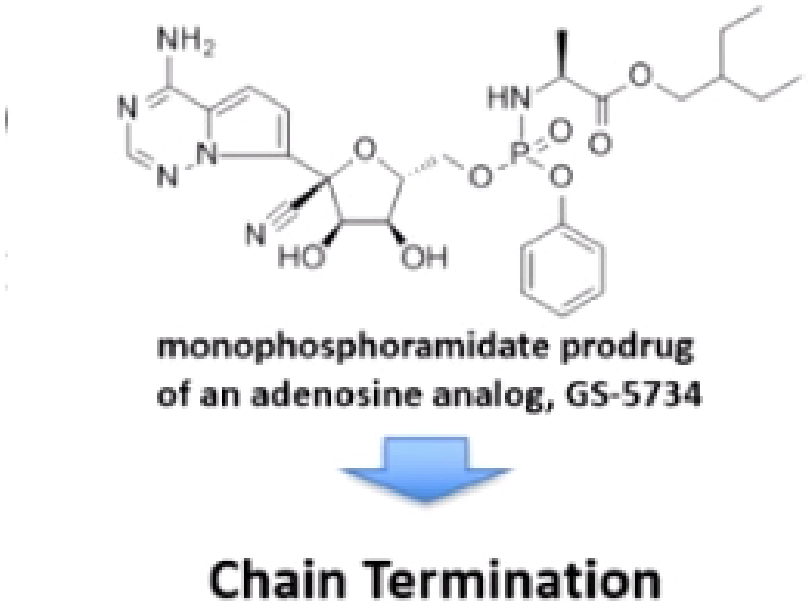
Remdesivir

- Received emergency use authorization by the FDA on May 1, 2020 and was approved on October 22, 2020
- It is a nucleotide prodrug that inhibits RNA-dependent RNA polymerase, the enzyme that is necessary to copy the genetic information of SARS-CoV-2, the virus that causes COVID-19
- Inhibitors of viral polymerases are used against other viruses such as HIV, HCV, and herpesviruses. Remdesivir has activity against Ebola and other coronaviruses
- It should be avoided in patients with ALT >= 10 x ULN
- eGFR < 30 is also a caution for remdesivir, which should be given when the benefits outweigh the risks



Remdesivir works like many antivirals that target the viral polymerase enzyme

Slide adapted from Arthur Kim, MD

Remdesivir (RDV) Data as of 11/4/2020

- Results from a randomized placebo-controlled trial from the NIH (ACTT-1) revealed:
  - Statistically significant reduction in time to recovery (11 days versus 15 days)
  - Non statistically significant reduction (HR 0.73) in mortality 6.7% (RDV) versus 11.9% (control)
  - Greatest benefit was seen in those on supplemental oxygen, compared to those on high-flow, NIPPV, or mechanical ventilation
- A large open-label (not blinded) randomized trial conducted did not show a statistically significant difference in outcomes; however this study has not yet been peer-reviewed

ACTT-1 Trial, NEJM 2020 Solidarity Trial pre-print

Slide courtesy of Arthur Kim, MD

Remdesivir – FDA Indications

- Treatment of COVID-19 in
  - Adults
  - Pediatric patients (12 years of age and older and weight at least 40 kg)
- Administered in a hospital or healthcare setting providing acute care comparable to inpatient hospital care
- Prior to starting need to check kidney function, liver function and prothrombin time (PT)

Remdesivir – FDA Indications

- 200 mg IV x 1 then 100 mg IV daily x 4-9 days
  - Not requiring invasive or mechanical ventilation or ECMO – 5 days total
  - Requiring invasive or mechanical ventilation or ECMO – 5 days with consideration to go 10 days depending on response
  - Okay to stop early if ready to go home
- Not recommended in patients with eGFR < 30 mL/min
- Side effects: infusion reaction, increased liver tests, potential for kidney dysfunction

NIH Guidelines

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] *or* **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**

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

NIH Guidelines

Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] *or* **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** *or* **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

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

Remdesivir –Emergency Use Authorization

- Pediatric patients < 12 years old and ≥ 3.5 kg
- Pediatric patients < 18 years old and < 40Kg
- Need assent from the patient and/or family member
- Patient info sheet must be given to patient and/or family member
- Documentation of assent and monitoring

https://www.gilead.com/remdesivir

Monoclonal Antibodies

- SARS-CoV-2 gains entry into cells through binding of its spike protein to receptors for angiotensin-converting enzyme 2 on target cells.

- Lilly product: LY-CoV555 (also known as LY3819253)
  - Anti-spike neutralizing monoclonal antibody that binds with high affinity to the receptor-binding domain
  - Derived from convalescent plasma obtained from a patient with Covid-19.
  - Passive protection against SARS-CoV-2 in nonhuman primates

- Regeneron product (REGN-COV2)
  - Monoclonal antibody cocktail

Chen P et al. NEJM 2020 ; Regeneron press release

Monoclonal Antibodies – Lilly Data

- Phase 2 preliminary data
- Outpatients
- Decreased viral load by day 11 more than placebo
- Decreased ED and hospital admissions in the 29 day follow-up
  - 1.6% (5 of 309) in monoclonal group vs 6.3% (9 of 143) in placebo group
  - High-risk patients (≥65 yo or a BMI ≥35) had the greatest benefit
- Well tolerated overall
  - Nausea was the most common (3.9%)
  - Infusion-related reactions

Chen P et al. NEJM 2020

Monoclonal Antibodies – Regeneron data

- Press release on Phase 2/3 trials
- Outpatients
- Reduces viral load and medical visits compared to placebo
  - Medical visits decreased to 2.8% in study vs 6.5% in placebo
- Most benefit in: higher viral load, pre-existing risk factors, or weak antibody response
- Adverse events
  - Infusion reactions

Monoclonal Antibodies – Inpatient data

- Inpatient trials halted due to safety concerns and lack of utility

Monoclonal Antibodies in a Nutshell

- Monoclonal antibodies against SARS-CoV-2 bind the virus and are part of a good immune response to COVID-19
- They are likely helpful earlier in disease
- They were not found to be helpful in hospitalized patients
- If offered under an emergency use authorization, permission or “assent” is required from patient or your family
- If receiving the medication, will need to be monitored closely
- Some patients may experience an infusion reaction that passes

Slide courtesy of Arthur Kim, MD

What is an Emergency Use Authorization (EUA)?

- Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives.
- Until full FDA-approval, agents under EUA are considered investigational
- Those receiving agents under EUA are not consenting to a study protocol but teams should obtain assent from patients or their families before writing the EPIC order

https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

Slide courtesy of Arthur Kim, MD

Vaccines

- Several vaccines in Phase 3 trials in the US
- Using several platforms
  - Inactivated vaccine (e.g. pertussis)
  - Live-attenuated vaccine (e.g. measles)
  - Protein subunit vaccines (e.g. hepatitis B)
  - DNA-based and RNA-based strategies

Vaccines

- Will need to await trial data for safety
- Followed by potential emergency use authorization
- Will need to prioritize recipients given initial limited supply
  - https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf

Questions?

MA/REGION 1 PARTNERSHIP *for*
Regional Disaster Health Response

THANK YOU!

To contact the MA/Region 1 Partnership:
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www.rdhrs.org