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School of Medicine and Surgery

SC Malattie Infettive
ASST Grande Ospedale Metropolitano Niguarda

COVID: quali terapie, in quale momento?

Conflitti d’interesse

- Speaker in evento FAD – Janssen
- Principal investigator in Trial Clinico – Eli Lilly

SARS-CoV-2 Data

630,653
SRA runs

570,941
Nucleotide records

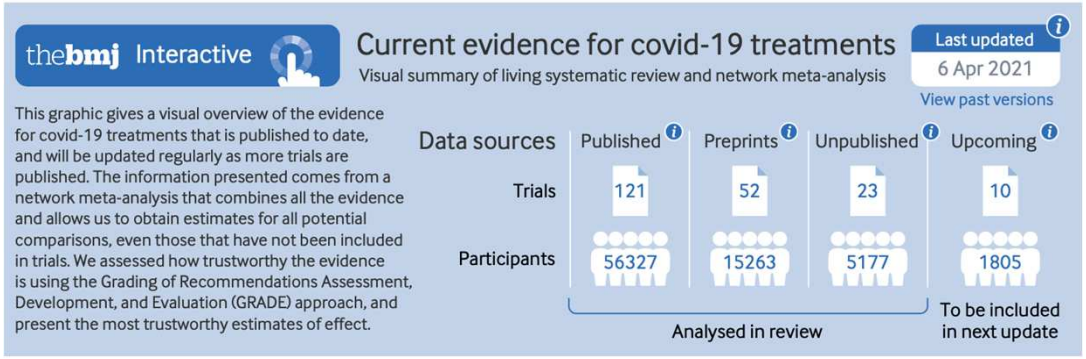
5,874
ClinicalTrials.gov

142,245
PubMed

159,721
PMC

Drug treatments for covid-19: living systematic review and network meta-analysis

BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2980 (Published 30 July 2020)Cite this as: *BMJ* 2020;370:m2980



	Mortality	Mechanical ventilation	Adverse events	Admission to hospital	Viral clearance at 7 days‡	Duration of hospital stay	ICU length of stay	Duration of mechanical ventilation	Time to symptom resolution	Time to viral clearance	Ventilator free days‡
Standard care*	130 per 1000	116 per 1000	9 per 1000	51 per 1000	500 per 1000	13 days	13 days	15 days	11 days	7 days	12 days
ACEi/ARB	-4 (-59 to 83)	-16 (-55 to 44)	8 (-5 to 58)†			-1.9 (-5.7 to 1.8)					
Anakinra		21 (-52 to 155)									
Anticoagulants	-2 (-33 to 34)										
Azithromycin	-4 (-25 to 21)	-6 (-33 to 28)				-0.9 (-1.7 to 0.3)†					-1.2 (-4.3 to 2.0)
Colchicine	-78 (-110 to -9)	-57 (-90 to 3)		-11 (-34 to 42)		-1.7 (-2.8 to -0.7)†					
Corticosteroids	-20 (-36 to -3)	-25 (-44 to -1)			-82 (-269 to 111)	-0.3 (-1.7 to 1.3)		-1.4 (-3.4 to 0.7)			2.6 (0.3 to 5.0)
Doxycycline + ivermectin	-130 (-130 to -123)		34 (-7 to 547)†								
Favipiravir	-41 (-113 to 207)	-14 (-74 to 120)	2 (-7 to 47)†		50 (-96 to 193)	-1.3 (-2.4 to -0.1)†			-4.3 (-5.9 to -2.14)	-0.6 (-3.2 to 4.2)	
Hydroxy-chloroquine	10 (-8 to 30)	15 (-9 to 45)	8 (-1 to 27)†	-10 (-31 to 26)	2 (-93 to 109)	0.1 (-1.8 to 2.0)			-1.5 (-3.0 to 0.2)	-0.9 (-2.9 to 2.1)	-1.4 (-4.9 to 2.2)
Hydroxy-chloroquine + azithromycin	-42 (-96 to 53)	54 (-22 to 174)	9 (-5 to 60)	-1 (-35 to 83)	-35 (-211 to 154)	0.4 (-1.4 to 2.1)†					
IL-6i	-15 (-30 to 6)	-30 (-46 to -10)	-4 (-9 to 67)†			-4.3 (-8.1 to -0.5)†			-0.7 (-2.7 to 1.7)		1.6 (-0.2 to 3.3)
Interferon beta	2 (-34 to 28)	-7 (-40 to 32)				-0.4 (-1.9 to 1.0)†			-1.8 (-4.0 to 1.0)		
Interferon gamma					419 (41 to 497)						
Interferon kappa + treefoil factor 2					284 (-54 to 451)						
Ivermectin	-103 (-117 to -78)	-54 (-100 to 80)	26 (-2 to 187)	-32 (-47 to 23)	118 (-13 to 241)	-0.5 (-1.7 to 1.1)†			-0.4 (-3.7 to 3.5)	-2.0 (-4.4 to 2.4)	
JAKi	-50 (-84 to 0)	-46 (-74 to -5)				-1.5 (-3.0 to 0.1)†		-3.8 (-7.5 to -0.1)†	-1.0 (-3.8 to 2.8)		
Lopinavir-ritonavir	3 (-17 to 25)	10 (-16 to 41)	46 (9 to 197)	-17 (-39 to 37)	-20 (-165 to 98)	0.7 (-1.1 to 2.7)†			0.1 (-2.5 to 3.5)		
Lopinavir-ritonavir + interferon b1a	62 (-20 to 176)	41 (-17 to 125)	136 (31 to 506)		-93 (-296 to 143)	5.0 (3.7 to 6.3)†			1.2 (-2.8 to 6.9)		
Nitazoxanide			63 (-3 to 725)	0 (-39 to 151)	159 (-97 to 350)						
Peginterferon					206 (-142 to 418)						
Proxalutimide	-130 (-130 to -118)	-116 (-116 to -111)		-50 (-51 to -38)†							
rhG-CSF	-102 (-124 to -43)	-96 (-107 to -76)				-0.7 (-1.8 to 0.5)†			-0.8 (-4.6 to 5.2)		
Remdesivir	-11 (-33 to 12)	-26 (-51 to -2)	1 (-6 to 26)		13 (-242 to 262)	0.4 (-0.1 to 1.4)†		-1.3 (-4.3 to 1.5)	-2.0 (-4.1 to 0.7)		
Sulodexide	-78 (-119 to 50)	-62 (-105 to 81)	3 (-7 to 65)	-24 (-41 to 20)							
Umifenovir	794 (-130 to 870)										
Vitamin C	-50 (-89 to 22)	17 (-41 to 110)				-1.6 (-3.3 to 1.3)†					
Vitamin D	-11 (-86 to 150)	-63 (-96 to 7)				0 (-1.2 to 1.2)†					

*The expected risk of each outcome with standard care is reported in the grey row. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care
† The best estimate of effect was obtained from direct evidence
‡ For this outcome, higher risk/mean is a benefit
Empty cells: there was no evidence for the specific intervention
IL-6i: Interleukin 6 inhibitors (tocilizumab, sarilumab); JAKi: Janus kinase inhibitors (bariticinib, ruxolitinib); rhG-CSF: Recombinant human granulocyte colony-stimulating factor

COVID-19 quali terapie in quale momento

- Fasi della malattia
- Terapia antivirale
  - Inibitori dell'entry
    - Anticorpi Monoclonali
    - Plasma di convalescente
  - Inibitori della polimerasi
- Terapia antinfiammatoria
  - Steroidi
  - Tocilizumab
  - Baricitinib
- Ad ogni tempo il suo farmaco

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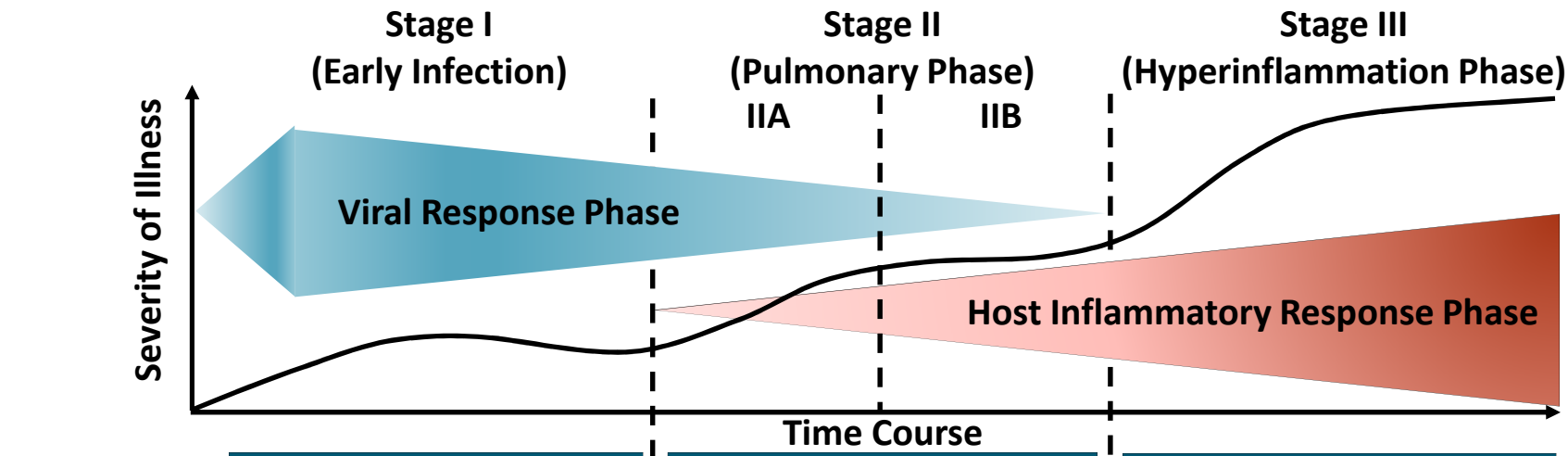
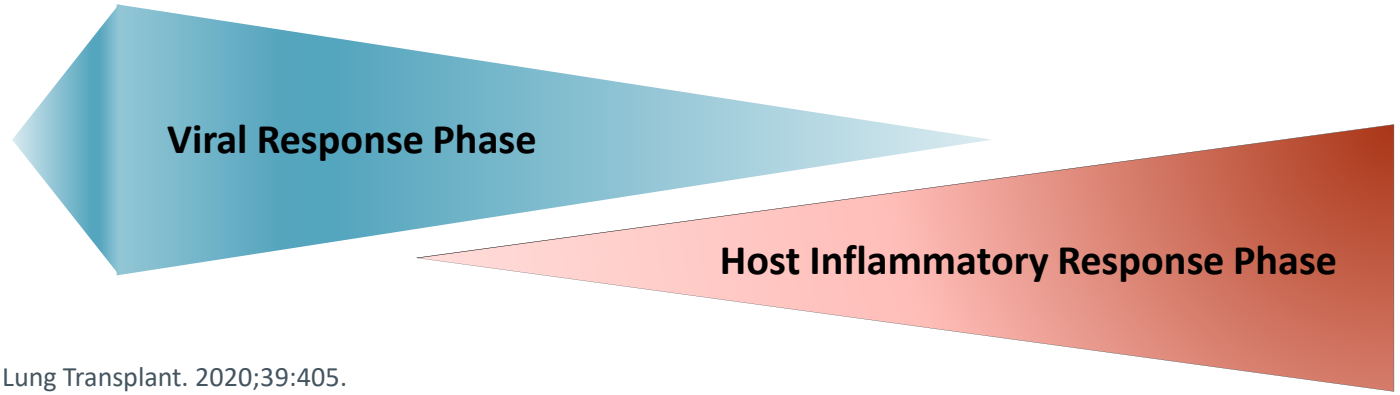


Clinical symptoms	Mild constitutional symptoms Fever > 99.6°F Dry cough	Shortness of breath without (IIA) and with hypoxia (IIB) (PaO_2/FiO_2 ≤ 300 mm Hg)	ARDS SIRS/shock Cardiac failure
Clinical signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

Highly replicating variants



Modified from Siddiqi. J Heart Lung Transplant. 2020;39:405.

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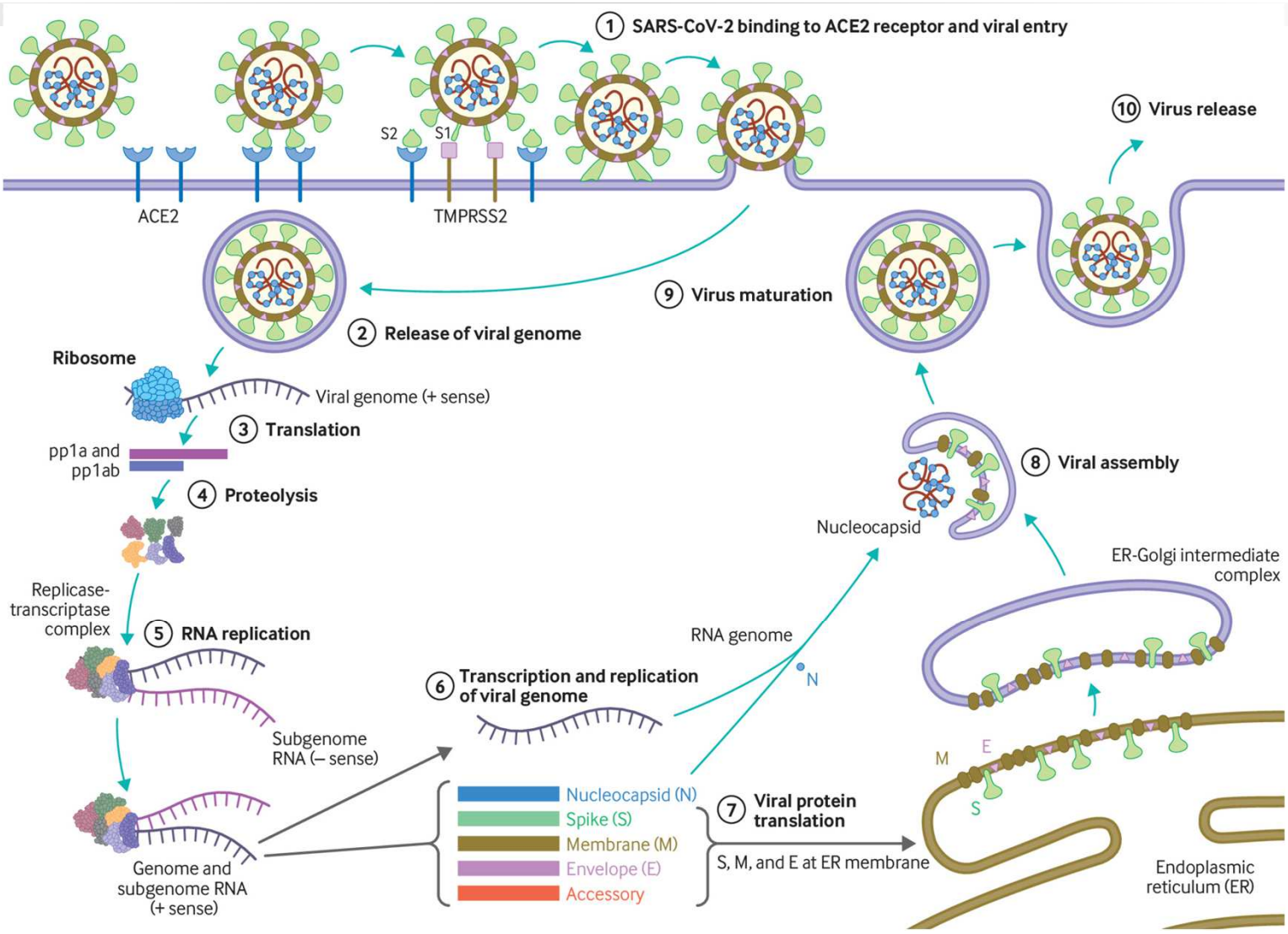
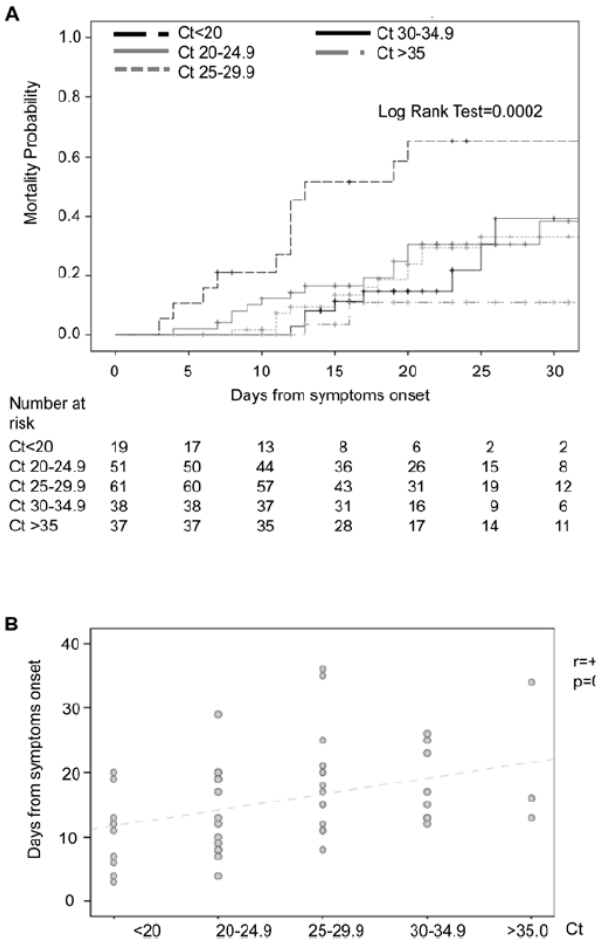
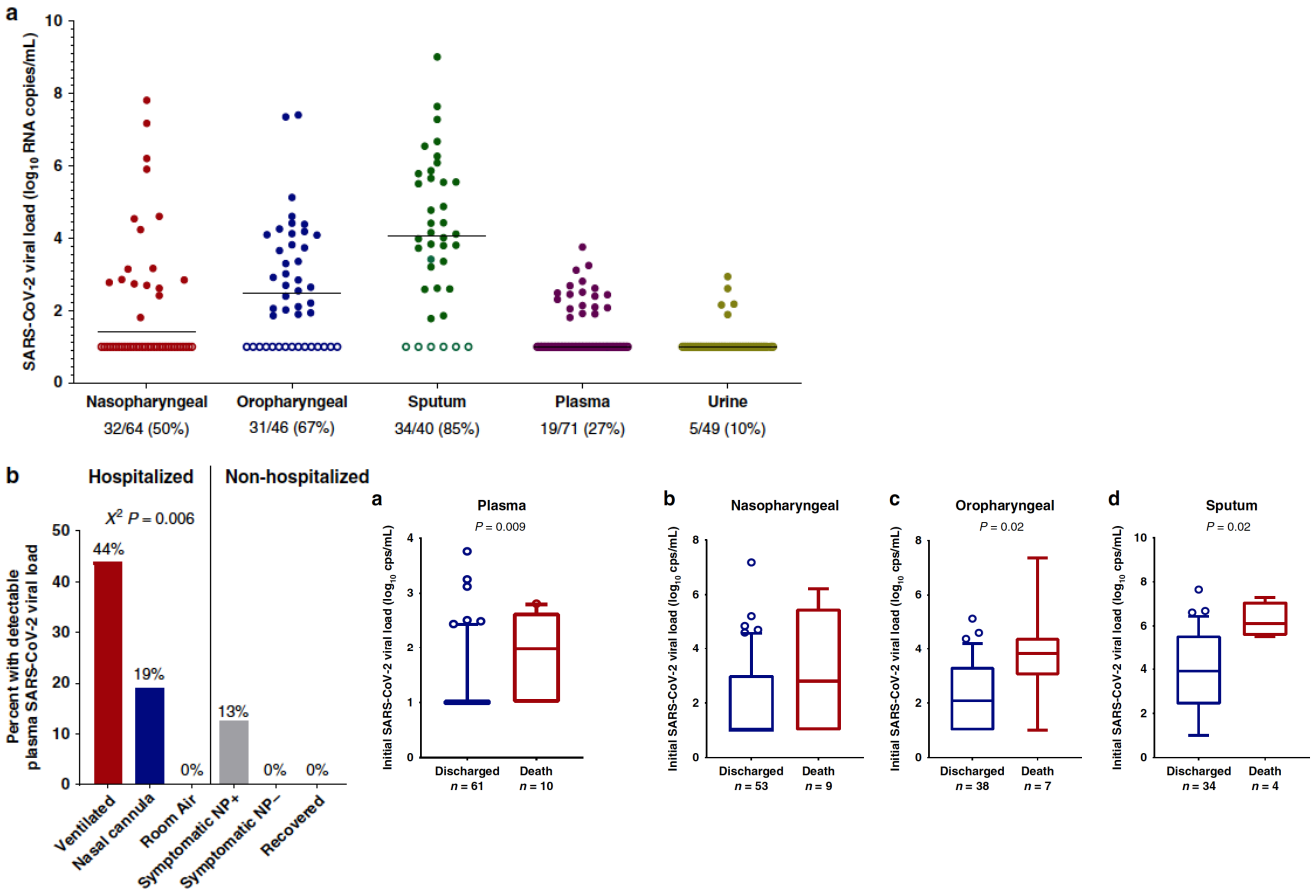


TMPRSS2 host's transmembrane serine protease 2 (cell surface protein), which is principally expressed in the airway epithelial cells and vascular endothelial cells.

Rationale of antiviral therapy: SARS-CoV-2 viral load is associated with increased disease severity and mortality





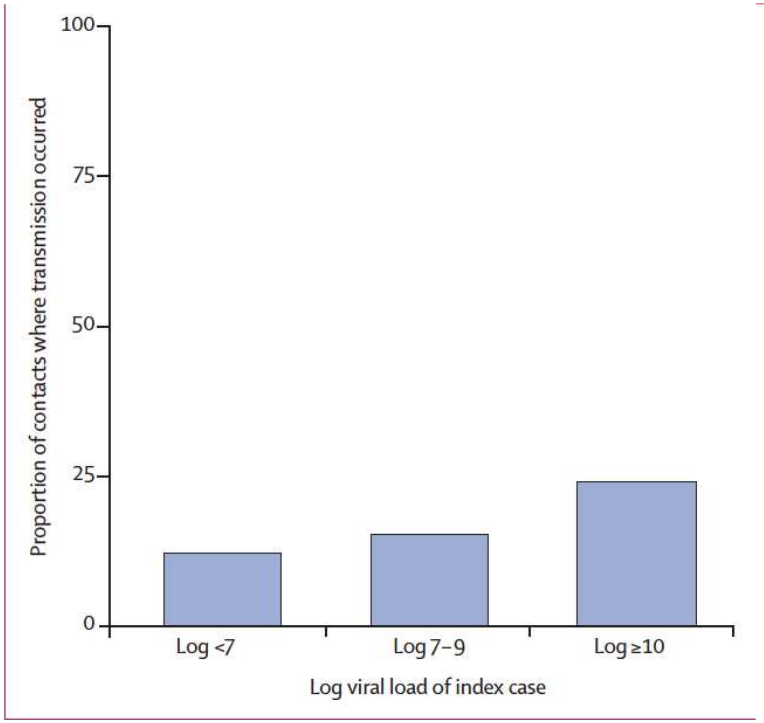
Alteri C et al CID 2020

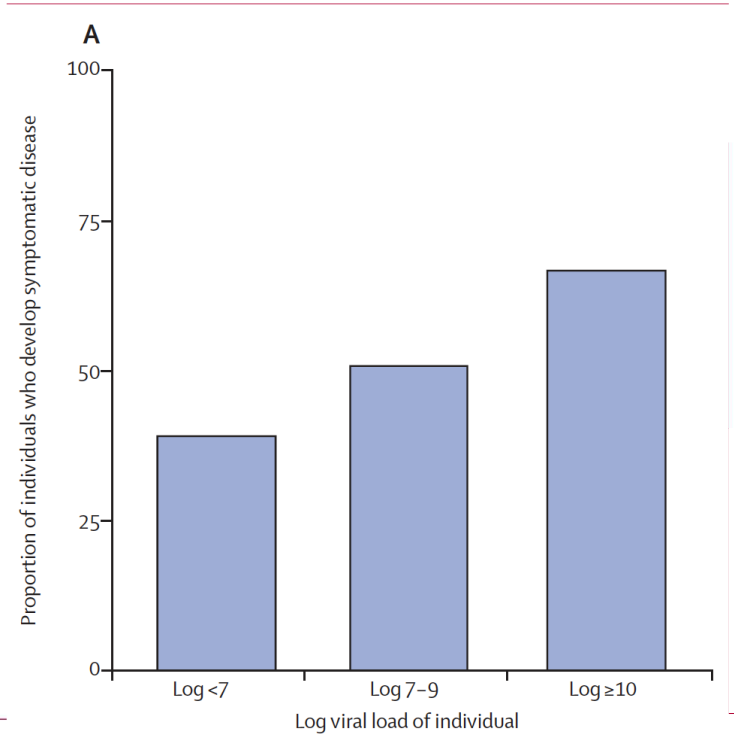
Fajnzylber J et al NATURE COMMUNICATIONS | (2020) 11:5493

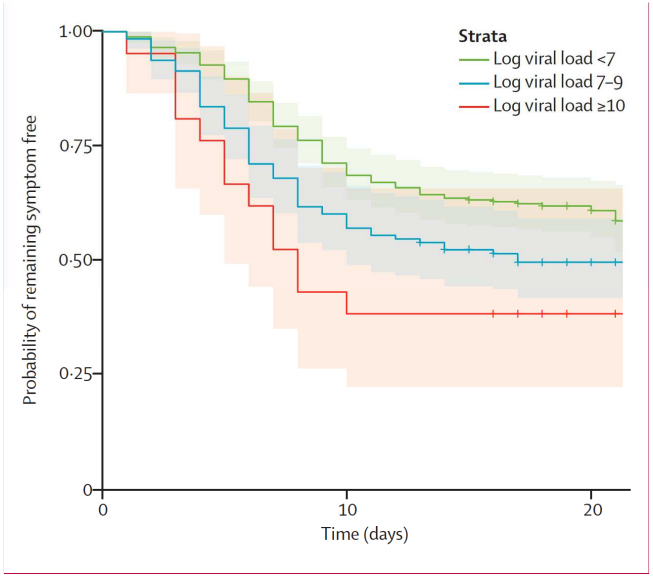
Rationale of antiviral therapy high viral load in the index case is associated with a higher number and worse severity of symptoms in contacts: treatment is prevention

Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study

Michael Marks, Pere Millat-Martinez, Dan Ouchi, Chrissy h Roberts, Andrea Alemany, Marc Corbacho-Monné, Maria Ubals, Aurelio Tobias, Cristian Tebé, Ester Ballana, Quique Bassat, Bàrbara Baro, Martí Vall-Mayans, Camila G-Beiras, Nuria Prat, Jordi Ara, Bonaventura Clotet, Oriol Mitjà







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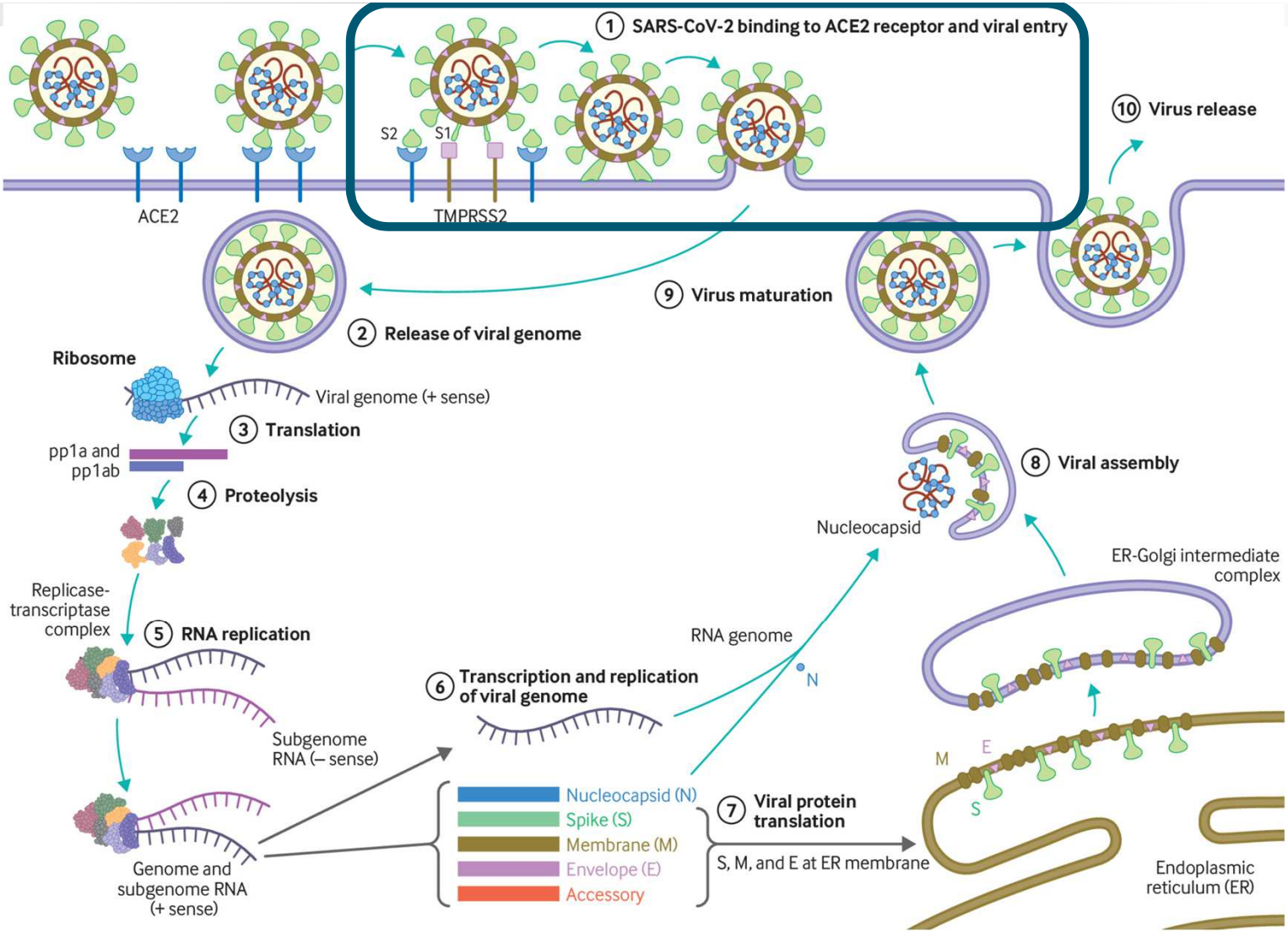
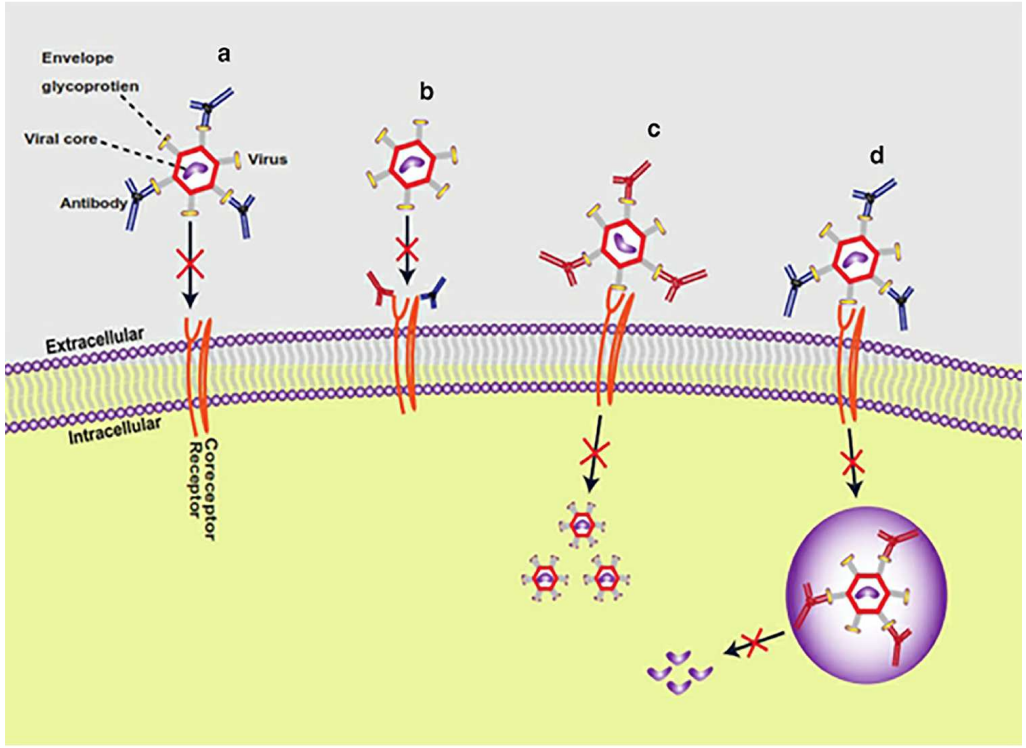

1 SARS-CoV-2 binding to ACE2 receptor and viral entry
S2
S1
ACE2
TMPRSS2
10 Virus release
9 Virus maturation
2 Release of viral genome
Ribosome
Viral genome (+ sense)
3 Translation
pp1a and pp1ab
4 Proteolysis
Replicase-transcriptase complex
5 RNA replication
Subgenome RNA (– sense)
Genome and subgenome RNA (+ sense)
6 Transcription and replication of viral genome
RNA genome
N
Nucleocapsid
8 Viral assembly
ER-Golgi intermediate complex
Nucleocapsid (N)
Spike (S)
Membrane (M)
Envelope (E)
Accessory
7 Viral protein translation
S, M, and E at ER membrane
M
E
S
Endoplasmic reticulum (ER)

Modes of activity of antiviral antibodies



Antibodies neutralize viruses by several mechanisms, either inhibition of virus entry into host cells as (a) Antibodies bind to an epitope in the viral glycoprotein envelope, lead to inhibit attachment to host cells. (b) Antibodies through the fab region can bind to host cell receptors or coreceptors (have Fcγr)) lead to inhibit viral entry. Or post binding inhibition of antibody-virus complex as (c) antibodies can bind to a non-binding region in the virus envelope lead to inhibit the conformational change to allow membrane fusion. (d) for certain viruses that need low endosomal PH for conformational change, antibodies bind to viral inside the endosome lead to inhibit the change in PH to achieve the membrane fusion, and antibodies can inhibit the release of the viral virio

Ali GM et al Immunologic Research (2020) 68:325–339

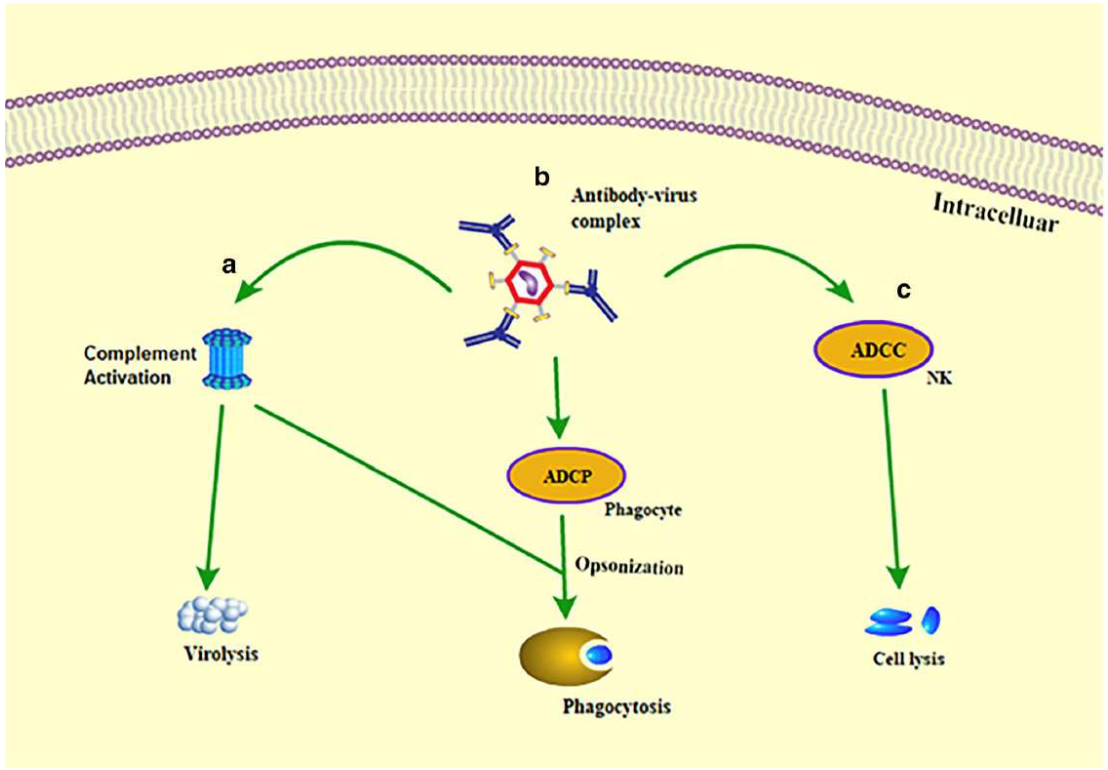


Fig. 3 The antiviral mechanism through antibody FC fragment. The Fc fragments of antibodies bind to the immune cells to perform neutralization activities. (a) Binding of complement to antibody activates complement-mediated virolysis and activation of phagocytosis. (b) Binding of antibodies to a phagocyte (Fcγr) via antibody-dependent cellular phagocytosis (ADCP) opsonizes the infected cell. (c) Antibodies bind to natural killer (NK) cells via antibody-dependent cellular cytotoxicity (ADCC) to lyse the infected cells

Table 1 | SARS-CoV-2 mAbs in clinical development

Product	Clinical stage	Trial ID	Study
REGN-COV2 (REGN10933 + REGN10987; human IgG1 mAbs targeting S protein epitope)	Phase 2/3	NCT04452318	2,000 healthy adults with infected people in household
REGN-COV2	Phase 2/3	NCT04426695	2,970 hospitalized adults with COVID-19
REGN-COV2	Phase 1/2	NCT04425629	2,104 ambulatory patients with COVID-19
LY3819253 or LY3819253 + LY3832479 (human IgG1 mAbs targeting S protein epitope)	Phase 3	NCT04427501	800 patients with mild to moderate COVID-19
LY3819253 or LY3819253 + LY3832479	Phase 3	NCT04497987	2,400 healthy staff or residents of skilled nursing facilities
LY3819253 versus remdesivir (small-molecule nucleotide analog antiviral that blocks viral RNA polymerase)	Phase 3	NCT04501978	10,000 hospitalized patients
VIR-7831/GSK4182136 (human IgG1 mAb targeting S protein epitope)	Phase 3	NCT04545060	1,360 non-hospitalized patients with COVID-19 at high risk
BGB-DXP593 (human IgG1 mAb targeting S protein epitope)	Phase 2	NCT04551898	180 patients with mild to moderate COVID-19
BGB-DXP593	Phase 1	NCT045332294	30 healthy adults 18–60 years olds
JS016 (human mAb targeting S protein epitope)	Phase 1	NCT04441918	40 healthy participants 15–45 years old
TY027	Phase 1	NCT04429529	32 healthy adults 21–50 years old
CT-P59 (human mAb targeting S protein epitope)	Phase 1	NCT04525079	32 healthy adults 19–55 years old
BRII-196 (human mAb targeting S protein epitope)	Phase 1	NCT04479631	12 healthy adults 18–49 years old
BRII-198 (human mAb targeting S protein epitope)	Phase 1	NCT04479644	12 healthy adults 18–49 years old
SCTA01 (humanized mAb targeting S protein epitopes)	Phase 1	NCT04483375	33 healthy adults
MW33 (human mAb targeting S protein epitope)	Phase 1	NCT05433048	42 healthy adults 18–45 years old
COVI-GUARD/STI-1499 (human mAb targeting S1 subunit of S protein)	Phase 1	NCT04454398	33 hospitalized patients with moderate COVID-19
AZD8895 + AZD1061 (IgG1 human mAbs targeting S protein epitopes)	Phase 1	NCT04507256	48 healthy adults 18–55 years old
HLX70 (human mAb targeting S protein epitope)	Phase 1	NCT04561076	24 healthy adults 18–60 years old

DeFrancesco L, *Nat Biotech* 2020

CLINICAL PROGRAM OVERVIEW

AMBULATORY (RECENTLY DIAGNOSED)

BLAZE-1

- Bamlanivimab alone and together with etesevimab
- 2400+ enrolled

BLAZE-4

- PD-focused study evaluating additional combinations and dose levels
- 700+ enrolled

BLAZE-5

- Real-world study of bamlanivimab in New Mexico
- 3000 subjects planned

ACTIV-2

- Bamlanivimab alone
- Partnership with NIH
- 1200+ enrolled

UNITED

- In-home infusion of bamlanivimab
- Partnership with United Health Group
- 7500 subjects planned

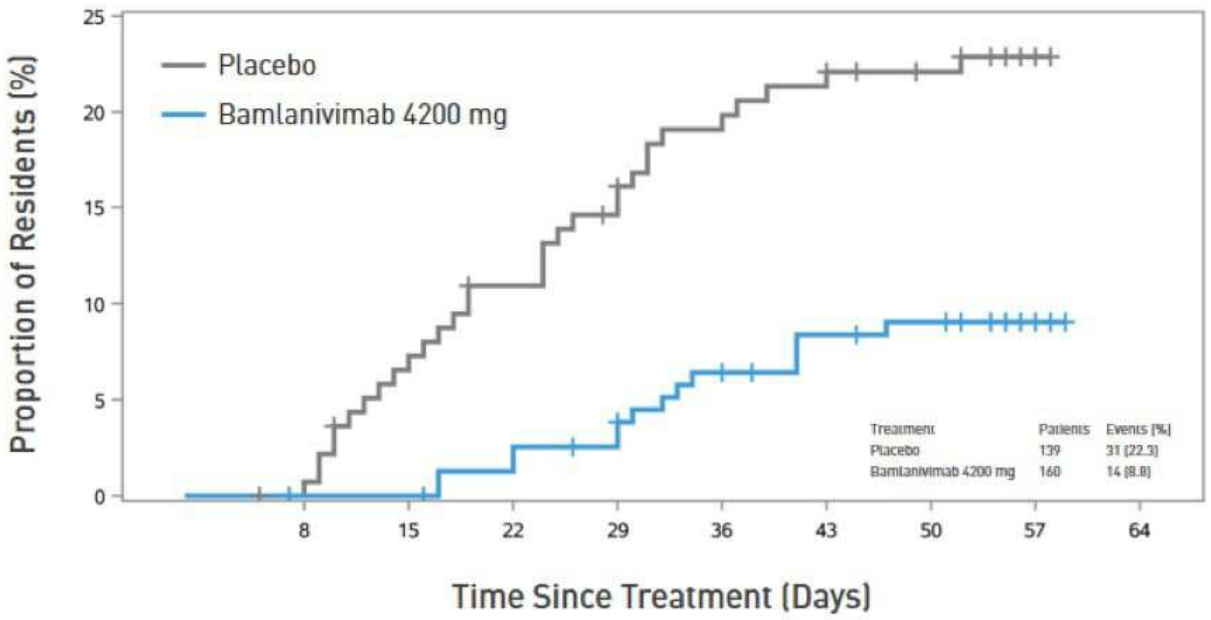
POST-EXPOSURE PROPHYLAXIS

BLAZE-2

- Bamlanivimab alone
- Residents and staff of long-term care facilities
- 1250+ enrolled

BLAZE-2: COVID-19 PREVENTION IN RESIDENTS

RESIDENTS WITH SYMPTOMATIC COVID-19 (Prevention Population)



COVID-19 PREVENTION

Odds ratio:	0.20
p-value:	0.00026

Up to 80% reduction in risk

DEATH DUE TO COVID-19

Placebo:	4 of 139 residents
Bamlanivimab:	0 of 160 residents

No deaths due to COVID-19 on bamlanivimab

BLAZE-1: AMBULATORY STUDY DESIGN

[redacted]

PHASE 2 PORTION

Bamlanivimab Monotherapy

- 7000 mg (N = 101)
- 2800 mg (N = 107)
- 700 mg (N = 101)
- Placebo (N = 100)

Bamlanivimab + Etesevimab

- 2800 mg + 2800 mg (N = 109)
- Placebo (N = 56)

Oct 7 Webcast Now Published

N Engl J Med
2021 Jan 21;384(3):229-237

JAMA
2021 Jan; Online ahead of print

Primary Endpoint: Virology
Population: Mild-to-Moderate COVID-19

PHASE 3 PORTION
(Higher Risk Population)

Bamlanivimab + Etesevimab

- 2800 mg + 2800 mg (N = 518)
- Placebo (N = 517)

Presented Today

- 700 mg + 1400 mg (N ~ 500)
- Placebo (N ~ 250)

Fully Enrolled

- Subcutaneous Dose Form
- 700 mg + 1400 mg IV

Planned

Primary Endpoint: Hospitalization or Death Through Day 29
Population: Mild-to-Moderate COVID-19 with Risk Factor(s)

BLAZE-1 PHASE 3: PRIMARY ENDPOINT

[redacted]

COVID-19 RELATED HOSPITALIZATION OR DEATH BY ANY CAUSE BY DAY 29

	N	Events	Rate	*p*
Placebo	517	36	7.0%	-
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	11	2.1%	0.0004

70% reduction vs. placebo

DEATH BY ANY CAUSE BY DAY 29

	N	Events	Rate
Placebo	517	10[†]	1.9%
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	0	0%

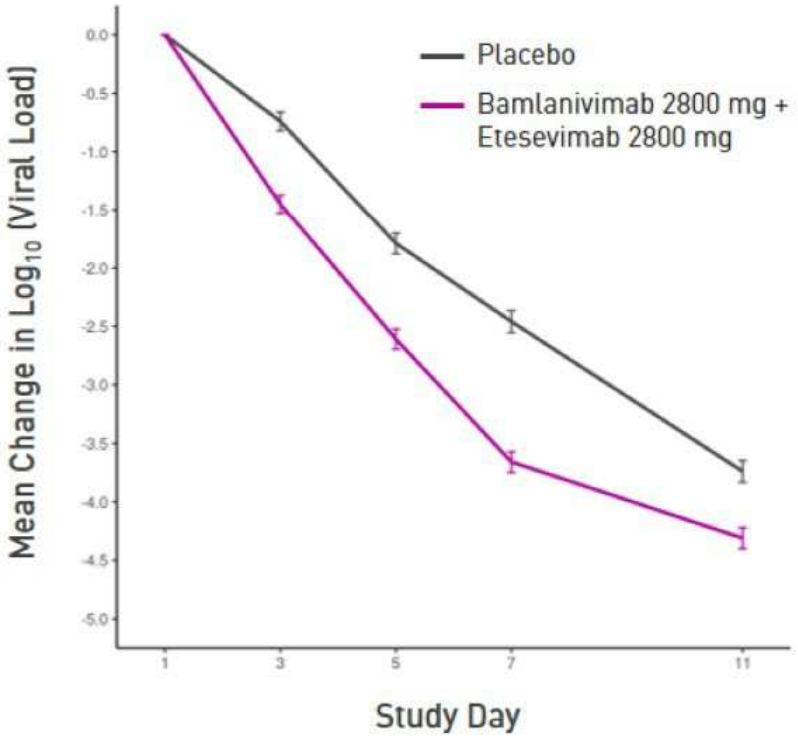
No deaths of any cause with antibody therapy

[†]8 of 10 deaths were deemed COVID-19 related

BLAZE-1 PHASE 3: IMPACT ON VIRAL LOAD

[redacted]

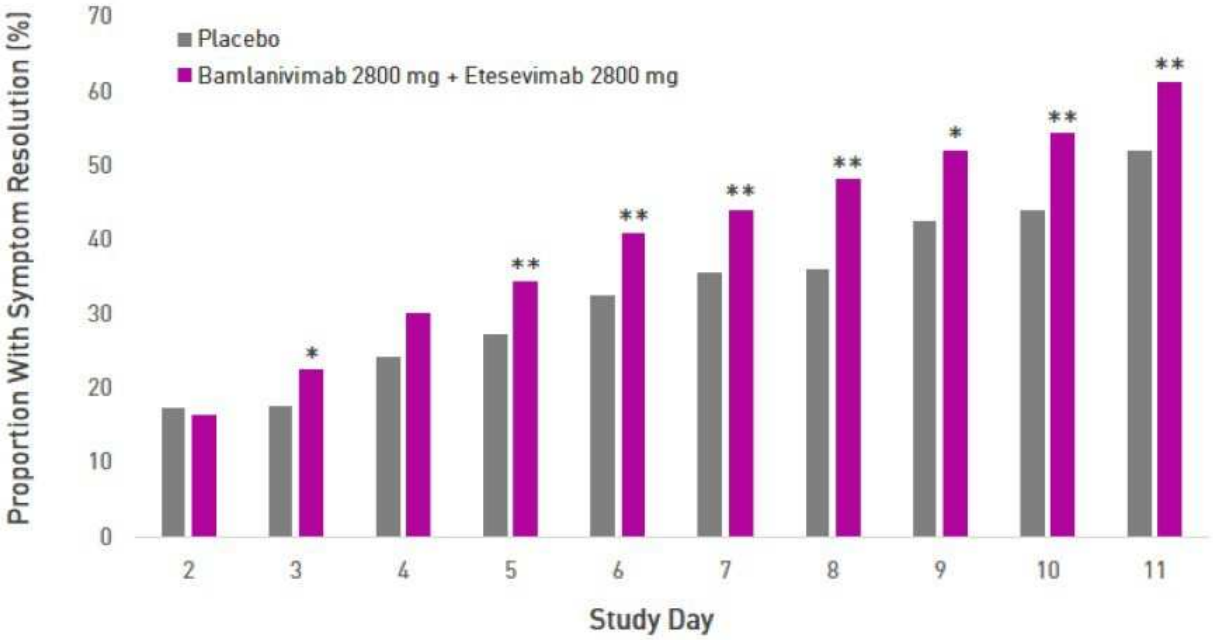
VIRAL LOAD CHANGE FROM BASELINE



MEAN VIRAL LOAD

	Placebo	Bamlanivimab + Etesevimab	*p*
Day 1	6.52	6.51	-
Day 3	5.74	5.04	<0.000001
Day 5	4.68	3.85	<0.000001
Day 7	4.05	2.87	<0.000001
Day 11	2.69	2.21	0.000011

BLAZE-1 PHASE 3: SYMPTOM RESOLUTION



- Symptom resolution defined as absence of all symptoms with an allowance for mild cough or fatigue
- Early and sustained impact on symptoms was similar to that observed in Phase 2 with bamlanivimab alone and bamlanivimab + etesevimab
- Time to sustained symptom resolution (two consecutive daily assessments) was significantly improved for bamlanivimab + etesevimab vs. placebo in this study (p = 0.007)

REGN-COV2 to Treat Nonhospitalized Patients With COVID-19

- Randomized, double-blind, placebo-controlled phase II/II trial

- Primary endpoints: change in viral load through Day 7 in patients and proportion of patients with at least 1 COVID-19–related medical visit

- Average daily change in viral load through Day 7 for combined REGN-COV2 dose groups vs placebo
  - Patients with high viral load (> 10^7 copies/mL): -0.68 (P < .0001)
  - All patients: -0.36 (P = .0003)
- REGN-COV2 reduced COVID-19–related medical visits by 57% through Day 29
  - 2.8% with REGN-COV2 vs 6.5% with placebo (P = .0065)

NCT04425629. https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates/. Press release only, not peer reviewed.

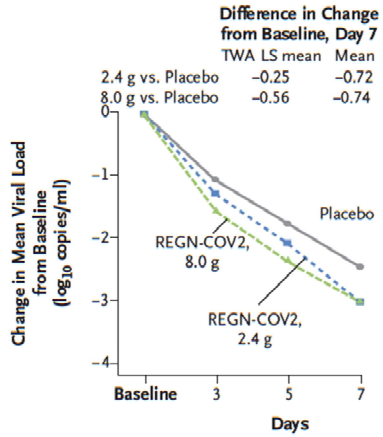
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

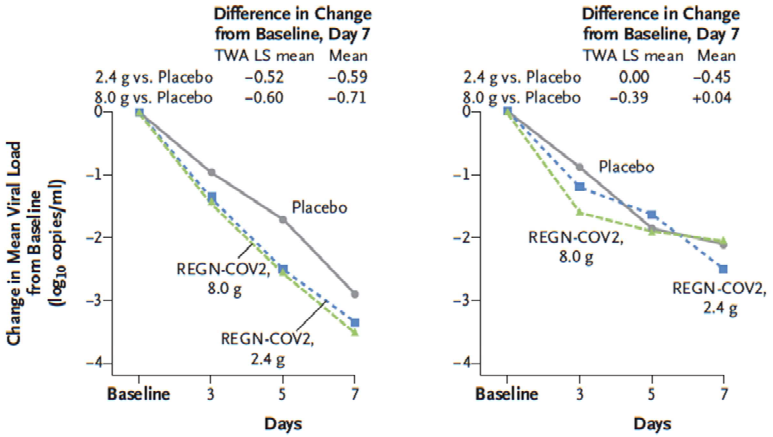
D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore, B.J. Musser, Y. Soo, D. Rofail, J. Im, C. Perry, C. Pan, R. Hosain, A. Mahmood, J.D. Davis, K.C. Turner, A.T. Hooper, J.D. Hamilton, A. Baum, C.A. Kyratsous, Y. Kim, A. Cook, W. Kampman, A. Kohli, Y. Sachdeva, X. Graber, B. Kowal, T. DiCioccio, N. Stahl, L. Lipsich, N. Braunstein, G. Herman, and G.D. Yancopoulos, for the Trial Investigators*

A Viral Load over Time in the Overall Population



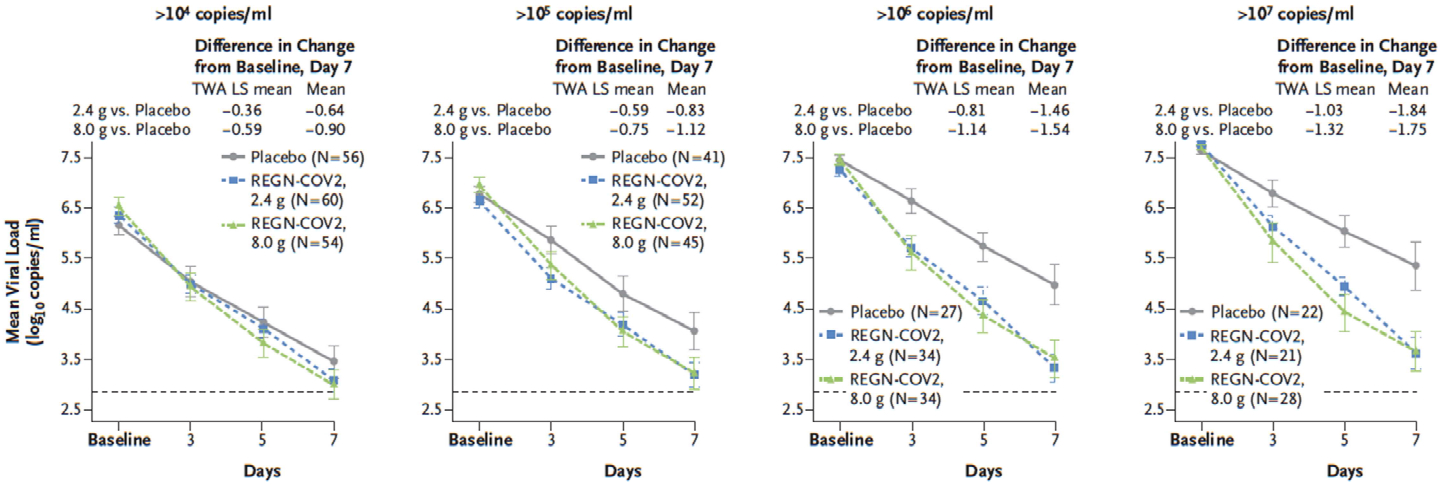
No. at Risk				
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

B Viral Load over Time According to Baseline Antibody Status



No. at Risk								
Placebo	30	23	28	28	38	35	37	37
REGN-COV2, 2.4 g	35	32	34	34	27	26	27	27
REGN-COV2, 8.0 g	36	34	35	35	29	38	29	29

C Viral Load over Time According to Baseline Viral Load Category



Dual mAb Prevents Symptomatic COVID-19 in Household-Exposed Group: Interim Results of Placebo-Controlled Trial

- Ongoing phase 3 placebo-controlled trial includes adults and adolescents who are asymptomatic household contacts of a person diagnosed with SARS-CoV-2 infection
- Participants get tested for SARS-CoV-2 and assigned to cohort A if negative and to cohort B if positive. This analysis involved cohort A members who completed at least 29 days of the study after being assigned to placebo or REGEN-COV at a dose of 1200 mg (600 mg of each mAb) given within 96 hours of their household contact's positive SARS-CoV-2 test.

	Placebo	REGEN-COV 1200 mg
N	223	186
Median age (IQR)	45 (30-55)	43 (28 -56)
Female	52%	57%
Hispanic	78%	78.5%
symptomatic PCR-positive SARS-CoV-2 infection	8 (3,6%)	0
any PCR-positive test	23 (10.3%)	10 (5,4%)*
viral load > 10,000 copies/mL.	13/212 (6,1%)	0
Viral load > 1000 copies/mL	19/212 (9.5%)	8/179 (4,5%)§
serious treatment-emergent adverse events	1.4%	1.1%

- * OR 0.49, 95% CI 0.20 - 1.12, not significant
- § OR 0.48, 95% CI 0.18 -1.17, not significant

O'Brien MP, et al. CROI 2021, Abstract 123. 2

Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions

Bamlanivimab + Etesevimab

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	>45[c]
P.1 (Brazil origin)	K417T + E484K + N501Y	>511[c]
B.1.427/B.1.429 (California origin)	L452R	7.4
B.1.526 (New York origin)[d]	E484K	17

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.
[b] No change: <5-fold reduction in susceptibility.
[c] No activity observed at the highest concentration tested. Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

Casirivimab + Imdevimab

Lineage with Spike Protein Substitution	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y[a]	no change[c]
B.1.351 (South Africa origin)	K417N, E484K, N501Y[b]	no change[c]
P.1 (Brazil origin)	K417T + E484K	no change[c]
B.1.427/B.1.429 (California origin)	L452R	no change[c]
B.1.526 (New York origin)[d]	E484K	no change[c]

[a] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.
[b] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.
[c] No change: <2-fold reduction in susceptibility.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

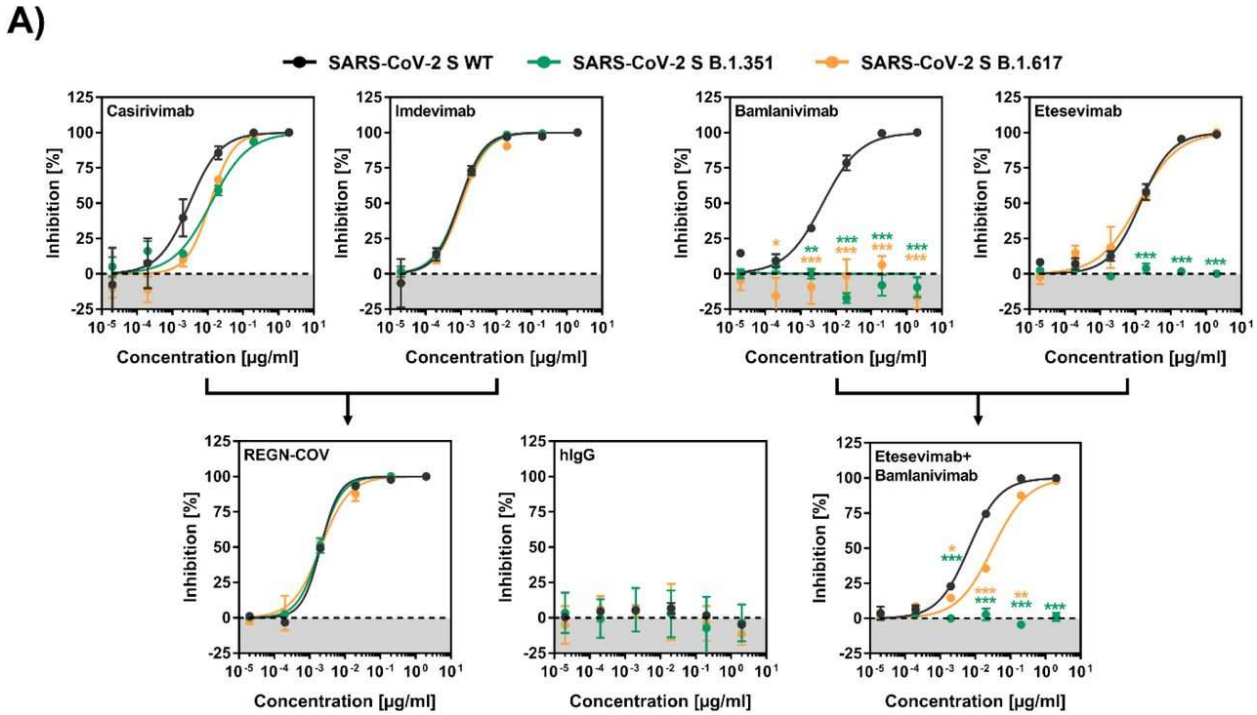
Bamlanivimab

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	E484K	>2,360[c]
P.1 (Brazil origin)	E484K	>2,360[c]
B.1.427/B.1.429 (California origin)	L452R	>1,020[c]
B.1.526 (New York origin)[d]	E484K	>2,360[c]

[a] For variants with more than one substitution of concern, only the one with the greatest impact on activity is listed.
[b] No change: <5-fold reduction in susceptibility.
[c] No activity was observed at the highest concentration tested. Bamlanivimab alone is unlikely to be active against variants from this lineage.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

FDA : FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF: BAMLANIVIMAB, BAMLANIVIMAB AND ETESEVIMAB, REGEN-COVTM (casirivimab with imdevimab)

SARS CoV-2 variants B 1.617 e B1.351 and neutralization in vitro by mon oclonal antibodies



Hoffman M et al. https://www.biorxiv.org/content/10.1101/2021.05.04.442663v1.full

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

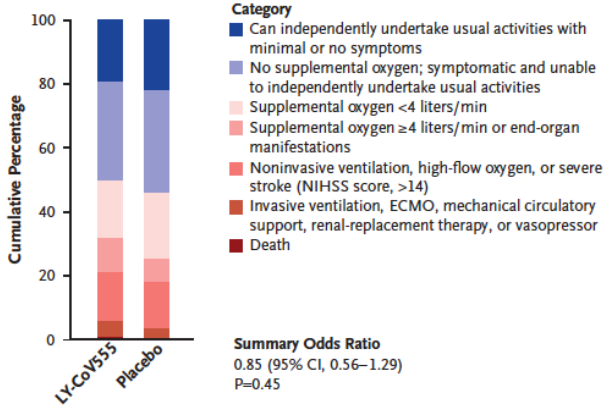
A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19

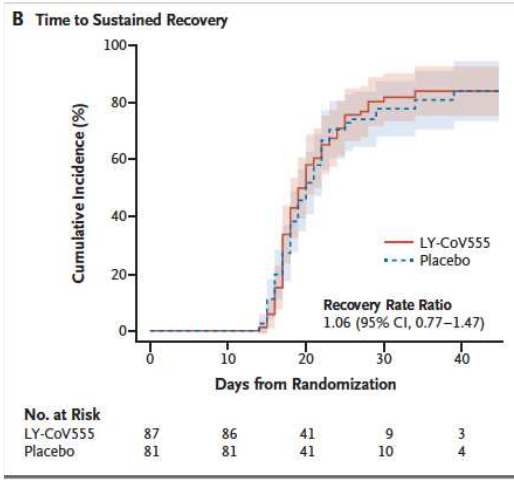
ACTIV-3/TICO LY-CoV555 Study Group*

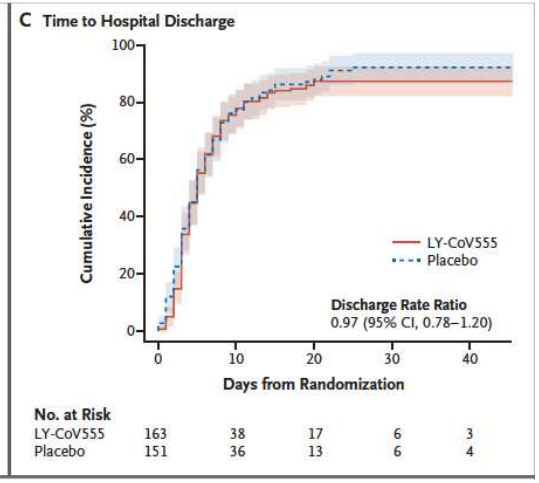
Monoclonal antibody LY-CoV555, when coadministered with remdesivir, did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure. (Funded by Operation Warp Speed and others; TICO ClinicalTrials.gov number, NCT04501978.)

A Pulmonary Ordinal Outcome on Day 5

Category		LY-CoV555	Placebo
		no. of patients (%)	
Better	1	31 (19.3)	33 (22.0)
	2	50 (31.1)	48 (32.0)
	3	29 (18.0)	31 (20.7)
	4	17 (10.6)	11 (7.3)
	5	25 (15.5)	22 (14.7)
	6	8 (5.0)	5 (3.3)
Worse	7	1 (0.6)	0 (0.0)







Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19
Published by IDSA on 4/11/2020. Last updated, 4/14/2021

- Among **ambulatory patients with mild to moderate COVID-19** at **high risk for progression** to severe disease, the IDSA guideline panel suggests **bamlanivimab/etesevimab or casirivimab/imdevimab** rather than no neutralizing antibodies. (Conditional recommendation, low certainty of evidence)
- Remarks:
  - Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab or casirivimab/imdevimab.
  - Local variant susceptibility may be considered in the choice of the most appropriate neutralizing antibody therapy.
  - There are limited data on efficacy of bamlanivimab/etesevimab or casirivimab/imdevimab in high-risk patients between 12 and 18 years of age.
- Among hospitalized patients with severe COVID-19, the IDSA guideline panel recommends against bamlanivimab monotherapy. (Strong recommendation, Moderate certainty of evidence)

Last updated, 4/14/2021 and posted online at www.idsociety.org/COVID19guidelines. Please check website for most updated version of these guidelines.

AGENZIA ITALIANA DEL FARMACO

DETERMINA 9 marzo 2021

Definizione delle modalita' e delle condizioni di impiego dell'anticorpo monoclonale bamlanivimab, ai sensi del decreto 6 febbraio 2021. (Determina DG n. 274/2021). (21A01534) (GU n.58 del 9-3-2021)

DETERMINA 17 marzo 2021

Definizione delle modalita' e delle condizioni di impiego dell'anticorpo monoclonale bamlanivimab-etesevimab. (Determina n. DG/318/2021). (21A01719) (GU n.66 del 17-3-2021)

DETERMINA 22 marzo 2021

Definizione delle modalita' e delle condizioni di impiego dell'anticorpo monoclonale casirivimab-imdevimab ai sensi del decreto 6 febbraio 2021. (Determina n. DG/340/2021). (21A01808) (GU n.71 del 23-3-2021)

Quali pazienti

Criteri di selezione dei pazienti

Tabella 1. Criteri di selezione dei pazienti candidabili alla terapia con anticorpi monoclonali per COVD-19 inclusi nel DM del 6 febbraio 2021 (GU n. 32 del 8-2-2021).
• BMI≥35
• Soggetti cronicamente sottoposti a dialisi peritoneale o emodialisi
• Diabete mellito non controllato (HbA1c≥9.0% 75 mmol/mol) o con complicanze croniche
• Immunodeficienze primitive
• Immunodeficienze secondarie con particolare riguardo ai pazienti onco-ematologici in trattamento con farmaci mielo/immunosoppressivi, mielosoppressivi o a meno di 6 mesi dalla sospensione delle cure.
• ≥65 anni (in questo caso deve essere presente almeno un ulteriore fattore di rischio)
• ≥ 55 anni con ○ malattia cardio-cerebrovascolare (inclusa ipertensione con concomitante danno d'organo) ○ BPCO e/o altre malattie respiratorie croniche (soggetti affetti da fibrosi polmonare o che necessitano di O2-terapia per ragioni differenti da SARS-CoV-2)
12-17 anni con: • BMI ≥ 85esimo percentile per età e genere; • anemia falciforme; • malattie cardiache congenite o acquisite; • malattia del neurosviluppo, • dipendenza da dispositivo tecnologico (p.es. soggetti con tracheotomia, gastrostomia, etc); • asma, o altre malattie respiratorie che richiedono medicazioni giornaliere per il loro controllo.
Sono esclusi soggetti ricoverati per COVID-19, o che ricevono ossigenoterapia per COVID-19

Quali prescrittori

a) la selezione del paziente e' affidata ai medici di medicina generale, ai pediatri di libera scelta, ai medici delle USCA(R) e, in generale, ai medici che abbiano l'opportunita' di entrare in contatto con pazienti affetti da COVID di recente insorgenza e con sintomi lievi-moderati e di indirizzarli rapidamente alla struttura presso la quale effettuare il trattamento e deve avvenire nel rispetto dei criteri fissati dalla CTS, di cui all'allegato 1;

b) la prescrivibilita' del prodotto e' limitata ai medici operanti nell'ambito delle strutture identificate a livello locale per la somministrazione;

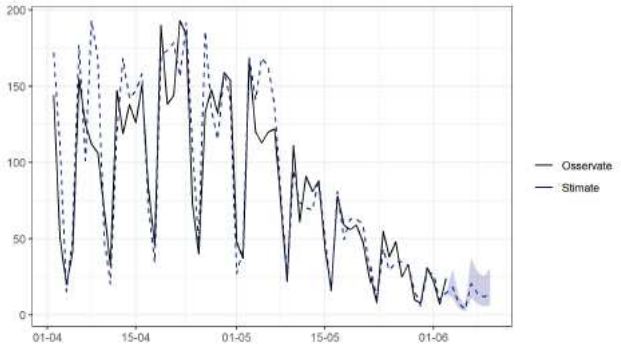
c) e' raccomandato il trattamento nell'ambito di una struttura ospedaliera o comunque in setting che consentano una pronta ed appropriata gestione di eventuali reazioni avverse gravi;

d) la prescrizione ed il trattamento devono garantire la somministrazione del prodotto il piu' precocemente possibile rispetto all'insorgenza dei sintomi, e comunque non oltre i dieci giorni dall'inizio degli stessi.

2. La definizione del percorso attraverso il quale vengono identificati i pazienti eleggibili al trattamento e' rimessa ai provvedimenti delle regioni e delle province autonome.

Monitoraggio Anticorpi Monoclonali per Covid-19
Ufficio Registri di Monitoraggio AIFA

Andamento a livello nazionale delle prescrizioni giornaliere di anticorpi monoclonali per il COVID-19 e proiezione alla settimana 4 giugno – 10 giugno



La predizione è stata effettuata con un modello s-arima.
Nel grafico, in blu, sono riportate le stime della prossima settimana (RF) con relative intervalli di confidenza. La linea tratteggiata blu indica il fit rispetto alla serie storica.

Riepilogo nazionale e regionale per principio attivo (periodo: apertura monitoraggio – 03/06/2021)*

REGIONE	bamlanivimab	bamlanivimab e etesevimab	casirivimab e imdevimab	Totale per Regione*	Inc%	%Bam	%BamEte	%Casimd
VENETO	201	489	83	773	13,2%	24,39	14,75	4,82
LAZIO	21	418	325	764	13,0%	2,55	12,61	18,87
TOSCANA	33	414	265	712	12,1%	4	12,49	15,39
PUGLIA	72	337	85	494	8,4%	8,74	10,17	4,94
CAMPANIA	157	233	86	476	8,1%	19,05	7,03	4,99
LOMBARDIA	26	233	176	435	7,4%	3,16	7,03	10,22
PIEMONTE	14	165	175	354	6,0%	1,7	4,98	10,16
LIGURIA	46	216	55	317	5,4%	5,58	6,52	3,19
SICILIA	73	139	102	314	5,4%	8,86	4,19	5,92
MARCHE	37	185	60	282	4,8%	4,49	5,58	3,48
EMILIA ROMAGNA	1	137	50	188	3,2%	0,12	4,13	2,9
VALLE D'AOSTA	33	61	72	166	2,8%	4	1,84	4,18
ABRUZZO	-	39	90	129	2,2%	0	1,18	5,23
FRIULI VENEZIA GIULIA	40	74	4	118	2,0%	4,85	2,23	0,23
CALABRIA	-	50	47	97	1,7%	0	1,51	2,73
UMBRIA	51	23	16	90	1,5%	6,19	0,69	0,93
BASILICATA	3	47	11	61	1,0%	0,36	1,42	0,64
SARDEGNA	-	34	16	50	0,9%	0	1,03	0,93
PROV. AUTON. TRENTO	4	19	2	25	0,4%	0,49	0,57	0,12
MOLISE	12	1	-	13	0,2%	1,46	0,03	0
PROV. AUTON. BOLZANO	-	1	2	3	0,1%	0	0,03	0,12
ITALIA	824	3.315	1.722	5.861	100%	14,1%	56,6%	29,4%

* I numeri indicano le prescrizioni anticorpi monoclonali (RF=richieste farmaco) al netto di quelle senza dispensazione

Early Covid-19 Treatment With SARS-CoV-2 I

- Ongoing, multicenter, double-blind, phase 3 trial,
  - nonhospitalized patients with
  - symptomatic Covid-19 and
  - at least one risk factor for disease progression
- were randomized (1:1)to an intravenous infusion of sotrovimab 500 mg or placebo.
- The primary efficacy endpoint was:
  - The proportion of patients with Covid-19 progression, defined as hospitalization longer than 24 hours or death, through day 29

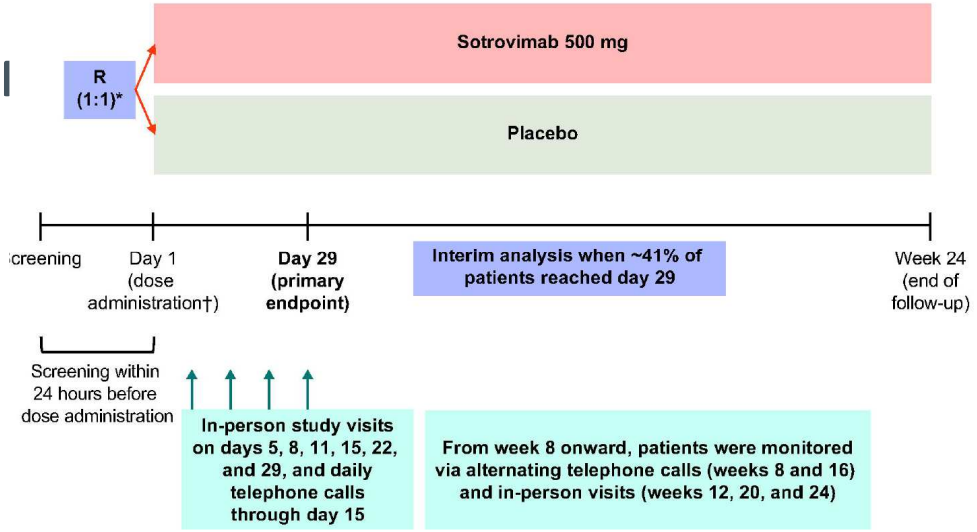


Table 2. Summary of Efficacy Outcomes Through Day 29 (ITT Population)

	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalized >24 hours or death for any cause – no. (%)	3 (1)	21 (7)
Hospitalized >24 hours for any cause	3 (1)	21 (7)
Death by any cause	0	1 (<1)
Alive and not hospitalized – no. (%)	284 (98)	270 (92)
Missing – no. (%)	4 (1)	1 (<1)
Withdrew consent prior to dosing – no. (%)	3 (1)	1 (<1)
Percent reduction (97.24% CI), P value	85% (44% to 96%); P = 0.002	

Gupta A et al. medRxiv preprint doi: https://doi.org/10.1101/2021.05.27.21257096

Sintesi degli studi disponibili su plasma di soggetti convalescenti nel trattamento di soggetti con COVID-19: Studi Non Randomizzati Interventistici (NRI)

Autore	Tipo di studio	Tipo di plasma (% donatori con anticorpi neutralizzanti/ anticorpi)	N pazienti Trattati/controlli	Mortalità intraospedaliera RR (95% CI)	Sopravvivenza HR (95% CI)	Dimissione RR (95% CI)	Miglioramento clinico a 15 gg RR (95% CI)	Miglioramento clinico a 30 gg RR ()5% CI)
Piechotta	Metanalisi studi NRI		195		0.46 (0.22-0.96)			
Perotti	**NRI**	**HIP (100%)**	**46/23**	**6.5% vs 30% 0.21 (0.0610 to 0.7528)**				
Rogers	NRI	CP (non nota;/ 13%)	64/177	0.93 (0.39-2.2)		1.28 (0.91-1.81) > 65 1.86 (1.03-3.36)		
Altuntas	NRI	CP (non nota)	888/888	24.7% vs 27.7%*				
Duan	NRI	HIP (100% +)	10/11	0.89 (0.61-1.31)				
Liu	**NRI**	**HIP 100%**	**39/156 (propensity score matched controls)**	**0.34 (0.16-0.89)**			**0.86; (0.75–0.98);**	
Salazar	**NRI**	**HIP**	**136/251**	**Transfused < 72 h from admission titre > 1:3125 Survival 5.92 (0.90 to 38.84)**		**Transfused < 72 h from admission titre > 1:3125 3.64 (1.05 to 12.62)**		

JAMA | Original Investigation

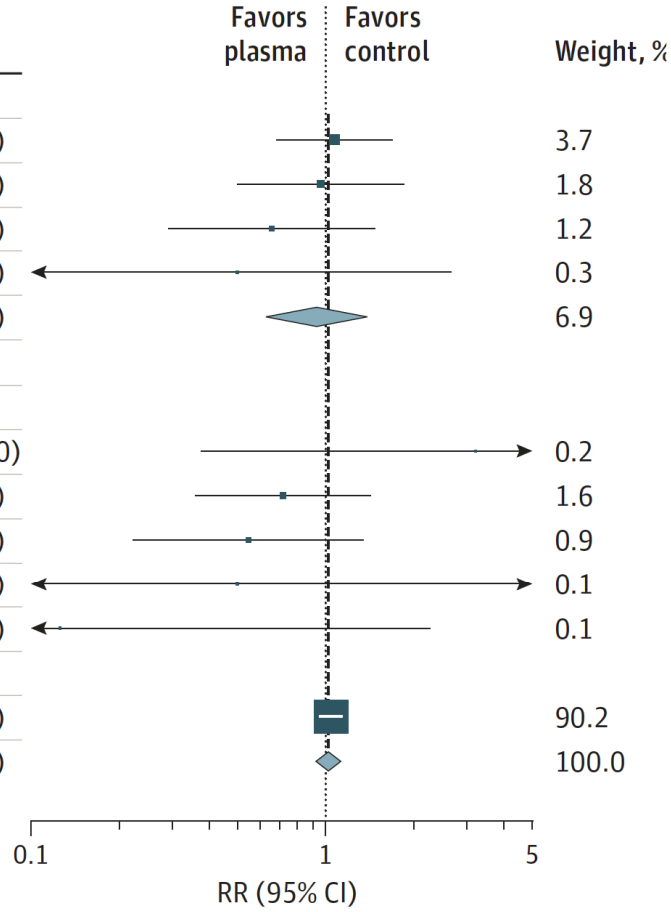
Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19

A Systematic Review and Meta-analysis

Perrine Janiaud, PhD; Cathrine Axfors, MD, PhD; Andreas M. Schmitt, MD; Viktoria Gloy, PhD; Fahim Ebrahimi, MD, MSc; Matthias Hepprich, MD; Emily R. Smith, ScD, MPH; Noah A. Haber, ScD; Nina Khanna, MD; David Moher, PhD; Steven N. Goodman, MD, PhD; John P. A. Ioannidis, MD, DSc; Lars G. Hemkens, MD, MPH

A All-cause mortality

Trial	Events, No./total: Plasma	Control	RR (95% CI)	Weight, %
Studies published in peer-reviewed journals				
PLACID[17]	34/235	31/229	1.07 (0.68-1.68)	3.7
PlasmAr[18]	25/228	12/105	0.96 (0.50-1.83)	1.8
ChiCTR2000029757[19]	8/52	12/51	0.65 (0.29-1.47)	1.2
NCT04479163[16]	2/80	4/80	0.50 (0.09-2.65)	0.3
Summary for peer-reviewed studies			0.93 (0.63-1.38)	6.9
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .65$				
Studies published as preprints				
ILBS-COVID-02[21]	3/14	1/15	3.21 (0.38-27.40)	0.2
PICP19[24]	10/40	14/40	0.71 (0.36-1.41)	1.6
ConCOVID[22]	6/43	11/43	0.55 (0.22-1.34)	0.9
NCT04356534[20]	1/20	2/20	0.50 (0.05-5.08)	0.1
ConPlas-19[23]	0/38	4/43	0.13 (0.01-2.26)	0.1
Study published as press release				
RECOVERY[8]	NA/NA	NA/NA	1.04 (0.95-1.14)	90.2
Summary for all studies			1.02 (0.92-1.12)	100.0
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .48$				
Test for overall effect: $P = .68$				



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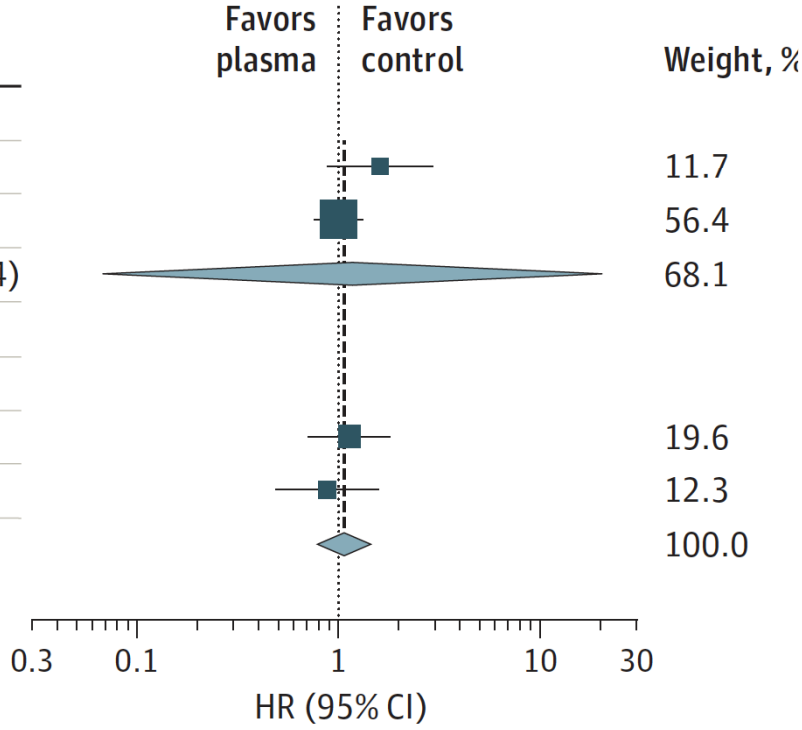
B Length of hospital stay

Trial	Events, No./total: Plasma	Events, No./total: Control	HR (95% CI)
Studies published in peer-reviewed journals			
ChiCTR2000029757[19]	NA/52	NA/51	1.61 (0.88-2.95)
PlasmAr[18]	NA/228	NA/105	1.00 (0.76-1.32)
Summary for peer-reviewed studies			1.17 (0.07-20.34)
Heterogeneity: $I^2 = 49\%$, $\tau^2 = 0.0559$, $P = .16$			
Studies published as preprints			
ConPlas-19[23]	NA/38	NA/43	1.13 (0.71-1.80)
ConCOVID[22]	NA/43	NA/43	0.88 (0.49-1.59)
Summary for all studies[a]			1.07 (0.79-1.45)
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .48$			
Test for overall effect: $P = .55$			



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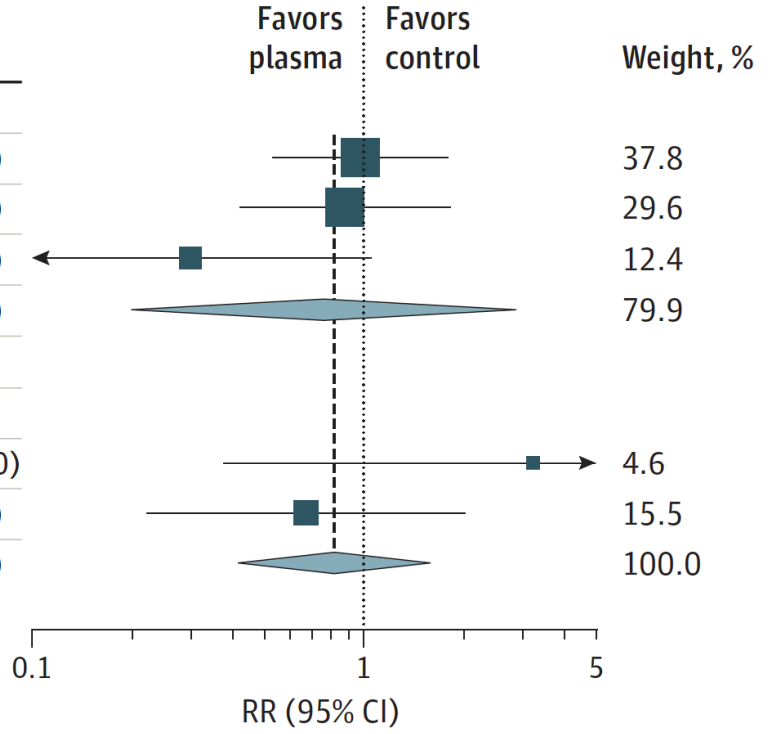
C Mechanical ventilation use

Trial	Events, No./total: Plasma	Control	RR (95% CI)
Studies published in peer-reviewed journals			
PLACID[17]	19/235	19/229	0.97 (0.53-1.79)
PlasmAr[18]	19/228	10/105	0.87 (0.42-1.82)
NCT04479163[16]	3/80	10/80	0.30 (0.09-1.05)
Summary for peer-reviewed studies			0.76 (0.20-2.87)
Heterogeneity: $I^2 = 29\%$, $\tau^2 = 0.1194$, $P = .25$			
Studies published as preprints			
ILBS-COVID-02[21]	3/14	1/15	3.21 (0.38-27.40)
NCT04356534[20]	4/20	6/20	0.67 (0.22-2.01)
Summary for all studies[a]			0.81 (0.42-1.58)
Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0559$, $P = .34$			
Test for overall effect: $P = .44$			



The NEW ENGLAND JOURNAL of MEDICINE

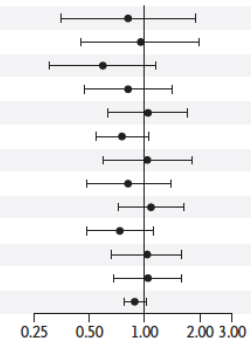
ORIGINAL ARTICLE

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

M.J. Joyner, R.E. Carter, J.W. Senefeld, S.A. Klassen, J.R. Mills, P.W. Johnson, E.S. Theel, C.C. Wiggins, K.A. Bruno, A.M. Klompas, E.R. Lesser, K.L. Kunze, M.A. Sexton, J.C. Diaz Soto, S.E. Baker, J.R.A. Shepherd, N. van Helmond, N.C. Verdun, P. Marks, C.M. van Buskirk, J.L. Winters, J.R. Stubbs, R.F. Rea, D.O. Hodge, V. Herasevich, E.R. Whelan, A.J. Clayburn, K.F. Larson, J.G. Ripoll, K.J. Andersen, M.R. Buras, M.N.P. Vogt, J.J. Dennis, R.J. Regimbal, P.R. Bauer, J.E. Blair, N.S. Paneth, D.L. Fairweather, R.S. Wright, and A. Casadevall

A Medium vs. Low Antibody Levels

Subgroup	No. of Patients	Mortality at 30 Days
Before May 15, no mechanical ventilation, 18–59 yr	239	0.81 (0.35–1.89)
May 15 or later, no mechanical ventilation, 18–59 yr	428	0.95 (0.45–1.97)
Before May 15, no mechanical ventilation, 60–69 yr	181	0.59 (0.30–1.14)
May 15 or later, no mechanical ventilation, 60–69 yr	265	0.81 (0.47–1.40)
Before May 15, no mechanical ventilation, ≥70 yr	220	1.04 (0.63–1.70)
May 15 or later, no mechanical ventilation, ≥70 yr	329	0.75 (0.54–1.05)
Before May 15, mechanical ventilation, 18–59 yr	194	1.03 (0.59–1.80)
May 15 or later, mechanical ventilation, 18–59 yr	109	0.81 (0.48–1.38)
Before May 15, mechanical ventilation, 60–69 yr	177	1.08 (0.72–1.62)
May 15 or later, mechanical ventilation, 60–69 yr	106	0.73 (0.48–1.11)
Before May 15, mechanical ventilation, ≥70 yr	158	1.03 (0.66–1.59)
May 15 or later, mechanical ventilation, ≥70 yr	105	1.04 (0.68–1.58)
All subgroups	2511	0.88 (0.77–1.02)



B High vs. Low Antibody Levels

Subgroup	No. of Patients	Mortality at 30 Days
Before May 15, no mechanical ventilation, 18–59 yr	109	0.47 (0.14–1.57)
May 15 or later, no mechanical ventilation, 18–59 yr	196	0.74 (0.26–2.13)
Before May 15, no mechanical ventilation, 60–69 yr	93	0.62 (0.26–1.47)
May 15 or later, no mechanical ventilation, 60–69 yr	117	0.66 (0.31–1.38)
Before May 15, no mechanical ventilation, ≥70 yr	74	0.57 (0.26–1.22)
May 15 or later, no mechanical ventilation, ≥70 yr	128	0.73 (0.45–1.20)
Before May 15, mechanical ventilation, 18–59 yr	81	1.35 (0.72–2.54)
May 15 or later, mechanical ventilation, 18–59 yr	47	0.31 (0.10–0.97)
Before May 15, mechanical ventilation, 60–69 yr	75	1.14 (0.70–1.88)
May 15 or later, mechanical ventilation, 60–69 yr	44	0.60 (0.30–1.19)
Before May 15, mechanical ventilation, ≥70 yr	48	1.29 (0.76–2.21)
May 15 or later, mechanical ventilation, ≥70 yr	46	0.91 (0.50–1.66)
All subgroups	1058	0.80 (0.65–0.97)

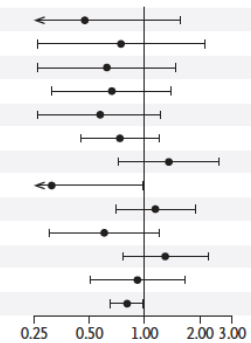


Figure 2. Relative Risk of Death within 30 Days after Convalescent Plasma Transfusion.

Forest plots of the relative risks of death associated with medium versus low antibody levels (Panel A) and high versus low antibody levels (Panel B) are shown. The subgroups are 12 mutually exclusive categories of the time period of the study in 2020, patient age, and ventilator support in patients who received transfusions of convalescent plasma. Shown are the estimated relative risks of death among patients who received convalescent plasma with IgG signal-to-cutoff ratios in the range of 4.62 to 18.45 (medium titer) or more than 18.45 (high titer), as compared with the relative risks among those who received plasma with IgG signal-to-cutoff ratios below 4.62 (low titer). The pooled estimates from all the subgroups are based on the Mantel–Haenszel estimator. Table S5 provides the sample sizes and number of deaths in each subgroup. I bars indicate 95% confidence intervals.

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial

RECOVERY Collaborative Group*

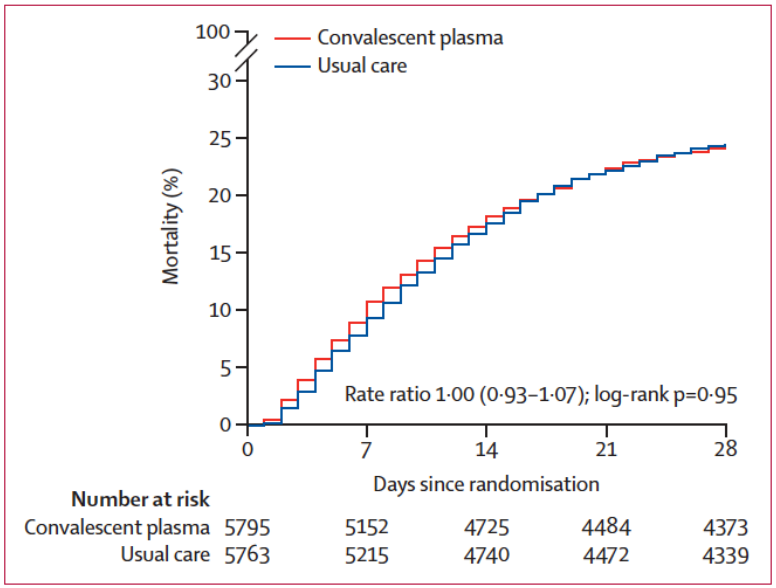


Figure 2: **Effect of allocation to convalescent plasma on 28-day mortality**

	Convalescent plasma group	Usual care group	RR (95% CI)
Age, years (χ^2_1=0·4; p=0·53)			
<70	534/3705 (14%)	545/3748 (15%)	1·00 (0·89–1·13)
70–79	495/1310 (38%)	494/1281 (39%)	0·99 (0·87–1·13)
≥80	370/780 (47%)	369/734 (50%)	0·94 (0·81–1·09)
Sex (χ^2_1=1·3; p=0·25)			
Men	953/3643 (26%)	972/3787 (26%)	1·03 (0·95–1·13)
Women	446/2152 (21%)	436/1976 (22%)	0·94 (0·82–1·07)
Ethnicity (χ^2_1=0·8; p=0·37)			
White	1111/4493 (25%)	1129/4421 (26%)	0·97 (0·90–1·06)
Black, Asian or minority ethnic	198/833 (24%)	199/887 (22%)	1·07 (0·88–1·31)
Days since symptom onset (χ^2_1=3·4; p=0·06)			
≤7	606/2226 (27%)	660/2240 (29%)	0·92 (0·82–1·03)
>7	790/3564 (22%)	748/3522 (21%)	1·06 (0·96–1·17)
Respiratory support received (χ^2_1=3·5; p=0·06)			
No oxygen received	56/442 (13%)	69/455 (15%)	0·83 (0·58–1·18)
Oxygen only	1185/5051 (23%)	1194/4993 (24%)	0·99 (0·91–1·07)
Invasive mechanical ventilation	158/302 (52%)	145/315 (46%)	1·19 (0·95–1·50)
Use of corticosteroids (χ^2_1=2·7; p=0·10)			
Yes	1314/5370 (24%)	1299/5311 (24%)	1·01 (0·94–1·09)
No	74/391 (19%)	100/413 (24%)	0·78 (0·58–1·05)
Patient SARS-CoV-2 antibody test result (χ^2_1=1·4; p=0·23)			
Positive	575/3078 (19%)	501/2810 (18%)	1·06 (0·94–1·19)
Negative	642/2016 (32%)	558/1660 (34%)	0·96 (0·85–1·07)
Not done	182/701(26%)	349/1293 (27%)	0·98 (0·82–1·17)
All participants	**1399/5795 (24%)**	**1408/5763 (24%)**	**1·00 (0·93–1·07) p=0·95**

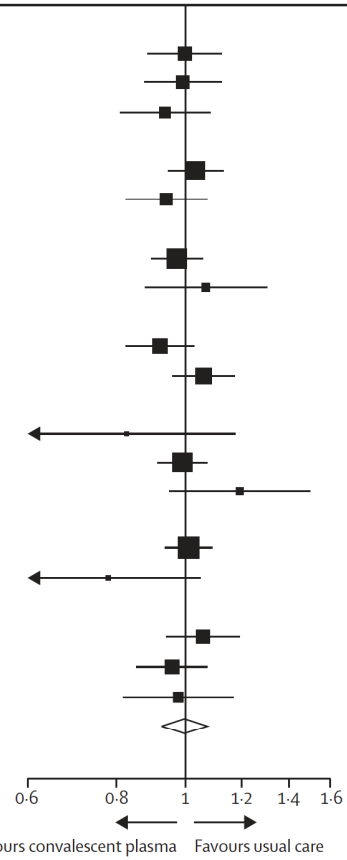
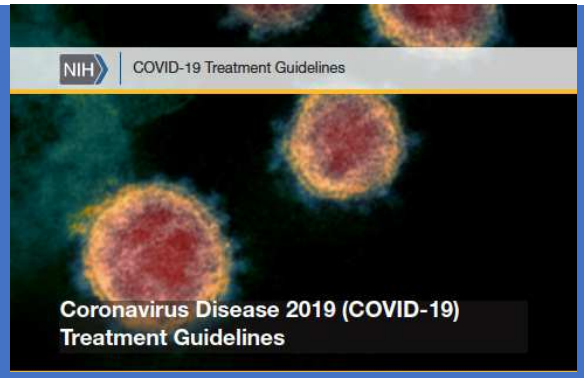


Figure 3: **Effect of allocation to convalescent plasma on 28-day mortality by prespecified characteristics at randomisation**
The ethnicity, days since onset, and use of corticosteroids subgroups exclude those with missing data, but these patients are included in the overall summary. Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. RR=rate ratio.

COVID-19: Tsunami Study, plasma does not reduce the risk of respiratory damage or death

- Tsunami study compared the effect of convalescent plasma with high titer of neutralizing antibodies (≥1: 160) associated with standard therapy versus standard therapy alone in patients with
- COVID-19 and pneumonia with mild to moderate ventilatory impairment (defined from a PaO2/FiO2 ratio between 350 and 200).
- 27 clinical centres distributed throughout Italy participated in the study.
- 487 patients were enrolled (of which 324 in Tuscany, 77 in Umbria, 66 in Lombardy and 20 from other regions).
- Demographics, existing comorbidities and concomitant therapies were similar in the two patient groups, 241 assigned to plasma and standard therapy (231 evaluable) and 246 to standard therapy alone (239 evaluable).
- There was no statistically significant difference in the primary end-point ("need for invasive mechanical ventilation, defined by a PaO2/FiO2 ratio<150, or death within thirty days from randomisation date") between the group treated with plasma and the one treated with standard therapy.
- Overall, TSUNAMI did not show a plasma benefit in terms of reducing the risk of respiratory worsening or death in the first thirty days.
- Only in the case of patients with less severe respiratory impairment (with a PaO2/FiO2 ratio ≥ 300 at enrollment), a signal emerged in favour of plasma which, however, did not reach statistical significance (p=0.059).
- This could suggest the opportunity to further study the potential therapeutic role of plasma in subjects with mild-moderate COVID and in the very early stages of the disease.

https://www.aifa.gov.it/en/-/covid-19-studio-tsunami-il-plasma-non-riduce-il-rischio-di-peggioramento-respiratorio-o-morte



- 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.

IDSA
Infectious Diseases Society of America

- Among patients hospitalized with COVID-19, the IDSA guideline panel suggests against COVID-19 convalescent plasma. (Conditional recommendation, Low certainty of evidence)

ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem, I. Esteban, M.T. Caballero, C. Wood, M. Berrueta, A. Rondan, G. Lescano, P. Cruz, Y. Ritou, V. Fernández Viña, D. Álvarez Paggi, S. Esperante, A. Ferreti, G. Ofman, Á. Ciganda, R. Rodriguez, J. Lantos, R. Valentini, N. Itcovici, A. Hintze, M.L. Oyarvide, C. Etchegaray, A. Neira, I. Name, J. Alfonso, R. López Castelo, G. Caruso, S. Rapelius, F. Alvez, F. Etchenique, F. Dimase, D. Alvarez, S.S. Aranda, C. Sánchez Yanotti, J. De Luca, S. Jares Baglivo, S. Laudanno, F. Nowogrodzki, R. Larrea, M. Silveyra, G. Leberzstein, A. Debonis, J. Molinos, M. González, E. Perez, N. Kreplak, S. Pastor Argüello, L. Gibbons, F. Althabe, E. Bergel, and F.P. Polack, for the Fundación INFANT–COVID-19 Group*

Randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers) in **older adult** patients **within 72 hours** after the onset of **mild Covid-19 symptoms**.

The primary end point was severe respiratory disease,

160 patients underwent randomization

Inclusion criteria

- > 75 years between
- 65 -74 with at least one
  - hypertension
  - diabetes on pharmacological treatment ,
  - obesity,
  - Chroni crenal failure,
  - cardiovascular disease,
  - COPD

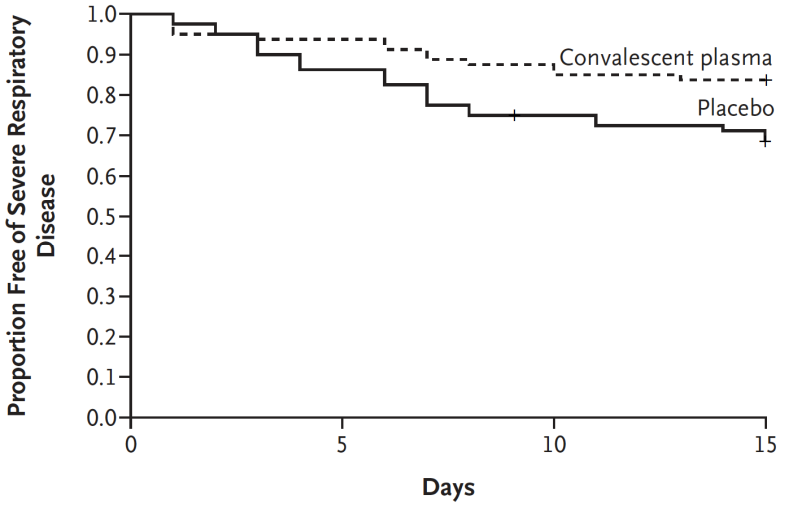


Figure 1. Time to the Development of Severe Respiratory Disease Due to Coronavirus Disease 2019, According to Trial Group in the Intention-to-Treat Analysis.

Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

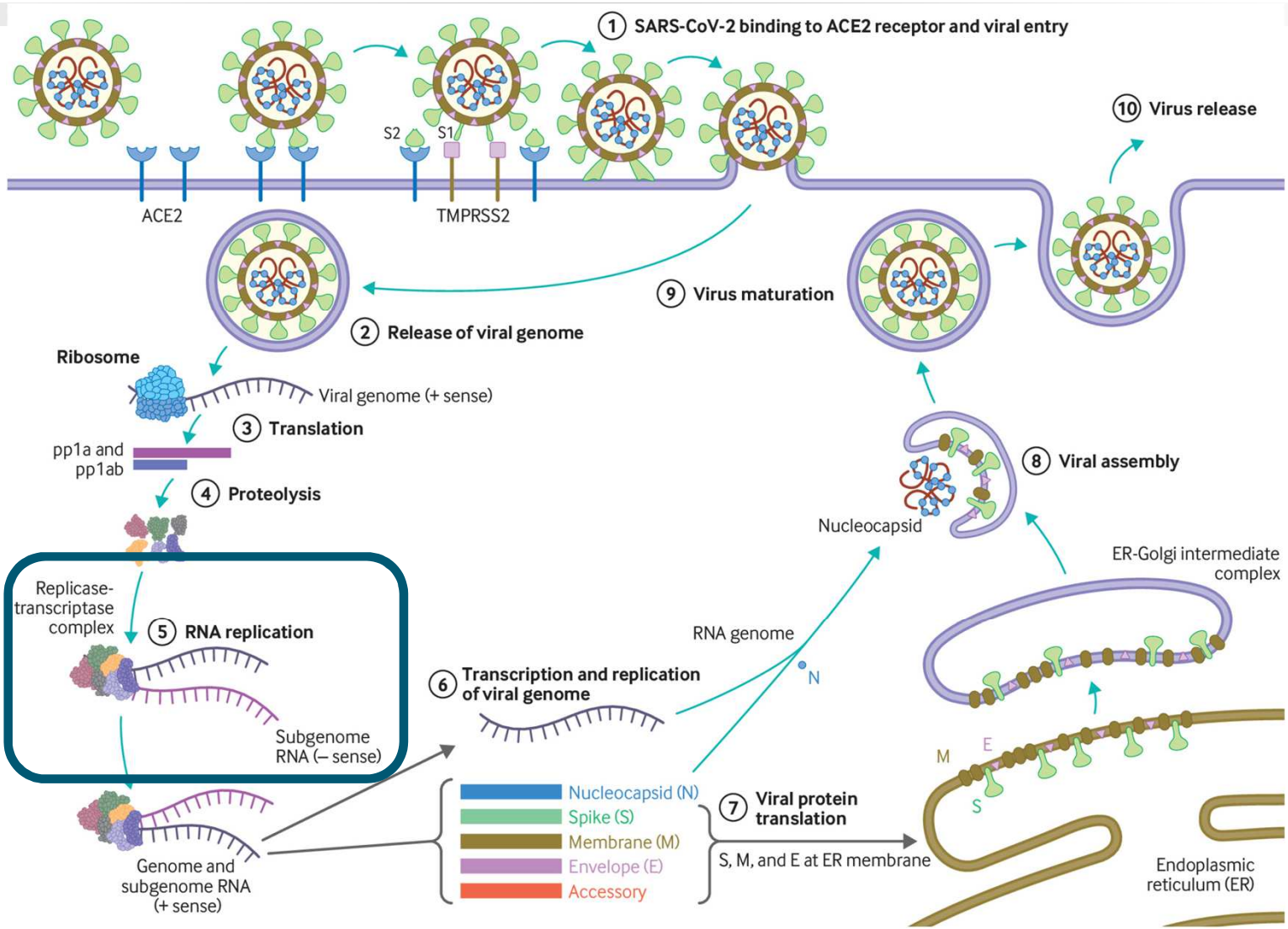
Patient Group	Patients with Severe Respiratory Disease	Relative Risk (95% CI)	Relative Risk Reduction
	no./total no. (%)		*percent*
Placebo group	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08–0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34–1.31)	31.4

* The median concentration is a SARS-CoV-2 S IgG titer of 1:3200.

COVID-19 quali terapie in quale momento

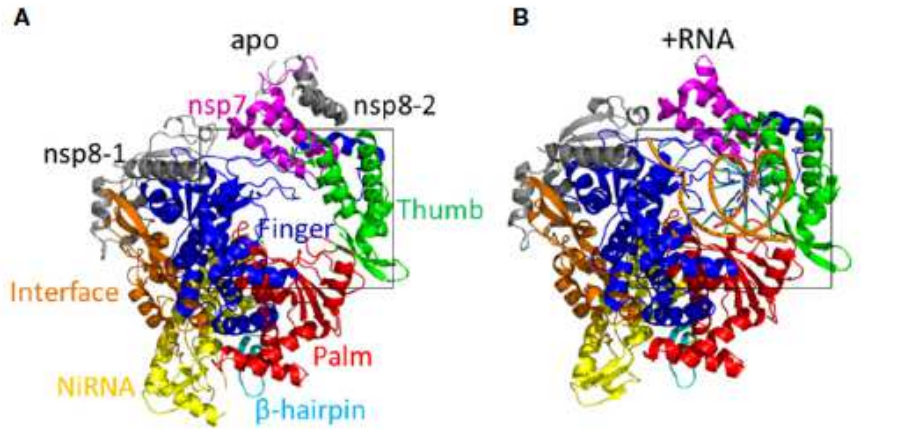
- Fasi della malattia
- Terapia antivirale
  - Inibitori dell'entry
    - Anticorpi Monoclonali
    - Plasma di convalescente
  - Inibitori della polimerasi
- Terapia antinfiammatoria
  - Steroidi
  - Tocilizumab
  - Baricitinib
- Ad ogni tempo il suo farmaco

Remdesivir
AT-527
Molnupiravir



TMPRSS2 host's transmembrane serine protease 2 (cell surface protein), which s principally expressed in the airway epithelial cells and vascular endothelial cells.

Il complesso nsp12-nsp7-nsp8: inibitori della polimerasi



structure of nsp12-nsp7-nsp8 complex

nsp12-nsp7-nsp8 complex bound to the template-primer RNA

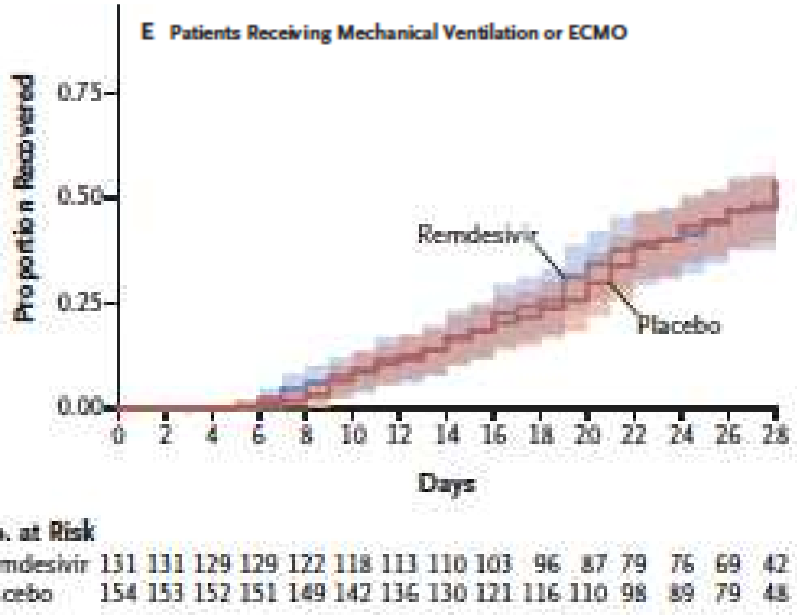
FIGURE 3 | **(A)** The structure of nsp12-nsp7-nsp8 complex. Color marks: nsp7, magenta; nsp8-1 and nsp8-2, grey; β-hairpin, cyan; NiRAN, yellow; the interface, orange; the fingers domain, blue; the palm domain, red; the thumb domain, green. (PDB: 6M71) **(B)** The structure of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) in active form. The nsp12-nsp7-nsp8 complex bound to the template-primer RNA. (PDB: 7BV2).

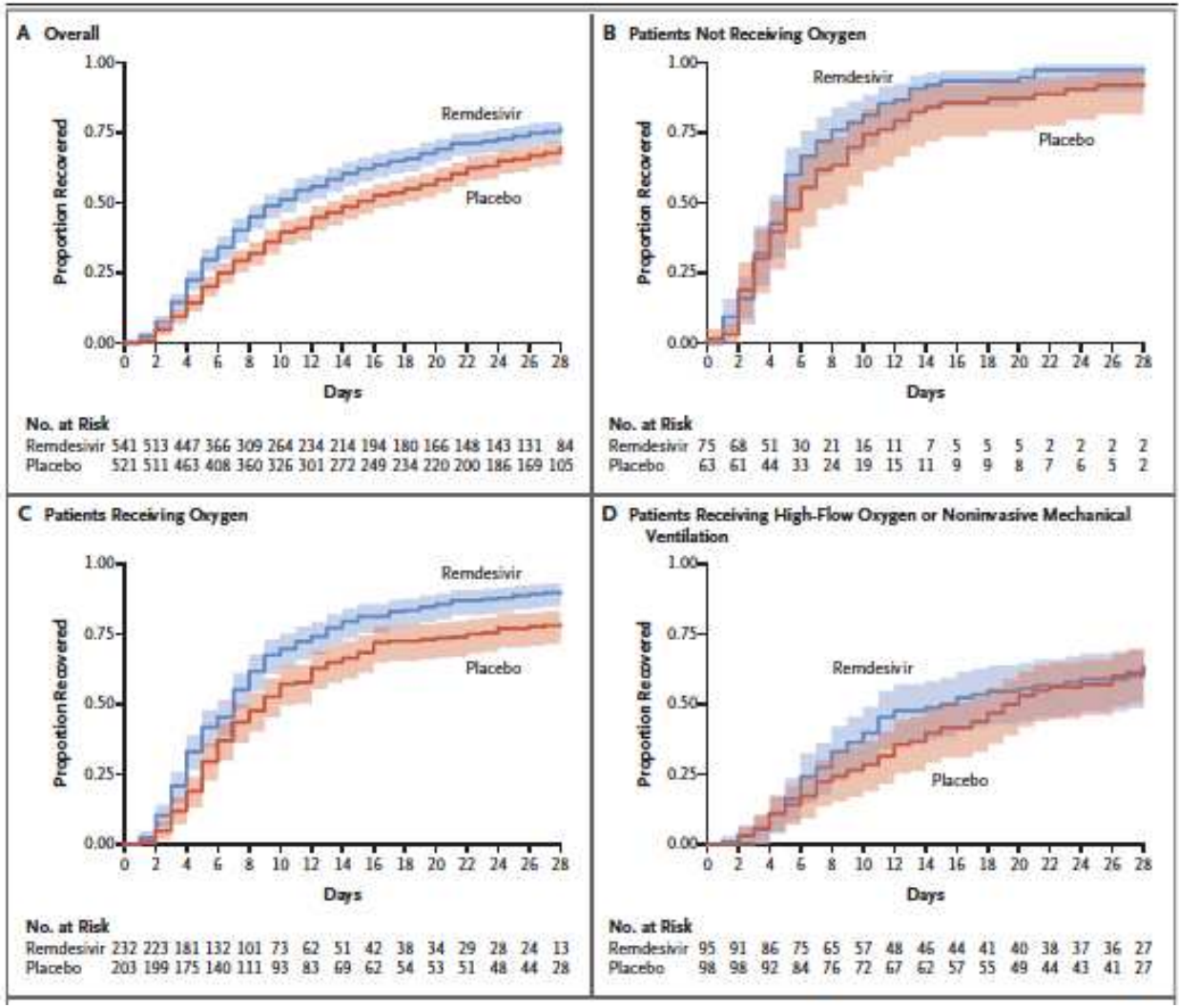
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Final Report

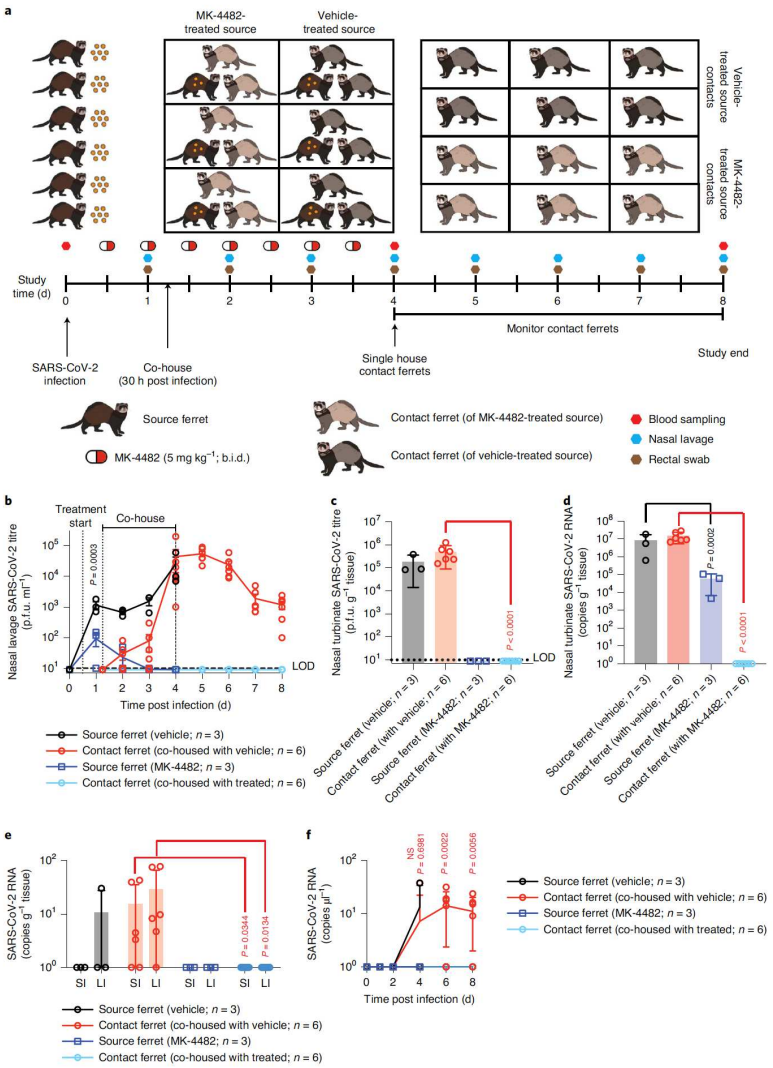
J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*





MK-4482/EIDD-2801 (Molnupiravir)

- MK-4482, orally administered nucleoside analog, orally administered bioavailable prodrug (5’-isopropylester form) of the cytidine nucleoside analogue EIDD-1931 act as a mutagen on RNA polymerase[1]
- In mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of EIDD-2801, an orally bioavailable NHC-prodrug (β-D-N4-hydroxycytidine-5’-isopropyl ester), improved pulmonary function, and reduced virus titer and body weight loss[1]
- Therapeutic treatment of infected ferrets with MK-4482/ EIDD-2801 twice a day significantly reduced the SARS-CoV-2 load in the upper respiratory tract and completely suppressed spread to untreated contact animals.[2]
- Inhibits SARS-CoV-2 replication in the Syrian hamster model. either beginning 12 hours before or 12 hours following infection in a high-risk exposure model3



1 Sheahan T. P. et al., Sci. Transl. Med. 10.1126/scitranslmed.abb5883 (2020).
2 Cox RM et al Nature Microbiology | VOL 6 | Januar y 2021 | 11–18
3 Rosenke K et al. Research square 2021

Significant Reduction in Infectious Virus in Molnupiravir-Treated Participants

- Of 182 participants with evaluable swabs, 78 (42.9%) had positive baseline cultures
- Overall, there was a significant reduction in positive viral culture at day 5 in molnupiravir-treated participants (**Figure 1**)
- By dose group (**Figure 2**), a statistically significant difference vs placebo was demonstrated for the 800 mg group at day 5 (pair-wise comparisons by Fisher's exact test, not adjusted for multiplicity)
- At day 5, infectious virus was not recovered in any molnupiravir-treated participants
- Of 202 treated participants (blinded data), 4 experienced a serious AE (0 drug-related) and 7 discontinued study drug (3 due to an AE)

Figure 1. Proportion of overall participants with positive viral culture by RT-PCR (for participants positive at baseline)

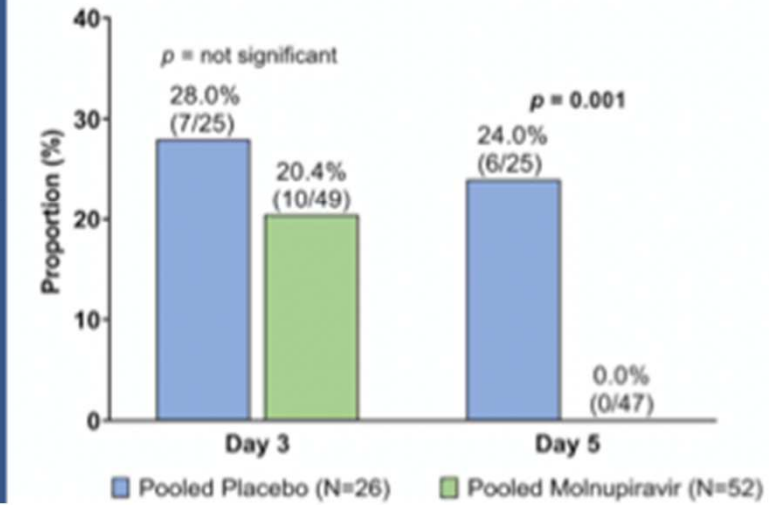
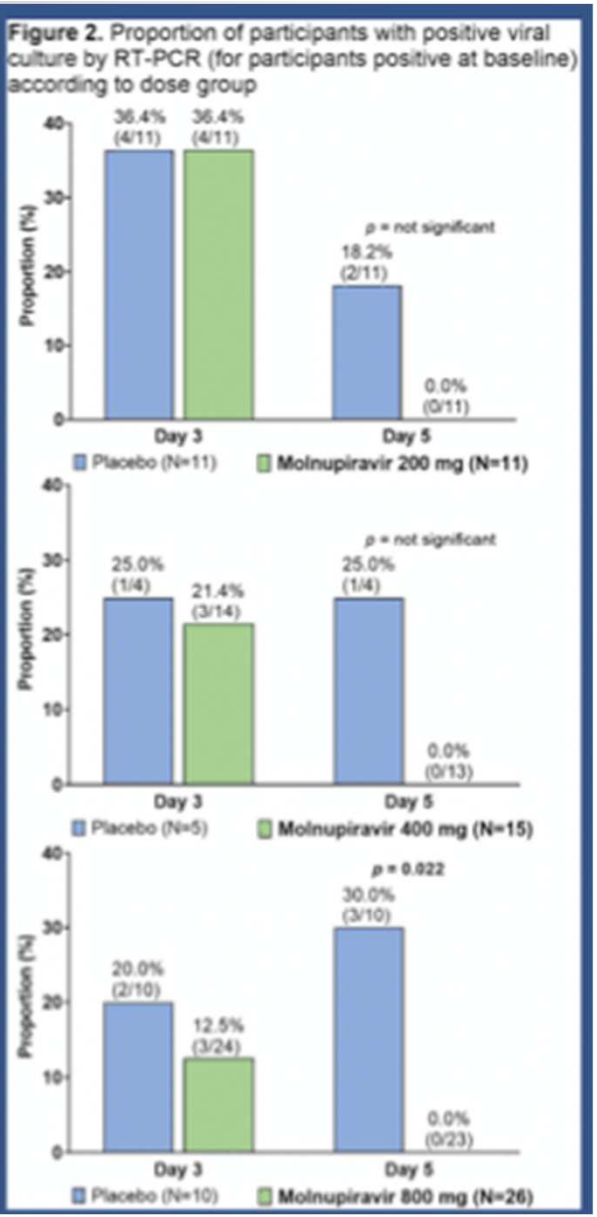


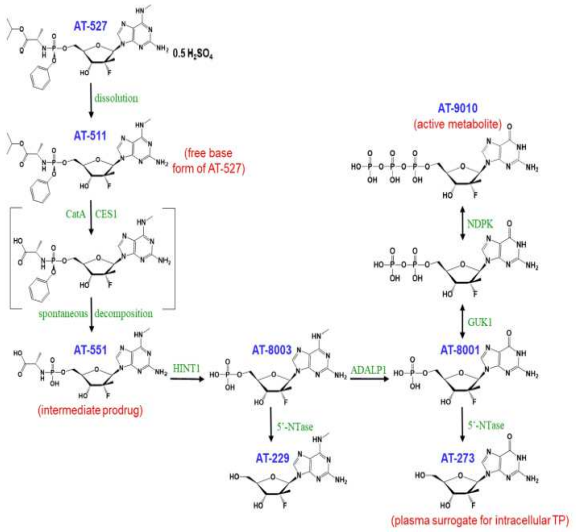
Figure 2. Proportion of participants with positive viral culture by RT-PCR (for participants positive at baseline) according to dose group



Painter WP et al CROI 2021 Abstract SS777. Presented March 6, 2021

AT-527

- Guanosine analogue active intracellular metabolite AT-511 is the free base of AT-527 and AT -9010 is the triphosphate intrac ellular active metabolit.
- AT-9010 is a nonobligate chain terminator of viral RNA replication and target the nucleotide binding site in the NiRAN domain of nsp12
- In normal human airway epithelial cells, the concentration of AT-511 required to inhibit replication of SARS-CoV-2 by 90% (EC90) was 0.47mM
- Little to no cytotoxicity was observed for AT-511 at concentrations up to 100mM
- Pharmacokinetic data from subjects given daily oral doses of AT-527, predict that twice daily oral doses of 550mg AT-527 will produce AT-9010 trough concentrations in human lung that exceed the EC90 observed for the prodrug against SARS-CoV-2 replication.



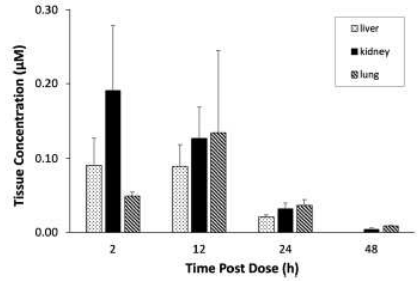


FIG 4 Tissue concentrations of AT-9010 in nonhuman primates. Cynomolgus monkeys were given a loading dose of 60 mg/kg AT-527 followed by 30 mg/kg maintenance doses every 12 h for 3 days to achieve steady state. Tissue samples were collected under anesthesia at the indicated time points after the last dose, flash frozen, and homogenized, and AT-9010 concentrations were determined by LC-MS/MS. Data are expressed as means ± SEs (n = 3).

TABLE 1 *In vitro* activity of AT-511 and other oral antiviral drugs against various human coronaviruses[a]

Virus (genus)	Cell line	Compound	CPE assay EC_{50} (μM [n])	CPE assay CC_{50} (μM)	VYR assay EC_{90} (μM [n])	Selectivity index (CC_{50}/EC_{50})
HCoV-229E (*Alphacoronavirus*)	BHK-21	AT-511	1.8 ± 0.3 [2]	>100	ND	>55
	BHK-21	Sofosbuvir	>100	>100	ND	ND
	Huh-7	AT-511	1.7 ± 0.1 [2]	>86	1.2 ± 0.1 [2]	>50
HCoV-OC43 (*Betacoronavirus*)	Huh-7	AT-511	ND[b]	>86	0.5	>170[c]
	RD	AT-511	2.8	>86	2.2	>30
MERS-CoV (*Betacoronavirus*)	Huh-7	AT-511	26 ± 15 [2]	>86	37 ± 28 [2]	>3.3
SARS-CoV (*Betacoronavirus*)	Huh-7	AT-511	ND[b]	>86	0.34	>250[c]
SARS-CoV-2 (*Betacoronavirus*)	HAE	AT-511	ND[b]	>86[d]	0.47 ± 0.12 [5]	>160[c]
	HAE	Molnupiravir	ND[b]	>19[d]	2.8 ± 1.0 [3]	>4.9[c]

[a]The activity of AT-511 and other antiviral compounds was measured in cells infected with different coronaviruses, using the cytopathic effect (neutral red dye) assay and/or the virus yield reduction (VYR) assay as described in Materials and Methods, to determine the effective concentration required to achieve 50% inhibition (EC_{50}) of the virus-induced cytopathic effect (CPE), the concentration to reduce virus yield by 1 $\log_{10}$ (EC_{90}), and the cytotoxic concentration of the drug to cause death to 50% of viable cells without virus (CC_{50}). Values represent results from single or multiple (mean ± SD [n]) experiments.
[b]Not determined because no cytopathic effect was produced by this virus in this cell line.
[c]CC_{50}/EC_{90}, since EC_{50} could not be determined by measuring CPE in the neutral red assay.
[d]Cytotoxicity assessed by visual inspection of cell monolayers.

Good SS et al. Antimicrobial Agents and Chemotherapy 2021; 65; e02479-20 (April 2021)

AT-527 Phase I study

- AT-527 has demonstrated clinical tolerability and potent antiviral activity in patients with HCV infection, as well as a favorable human pharmacokinetic (PK) profile.
- Well-tolerated in 30 COVID-19 patients (550 mg, twice-daily, 5 days treatment) and in 28 HCV-infected patients (550 mg, once-daily, 7 days or up to 12 weeks).
- **20 healthy participants who were randomly given oral AT-527 550mg twice daily (BID) or placebo for five days.**
- **According to the study data, twice daily 550mg dose of AT-527 aided in rapidly achieving steady-state levels of AT-273 in two days of dosing.**
- **Results showed that no discontinuations, serious adverse events, clinically significant changes in vital signs, or electrocardiograms were noted in the study.**
- **Furthermore, predicted lung AT-9010 levels were steadily above the EC90 level of 0.5µM for in vitro inhibition by the drug of SARS-CoV-2 replication starting as early as three hours after the first dose and preserved through the five days of dosing.**

https://www.pharmaceutical-technology.com/news/atea-antiviral-agent-trial/

AT- 527 MORNINGSKY TRIAL

- Phase 3 multicenter, randomized, double-blind, placebo-controlled, outpatient study to evaluate the efficacy, safety, pharmacokinetic profile and antiviral activity of AT-527 in patients with mild or moderate COVID-19.
- 1,400 non-hospitalized patients, including adolescents with confirmed mild to moderate acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.
- Patients will be randomized within 5 days of symptom onset.
- At the time of enrollment, patients must be stable and not require hospitalization.
- The primary endpoins:
  - the time to alleviation or improvement of COVID-19 symptoms.
  - Number of patients requiring medically attended visits or hospitalization for COVID-19.

segnalare possibili candidati a malattie infettive@ospedaleniguarda.it

COVID-19 quali terapie in quale momento

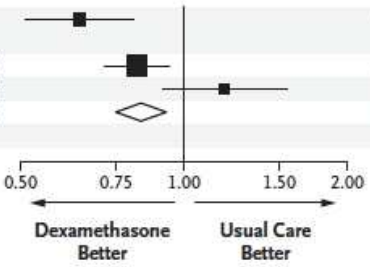
- Fasi della malattia
- Terapia antivirale
  - Inibitori dell'entry
    - Anticorpi Monoclonali
    - Plasma di convalescente
  - Inibitori della polimerasi
- Terapia antinfiammatoria
  - Steroidi
  - Tocilizumab
  - Baricitinib
- Ad ogni tempo il suo farmaco

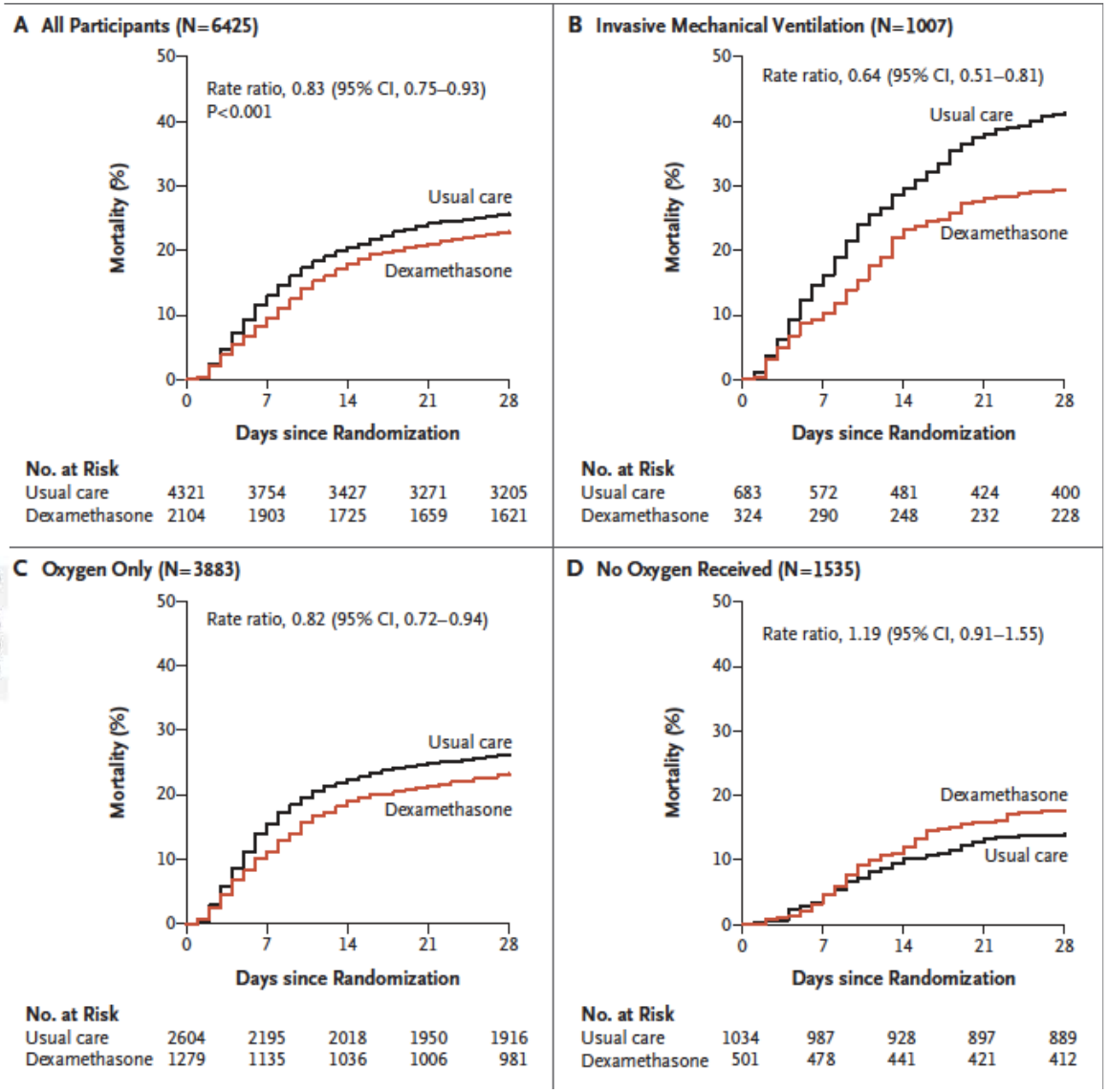
Steroids

RECOVERY Trial

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





RECOVERY Collaborative GroupDexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020 Jul 17:NEJMoa2021436. doi: 10.1056/NEJMoa2021436.

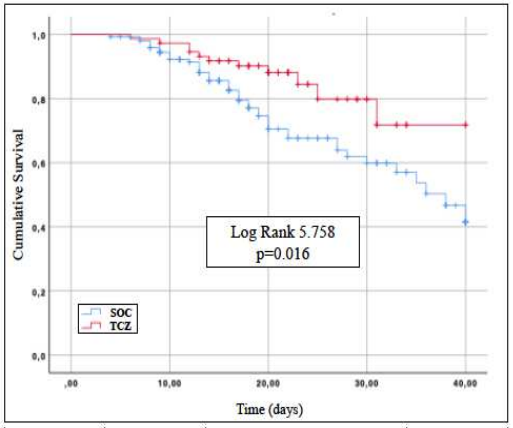
Tocilizumab

TOCILIZUMAB

- Retrospective matched case control study
- 74 treated with Tocilizumab vs 148 matched controls.
- Critical disease in 69·8%. TCZ use was associated with a better overall survival (HR 0·499 [95% CI 0·262-0·952], p=0·035) compared to controls but with a longer hospital stay (HR 1·658 [95% CI 1·088-2·524], p=0·019) mainly due to biochemical, respiratory and infectious adverse events.

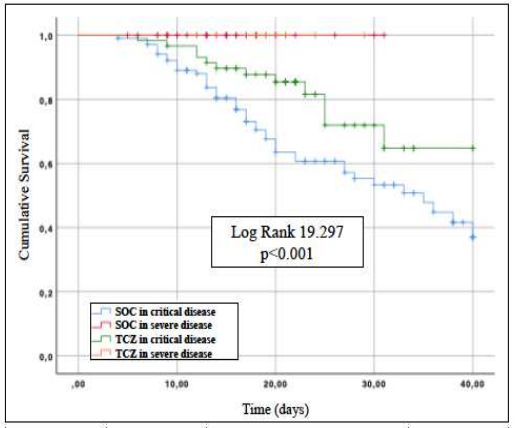
Figure 1. Kaplan Meier probability curves and Cox regression models for survival in the overall population (**A**) and stratified according to disease severity (**B**).

A. Survival in Overall Study Population



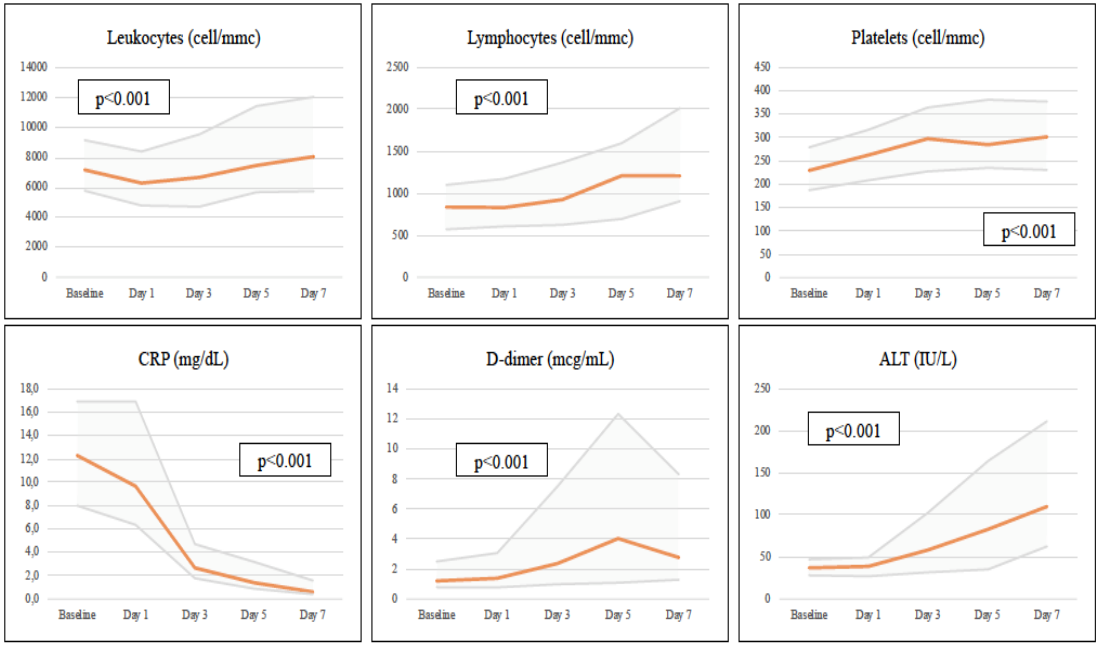
Factor	HR	95% CI		p
TCZ	0.499	0.262	0.952	0.035
REMDESIVIR	0.595	0.235	1.508	0.274

B. Survival Stratified according to Disease Severity



Factor	HR	95% CI		p
Critical Disease	30.055	1.420	636.284	0.029
P/F <150 mmHg	3.837	1.195	12.313	0.024

Figure 3. Trends of hematologic and biochemical parameters (median with IQR) after TCZ administration.

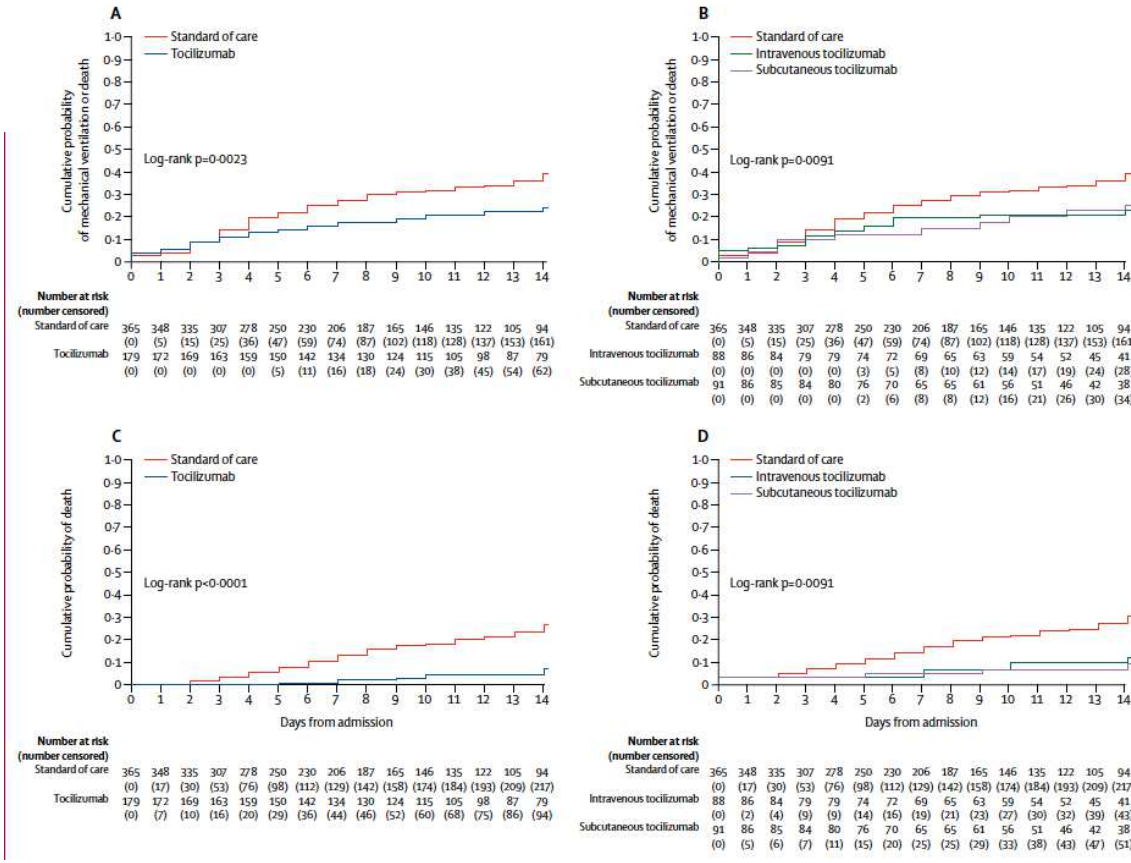


Rossotti R et al J of Infection 2021

Tocilizumab in patients with severe COVID-19: a retrospective cohort study

Giovanni Guaraldi, Marianna Meschiari*, Alessandro Cozzi-Lepri, Jovana Milic, Roberto Tonelli, Marianna Menozzi, Erica Franceschini, Gianluca Cuomo, Gabriella Orlando, Vanni Borghi, Antonella Santoro, Margherita Di Gaetano, Cinzia Puzzolante, Federica Carli, Andrea Bedini, Luca Corradi, Riccardo Fantini, Ivana Castaniere, Luca Tabbi, Massimo Girardis, Sara Tedeschi, Maddalena Giannella, Michele Bartoletti, Renato Pascale, Giovanni Dolci, Lucio Brugioni, Antonello Pietrangelo, Andrea Cossarizza, Federico Pea, Enrico Clini, Carlo Salvarani, Marco Massari, Pier Luigi Viale, Cristina Mussini*

- 57 (16%) of 365 patients in the standard care group needed mechanical ventilation, compared with 33 (18%) of 179 patients treated with tocilizumab (p=0·41)
- 73 (20%) patients in the standard care group died, compared with 13 (7%; p<0·0001) patients treated with tocilizumab .
- After adjustment for sex, age, recruiting centre, duration of symptoms, and SOFA score, tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p=0·020).
- 24 (13%) of 179 patients treated with tocilizumab were diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone (p<0·0001).



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FAST TRACK

Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial

Viviane C Veiga,[1,2] João A G G Prats,[1] Danielle L C Farias,[1] Regis G Rosa,[2,3] Leticia K Dourado,[4] Fernando G Zampieri,[2,4] Flávia R Machado,[2,5] Renato D Lopes,[6,7] Otavio Berwanger,[8] Luciano C P Azevedo,[2,9] Álvaro Avezum,[10] Thiago C Lisboa,[2,4] Salomón S O Rojas,[1] Juliana C Coelho,[1] Rodrigo T Leite,[1] Júlio C Carvalho,[1] Luis E C Andrade,[11] Alex F Sandes,[11] Maria C T Pintão,[11] Claudio G Castro Jr,[8,12] Sueli V Santos,[4] Thiago M L de Almeida,[5] André N Costa,[9] Otávio C E Gebara,[13] Flávio G Rezende de Freitas,[2,14] Eduardo S Pacheco,[14] David J B Machado,[15] Josiane Martin,[15] Fábio G Conceição,[15] Suellen R R Siqueira,[15] Lucas P Damiani,[4,16] Luciana M Ishihara,[16] Daniel Schneider,[3] Denise de Souza,[3] Alexandre B Cavalcanti,[2,4] Phillip Scheinberg[1]; on behalf of the Coalition covid-19 Brazil VI Investigators

RESULTS

A total of 129 patients were enrolled (mean age 57 (SD 14) years; 68% men) and all completed follow-up. All patients in the tocilizumab group and two in the standard care group received tocilizumab. 18 of 65 (28%) patients in the tocilizumab group and 13 of 64 (20%) in the standard care group were receiving mechanical ventilation or died at day 15 (odds ratio 1.54, 95% confidence interval 0.66 to 3.66; P=0.32). Death at 15 days occurred in 11 (17%) patients in the tocilizumab group compared with 2 (3%) in the standard care group (odds ratio 6.42, 95% confidence interval 1.59 to 43.2). Adverse events were reported in 29 of 67 (43%) patients who received tocilizumab and 21 of 62 (34%) who did not receive tocilizumab.

CONCLUSIONS

In patients with severe or critical covid-19, tocilizumab plus standard care was not superior to standard care alone in improving clinical outcomes at 15 days, and it might increase mortality.

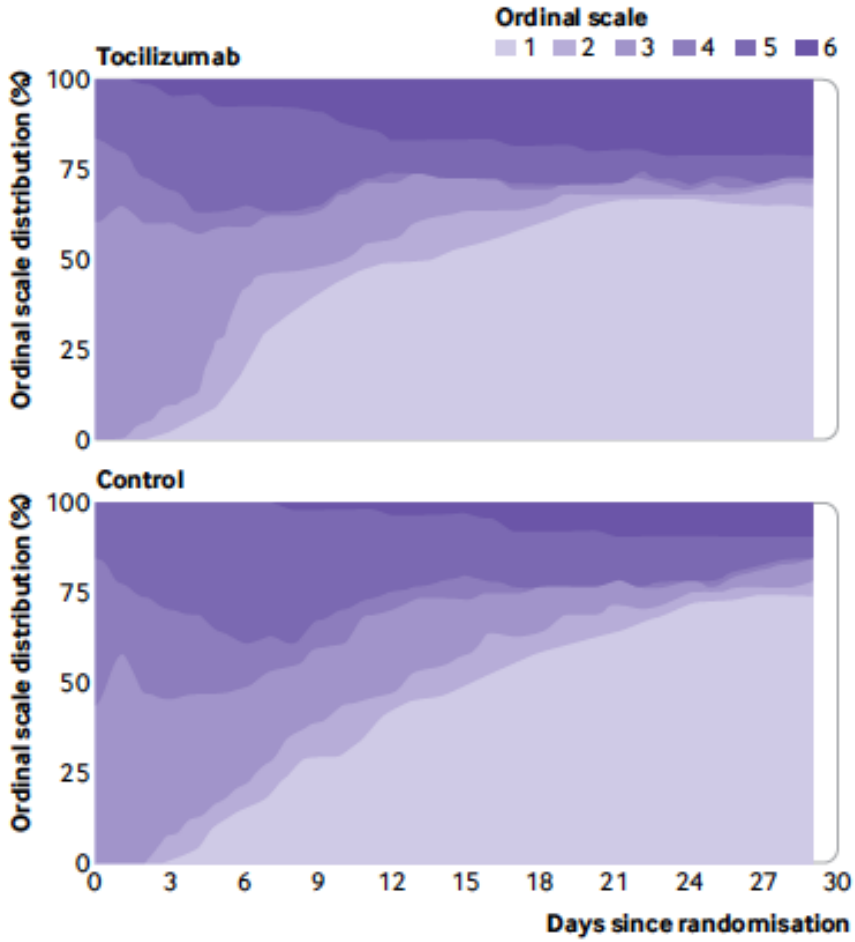

Fig 2 | Relative distribution of patient status over time stratified by treatment group. Six level ordinal scale—1: not admitted to hospital; 2: admitted to hospital, not receiving supplemental oxygen; 3: admitted to hospital, receiving supplemental oxygen; 4: admitted to hospital, receiving non-invasive ventilation or high flow oxygen through a nasal cannula; 5: receiving mechanical ventilation; 6: death

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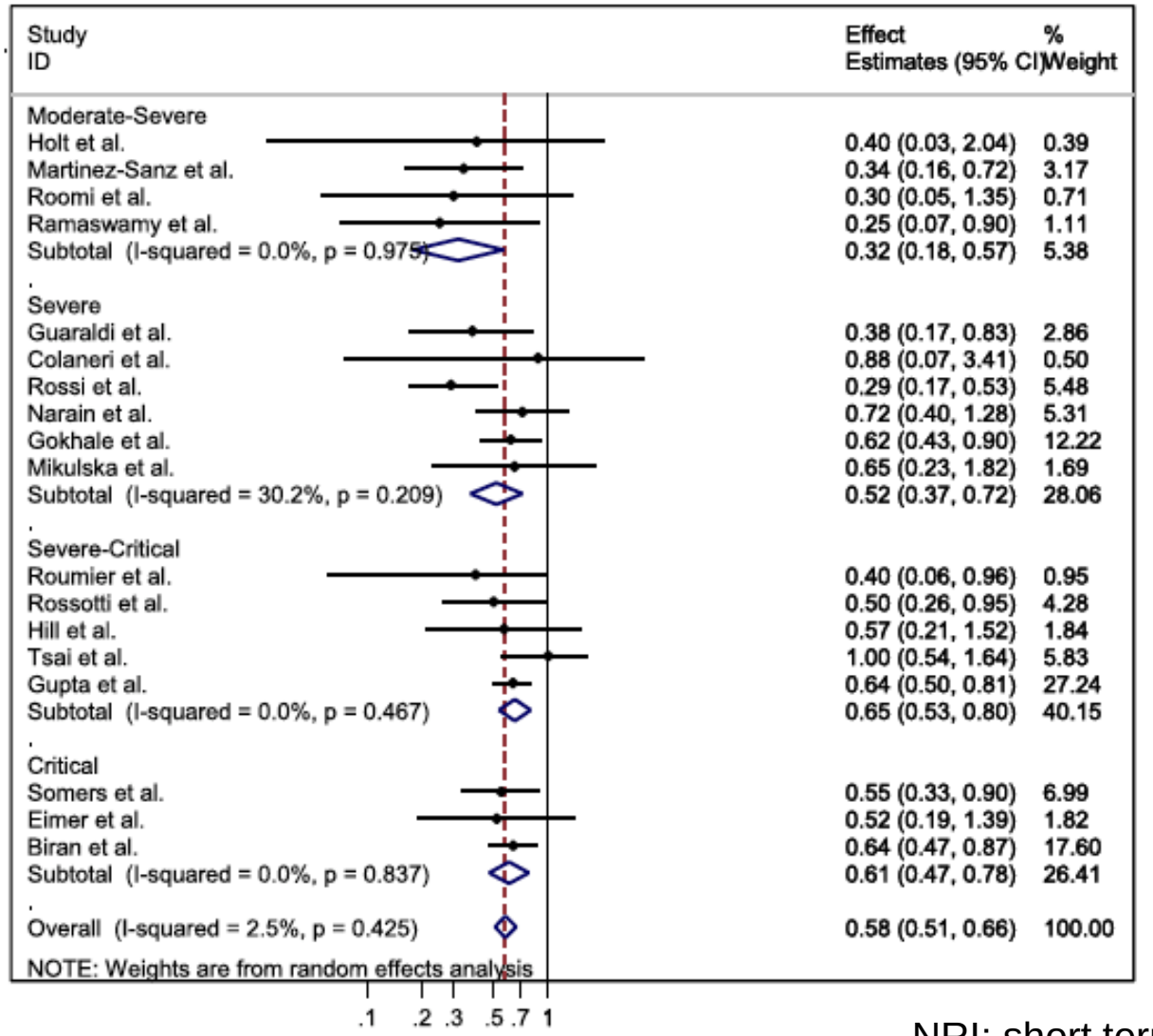
Systematic Review

Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis

Imad M. Tleyjeh [1, 2, 3, 4, *], Zakariya Kashour [5], Moussab Damlaj [6, 7, 8], Muhammad Riaz [9], Haytham Tlayjeh [7, 8, 10], Mustafa Altannir [2], Youssef Altannir [2], Mohamad Al-Tannir [11], Rana Tleyjeh [2], Leslie Hassett [12], Tarek Kashour [13]



NRI: short term mortality

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

*RECOVERY Collaborative Group**

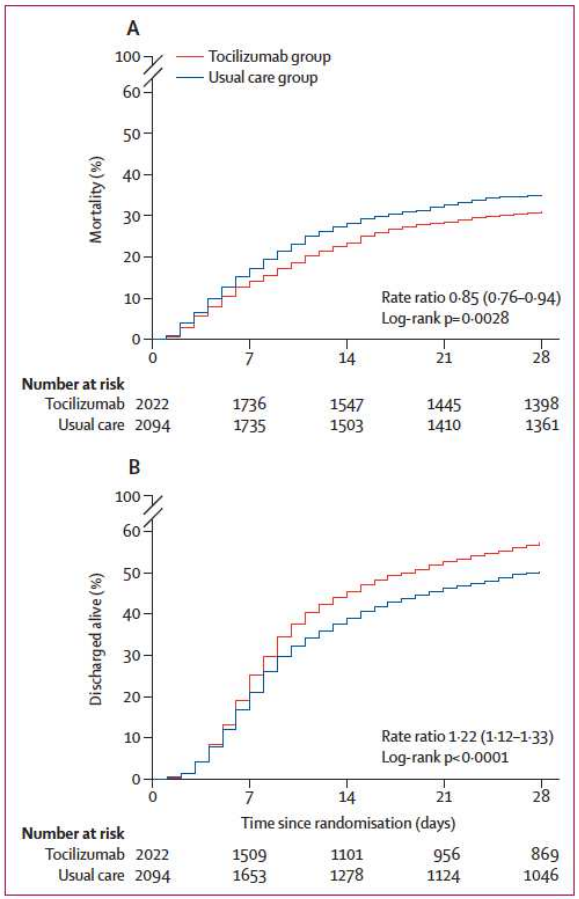


Figure 2: **Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)**

	Tocilizumab group	Usual care group	Risk ratio (95% CI)
Age, years (χ^2_1=0·0; p=0·88)			
<70	273/1331 (21%)	309/1355 (23%)	0·88 (0·74–1·03)
70–79	212/478 (44%)	245/480 (51%)	0·82 (0·68–0·99)
≥80	136/213 (64%)	175/259 (68%)	0·92 (0·73–1·15)
Sex (χ^2_1=2·4; p=0·12)			
Men	417/1337 (31%)	529/1437 (37%)	0·80 (0·71–0·91)
Women	204/685 (30%)	200/657 (30%)	0·97 (0·80–1·18)
Ethnicity (χ^2_1=0·0; p=0·98)			
White	476/1530 (31%)	573/1597 (36%)	0·83 (0·73–0·94)
Black, Asian, or minority ethnic	99/354 (28%)	123/378 (33%)	0·83 (0·64–1·09)
Unknown	46/138 (33%)	33/119 (28%)	1·20 (0·77–1·88)
Days since symptom onset (χ^2_1=1·1; p=0·30)			
≤7	214/668 (32%)	256/660 (39%)	0·78 (0·65–0·94)
>7	407/1354 (30%)	473/1433 (33%)	0·88 (0·77–1·01)
Respiratory support at randomisation (χ^2_1=0·8; p=0·38)			
No ventilator support*	180/935 (19%)	214/933 (23%)	0·81 (0·67–0·99)
Non-invasive ventilation†	310/819 (38%)	366/867 (42%)	0·86 (0·74–1·00)
Invasive mechanical ventilation‡	131/268 (49%)	149/294 (51%)	0·93 (0·74–1·18)
Use of corticosteroids§ (χ^2_1=7·7; p=0·01)			
Yes	482/1664 (29%)	600/1721 (35%)	0·79 (0·70–0·89)
No	139/357 (39%)	127/367 (35%)	1·16 (0·91–1·48)
Unknown	0/1 (0%)	2/6 (33%)	..
All participants	**621/2022 (31%)**	**729/2094 (35%)**	**0·85 (0·76–0·94) p=0·0028**

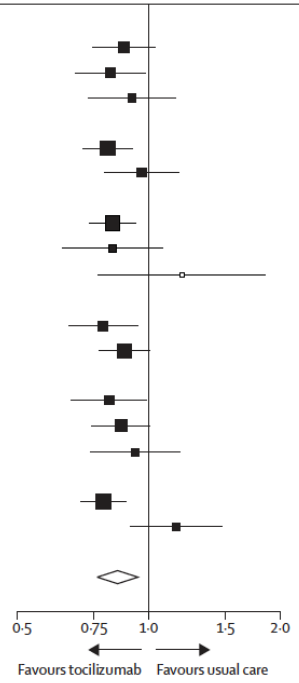


Figure 3: **Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics**
Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. *Includes nine patients not receiving any oxygen and 1859 patients receiving simple oxygen only. †Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure ventilation, and other non-invasive ventilation. ‡Includes patients receiving invasive mechanical ventilation and extracorporeal membranous oxygenation. §Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation before this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids. In a model adjusted for all six baseline subgroups (in the categories shown) the overall rate ratio was 0·88 (95% CI 0·79–0·98).

	Deaths/patients randomly assigned (%)		Observed minus expected deaths*		Ratio of death rates, rate ratio (95% CI)
	Tocilizumab group	Usual care group	(O–E)	Var (O–E)	
CORIMUNO–TOCI[10]	7/64 (11%)	8/67 (12%)	–0·3	3·3	0·91 (0·31–2·65)
RCT–TCZ–COVID-19[11]	2/60 (3%)	1/66 (2%)	0·6	0·7	2·17 (0·22–21·3)
BACC Bay[12]	9/161 (6%)	(3/82) ×2† (4%)	1·0	2·6	1·51 (0·44–5·13)
COVACTA[9]	58/294 (20%)	(28/144) ×2† (19%)	0·3	15·3	1·02 (0·62–1·68)
EMPACTA[13]	26/249 (10%)	(11/128) ×2† (9%)	1·6	7·5	1·23 (0·60–2·52)
REMAP–CAP[15]	98/353 (28%)	142/402 (35%)	–14·2	40·8	0·71 (0·52–0·96)
TOCIBRAS[8]	14/65 (22%)	6/64 (9%)	3·9	4·3	2·51 (0·97–6·50)
COVINTOC[14]	11/91 (12%)	15/89 (17%)	–2·1	5·6	0·68 (0·30–1·56)
Subtotal: eight trials	**225/1337 (17%)**	**256/1396 (18%)**	**–9·3**	**80·1**	**0·89 (0·72–1·11)**
RECOVERY	621/2022 (31%)	729/2094 (35%)	–54·4	330·6	0·85 (0·76–0·94)
All trials	**846/3359 (25%)**	**985/3490 (28%)**	**–63·7**	**410·7**	**0·86 (0·78–0·94)**
					p=0·0017

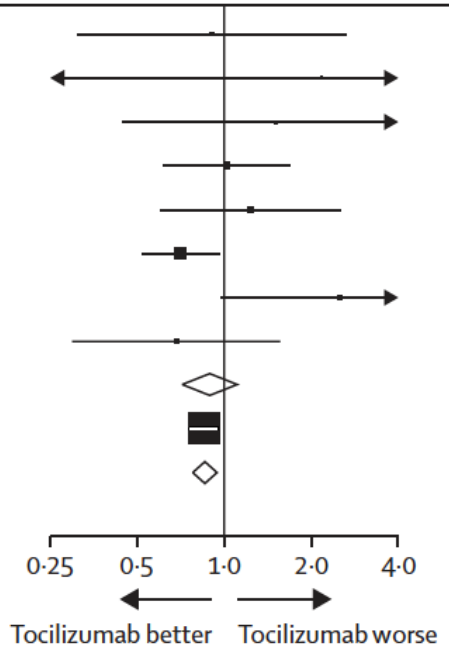


Figure 4: **Meta-analysis of mortality in randomised, controlled trials of tocilizumab in patients hospitalised with COVID-19**
O–E=observed–expected. Var=variance. *Log–rank O–E for RECOVERY, O–E from 2 × 2 contingency tables for the other trials. Rate ratio is calculated by taking ln rate ratio to be (O–E)/V with normal variance 1/V, where V=Var (O–E). Subtotals or totals of (O–E) and of V yield inverse-variance weighted averages of the ln rate ratio values. †For balance, controls in the 2:1 studies count twice in the control totals and subtotals, but do not count twice when calculating their O–E or V values. Heterogeneity between RECOVERY and eight previous trials combined, χ_1^2=0·2 (p=0·7).

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19
Published by IDSA on 4/11/2020. Last updated, 6/3/2021

IDSA
Infectious Diseases Society of America

- Among hospitalized adults with **progressive severe* or critical** COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care** (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)

- Remarks:
  - Patients, particularly **those who respond to steroids alone**, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, **would reasonably decline tocilizumab**.
  - In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥75 mg/L.

- Severity definitions:

- *Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen.

Last updated, 4/14/2021 and posted online at www.idsociety.org/COVID19guidelines. Please check website for most updated version of these guidelines.

Baricitinib

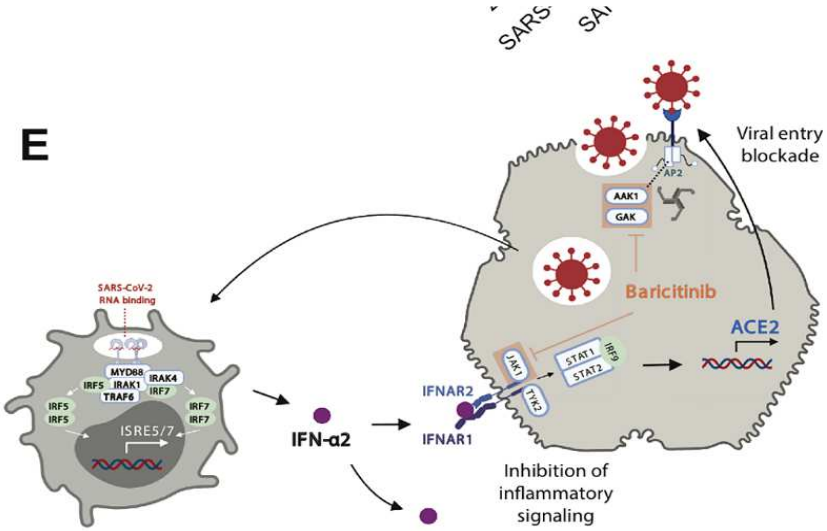
Science Advances Publish Ahead of Print, published on November 13, 2020 as doi:10.1126/sciadv.abe4724

ScienceAdvances RESEARCH ARTICLES

Cite as: J. Stebbing *et al.*, *Sci. Adv.* 10.1126/sciadv.abe4724 (2020).

JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality

Justin Stebbing[21]*, Ginés Sánchez Nievas[2†], Marco Falcone[3†], Sonia Youhanna[4†], Peter Richardson[5], Silvia Ottaviani[1], Joanne X. Shen[4], Christian Sommerauer[6], Giusy Tiseo[3], Lorenzo Ghiadoni[3], Agostino Virdis[3], Fabio Monzani[3], Luis Romero Rizos[7,8], Francesco Forfori[9], Almudena Avendaño-Céspedes[7,8], Salvatore De Marco[10], Laura Carrozzi[9], Fabio Lena[11], Pedro Manuel Sánchez-Jurado[7,8], Leonardo Gianluca Lacerenza[11], Nencioni Cesira[12], David Caldevilla-Bernardo[13], Antonio Perrella[12], Laura Niccoli[14], Lourdes Sáez Méndez[15], Daniela Matarrese[16], Delia Goletti[17], Yee-Joo Tan[18], Vanessa Monteil[19], George Dranitsaris[20], Fabrizio Cantini[14], Alessio Farcomeni[21], Shuchismita Dutta[22], Stephen K. Burley[22], Haibo Zhang[23], Mauro Pistello[24], William Li[25], Marta Mas Romero[7], Fernando Andrés Pretel[26], Rafaela Sánchez Simón-Talero[27], Rafael García-Molina[7], Claudia Kutter[6], James H. Felce[28], Zehra F. Nizami[28], Andras G. Miklosi[28], Josef M. Penninger[29,30],Francesco Menichetti[31], Ali Mirazimi[18‡], Pedro Abizanda[7,8‡] and Volker M. Lauschke[4‡*]



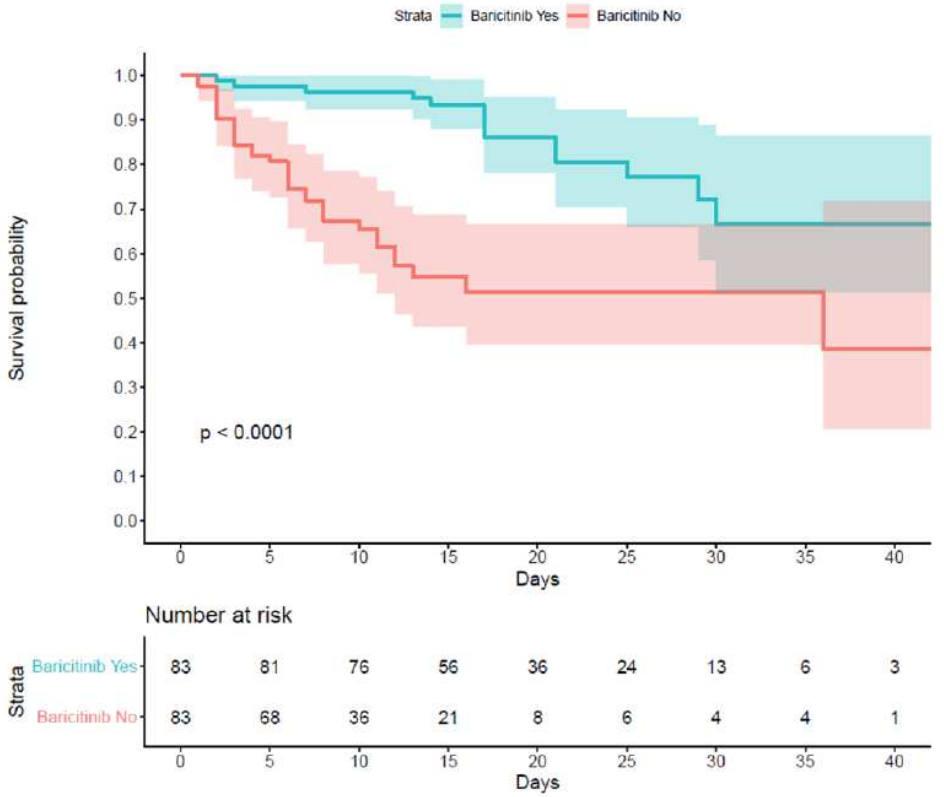
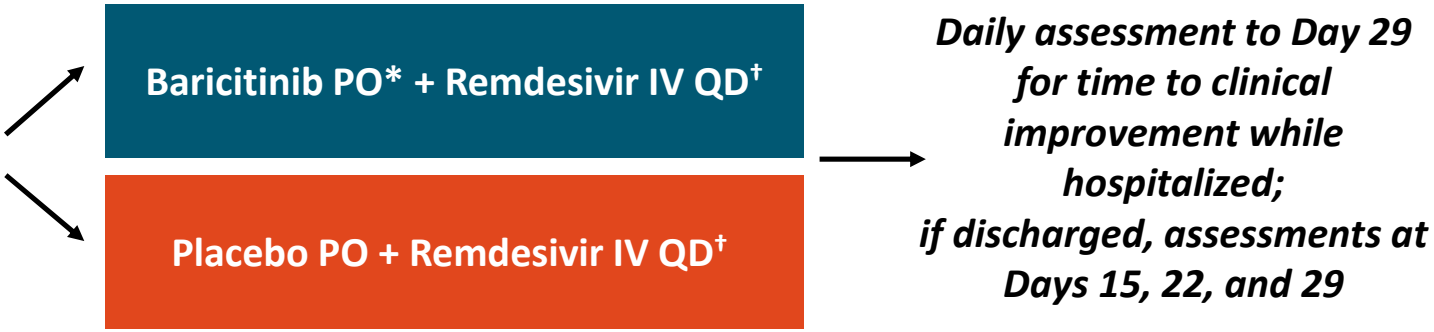


Fig. 2. Kaplan-Meier analysis of the propensity score matched cohorts from Pisa University and Albacete Hospital cohorts.

NIAID ACTT-2: Baricitinib + Remdesivir vs Remdesivir in Hospitalized Patients With Severe COVID-19

- Multicenter, adaptive, randomized, double-blind, placebo-controlled phase III trial[1]

Adult patients ≥ 18 yrs of age; hospitalized with confirmed SARS-CoV-2 infection and ≥ 1 of following: radiographic infiltrates by imaging; SpO_2 ≤ 94% on room air; requiring supplemental oxygen; or requiring mechanical ventilation
(**N = 1034**)



***4 mg** administered for duration of hospitalization, up to 14 days.
†200 mg on Day 1 followed by 100 mg on Days 2-10.

- Primary endpoint: time to recovery by Day 29 defined as the first day patient satisfies 1 of these categories from ordinal scale: 1) hospitalized, not requiring supplemental oxygen or ongoing medical care; 2) not hospitalized, limitation on activities and/or requiring home oxygen; or 3) not hospitalized, no limitations on activities
  - **Press release report of 1-day reduction in median recovery time[2]**

1. NCT04401579. 2. https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery. Press release only, not peer reviewed.

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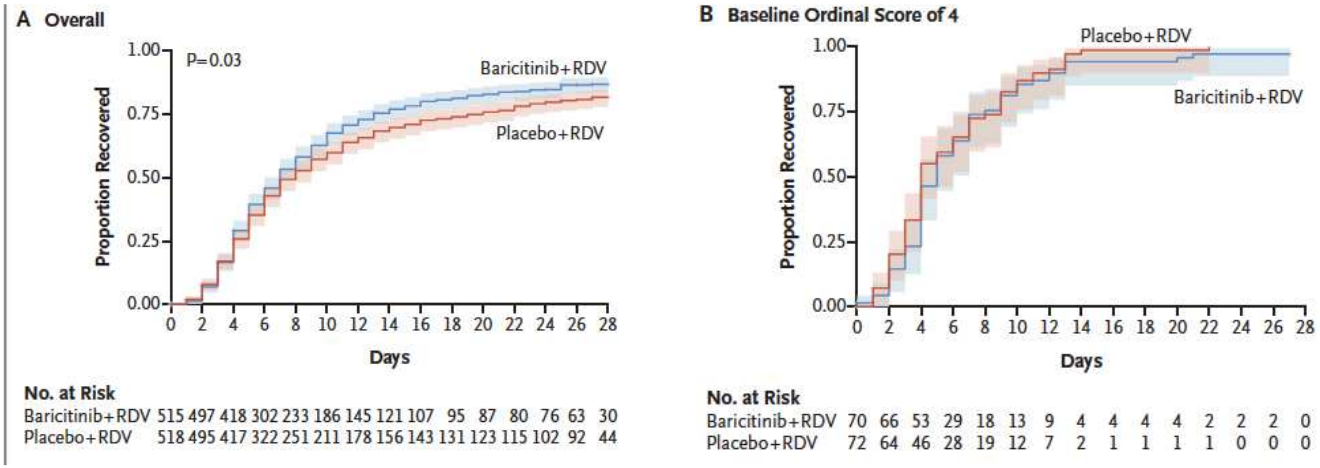
The NEW ENGLAND JOURNAL of MEDICINE

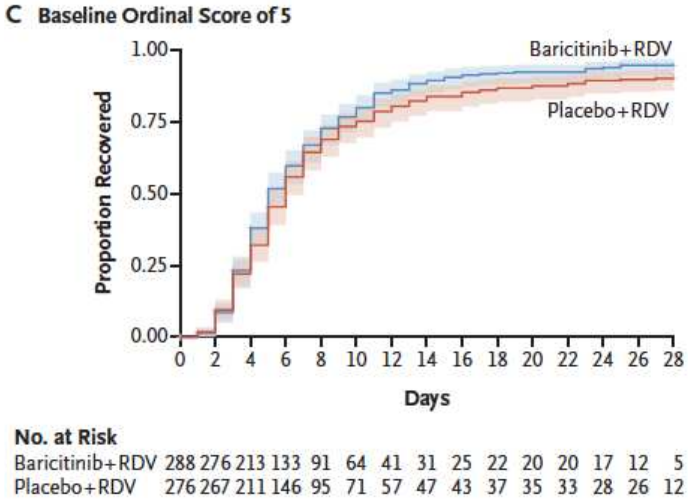
ORIGINAL ARTICLE

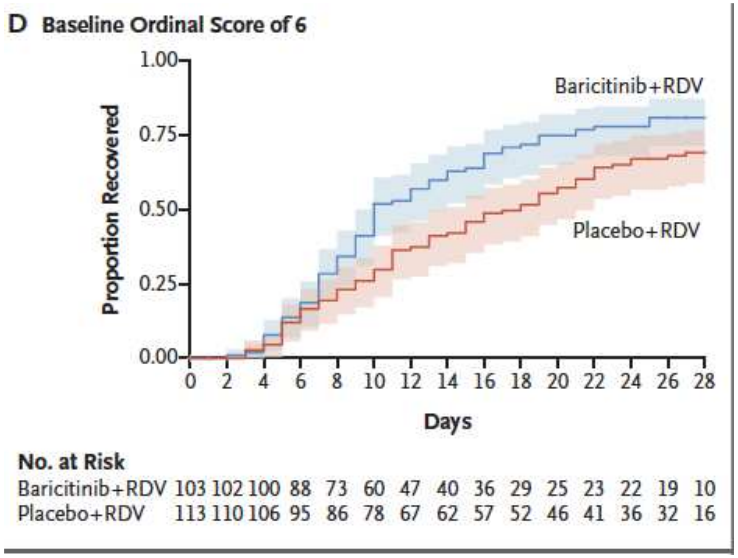
Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

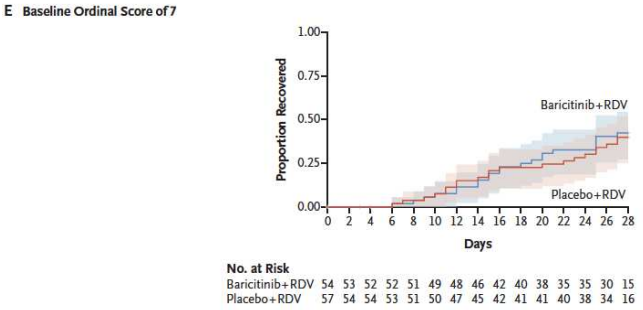
A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G.A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, and J.H. Beigel, for the ACTT-2 Study Group Members*



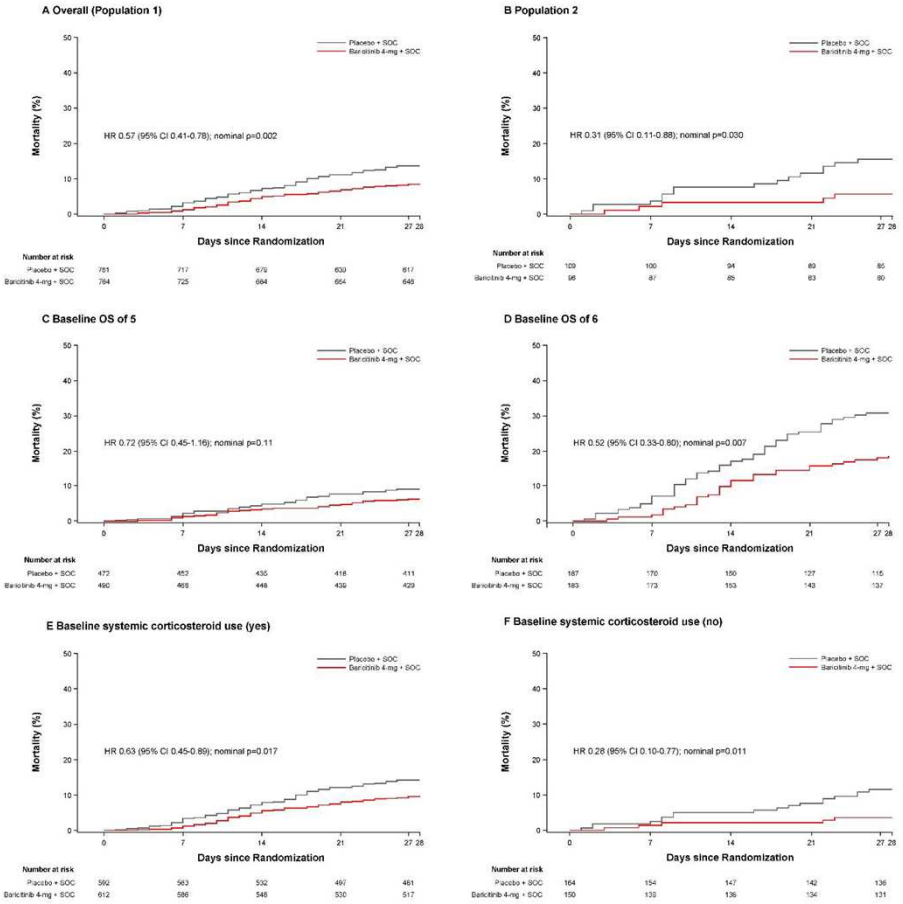
Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not requiring oxygen; Panel B), in those with a baseline score of 5 (requiring oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or extracorporeal membrane oxygenation [ECMO]; Panel E). Shaded areas indicate 95% confidence intervals.

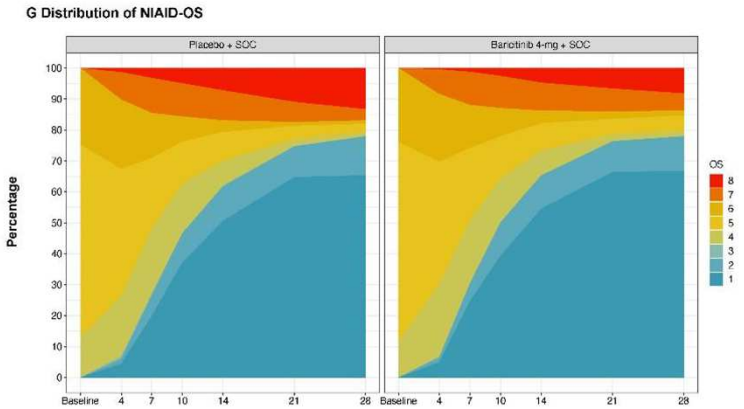


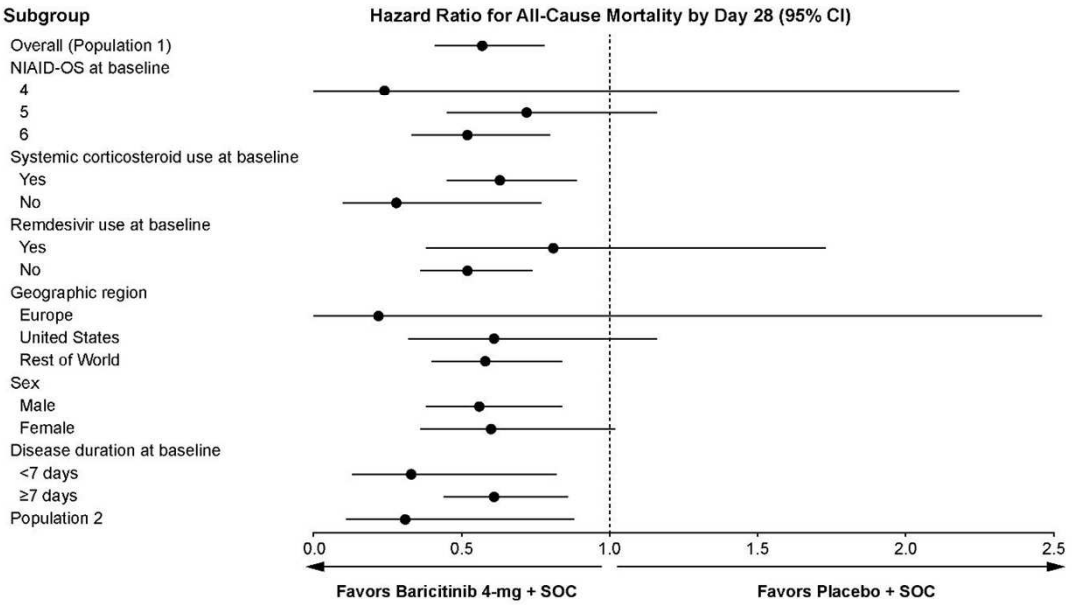




Baricitinib plus Standard of Care for Hospitalized Adults with COVID-19 (COV-BARRIER TRIAL)







Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19
Published by IDSA on 4/11/2020. Last updated, 6/3/2021

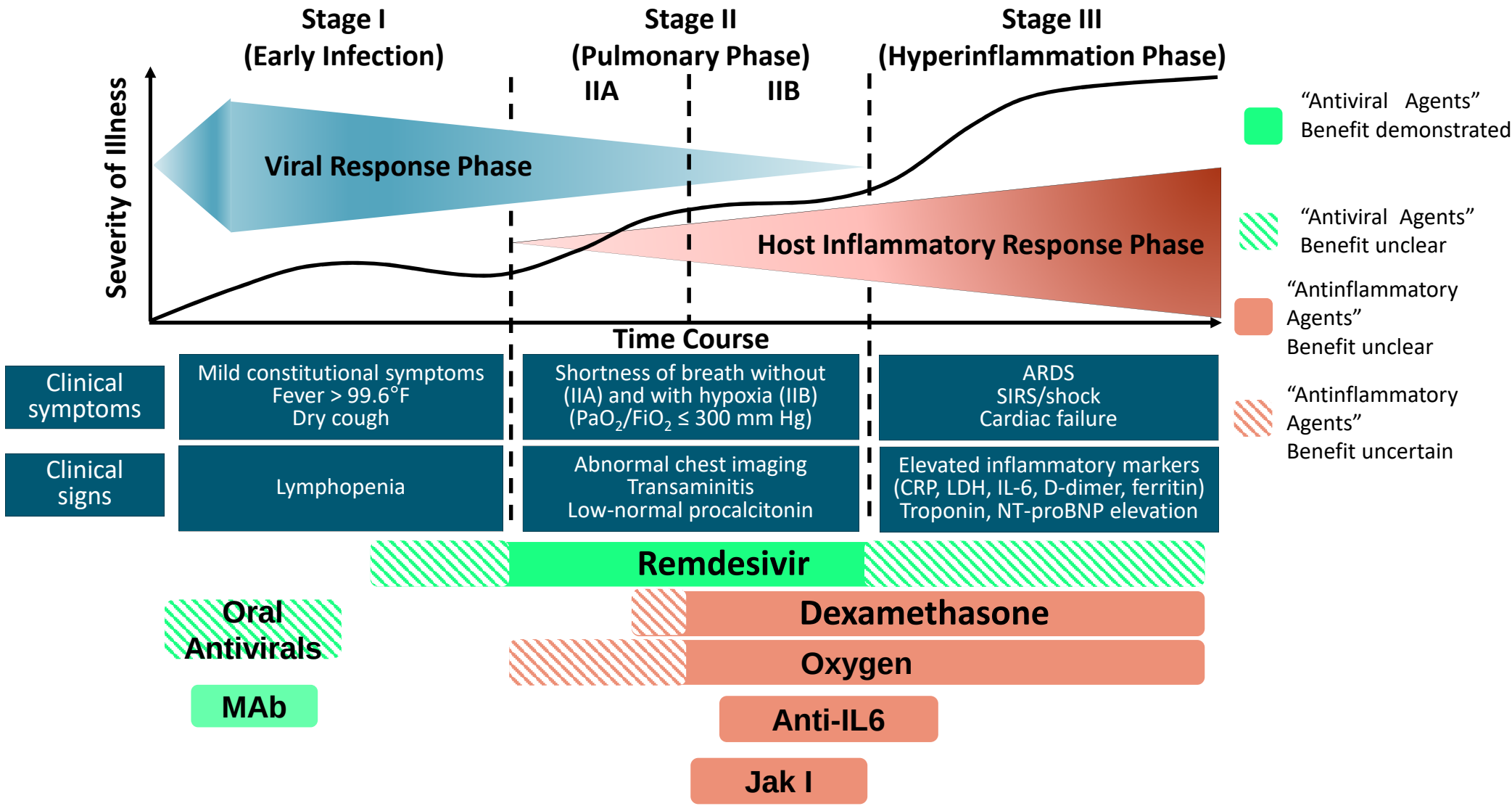
IDSA
Infectious Diseases Society of America

- Among hospitalized adults with severe* COVID-19 **having elevated inflammatory markers but not on invasive mechanical ventilation, the IDSA panel suggests baricitinib rather than no baricitinib**. (Conditional recommendation, Moderate certainty of evidence)
  - Remarks:
    - Baricitinib 4 mg per day up to 14 days or until discharge from hospital.
    - Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high-flow oxygen/non-invasive ventilation at baseline.
- Among hospitalized patients with severe* COVID-19 **who cannot receive a corticosteroid (which is standard of care) because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone**. (Conditional recommendation, Low certainty of evidence)
  - Remark: Baricitinib 4 mg daily dose for 14 days or until hospital discharge. The benefits of baricitinib plus remdesivir for persons on mechanical ventilation are uncertain.

Last updated, 4/14/2021 and posted online at www.idsociety.org/COVID19guidelines. Please check website for most updated version of these guidelines.

COVID-19 quali terapie in quale momento

- Fasi della malattia
- Terapia antivirale
  - Inibitori dell'entry
    - Anticorpi Monoclonali
    - Plasma di convalescente
  - Inibitori della polimerasi
- Terapia antinfiammatoria
  - Steroidi
  - Tocilizumab
  - Baricitinib
- Ad ogni tempo il suo farmaco



Modified from Siddiqi. J Heart Lung Transplant. 2020;39:405.

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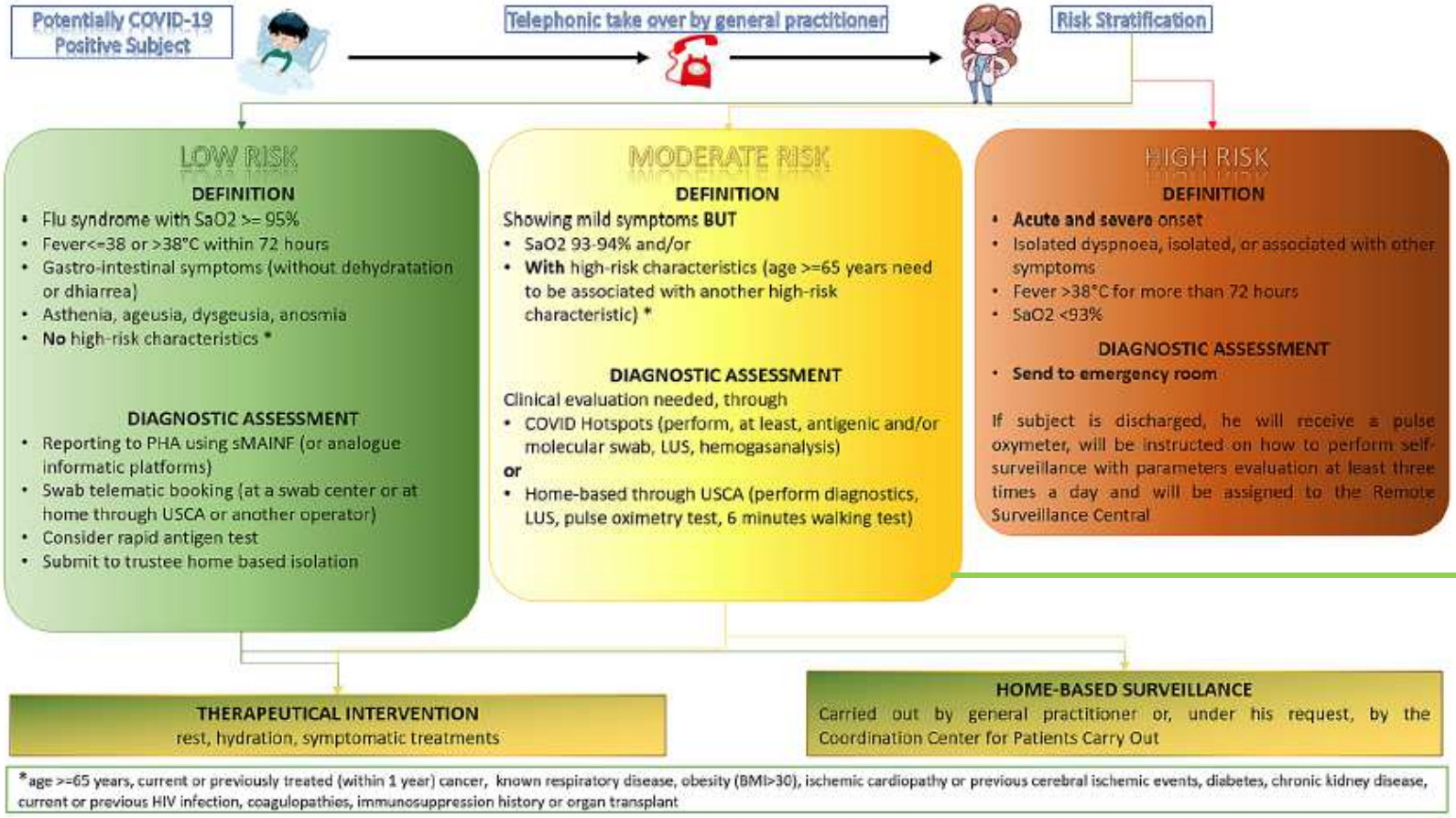

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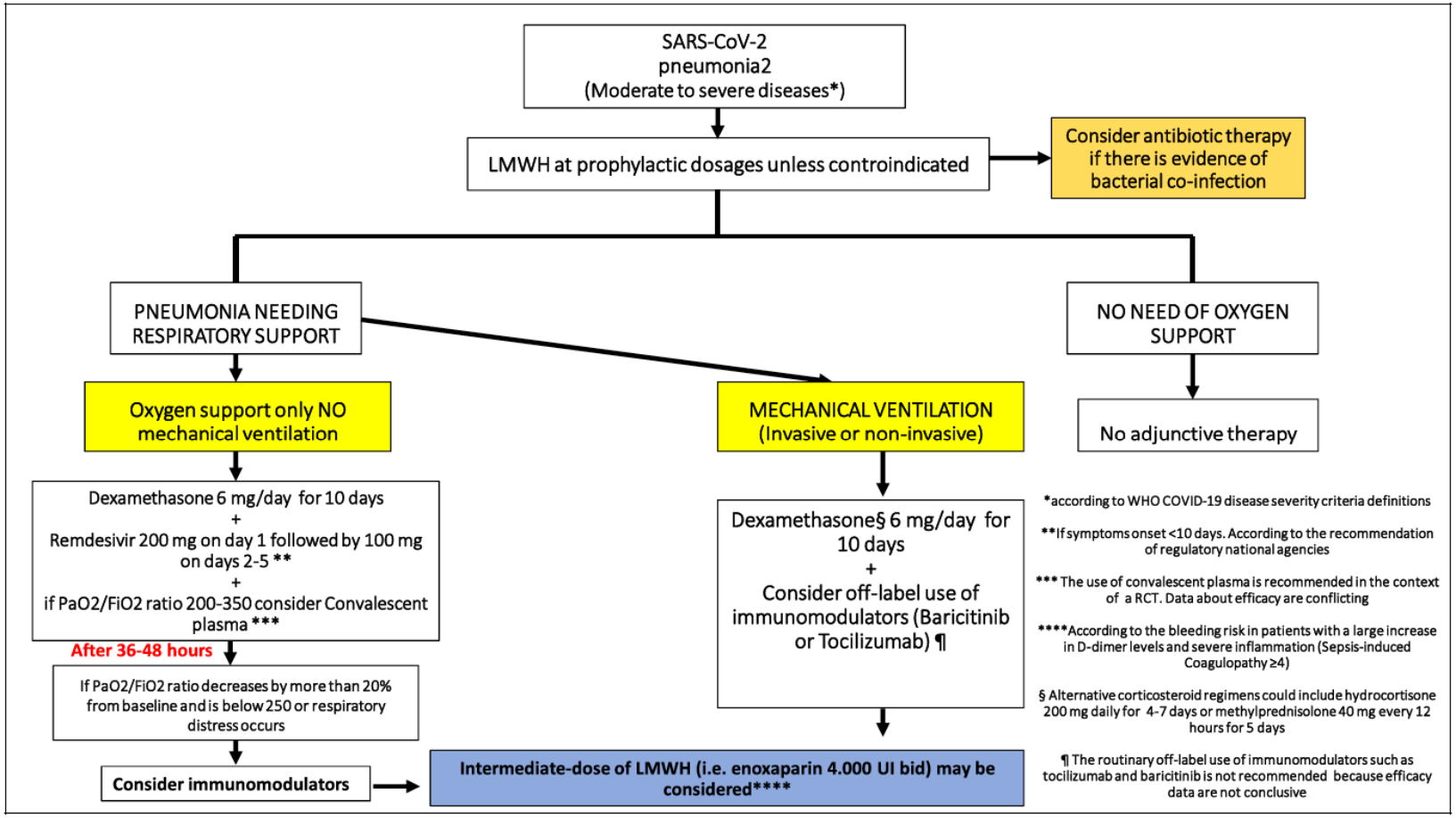

Fig. 1. Flowchart for treatment of severe cases of coronavirus disease 2019 (COVID-19).

COVID-19 Quali terapie in quale momento

- La malattia si sviluppa attraverso l'embricazione di una fase di replicazione virale il cui mancato controllo innesca una alterata regolazione della risposta infiamatoria
- Per il trattamento occorre embricare
  - Farmaci antivirali da impiegare precocemente (anticorpi monoclonali ed inibitori della polimerasi)
  - Farmaci antinfiammatori da impiegae in pazienti con insufficienza respiratoria (steroidi, baricitinib, tocilizumab) secondo una strategia di escalation
- Nella fase di insufficienza respiratoria grave (ARDS) è necessaria una saggia supplementazione di ossigeno

Terapia del COVID-19:

.... come un Presepe

Infettivologa

Pneumologi Urgentisti ed Intensivisti