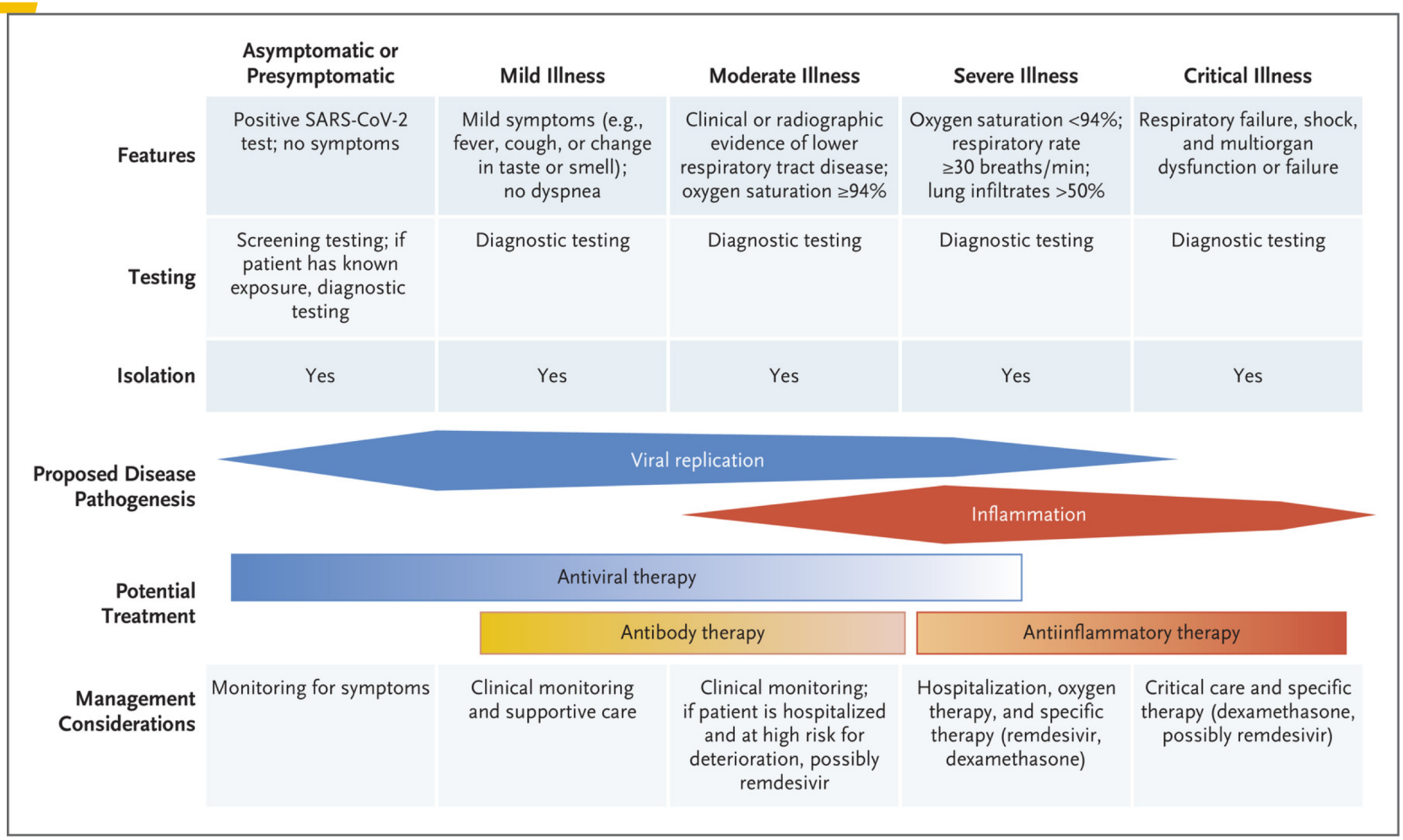
UWTASP
tele-antimicrobial stewardship program

COVID-19 Update

- Remdesivir
- Masking
- Case discussion

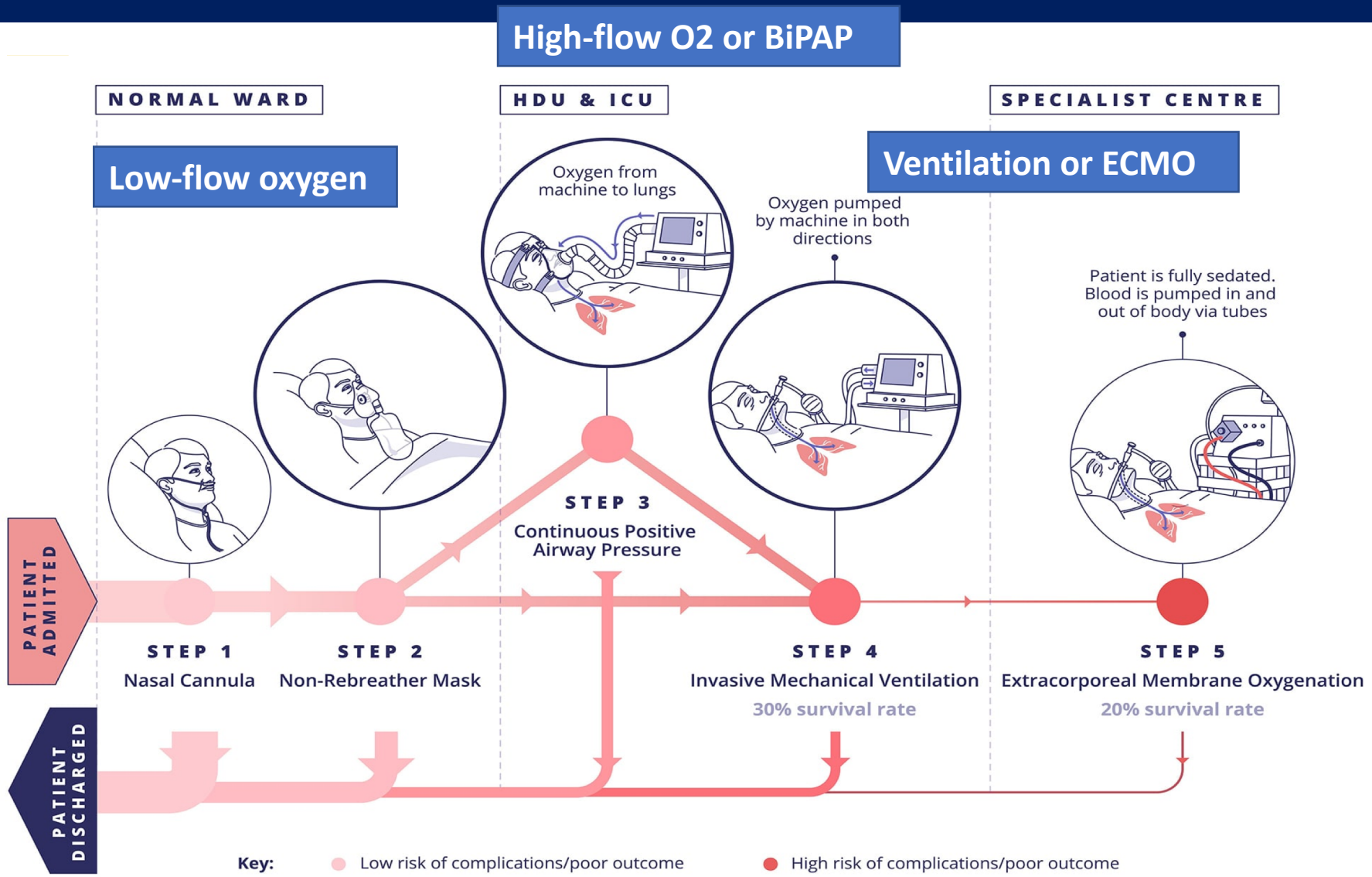
August 3rd, 2021

COVID-19 disease progression



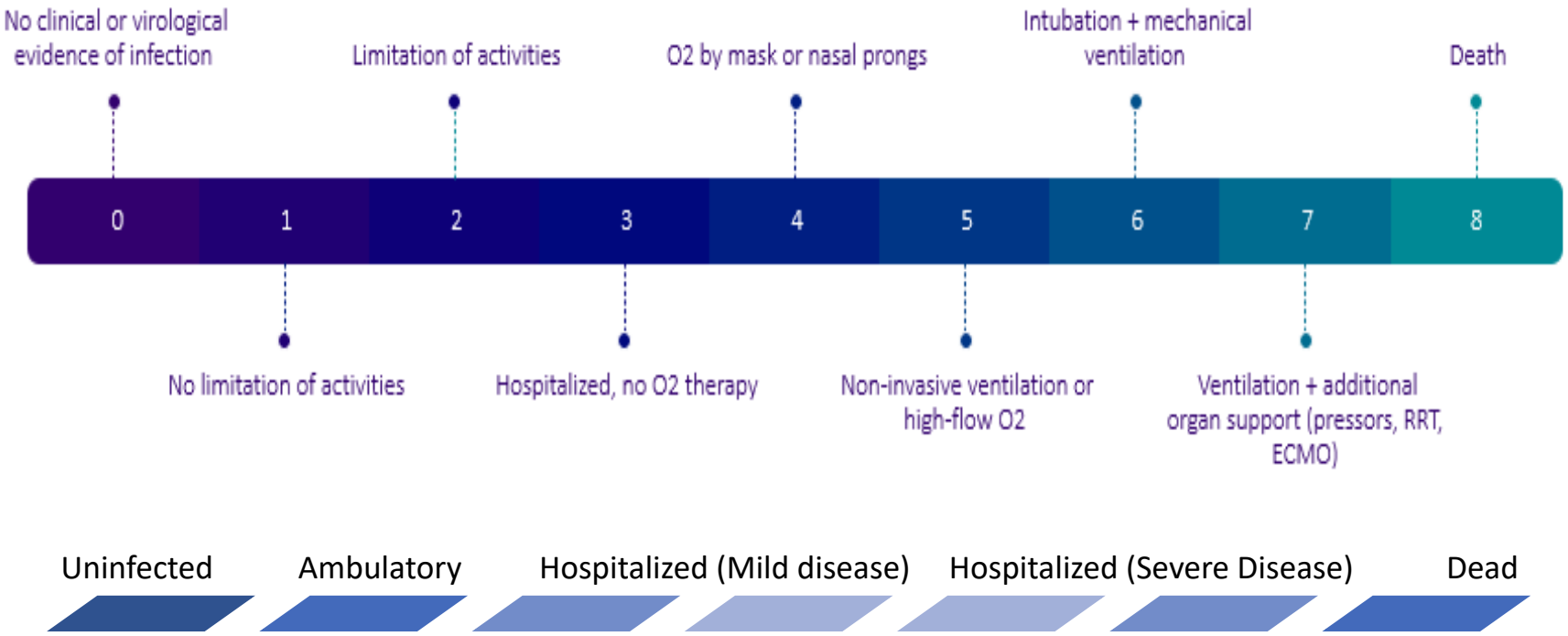
Gandhi, R. T., Lynch, J. B., & del Rio, C. (2020). Mild or Moderate Covid-19. *New England Journal of Medicine*, *383*(18), 1757–1766. https://doi.org/10.1056/NEJMcp2009249

Respiratory progression



How is coronavirus disease treated in hospital? - Coronavirus: the science explained - UKRI. (n.d.). Retrieved May 5, 2021, from https://coronavirusexplained.ukri.org/en/article/vdt0008/

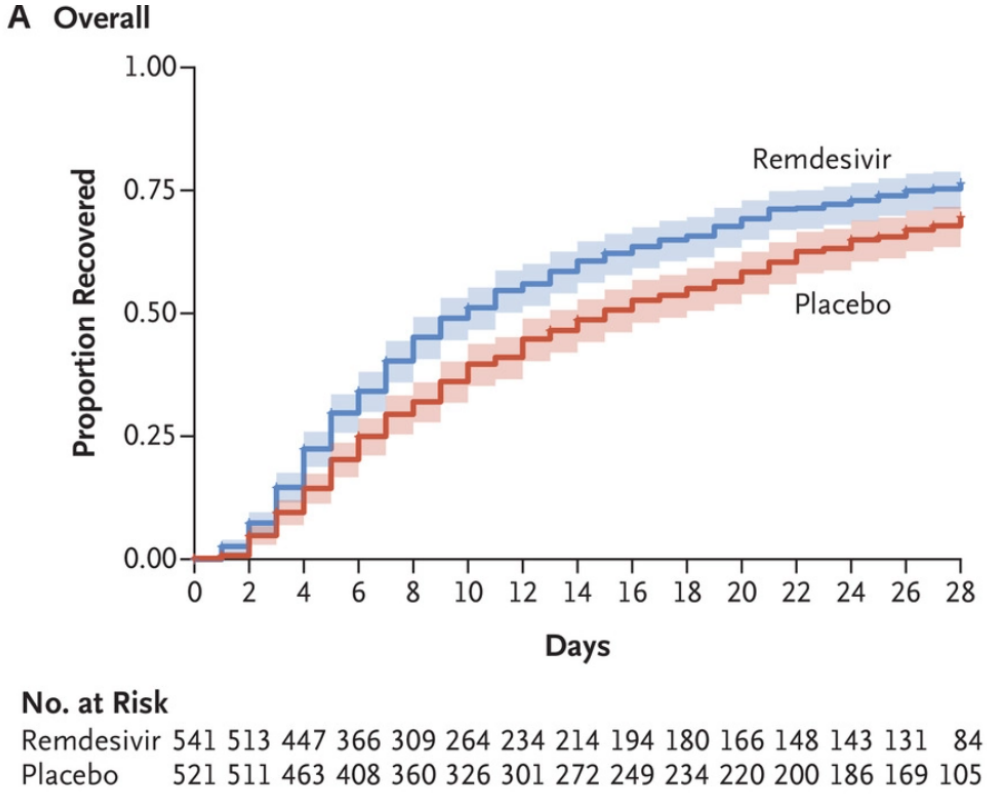
WHO Ordinal Scale for Clinical Improvement



WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. (2020).

Remdesivir: ACTT-1

ACTT: Double-Blind, Randomized, Placebo-Controlled Trial
N = 1062, 541 RDV/521 Placebo
Time to Recovery: 10 days RDV vs. 15 days placebo (RR 1.29, 1.12-1.49)

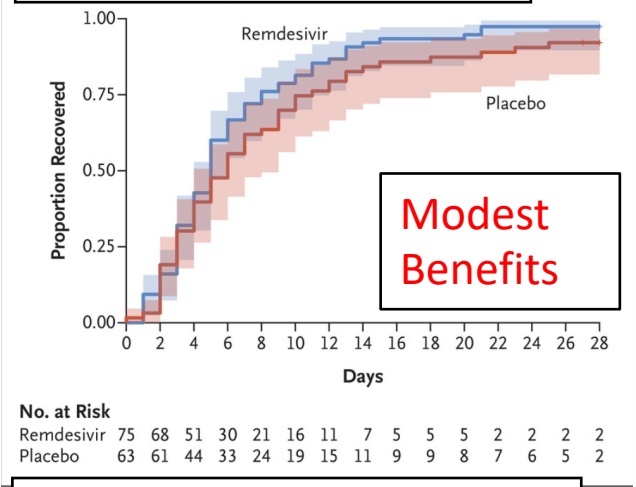


Bottom line:
Remdesivir shortened time to recovery vs. placebo in patients hospitalized with COVID-19 with lower respiratory tract disease

Beigel JH, Tomashek, Dodd, Mehta, Zingman, Kalil, Hohmann, **Chu Helen Y.,** Luetkemeyer A, Kline S, Lopez de Castilla, Finberg et al. DOI: 10.1056/NEJMoa2007764

ACTT -1

Not receiving oxygen

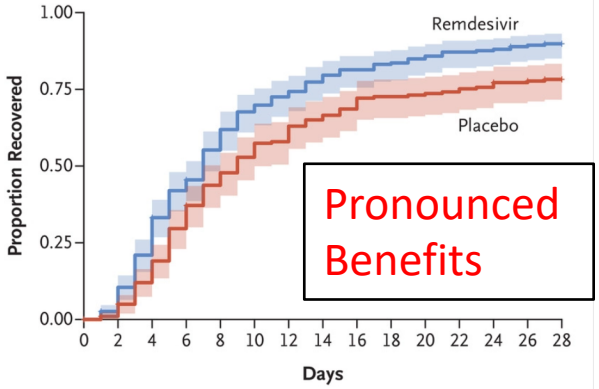


Modest Benefits

No. at Risk

Remdesivir	75	68	51	30	21	16	11	7	5	5	5	2	2	2	2
Placebo	63	61	44	33	24	19	15	11	9	9	8	7	6	5	2

Receiving oxygen

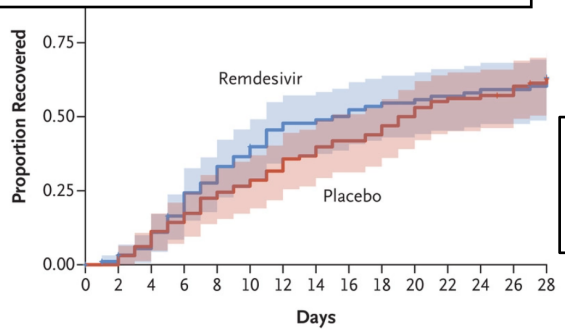


Pronounced Benefits

No. at Risk

Remdesivir	232	223	181	132	101	73	62	51	42	38	34	29	28	24	13
Placebo	203	199	175	140	111	93	83	69	62	54	53	51	48	44	28

High flow oxygen or noninvasive mech vent

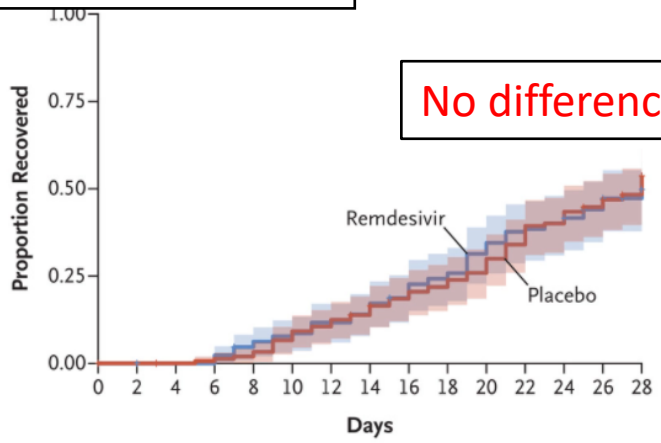


Maybe Benefits

No. at Risk

Remdesivir	95	91	86	75	65	57	48	46	44	41	40	38	37	36	27
Placebo	98	98	92	84	76	72	67	62	57	55	49	44	43	41	27

Mech Vent or ECMO



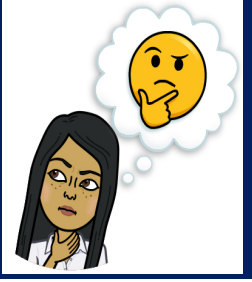
No difference

No. at Risk

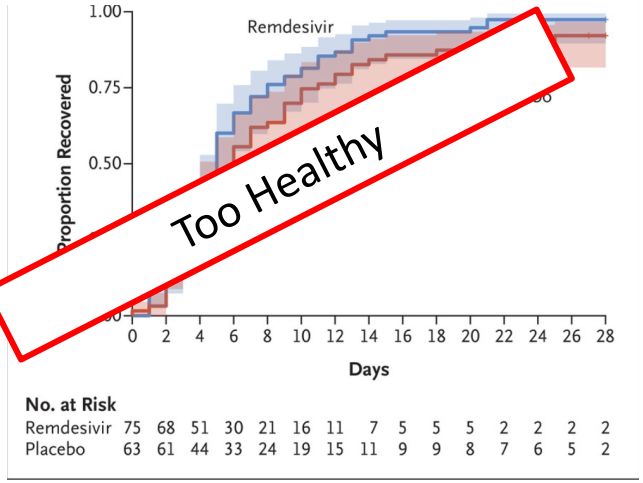
Remdesivir	131	131	129	129	122	118	113	110	103	96	87	79	76	69	42
Placebo	154	153	152	151	149	142	136	130	121	116	110	98	89	79	48

DOI: 10.1056/NEJMoa2007764

ACTT-1 Interpreted by Zahra

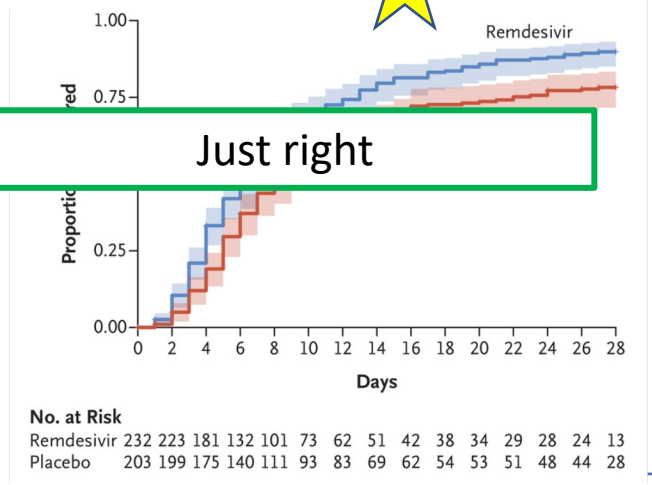


Not receiving oxygen



Too Healthy

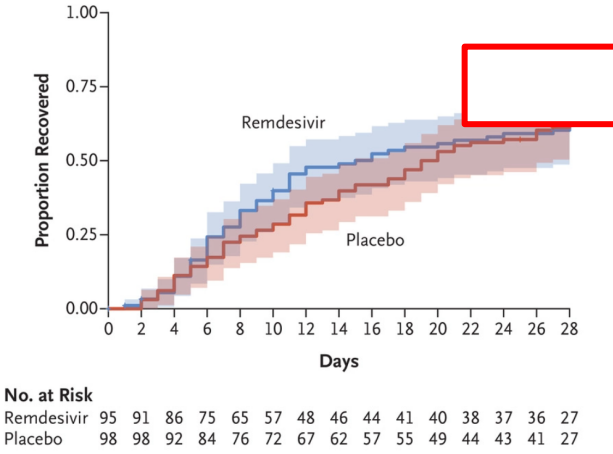
Receiving oxygen



Just right

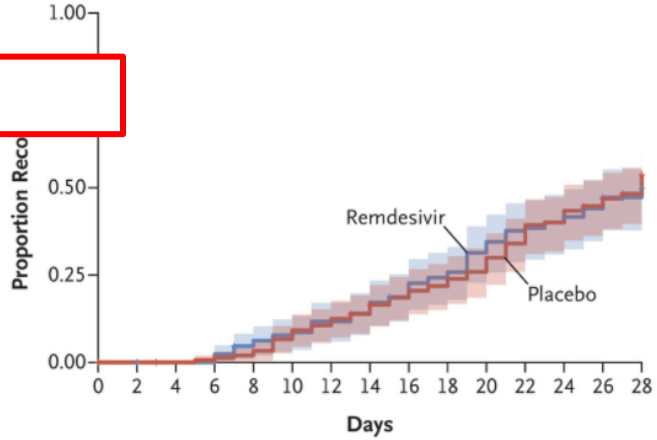
Goldilocks Window

High flow oxygen or noninvasive mech vent



Too Sick

Mech Vent or ECMO



DOI: 10.1056/NEJMoa2007764

Repurposed Antiviral Drugs for COVID-19 (SOLIDARITY Trial)

Population
- Hospitalized COVID patients

Intervention
- Placebo
- Remdesivir (200 mg Day1, then 100 mg for 9 days)

Comparison
- In-hospital mortality

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

ABSTRACT

BACKGROUND

World Health Organization expert groups recommended mortality trials of four repurposed antiviral drugs — remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a — in patients hospitalized with coronavirus disease 2019 (Covid-19).

METHODS

The members of the writing and steeri committees (H. Pan, R. Peto, A.-Henao-Restrepo, M.-P. Preziosi, V. Sat yamoorthy, Q. Abdool Karim, M.M. A jandria, C. Hernández García, M.-P. K

WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511. doi:10.1056/NEJMoa2023184

SOLIDARITY: Results

Figure S1. Effects on in-hospital mortality of (a) remdesivir,

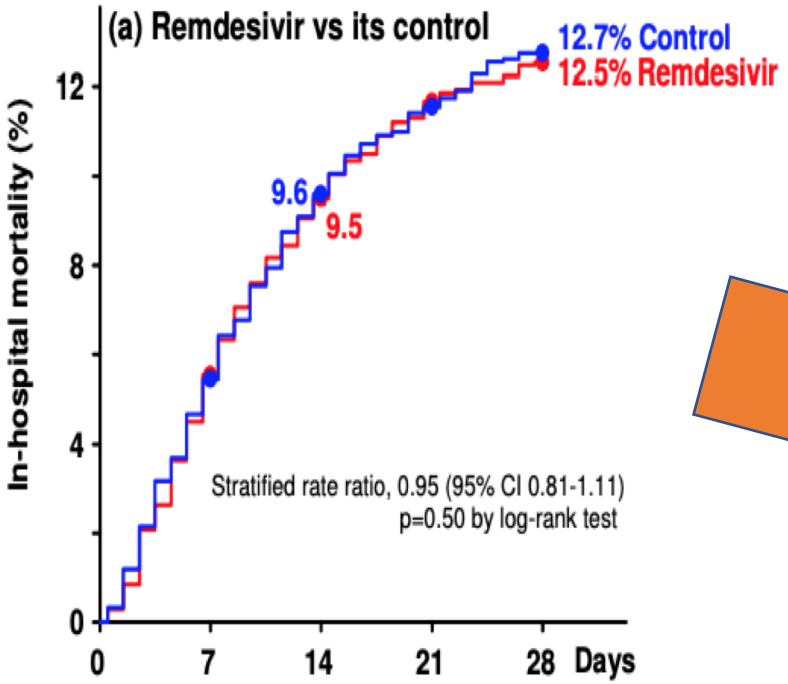
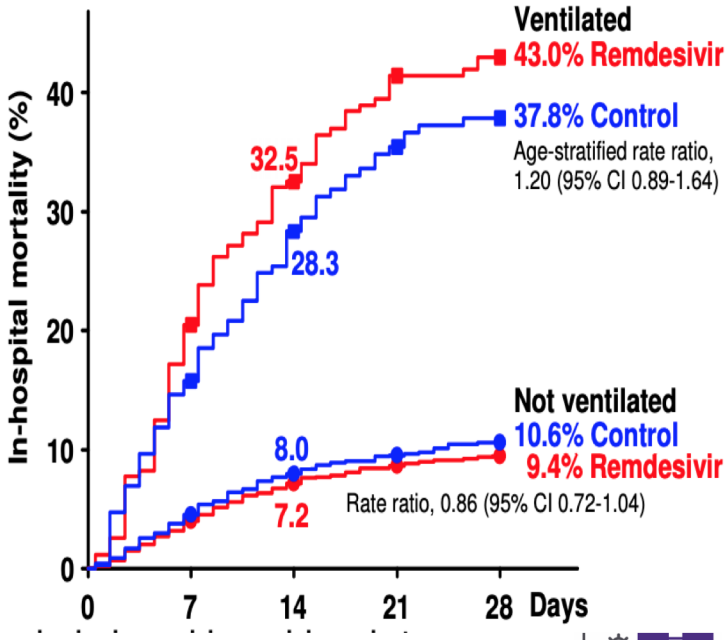


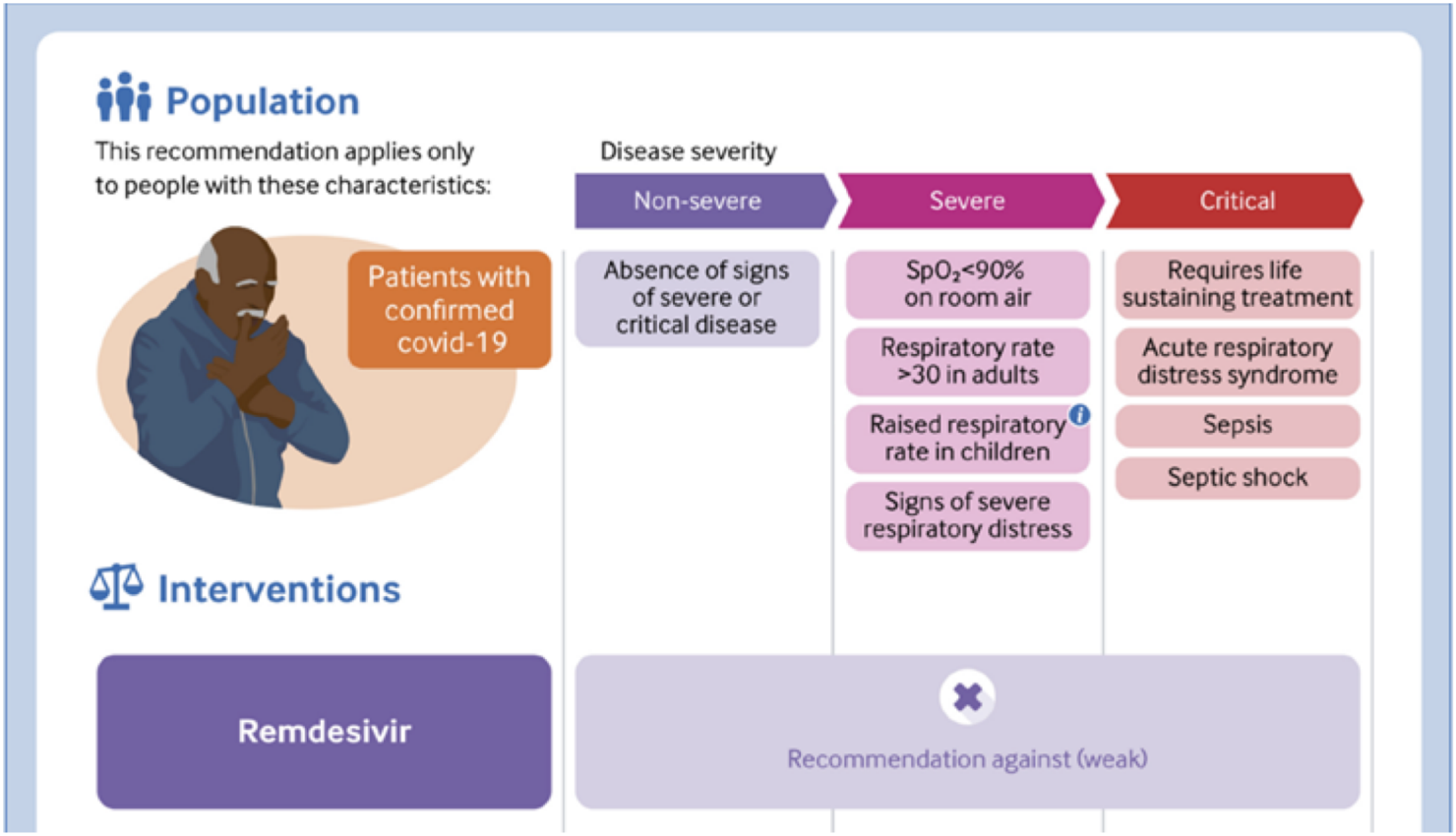
Figure S2. Subdivision by ventilation at randomization of the apparent effects of remdesivir on the probability of death in hospital from any cause



- No diff in survival, irrespective of ventilation status

Supplementary Appendix Supplementary online material for. (n.d.). https://doi.org/10.1056/NEJMoa2023184

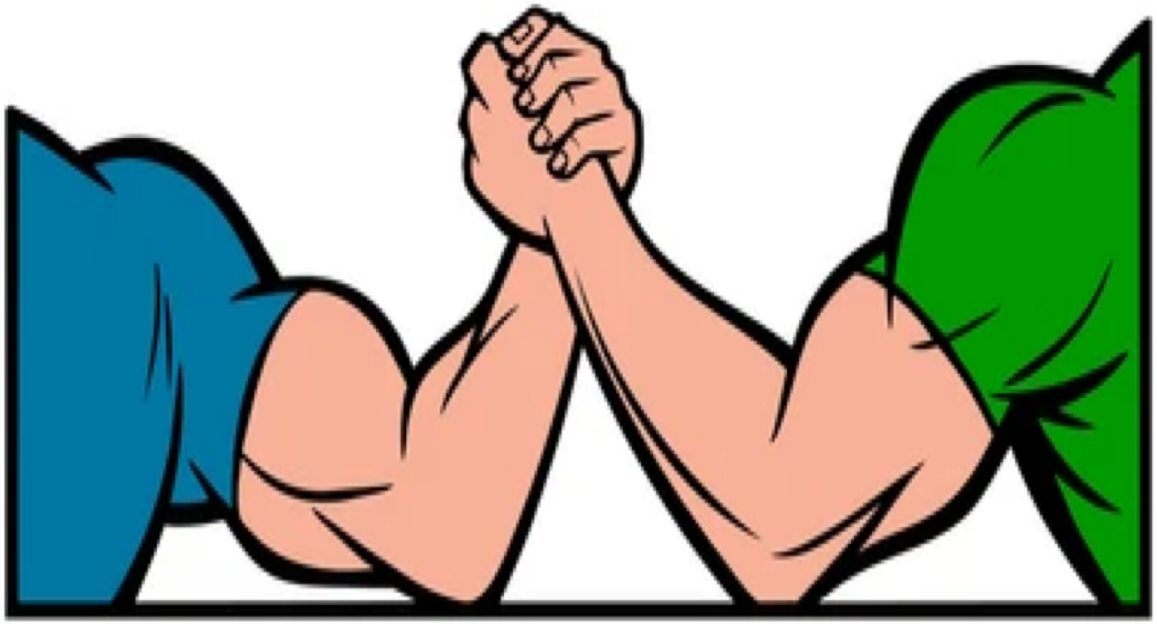
WHO Recommendation



The panel acknowledged, however, there will be patients and clinicians who choose to use remdesivir given that the evidence has *not* excluded the possibility of benefits

For or Against Remdesivir?

WHO



NIH

Slide courtesy of Sharon Zhong,PharmD

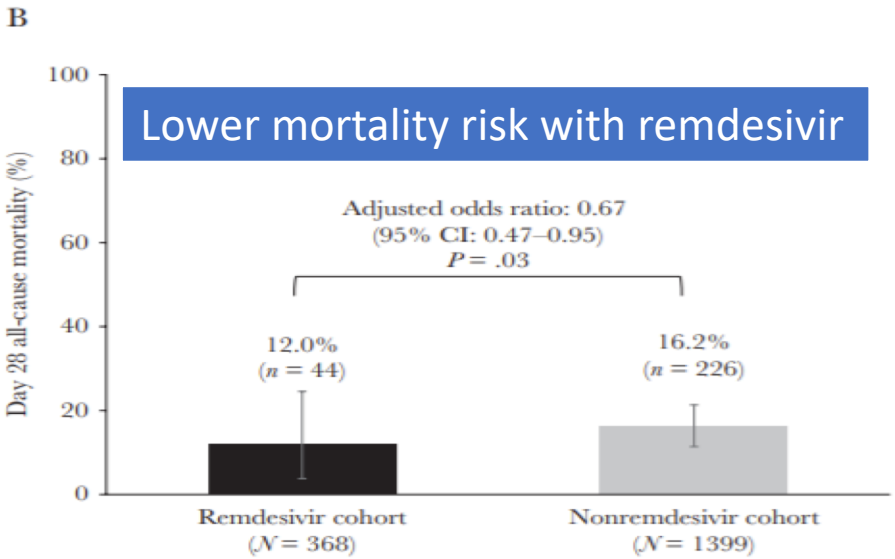
Open Forum Infectious Diseases
MAJOR ARTICLE

Remdesivir Versus Standard-of-Care for Severe Coronavirus Disease 2019 Infection: An Analysis of 28-Day Mortality

Study Design

- Phase 3, randomized, open-label study comparing Remdesivir 5 vs 10 days (previously published data, RDV cohort)
- Real world longitudinal cohort receiving standard of care (non-RDV cohort)
- Propensity score matching to compare populations

Outcome



Limitations

- Comparing prospective and retrospective data
open-label treatment
- Unproven treatments used
- Time period before steroids used

https://doi.org/10.1093/ofid/ofab278

JAMA Network | Open

Original Investigation | Infectious Diseases

Comparison of Time to Clinical Improvement With vs Without Remdesivir Treatment in Hospitalized Patients With COVID-19

Brian T. Garibaldi, MD, MEHP; Kunbo Wang, MS; Matthew L. Robinson, MD; Scott L. Zeger, PhD; Karen Bandeen-Roche, PhD; Mei-Cheng Wang, PhD; G. Caleb Alexander, MD; Amita Gupta, MD; Robert Bollinger, MD, MPH; Yanxun Xu, PhD

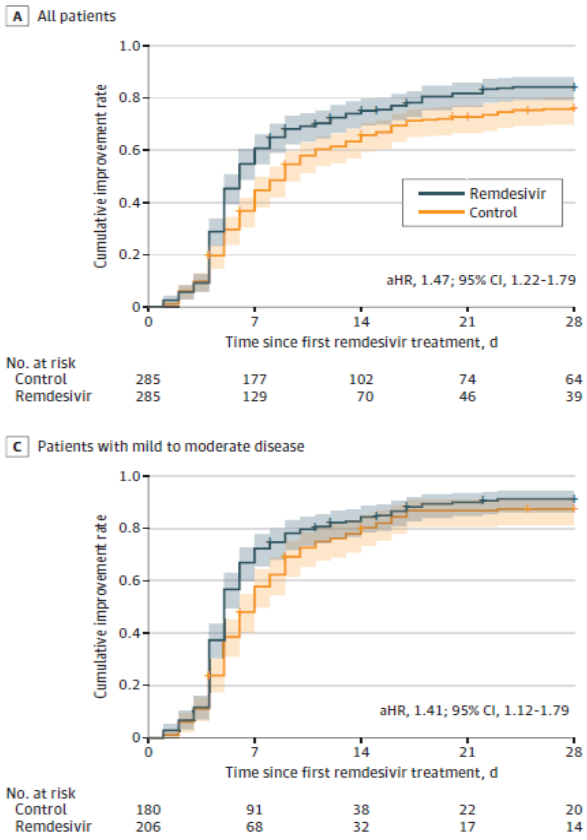
- Retrospective study
- March to August 2020
- Five hospitals in Maryland
- (>75%) were non-White
- Primary endpoint
  - time to clinical improvement (defined as hospital discharge or 2 points decrease in WHO ordinal score)
- Secondary endpoint
  - 28-d mortality

Characteristic	Propensity score-matched patients[b]		
	Matched remdesivir (n = 285)	Matched control (n = 285)	Absolute standardized difference
Demographic characteristics			
Sex, No. (%)			
Male	160 (56.1)	158 (55.4)	0.014
Female	125 (43.9)	127 (44.6)	
Race/ethnicity, No. (%)			
Black	95 (33.3)	100 (35.1)	0.037
Latinx	98 (34.4)	86 (30.2)	0.090
White	59 (20.7)	66 (23.2)	0.059
Other[c]	33 (11.6)	33 (11.6)	0
Age, median (IQR), y	60 (48-70)	62 (51-75)	0.167
BMI, median (IQR)	29.8 (25.9-34.7)	29.6 (25.4-35.0)	0.070
DNR or DNI, No. (%)	59 (20.7)	69 (24.2)	0.084
Oxygen devices, No. (%)			
No supplemental oxygen	16 (5.6)	15 (5.3)	0.015
Nasal cannula or face mask	189 (66.3)	173 (60.7)	0.117
High-flow nasal cannula	38 (13.3)	50 (17.5)	0.117
Noninvasive positive-pressure ventilation	5 (1.8)	5 (1.8)	0
Mechanical ventilator	37 (13.0)	39 (13.7)	0.021

Remdesivir was associated with faster clinical improvement

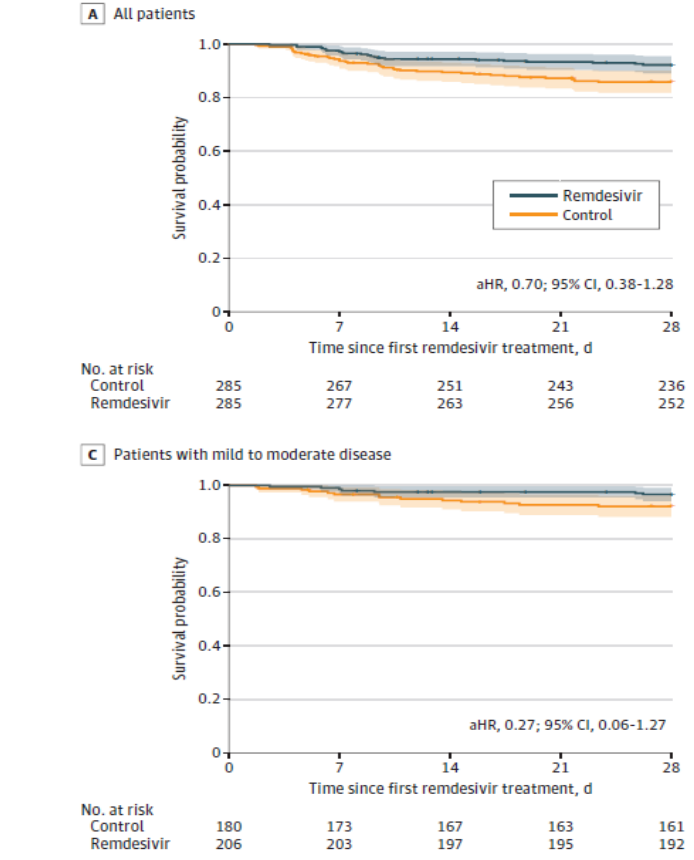
Faster Clinical Improvement

Figure 2. Time to Clinical Improvement



No Difference in Survival

Figure 3. Patient Survival



JAMA Network | Open

Original Investigation | Infectious Diseases

Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans Hospitalized With COVID-19

Michael E. Ohl, MD, MSPH; Donald R. Miller, ScD; Brian C. Lund, PharmD; Takaaki Kobayashi, MD; Kelly Richardson Miell, PhD; Brice F. Beck, MA; Bruce Alexander, PharmD; Kristina Crothers, MD; Mary S. Vaughan Sarrazin, PhD

Study design:

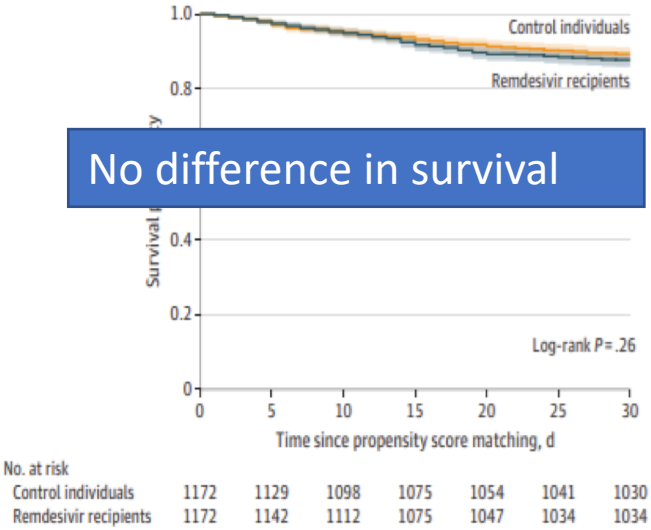
- Retrospective VA cohort study
- Propensity scoring to match
- Time period: May to Oct 20

Outcomes:

- No difference in survival regardless of dexamethasone
- Median LOS 6 vs. 3 days ($p<0.001$)

doi:10.1001/jamanetworkopen.2021.14741

Figure 2. Kaplan-Meier Survival Curves for Remdesivir Recipients and Control Individuals in the Propensity Score–Matched Cohort



Limitations:

-Only 50% had matching control

-Symptom onset and amount supplemental O2 not available

Clinical Infectious Diseases

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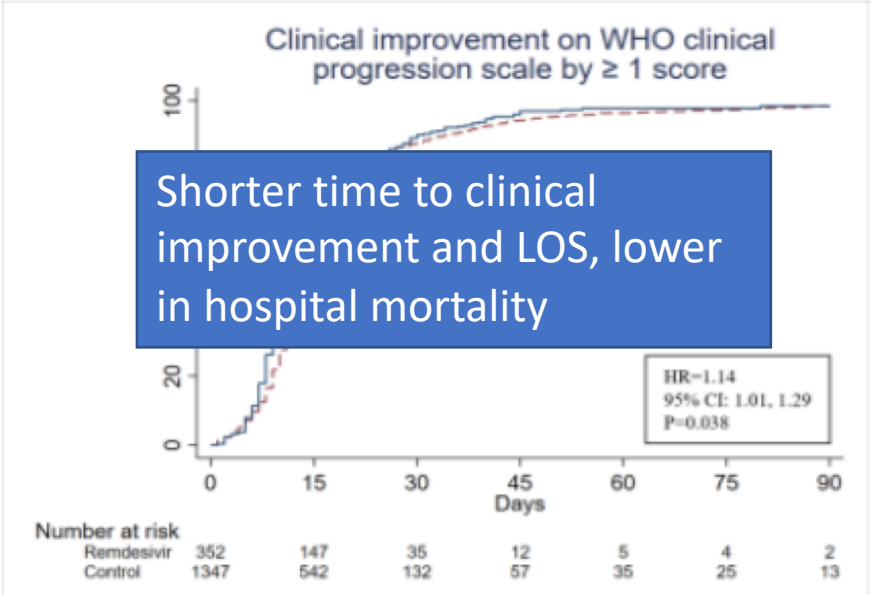
ACCEPTED MANUSCRIPT

Clinical improvement, outcomes, antiviral activity, and costs associated with early treatment with remdesivir for patients with COVID-19 FREE

Study Design:

- Retrospective cohort of hospitalized patients in Hong Kong
- Propensity matching
- RDV=352; Control=1,347
- Time period: Jan 20 to Jan 21

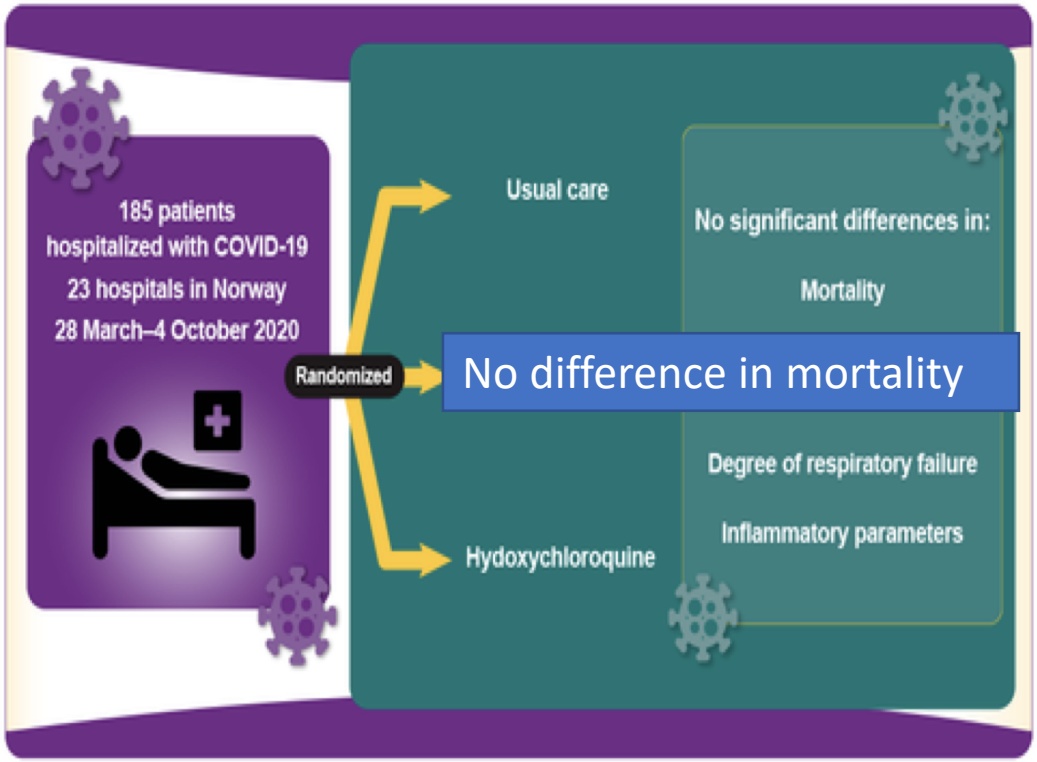


Limitations:

- Heterogeneity in study population; most with moderate COVID-19 without need for oxygen

https://doi.org/10.1093/cid/ciab631

Do remdesivir and hydroxychloroquine affect outcomes of patients hospitalized with COVID-19?



Annals of Internal Medicine

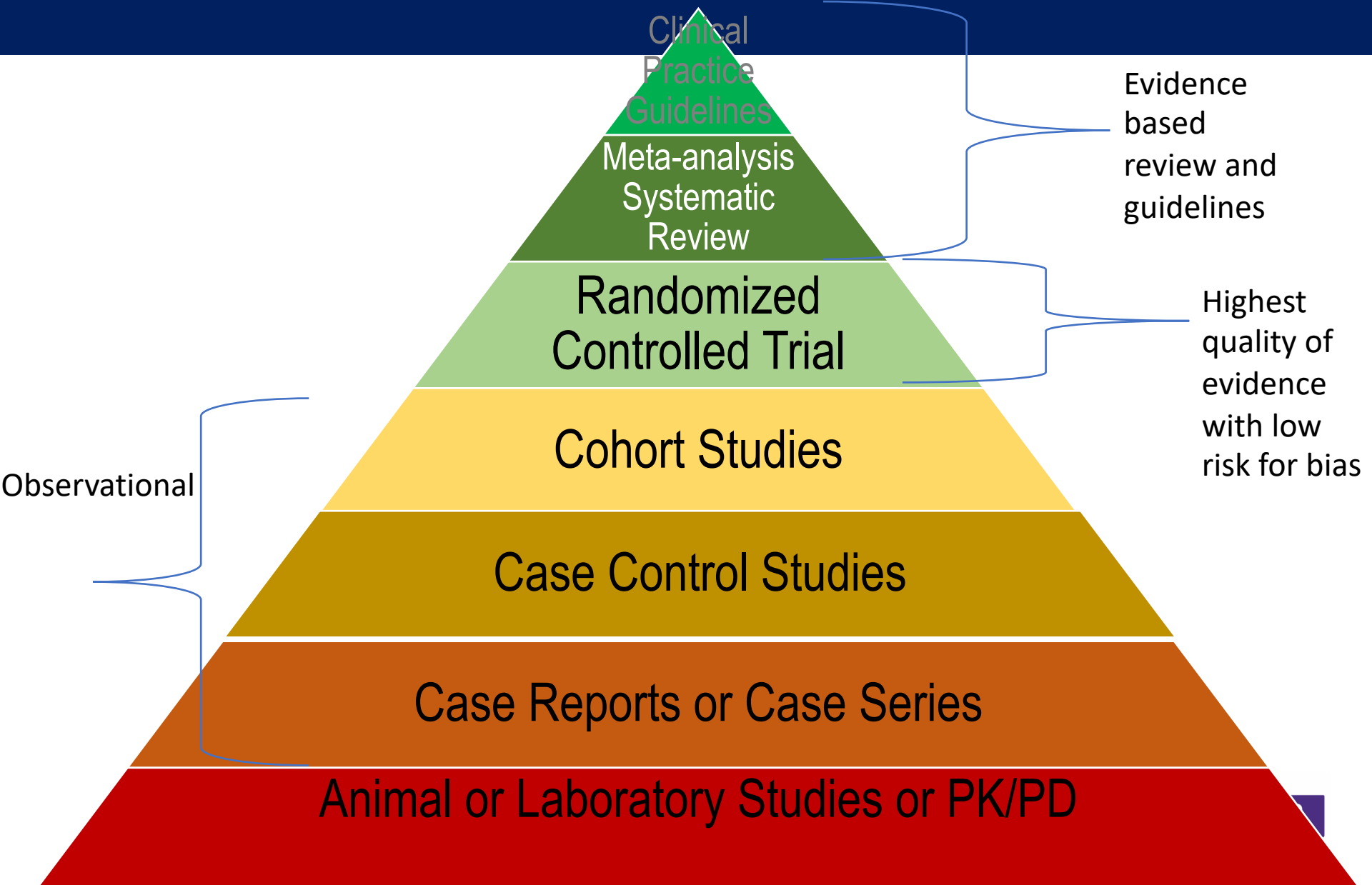
Limitation:

No placebo control

Only 43 patients received remdesivir

Feeling information overload yet?

How do you make sense of it all?



Annals of Internal Medicine

REVIEW

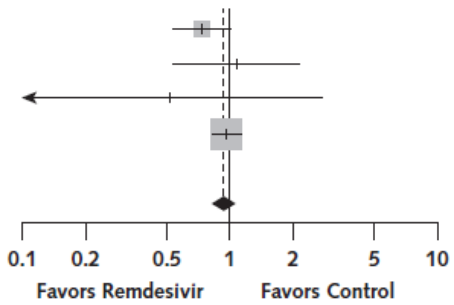
Major Update: Remdesivir for Adults With COVID-19

A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points

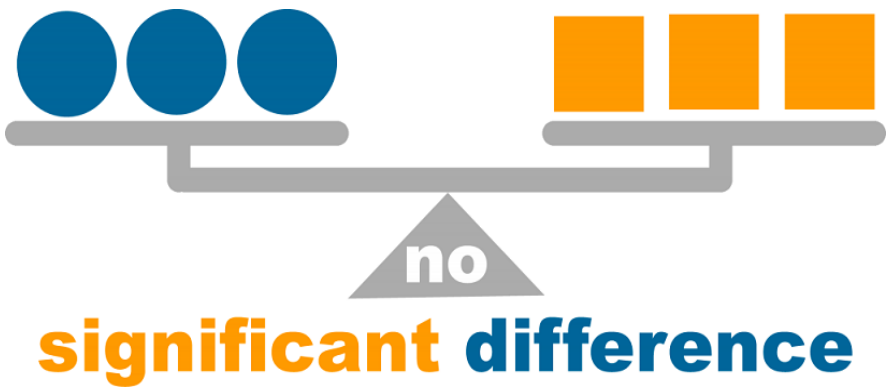
Anjum S. Kaka, MD; Roderick MacDonald, MS; Nancy Greer, PhD; Kathryn Vela, MLIS; Wei Duan-Porter, MD, PhD; Adam Obley, MD; and Timothy J. Wilt, MD, MPH

Figure 1. Mortality for remdesivir 10-d course vs. control (placebo or standard care).

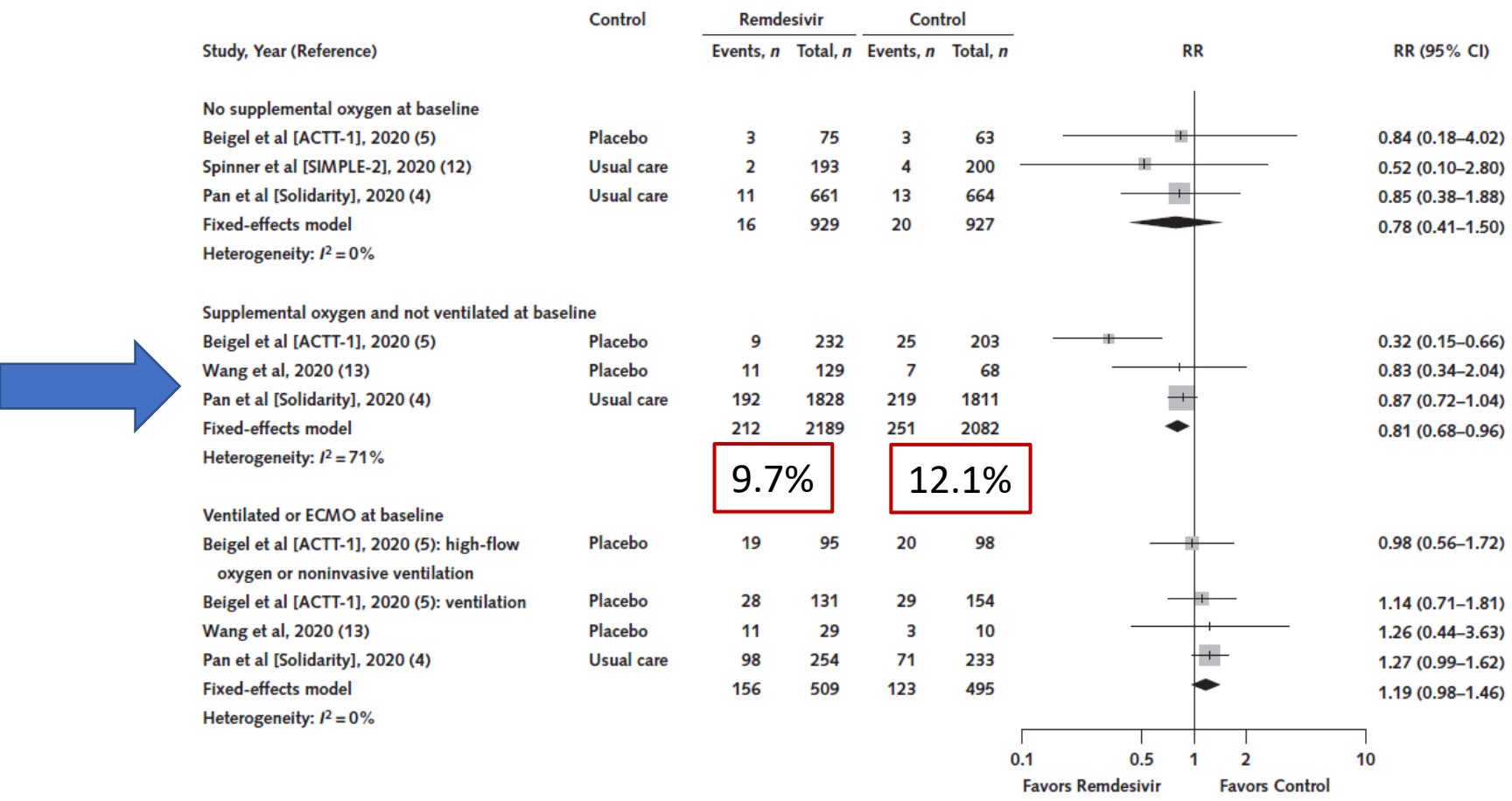
Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
Beigel et al [ACTT-1], 2020 (5)	Placebo	59	541	77	521	0.74 (0.54–1.01)
Wang et al, 2020 (13)	Placebo	22	158	10	78	1.09 (0.54–2.18)
Spinner et al [SIMPLE-2], 2020 (12)	Usual care	2	193	4	200	0.52 (0.10–2.80)
Pan et al [Solidarity], 2020 (4)	Usual care	301	2743	303	2708	0.98 (0.84–1.14)
Fixed-effects model		384	3635	394	3507	0.93 (0.82–1.06)
Heterogeneity: $I^2 = 6\%$						



10.6% 11.2%



Small mortality benefit among patients with supplemental oxygen



Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
No supplemental oxygen at baseline						
Beigel et al [ACTT-1], 2020 (5)	Placebo	3	75	3	63	0.84 (0.18–4.02)
Spinner et al [SIMPLE-2], 2020 (12)	Usual care	2	193	4	200	0.52 (0.10–2.80)
Pan et al [Solidarity], 2020 (4)	Usual care	11	661	13	664	0.85 (0.38–1.88)
Fixed-effects model		16	929	20	927	0.78 (0.41–1.50)
Heterogeneity: $I^2 = 0\%$						
Supplemental oxygen and not ventilated at baseline						
Beigel et al [ACTT-1], 2020 (5)	Placebo	9	232	25	203	0.32 (0.15–0.66)
Wang et al, 2020 (13)	Placebo	11	129	7	68	0.83 (0.34–2.04)
Pan et al [Solidarity], 2020 (4)	Usual care	192	1828	219	1811	0.87 (0.72–1.04)
Fixed-effects model		212	2189	251	2082	0.81 (0.68–0.96)
Heterogeneity: $I^2 = 71\%$		9.7%		12.1%		
Ventilated or ECMO at baseline						
Beigel et al [ACTT-1], 2020 (5): high-flow oxygen or noninvasive ventilation	Placebo	19	95	20	98	0.98 (0.56–1.72)
Beigel et al [ACTT-1], 2020 (5): ventilation	Placebo	28	131	29	154	1.14 (0.71–1.81)
Wang et al, 2020 (13)	Placebo	11	29	3	10	1.26 (0.44–3.63)
Pan et al [Solidarity], 2020 (4)	Usual care	98	254	71	233	1.27 (0.99–1.62)
Fixed-effects model		156	509	123	495	1.19 (0.98–1.46)
Heterogeneity: $I^2 = 0\%$						

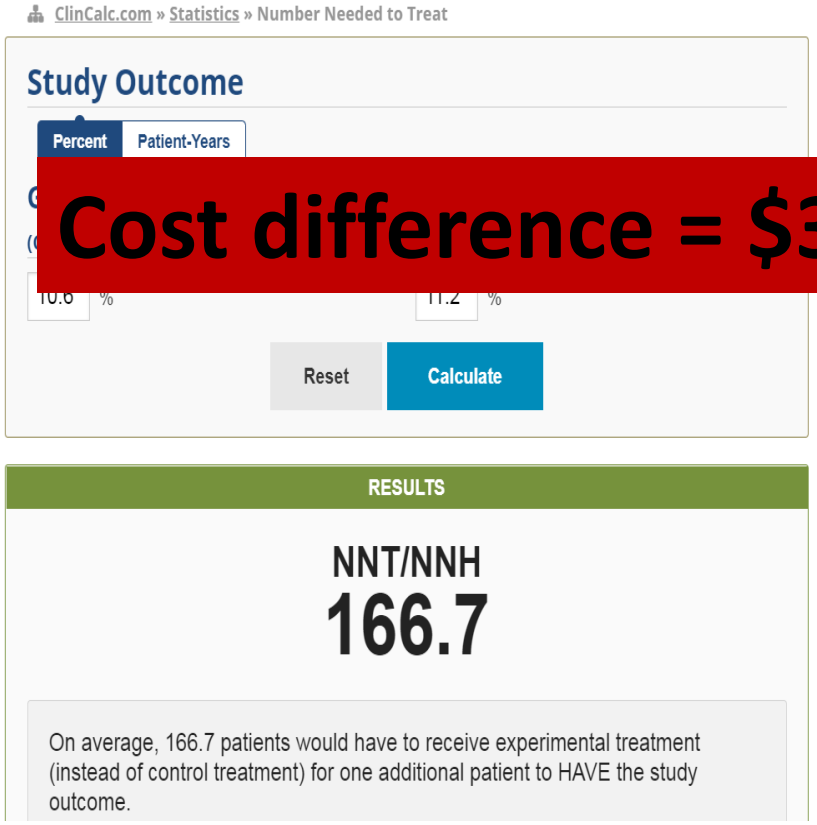
Putting it all together….

- Absolute risk reduction (ARR)
  - Difference between the event rate in control group and experimental group
  - 12.1% - 9.7% = 2.4%

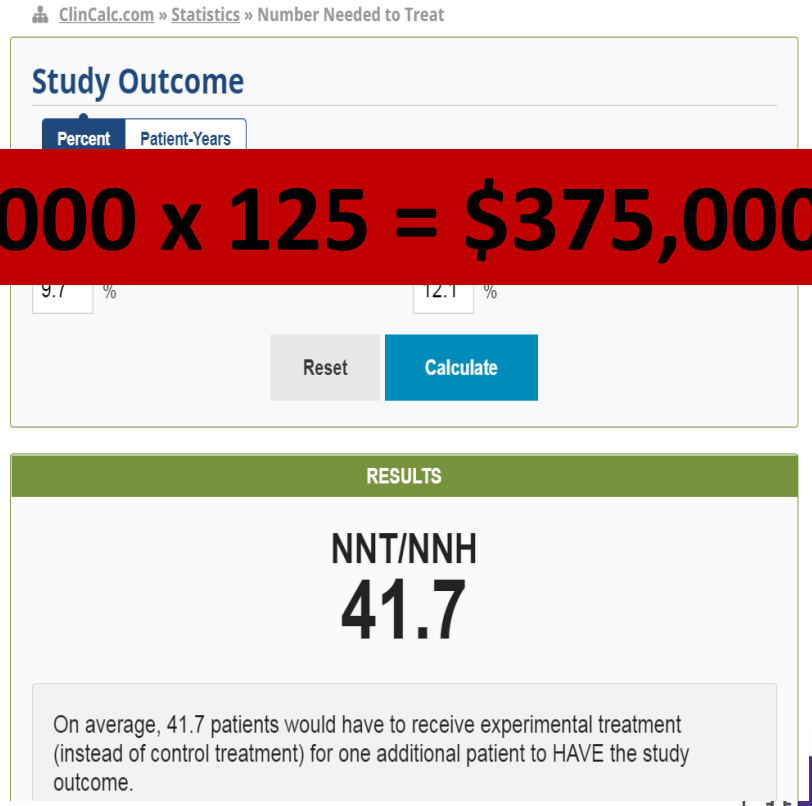
- Number needed to treat (NNT)
  - Inverse of the absolute risk reduction (ARR) expressed as a decimal.
  - NNT = 1/ARR
  - NNT = 1/0.024

What is the number needed to treat with remdesivir to prevent one death?

All hospitalized COVID-19 patients regardless of oxygenation status

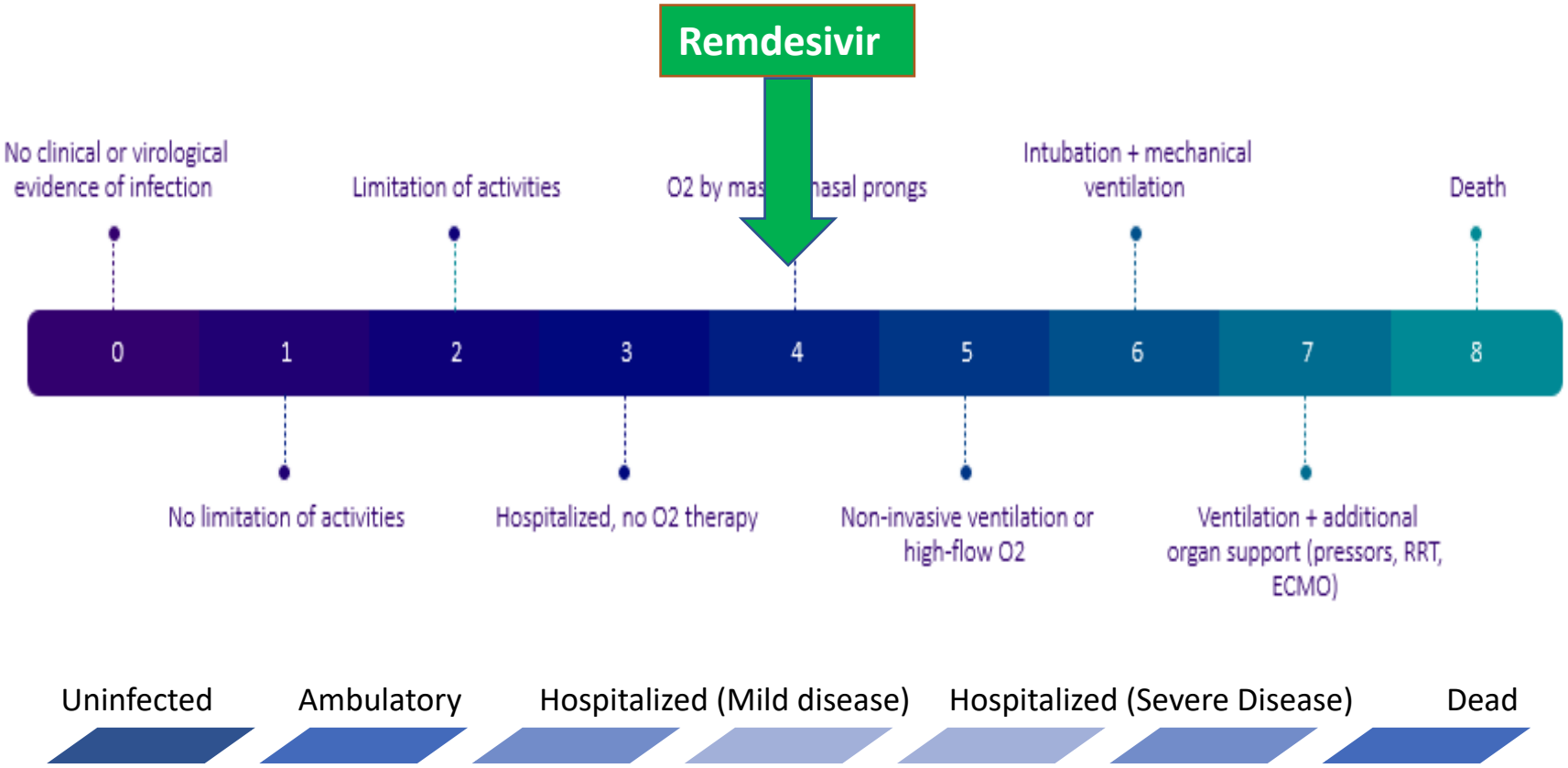


Patients requiring supplemental oxygen



Cost difference = $3000 x 125 = $375,000

Place of therapy



WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. (2020).

Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: July 8, 2021

Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity