COVID-19 Update from an Infectious Diseases Perspective

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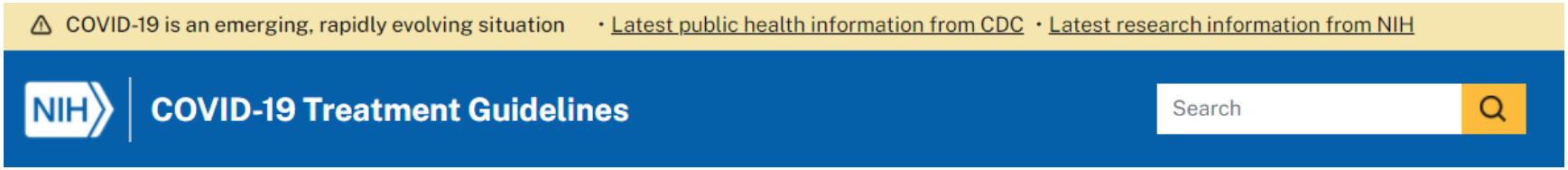
Disclaimers

- No conflicts of interest related to this presentation
- Data/knowledge on COVID-19 constantly evolving so information presented today as current as possible
- Too much data/information!
  - Focus will be highlights, key studies, and recent updates on ID-related management in adults



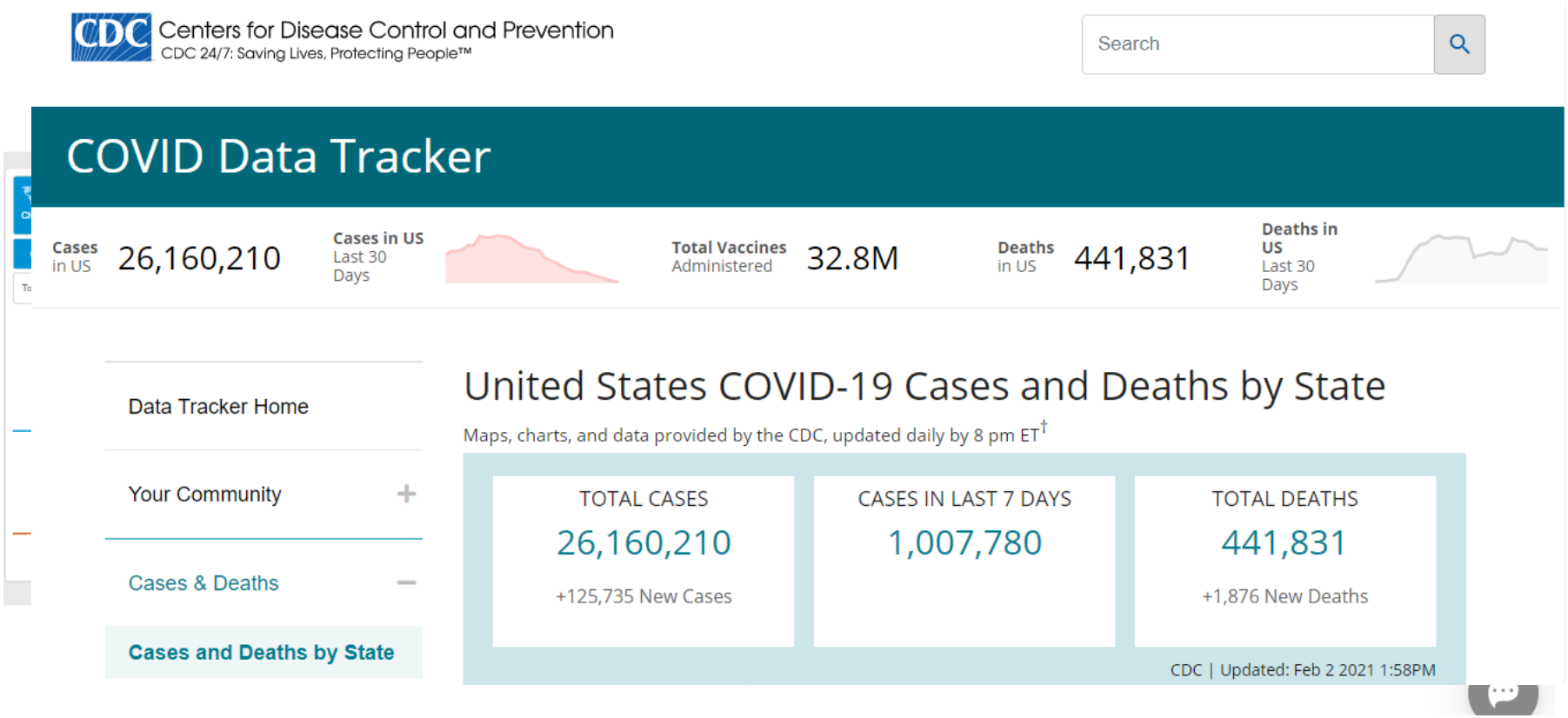
Objectives

- Review what we have learned about COVID-19 and what NOT to use (at least as of today)
- Discuss the current guidelines and evidence-based treatment options for hospitalized patients with COVID-19
- Evaluate the role of monoclonal antibodies for COVID-19
- Review the literature and operational considerations for COVID-19 vaccines and vaccine candidates

Introduction

- COVID-19 – disease caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  - Single-stranded RNA virus
  - Most common coronaviruses in clinical practice before this caused common colds
  - SARS-CoV-2 – 3rd coronavirus to cause severe disease
    - Severe acute respiratory syndrome (SARS) – 2002-2003
    - Middle East respiratory syndrome (MERS) – 2012

Statistics


CDC
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
Search
COVID Data Tracker
Cases in US 26,160,210
Cases in US Last 30 Days
Total Vaccines Administered 32.8M
Deaths in US 441,831
Deaths in US Last 30 Days
Data Tracker Home
Your Community
Cases & Deaths
Cases and Deaths by State
United States COVID-19 Cases and Deaths by State
Maps, charts, and data provided by the CDC, updated daily by 8 pm ET†
TOTAL CASES
26,160,210
+125,735 New Cases
CASES IN LAST 7 DAYS
1,007,780
TOTAL DEATHS
441,831
+1,876 New Deaths
CDC | Updated: Feb 2 2021 1:58PM

Pathophysiology

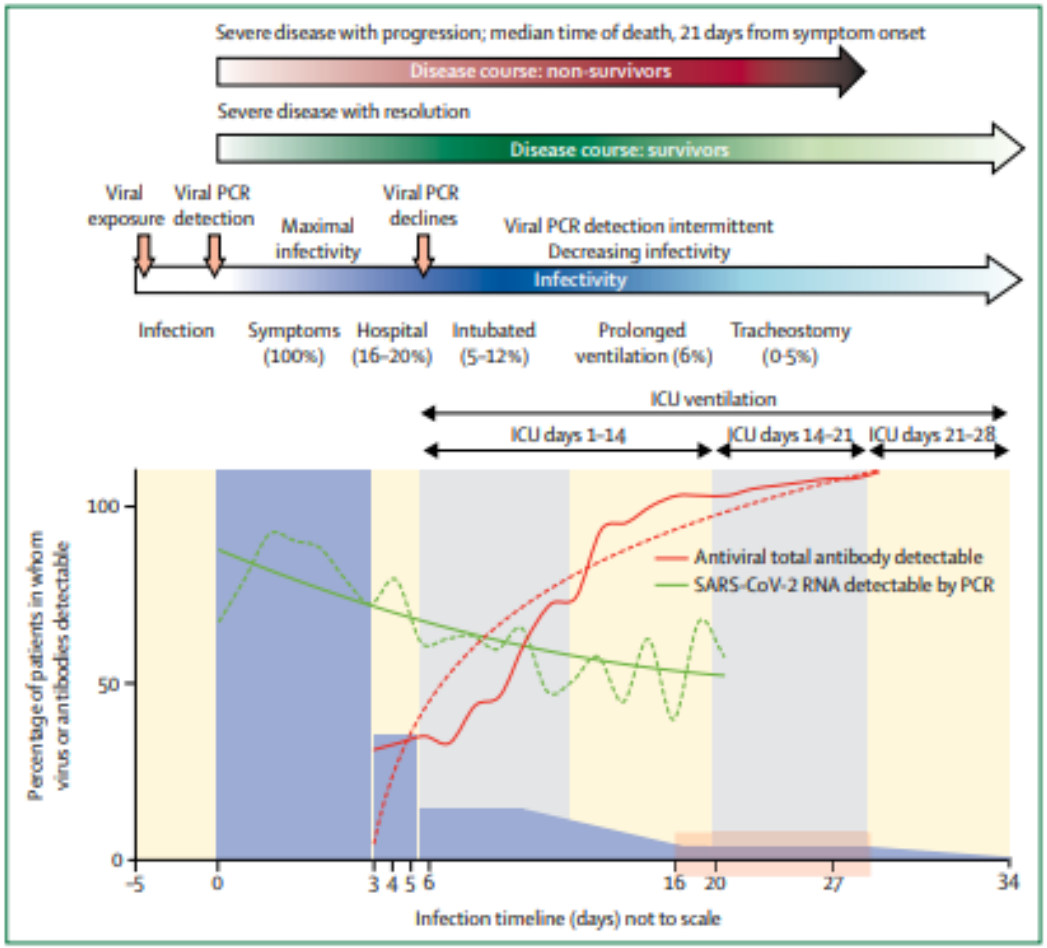
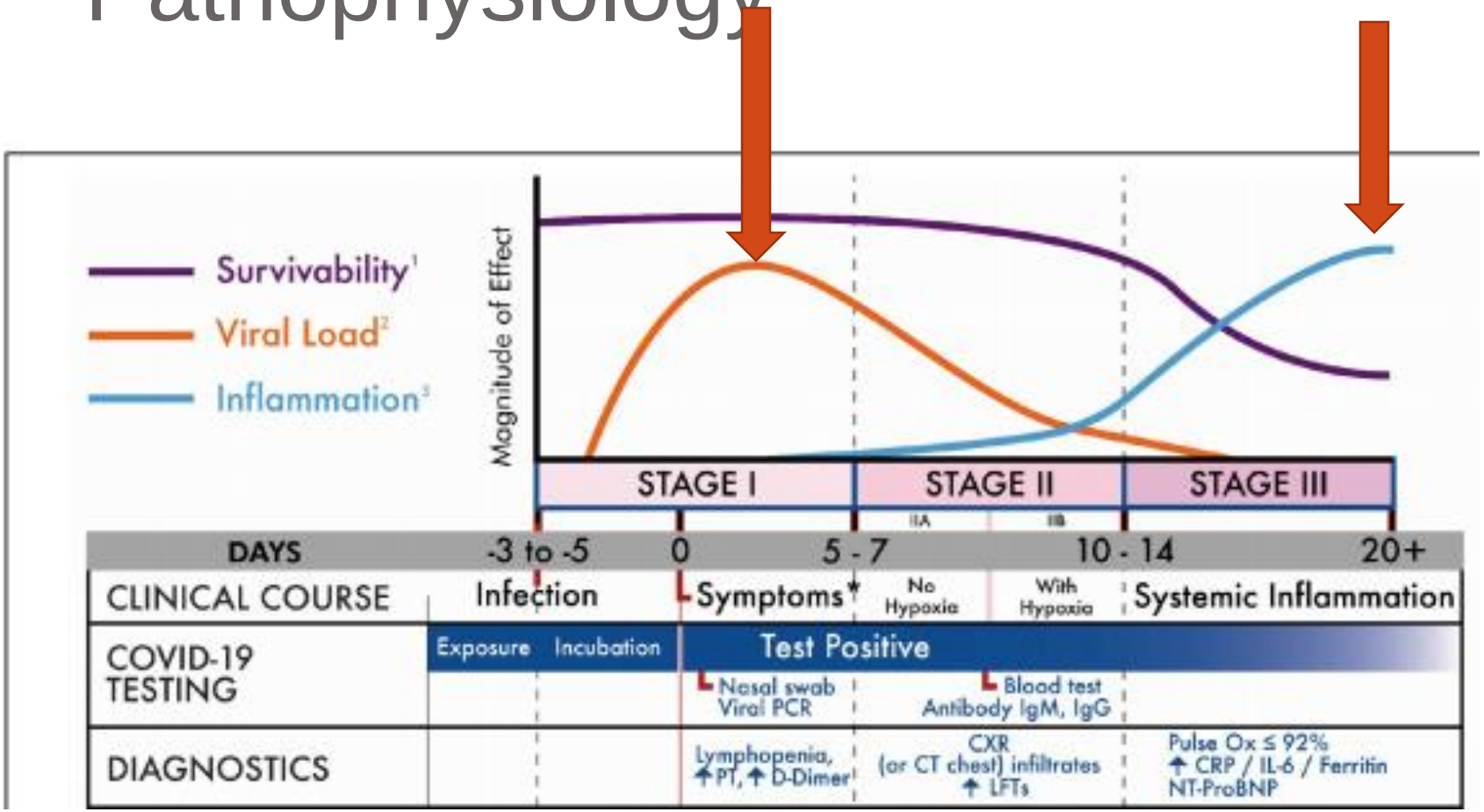


Figure 1: **Typical clinical course, viral PCR, and antiviral antibody detection and infectivity of severe SARS-CoV-2 infection**

McGrath, et al. *Lancet Resp Med.* July 2020.

Pathophysiology



Parasher. *Postgrad Med J.* Sept 2020.

Assessment Question #1

- Which of the following is the only medication to be recommended as a AI recommendation in current NIH COVID-19 treatment guidelines?
  A. Remdesivir
  B. Dexamethasone
  C. Tocilizumab
  D. Bamlanivimab
  E. Hydroxychloroquine

Outline

- Repurposed drugs
- Treatments aimed at inflammatory/immune response to virus
- Monoclonal antibodies
- Vaccines

Repurposed Drugs

- In vitro activity = in vivo activity?
  - Hydroxychloroquine (w or w/o azithromycin)
    - In vitro studies – inhibition of fusion of SARS-CoV2 and host cell membrane[1]
    - Initial small, open-label trial in pre-print showed promising results[2,3] → EUA end of March 2020
    - Reports of adverse effects and lack of efficacy[4,5]
    - EUA revoked 6/15/20

1. Wang, et al. *Cell Res.* 2020.
2. Saag. *JAMA.* 2020
3. Gautret, et al. *Intl J Antimicrob Ag.* 2020.
4. Rosenberg, et al. *JAMA.* 2020.
5. Magagnoli, et al. *Med (N.Y.).* 2020.

Repurposed Drugs

- Lopinavir/ritonavir
  - In vitro studies – inhibition of protease SARS-CoV2 needs for replication[1]
  - Concentrations achieved with usual doses far below (60-120-fold) needed to inhibit SARS-CoV2 replication[1,2]
  - Early observational studies from China did not show benefit[1,3]

1. Yao, et al. *J Med Virol.* 2020.
2. Schoergenhofer, et al. *Ann Intern Med.* 2020.
3. Cao, et al. *NEJM.* 2020.

Repurposed Drugs

- March 20, 2020 – WHO announced launch of SOLIDARITY
  - Large, international, open-label, randomized, adoptive trial
  - Evaluate effects of 4 drugs on hospital mortality:
    - Remdesivir
    - Hydroxychloroquine
    - Lopinavir
    - Interferon beta-1a
  - Trials for hydroxychloroquine, lopinavir, and interferon discontinued for futility on June 19, July 4, and October 16, 2020

Remdesivir

- Inhibitor of viral RNA-dependent, RNA polymerase – affects viral replication
- Repurposed drug – did not work well for Ebola but in vitro activity against SARS-CoV2 and animal studies suggested lower viral loads and less lung damage when given early
- Several clinical trials
  - ACTT-1
  - SOLIDARITY

ACTT-1 Trial

- Randomized, placebo-controlled, double-blind
- Enrolled 1062 hospitalized patients with COVID-19 and evidence of LRTI in 60 international trial sites (45 in US) from Feb 21 – April 19, 2020
- Patients clinical status assessed daily with 8-category ordinal scale for 28 days
- Outcomes
  - Primary – Time to recovery (category 1-3 – not hospitalized or hospitalized but not for COVID-19 treatment)
  - Key secondary
    - Clinical status at day 15
    - Mortality at 15 and 29 days

Beigel, et al. *NEJM.* 2020.

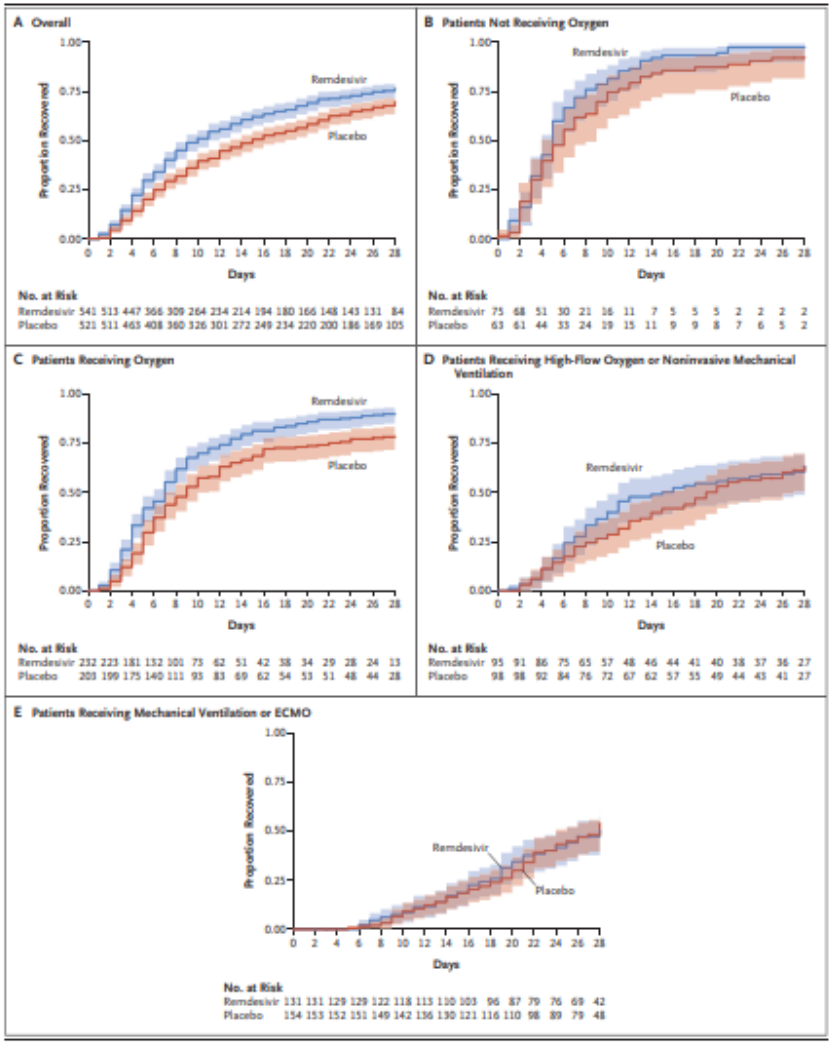
ACTT-1 Trial

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All (N=1062)	Remdesivir (N=541)	Placebo (N=521)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.4)	352 (65.1)	332 (63.7)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	135 (12.7)	79 (14.6)	56 (10.7)
Black or African American	226 (21.3)	109 (20.1)	117 (22.5)
White	566 (53.3)	279 (51.6)	287 (55.1)
Hispanic or Latino — no. (%)	250 (23.5)	134 (24.8)	116 (22.3)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	194/1048 (18.5)	97/531 (18.3)	97/517 (18.8)
One	275/1048 (26.2)	138/531 (26.0)	137/517 (26.5)
Two or more	579/1048 (55.2)	296/531 (55.7)	283/517 (54.7)
Coexisting conditions — no./total no. (%)			
Type 2 diabetes	322/1051 (30.6)	164/532 (30.8)	158/519 (30.4)
Hypertension	533/1051 (50.7)	269/532 (50.6)	264/519 (50.9)
Obesity	476/1049 (45.4)	242/531 (45.6)	234/518 (45.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	138 (13.0)	75 (13.9)	63 (12.1)
5. Hospitalized, requiring supplemental oxygen	435 (41.0)	232 (42.9)	203 (39.0)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	193 (18.2)	95 (17.6)	98 (18.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	285 (26.8)	131 (24.2)	154 (29.6)
Baseline score missing	11 (1.0)	8 (1.5)	3 (0.6)

Beigel, et al. *NEJM.* 2020.

ACTT-1 Trial



Beigel, et al. *NEJM.* 2020.

ACTT-1 Trial

Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=541)	Placebo (N=521)	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
Recovery										
No. of recoveries	399	352	73	58	206	156	57	61	63	77
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)	5 (4–6)	6 (4–7)	7 (6–8)	9 (7–10)	15 (10–27)	20 (14–26)	29 (24–NE)	28 (24–NE)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])		1.29 (0.91–1.83)		1.45 (1.18–1.79)		1.09 (0.76–1.57)		0.98 (0.70–1.36)	
Mortality through day 14‡										
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)		0.42 (0.04–4.67)		0.28 (0.12–0.66)		0.82 (0.40–1.69)		0.76 (0.39–1.50)	
No. of deaths by day 15	35	61	1	2	7	21	13	17	14	21
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)	1.3 (0.2–9.1)	3.2 (0.8–12.1)	3.1 (1.5–6.4)	10.5 (7.0–15.7)	14.2 (8.5–23.2)	17.3 (11.2–26.4)	10.9 (6.6–17.6)	13.8 (9.2–20.4)
Mortality over entire study period‡										
Hazard ratio (95% CI)	0.73 (0.52–1.03)		0.82 (0.17–4.07)		0.30 (0.14–0.64)		1.02 (0.54–1.91)		1.13 (0.67–1.89)	
No. of deaths by day 29	59	77	3	3	9	25	19	20	28	29
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)	4.1 (1.3–12.1)	4.8 (1.6–14.3)	4.0 (2.1–7.5)	12.7 (8.8–18.3)	21.2 (14.0–31.2)	20.4 (13.7–29.8)	21.9 (15.7–30.1)	19.3 (13.8–26.5)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	157 (29.0)	115 (22.1)	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
2	117 (21.6)	102 (19.6)	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
3	14 (2.6)	8 (1.5)	8 (10.7)	4 (6.3)	6 (2.6)	4 (2.0)	0	0	0	0
4	38 (7.0)	33 (6.3)	3 (4.0)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
5	58 (10.7)	60 (11.5)	3 (4.0)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)
6	28 (5.2)	24 (4.6)	1 (1.3)	0	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
7	95 (17.6)	121 (23.2)	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
8	34 (6.3)	58 (11.1)	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.5 (1.2–1.9)		1.5 (0.8–2.7)		1.6 (1.2–2.3)		1.4 (0.9–2.3)		1.2 (0.8–1.9)	

Beigel, et al. *NEJM.* 2020.

ACTT-1 Trial

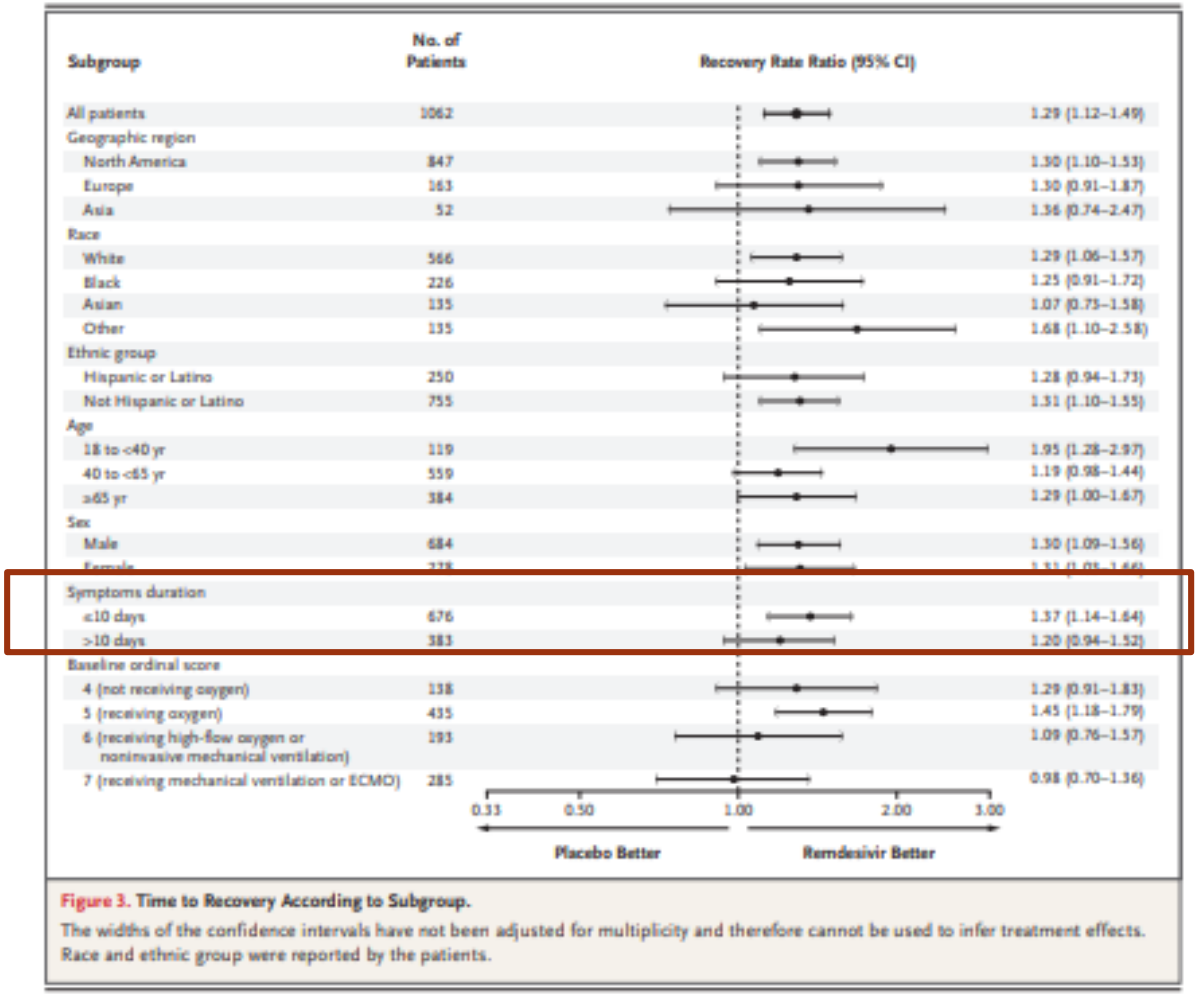


Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients.

Beigel, et al. *NEJM.* 2020.

Remdesivir

- ACTT-1 trial led to FDA approval on Oct 22 for treatment of adults and pediatric patients ≥12 years old and weighing ≥40 kg requiring hospitalization for COVID-19

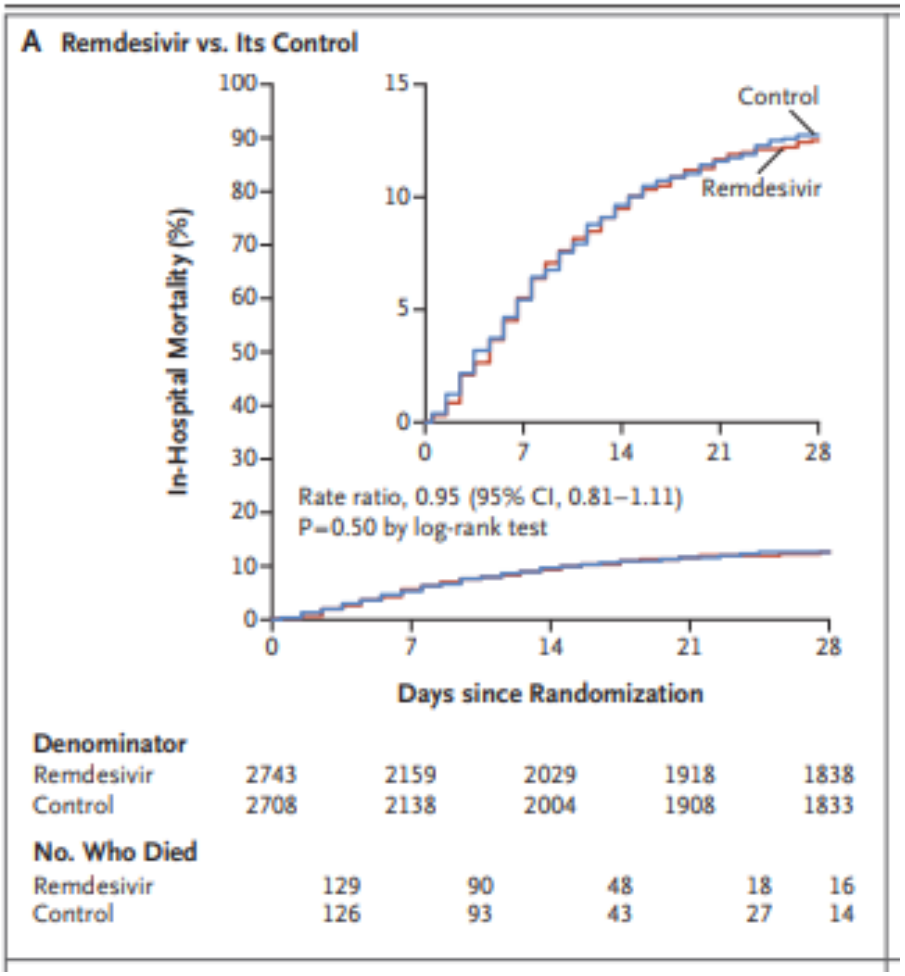
- However, SOLIDARITY trial…

SOLIDARITY Trial – Interim

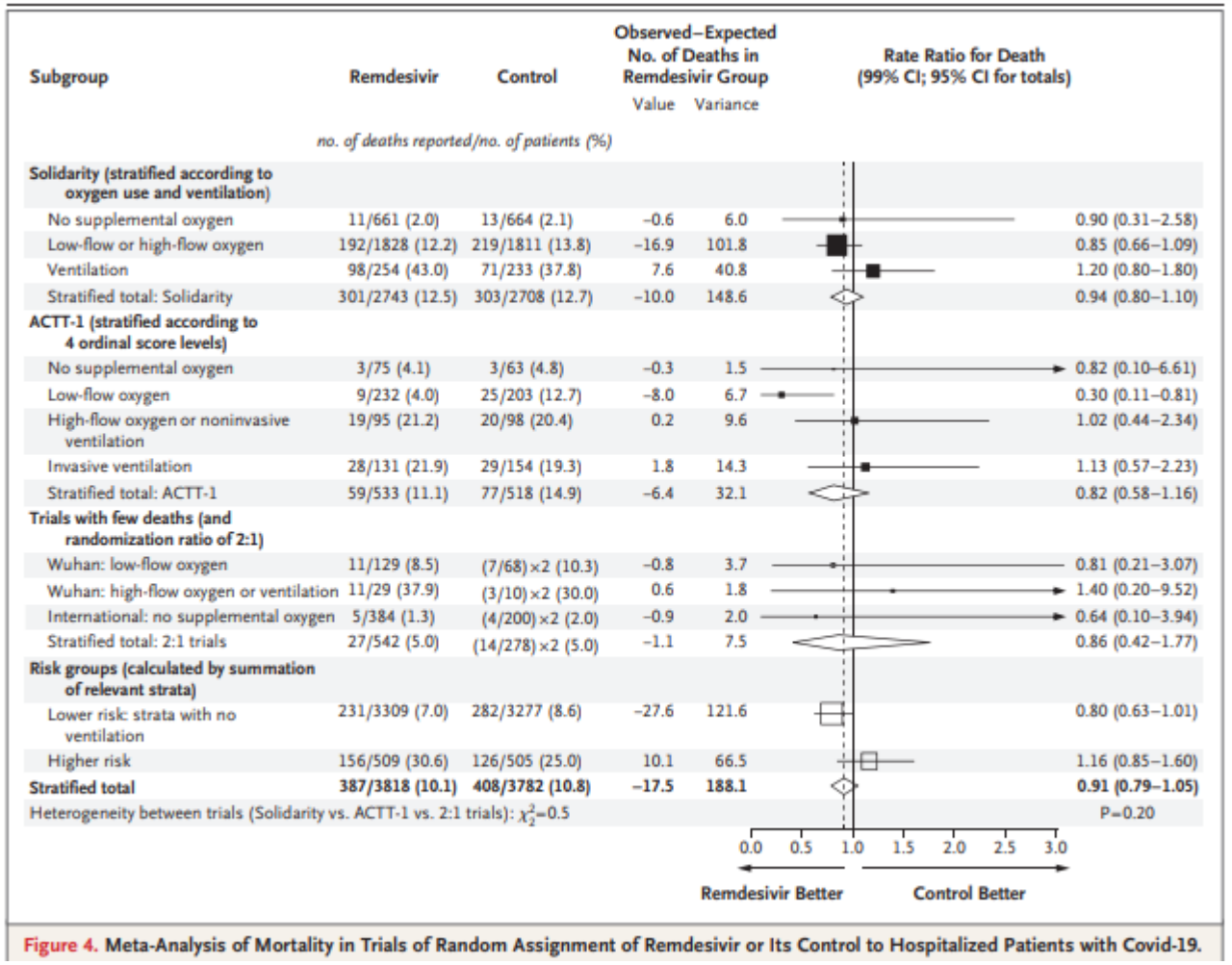
- Randomized, open-label, adaptive
- Enrolled 11,330 hospitalized patients with COVID-19 in 30 countries (405 hospitals) from March 22 – October 4, 2020
  - 2743 randomized to remdesivir, 2708 to standard of care
    - ~48% in each group received corticosteroids
- Outcomes
  - Primary – In-hospital mortality – 11% vs. 11.1% (p=0.50)
  - Secondary
    - Initiation of mechanical ventilation – 10.8 vs. 10.5%
    - Duration of hospitalization – no difference

WHO Solidarity Trial Consortium. *NEJM.* 2020.

SOLIDARITY Trial – Interim



SOLIDARITY Trial – Interim

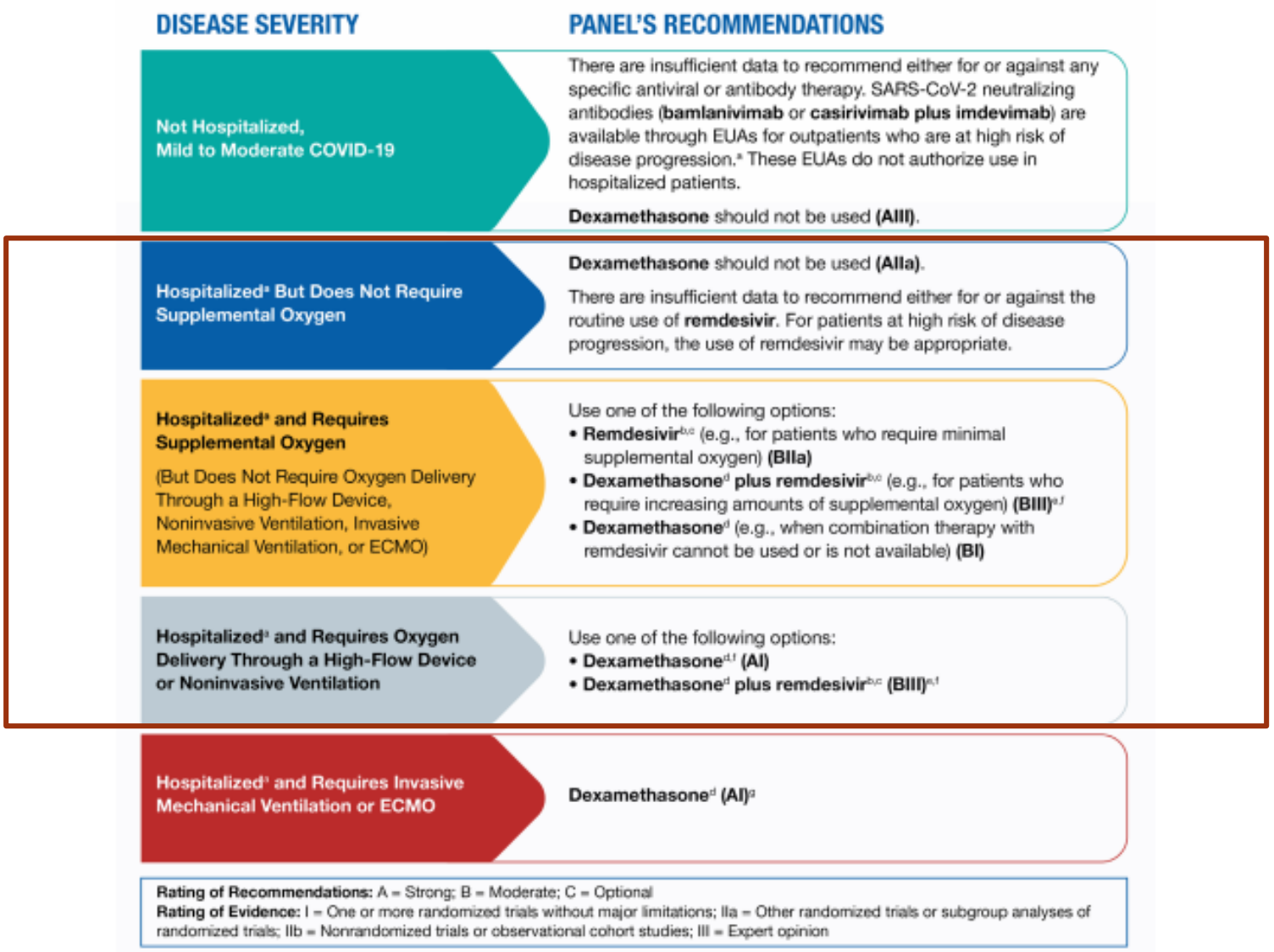


Subgroup	Remdesivir	Control	Observed–Expected No. of Deaths in Remdesivir Group: Value	Observed–Expected No. of Deaths in Remdesivir Group: Variance	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (2.1)	−0.6	6.0	0.90 (0.31–2.58)
Low-flow or high-flow oxygen	192/1828 (12.2)	219/1811 (13.8)	−16.9	101.8	0.85 (0.66–1.09)
Ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Stratified total: Solidarity	301/2743 (12.5)	303/2708 (12.7)	−10.0	148.6	0.94 (0.80–1.10)
ACTT-1 (stratified according to 4 ordinal score levels)					
No supplemental oxygen	3/75 (4.1)	3/63 (4.8)	−0.3	1.5	0.82 (0.10–6.61)
Low-flow oxygen	9/232 (4.0)	25/203 (12.7)	−8.0	6.7	0.30 (0.11–0.81)
High-flow oxygen or noninvasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 (0.44–2.34)
Invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.8	14.3	1.13 (0.57–2.23)
Stratified total: ACTT-1	59/533 (11.1)	77/518 (14.9)	−6.4	32.1	0.82 (0.58–1.16)
Trials with few deaths (and randomization ratio of 2:1)					
Wuhan: low-flow oxygen	11/129 (8.5)	(7/68)×2 (10.3)	−0.8	3.7	0.81 (0.21–3.07)
Wuhan: high-flow oxygen or ventilation	11/29 (37.9)	(3/10)×2 (30.0)	0.6	1.8	1.40 (0.20–9.52)
International: no supplemental oxygen	5/384 (1.3)	(4/200)×2 (2.0)	−0.9	2.0	0.64 (0.10–3.94)
Stratified total: 2:1 trials	27/542 (5.0)	(14/278)×2 (5.0)	−1.1	7.5	0.86 (0.42–1.77)
Risk groups (calculated by summation of relevant strata)					
Lower risk: strata with no ventilation	231/3309 (7.0)	282/3277 (8.6)	−27.6	121.6	0.80 (0.63–1.01)
Higher risk	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 (0.85–1.60)
Stratified total	**387/3818 (10.1)**	**408/3782 (10.8)**	**−17.5**	**188.1**	**0.91 (0.79–1.05)**
Heterogeneity between trials (Solidarity vs. ACTT-1 vs. 2:1 trials): χ^2_2=0.5					P=0.20

Figure 4. Meta-Analysis of Mortality in Trials of Random Assignment of Remdesivir or Its Control to Hospitalized Patients with Covid-19.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnote.



NIH COVID-19 Treatment Guidelines. Last update Jan 14, 2021.

Remdesivir Safety

- Adverse effect profile similar in ACTT-1 trial
- Transaminase elevations (2-8%)
  - Per package insert, consider discontinuing if ALT > 10x ULN or if any s/sx of liver failure
  - Monitoring at baseline and throughout therapy
- Renal disease/failure
  - Concern of accumulation of excipient SBECD[1]
    - Safety threshold 250mg/kg/day of SBECD
    - 100mg remdesivir powder, solution contains 3 and 6g of SBECD
  - Small case series in AKI/CKD
    - 20 patients[2], 18 patients[3], 46 patients[4] – no difference in ALT or SCr elevations

1. Adamsick, et al. *JASN.* 2020.
2. Pettit, et al. *CID.* 2020.
3. Estiverne, et al. *Kidney Int Rep.* 2020.
4. Thakare, et al. *Kidney Int Rep.* 2021.

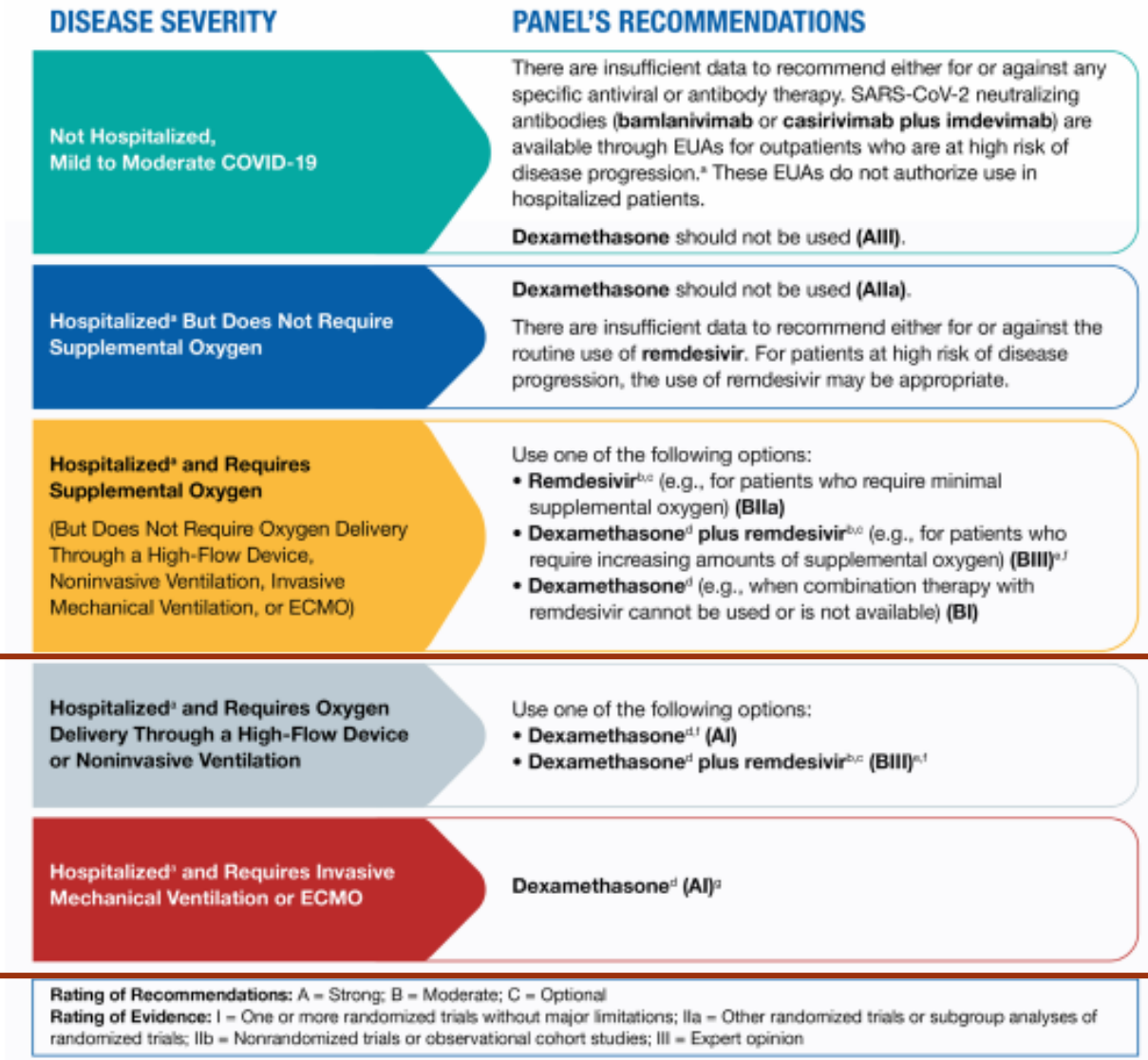
Last Word about Repurposed Drugs (for Now)

- Ivermectin
  - In vitro studies – inhibit replication of SARS-CoV2
  - Plasma concentrations for this would require 100-fold higher doses than approved
  - Clinical data difficult to interpret
  - NIH treatment guidelines updated recommendation from “against use” to “insufficient data to recommend either for or against” on January 14, 2021
- Colchicine (and many others)
  - Jury still out
  - Not mentioned in NIH or IDSA guidelines

NIH COVID-19 Treatment Guidelines. Last update Jan 14, 2021.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnote.



NIH COVID-19 Treatment Guidelines. Last update Jan 14, 2021.

Dexamethasone – RECOVERY Trial

- Multicenter, randomized, open-label trial in hospitalized patients with COVID-19 in UK
- Enrolled 2104 patients to receive dexamethasone (6mg IV/PO daily) vs. 4321 standard of care
- Outcomes
  - Primary – all-cause mortality within 28 days of randomization
  - Secondary
    - Time to discharge
    - Progression to mechanical ventilation or death

RECOVERY Collaborative Group. *NEJM.* 2020.

RECOVERY Trial

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

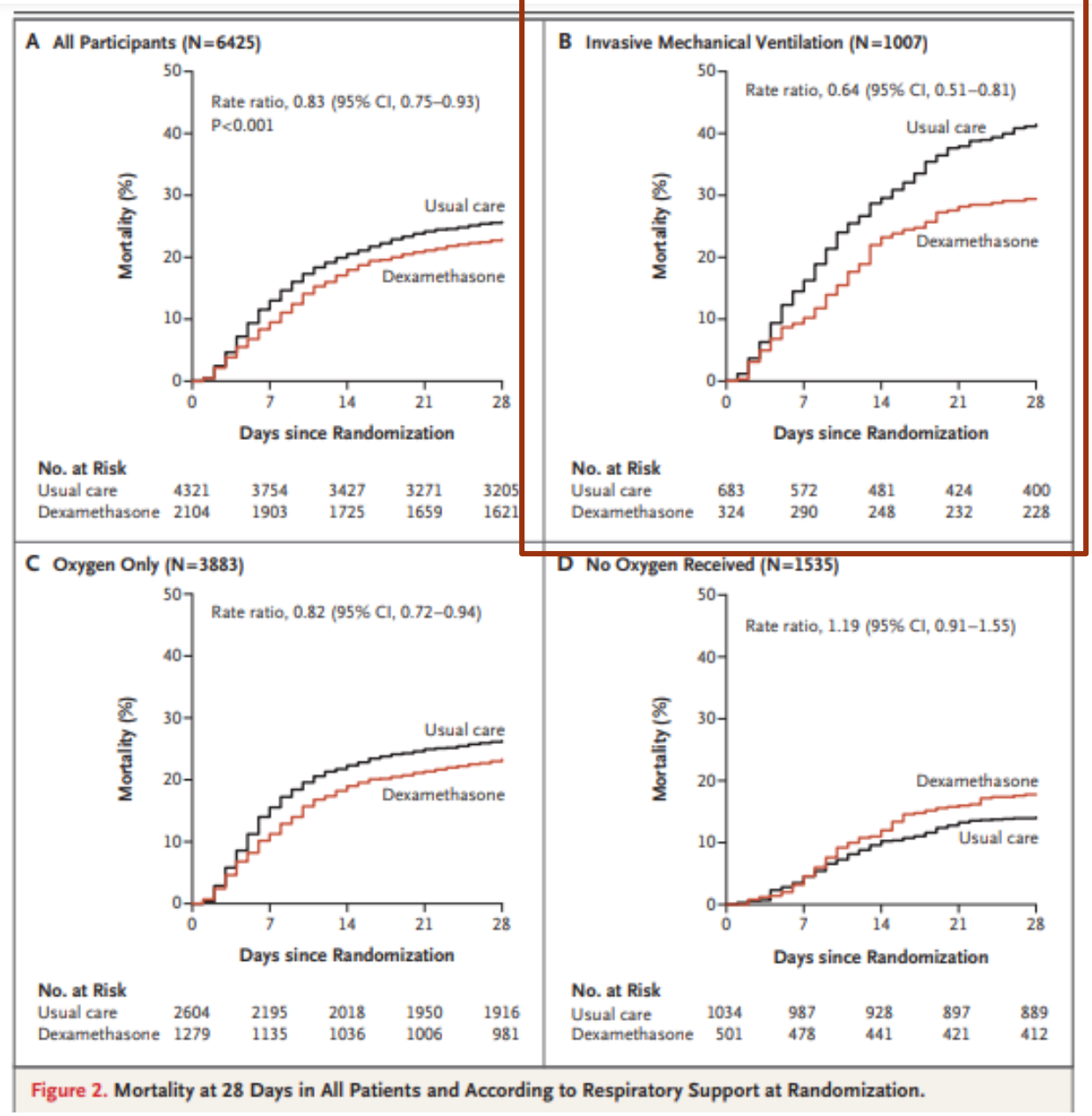


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

RECOVERY Trial

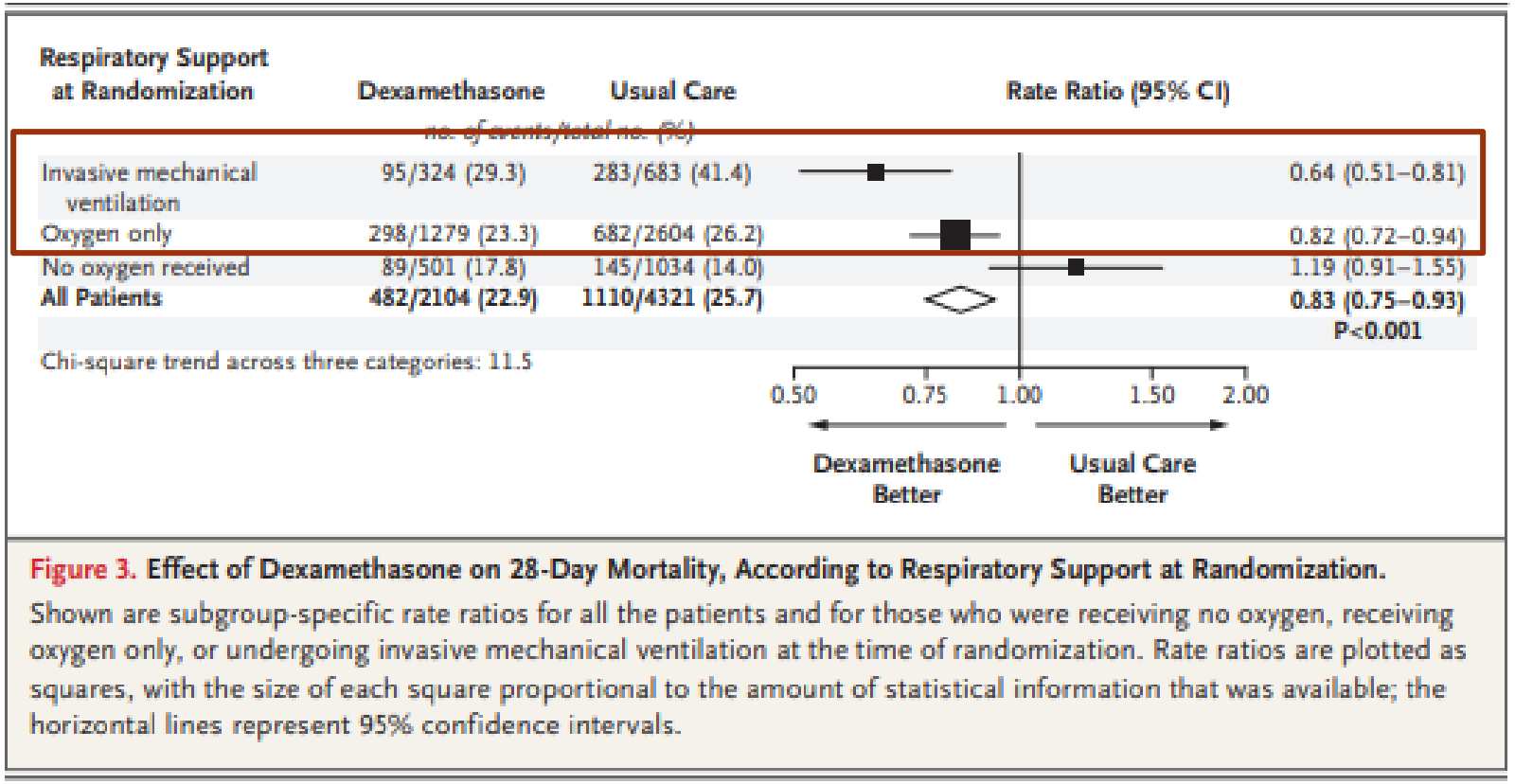


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

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.

Immunomodulators

- IL-1 inhibitors – anakinra
  - CORIMUNO-ANA-1 trial – stopped early for futility
  - NIH guidelines – insufficient data for or against – above not included
  - CORIMUNO-ANA-2 trial ongoing to evaluate severe COVID-19 in ICU patients

CORIMUNO-19 Collaborative Group. *Lancet Resp Med.* 2021.

Immunomodulators

- IL-6 inhibitors – particularly tocilizumab – 3 recent trials
  - EMPACTA – hospitalized with COVID-19 pneumonia not on mechanical ventilation
    - Modified Intention-to-Treat – 249 tocilizumab vs. 128 placebo
    - Primary outcome – combined mechanical ventilation or death 12% vs. 19.3% (p=0.04)
    - Secondary outcome – no difference in death from any cause

Salama, et al. *NEJM.* 2021.

Tocilizumab

- Veiga, et al[1] – severe or critical COVID-19 – supplemental oxygen or mechanical ventilation
  - Enrolled 129 patients from May 8 – July 17, 2020
  - Stopped early for excess deaths at 15 days in tocilizumab group (17 vs. 3%); in-hospital mortality 21 vs. 9% (p=0.02)
- REMAP-CAP[2] – ICU patients within 24 hours of resp support
  - Lower organ support-free days and hospital mortality

1. Veiga, et al. *BMJ.* 2021.
2. REMAP-CAP. medRxiv (pre-print). 2021.

Immunomodulators

- JAK inhibitors – baricitinib
  - EUA on Nov 19, 2020 – baricitinib + remdesivir in hospitalized patients w COVID-19 who require supplemental O2, mechanical ventilation, or ECMO
  - Primarily due to ACTT-2 results
    - Double-blind, placebo-controlled in 8 countries (May 8 – July 1)
    - Baricitinib (4mg daily x 14 days) + remdesivir (10 days) (n=515) vs. remdesivir alone (n=518)
    - Combination group recovered 1 day faster (7 vs. 8 days; p=0.03)
      - High flow or non-invasive ventilation most benefit (10 vs. 18 d)
    - No difference in mortality
  - NIH guidelines updated Dec 14 – insuff data for or against
  - Awaiting results of ACTT-4 – baricitinib + remdesivir vs. dexamethasone + remdesivir

Kalil, et al. *NEJM.* 2020.

Assessment Question #2

- Which of the following is true regarding the use of monoclonal antibodies for COVID-19?
  - A. Considered standard of care according to current NIH guidelines
  - B. Patient must be symptomatic to receive it per the EUA
  - C. Patients can receive it at any time during illness per EUA
  - D. Patient can receive it during hospitalization for COVID-19 per EUA

Monoclonal Antibodies

- Neutralizing monoclonal antibodies target receptor-binding protein of spike protein of SARS-CoV2
- Being evaluated for treatment and prophylaxis in early disease
  - ACTIV-3 trial in hospitalized pts stopped early for futility[1]
- EUAs
  - Bamlanivimab 700mg – Nov 9
  - Casirivimab/imdevimab (REGN10933) 2.4g – Nov 21
  - Treatment of non-hospitalized patients with mild-mod COVID-19 at high risk of severe dx or hospitalization
  - Administered ASAP after positive test and w/in 10 days of symptom onset
- New data evolving

1. ACTIV-3/TICO LY-CoV555 Study Group. *NEJM.* 2020.

Bamlanivimab – BLAZE-1

- Monotherapy vs. combination therapy with etesevimab
- Randomized, double-blind, placebo-controlled, single-infusion study
  - Mild-mod COVID-19 outpts w/in 3 days of positive test
  - 5 treatment groups (June 17 – Aug 21; Aug 22 – Sept 3):
    - Bamlanivimab monotx (700mg, n=101; 2800mg, n=107, 7000mg, n=101)
    - Combination w etesevimab (2800mg of each; n=112)
    - Placebo (n=156)
  - Outcomes
    - Primary – SARS-CoV-2 viral load from baseline to day 11
    - Secondary – 9 total, 1 clinical (hospitalization, ER visit, death at day 29)

Gottlieb, et al. *JAMA.* 2021.

BLAZE-1

- Patients received infusion median 4 days of symptom onset
- Results
  - Primary – Change of viral load only significantly different in any combination therapy group (p=0.01)
  - Secondary – Proportion of hospitalizations/ER visits lower in treatment groups, lowest in combination therapy (1 vs. 9, p=0.049) but only hypothesis generating
- NIH guidelines – based on interim results of bamlanivimab monotherapy
  - Insufficient evidence for or against
  - Should not be considered standard of care

Gottlieb, et al. *JAMA.* 2021.

REGN-COV2 Trial – Interim Results

- Multicenter, randomized, double-blind, placebo-controlled
- Symptomatic, non-hospitalized patients with COVID-19 to evaluate safety, efficacy, refine end points
  - Randomized no more than 7 days after symptom onset and 72 hours of positive test
  - 3 treatment groups:
    - Low dose – 2.4g (n=92)
    - High dose – 8g (n=90)
    - Placebo (n=93)
  - Outcomes
    - Change in viral load from baseline through day 7 – more in those antibody-negative or high viral loads at baseline
    - Numerically lower medically attended visits, esp Ab-

Weinreich, et al. *NEJM.* 2021.

More to Come on Monoclonal Antibodies – Prophylaxis?

- BLAZE-2 – press release
  - Randomized, double-blind, placebo-controlled trial
  - Efficacy and safety of bamlanivimab 4200mg vs placebo in preventing COVID-19 in skilled nursing and assisted living facility residents and staff
  - 80% reduced risk?

Antibiotic Stewardship and COVID-19

Co-infection and Use of Antibiotics

- NIH guidelines:

  Empiric Broad-Spectrum Antimicrobial Therapy

  Recommendations

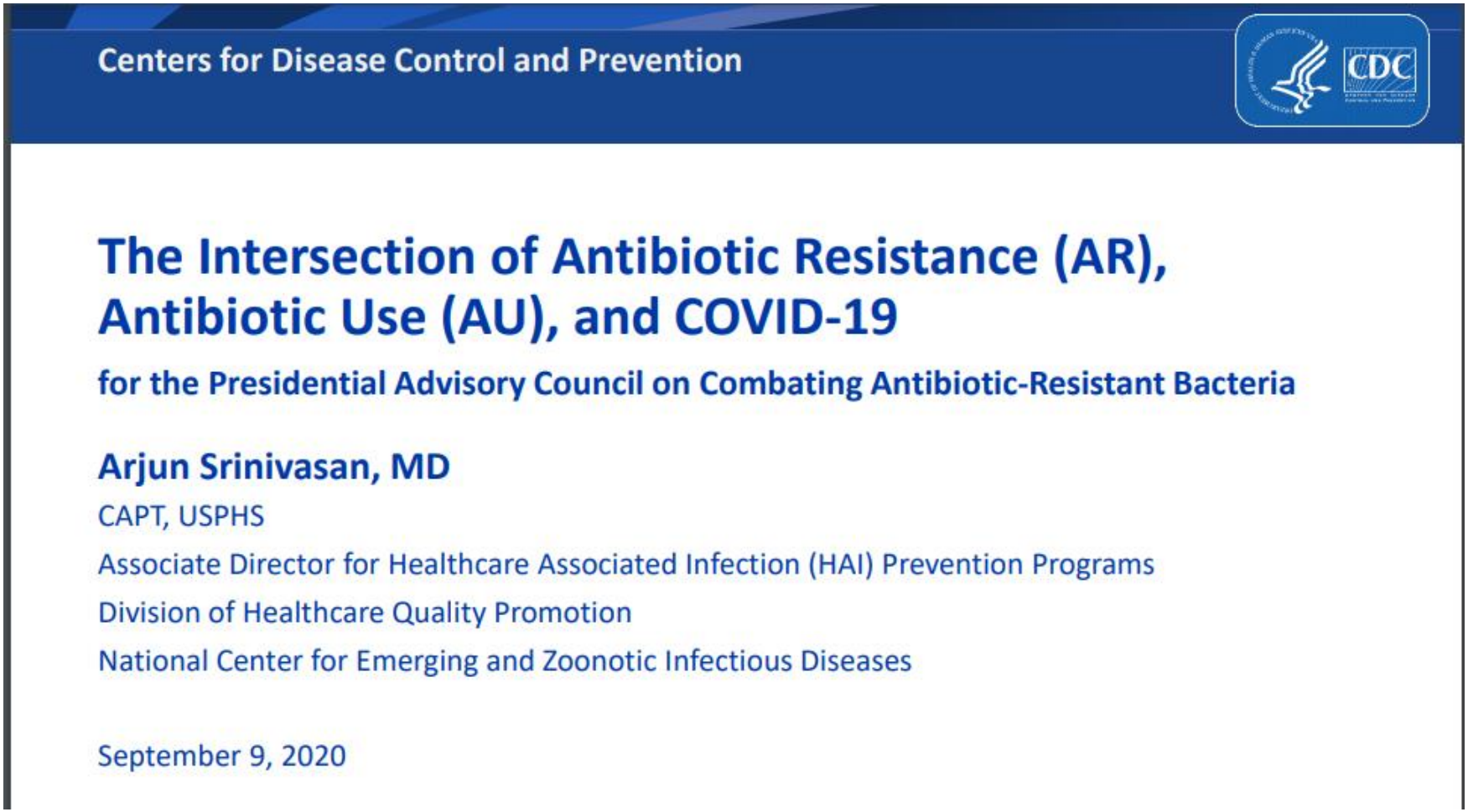
  - In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.
  - If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy **(AIII)**.

  Rationale

  There are no reliable estimates of the incidence or prevalence of copathogens with severe acute respiratory syndrome coronavirus 2 at this time.

- IDSA guidelines:
  - Bacterial coinfections with SARS-CoV-2 relatively infrequent (likely occurring in <10% of hospitalized COVID-19 patients) – literature does not support routine use of empiric antibiotics
  - Recent studies in COVID-19 patients
    - Antibiotics administered in 56 – 74.6%
    - Bacterial co-infection 3.5 – 31%

Impact on Resistance



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Antimicrobial resistance

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Preventing the COVID-19 pandemic from causing an antibiotic resistance catastrophe

19

18-11-2020

According to research conducted by WHO/Europe and reports from the field, the European Region now risks accelerated spread of antimicrobial resistance. The long-term problem of antibiotics being used inappropriately by individuals and in health care settings is worsening as a result of the COVID-19 pandemic. This year's World Antimicrobial Awareness Week, set to take place on 18–24 November, is an opportunity to focus attention on the evolving situation.

United Hospital Fund

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Publications

Antibiotic Resistance in the Era of COVID-19

Author: Pooja Kothari, RN, MPH

The New York Times

With All Eyes on Covid-19, Drug-Resistant Infections Crept In

The spread of other dangerous germs is surging — a result, in part, of the chaotic response to the pandemic.

A hospital worker disinfecting a room where a Covid patient had died. Focus on the coronavirus has helped a different set of germs spread. Shannon Stapleton/Reuters

By Matt Richtel

Jan. 27, 2021