Ventilation for COVID-19

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台灣胸腔暨重症加護醫學會
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新型冠狀病毒感染(COVID-19)

併發急性呼吸衰竭臨床處置指引

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台灣胸腔暨重症加護醫學會 編輯

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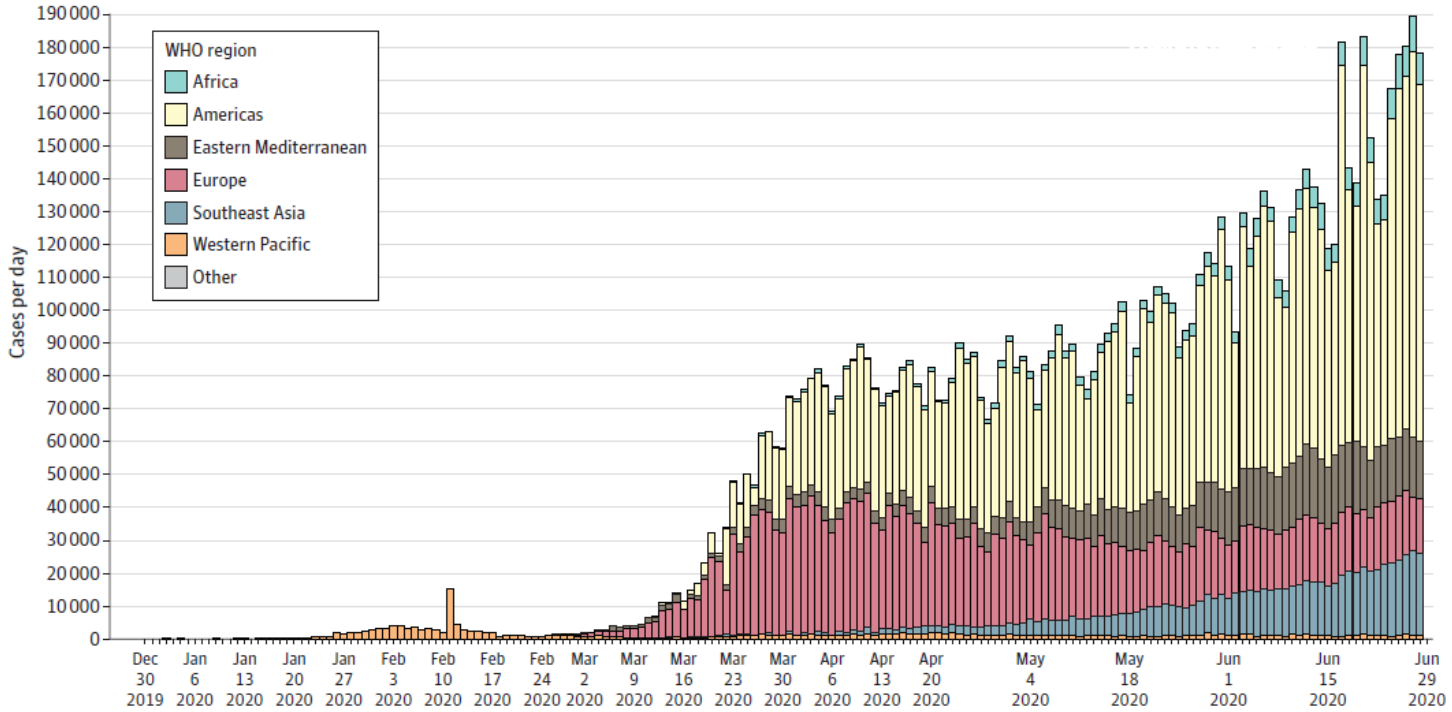
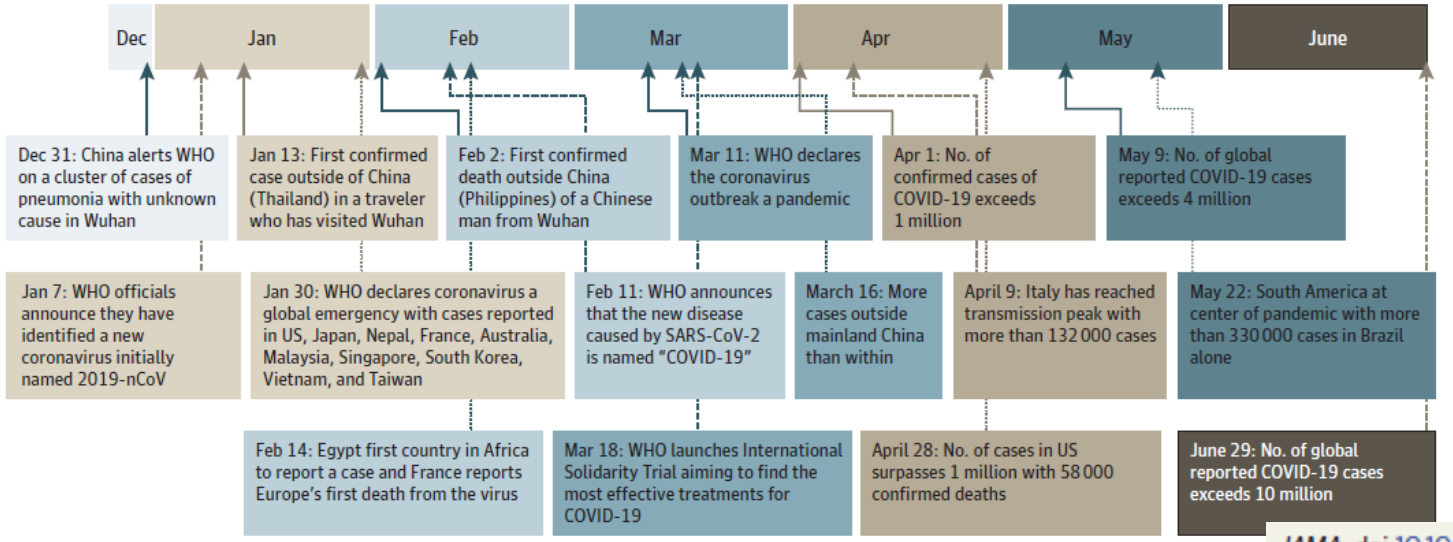
Key Events in the Early Coronavirus Disease 2019 (COVID-19) Pandemic





JAMA. doi:10.1001/jama.2020.12839
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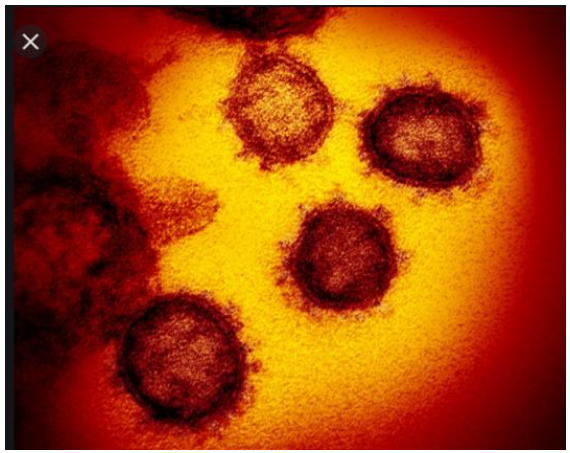
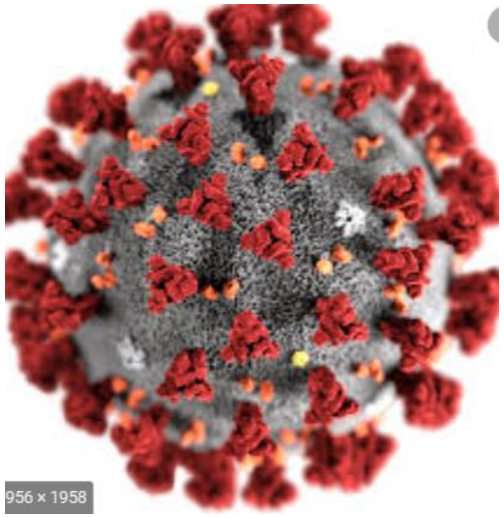
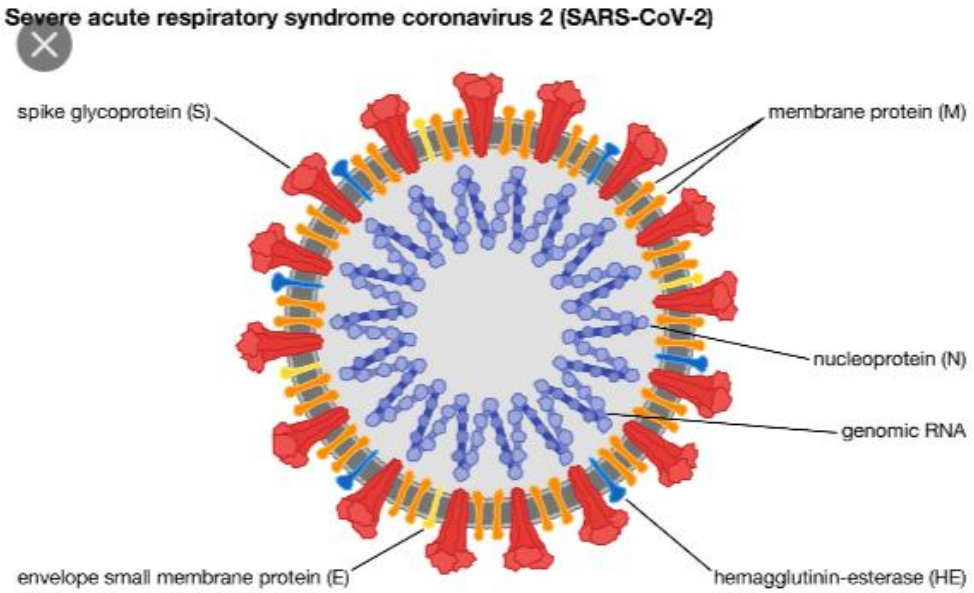
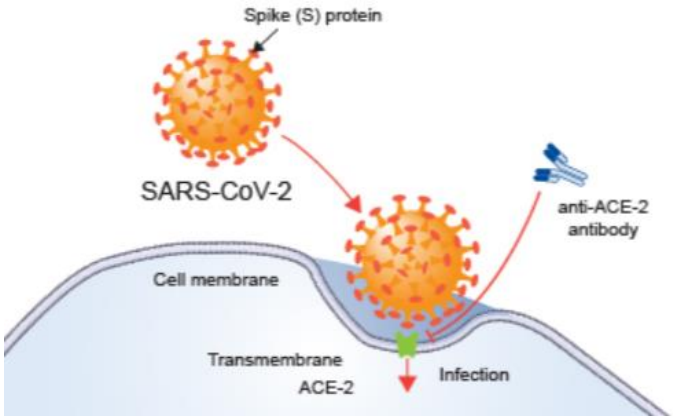
SARS-CoV-2



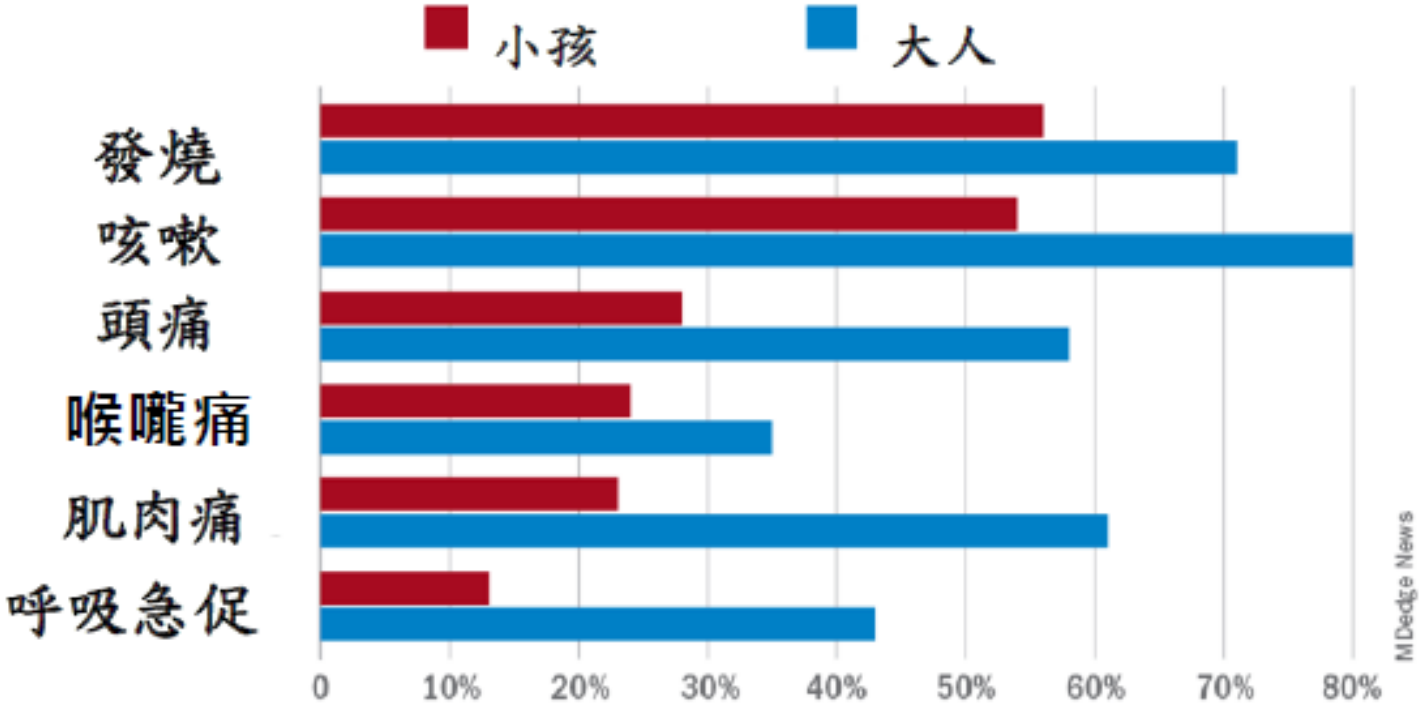

956 × 1958


Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
spike glycoprotein (S)
membrane protein (M)
nucleoprotein (N)
genomic RNA
envelope small membrane protein (E)
hemagglutinin-esterase (HE)


Spike (S) protein
SARS-CoV-2
anti-ACE-2
antibody
Cell membrane
Transmembrane
ACE-2
Infection

COVID-19的臨床症狀是什麼?

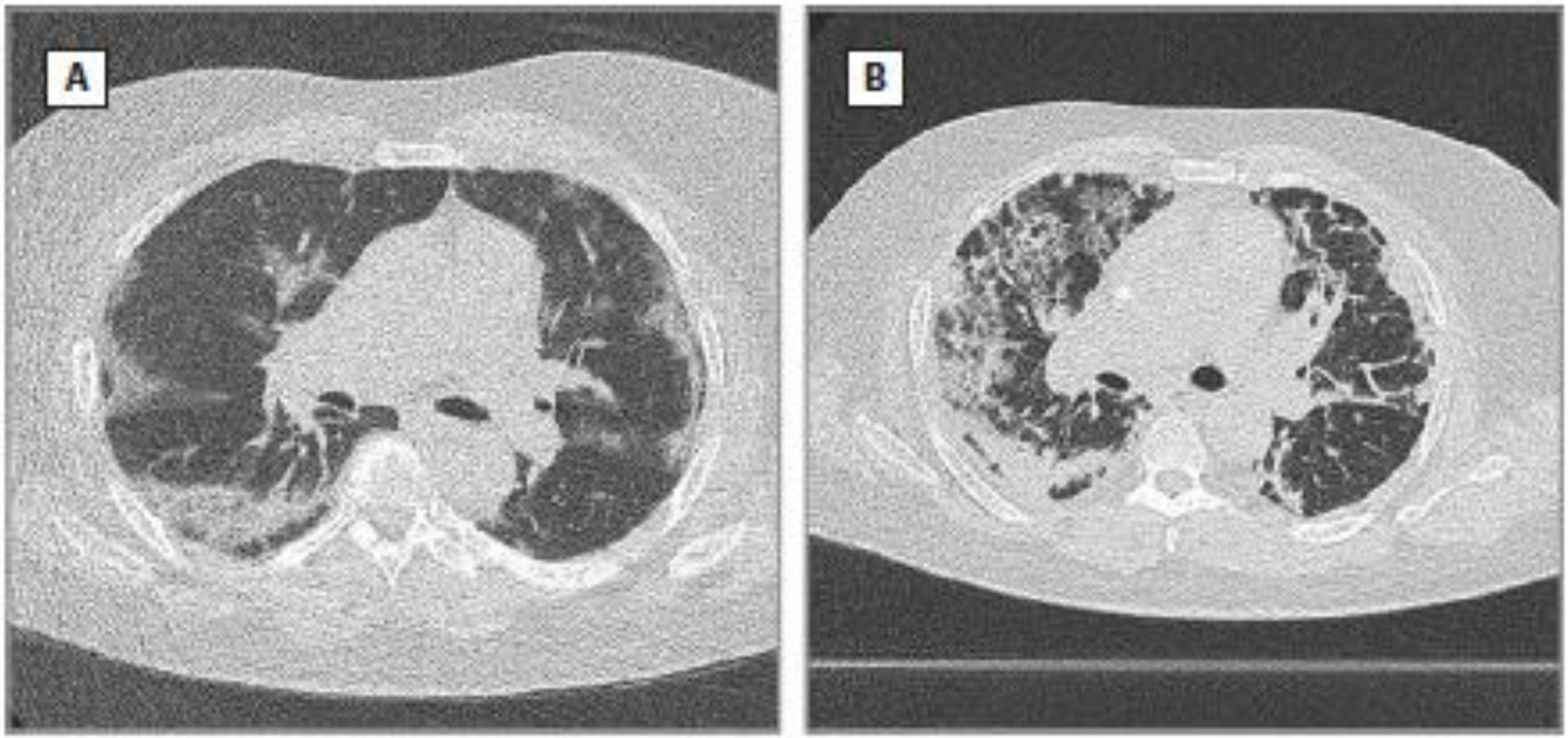
- 大人的前三大症狀是「咳嗽、發燒、肌肉痛」
- 小孩的症狀是「發燒、咳嗽、頭痛」。



Note: Based on data for 11% of pediatric cases and 9.6% of adult cases reported as of April 2.

Source: MMWR. 2020 Apr 6;69(early release):1-5

Radiological findings of COVID-19



A, Transverse thin-section computed tomographic scan of a 76-year-old man, 5 days after symptom onset, showing subpleural ground-glass opacity and consolidation with subpleural sparing. B, Transverse thin-section computed tomographic scan of a 76-year-old man, 21 days after symptom onset, showing bilateral and peripheral predominant consolidation, ground-glass with reticulation, and bronchodilatation. C, Pathological manifestations of lung tissue

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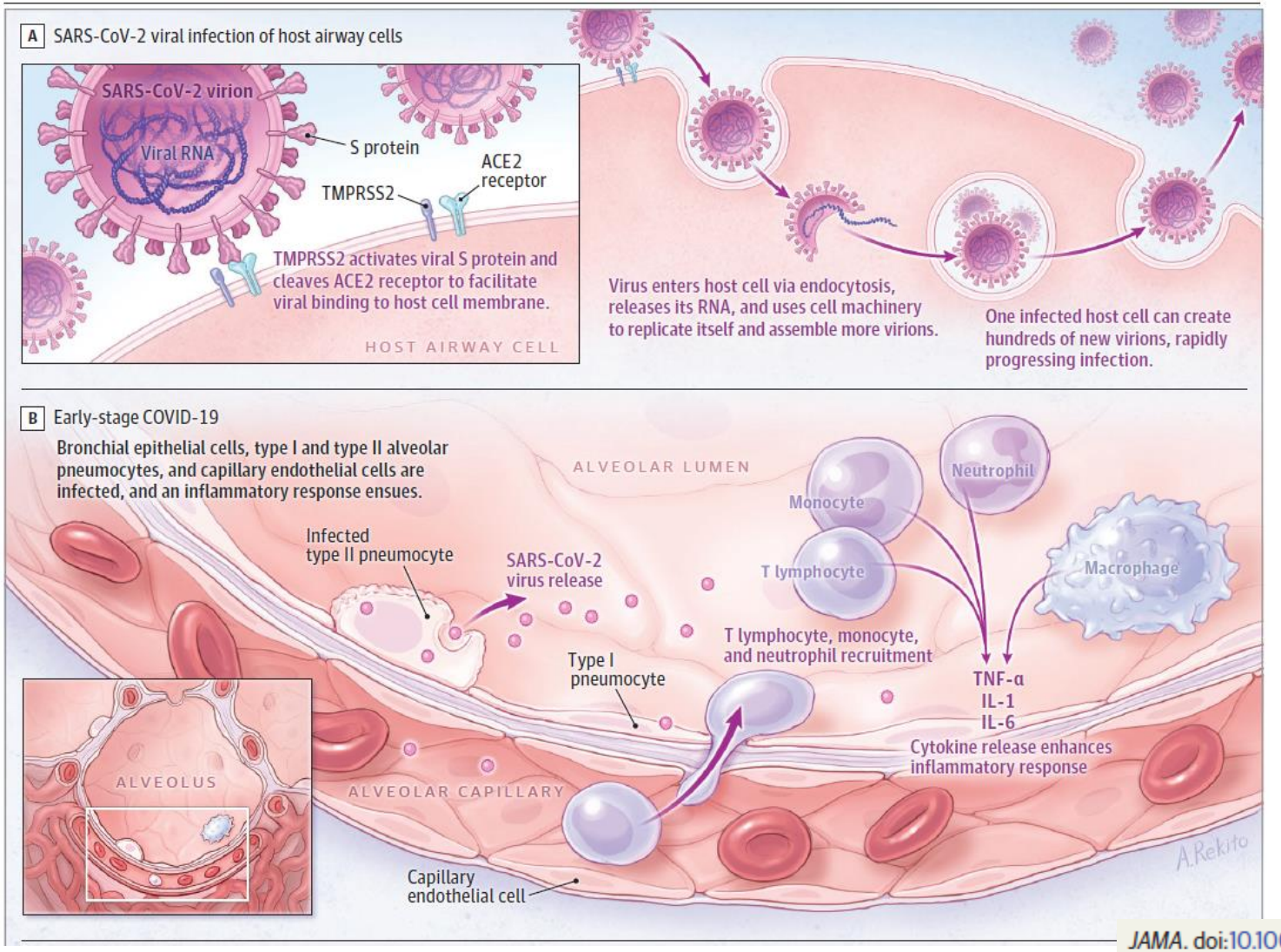
Immunopathogenesis of COVID-19 (1)



JAMA. doi:10.1001/jama.2020.12839
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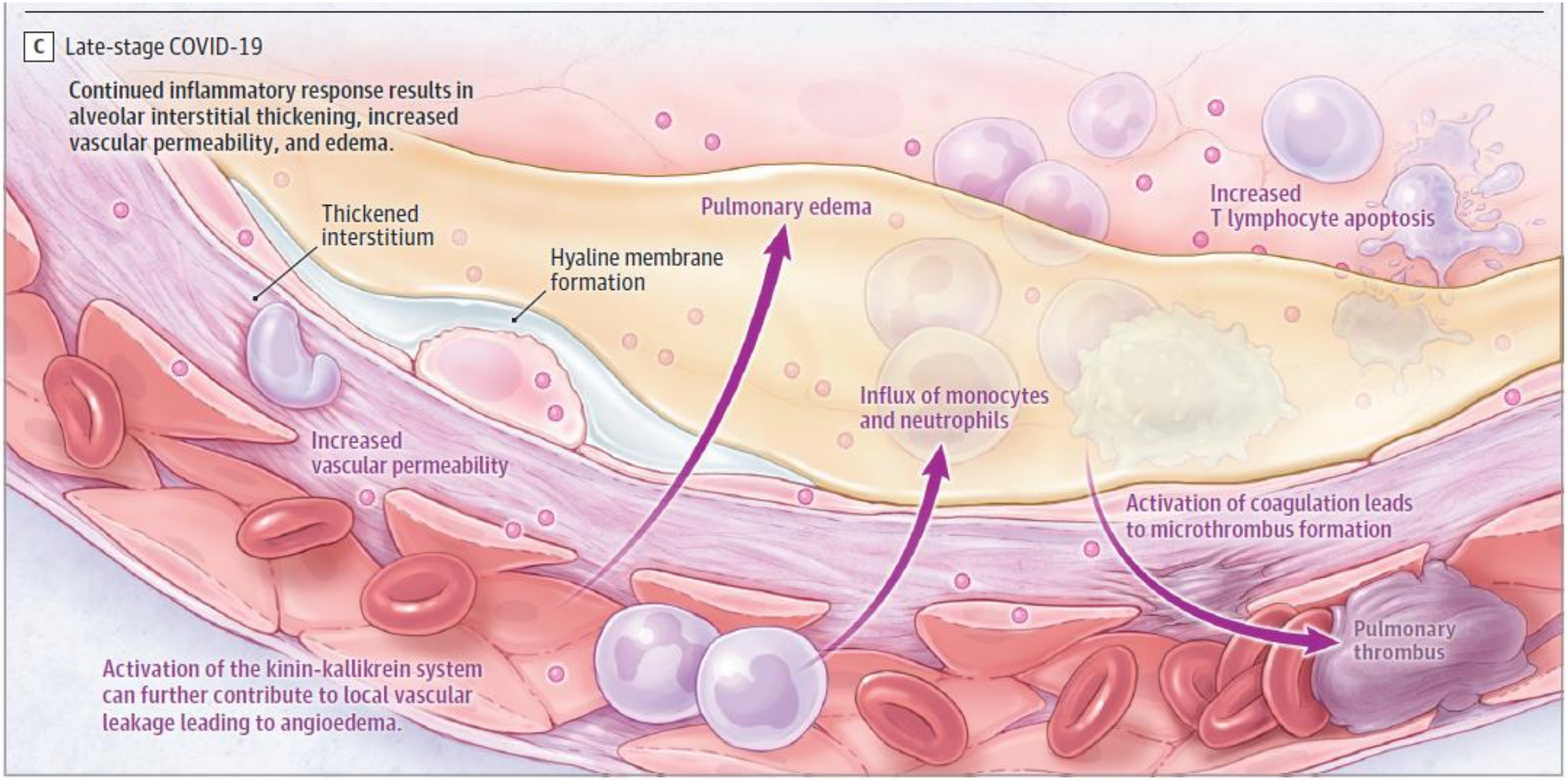
Immunopathogenesis of COVID-19 (2)



JAMA. doi:10.1001/jama.2020.12839
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Immunological landscape in Sepsis and COVID-19

Polymicrobial sepsis

COVID-19

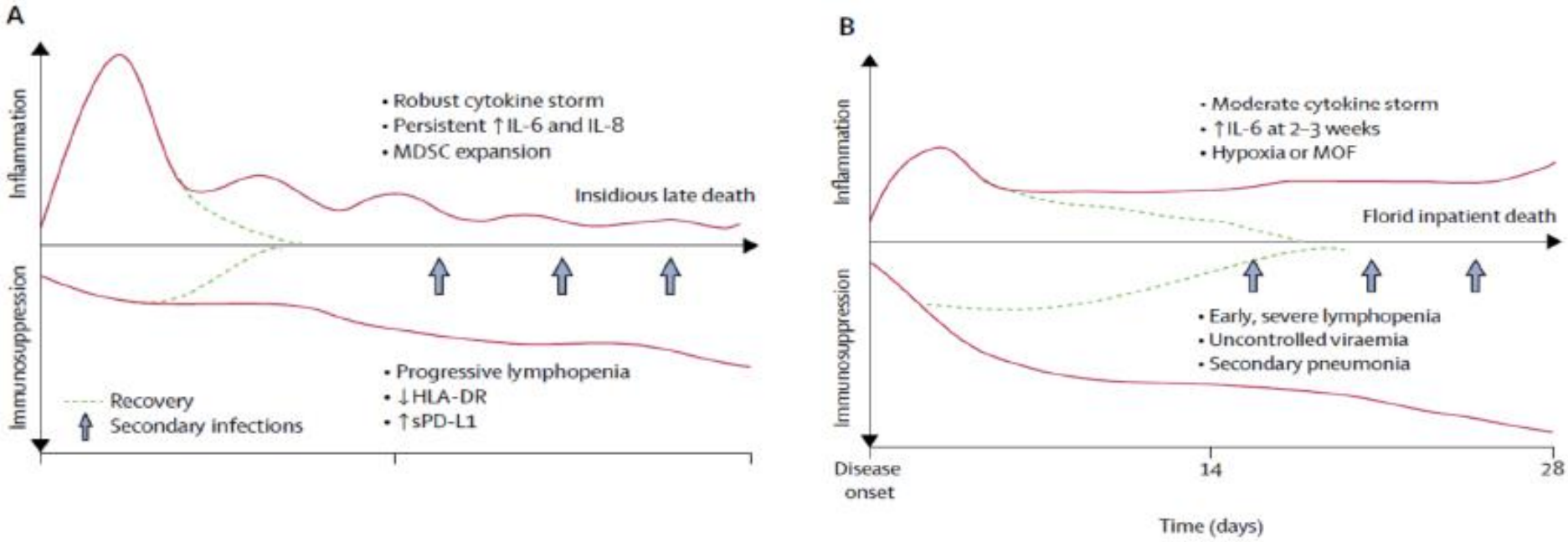
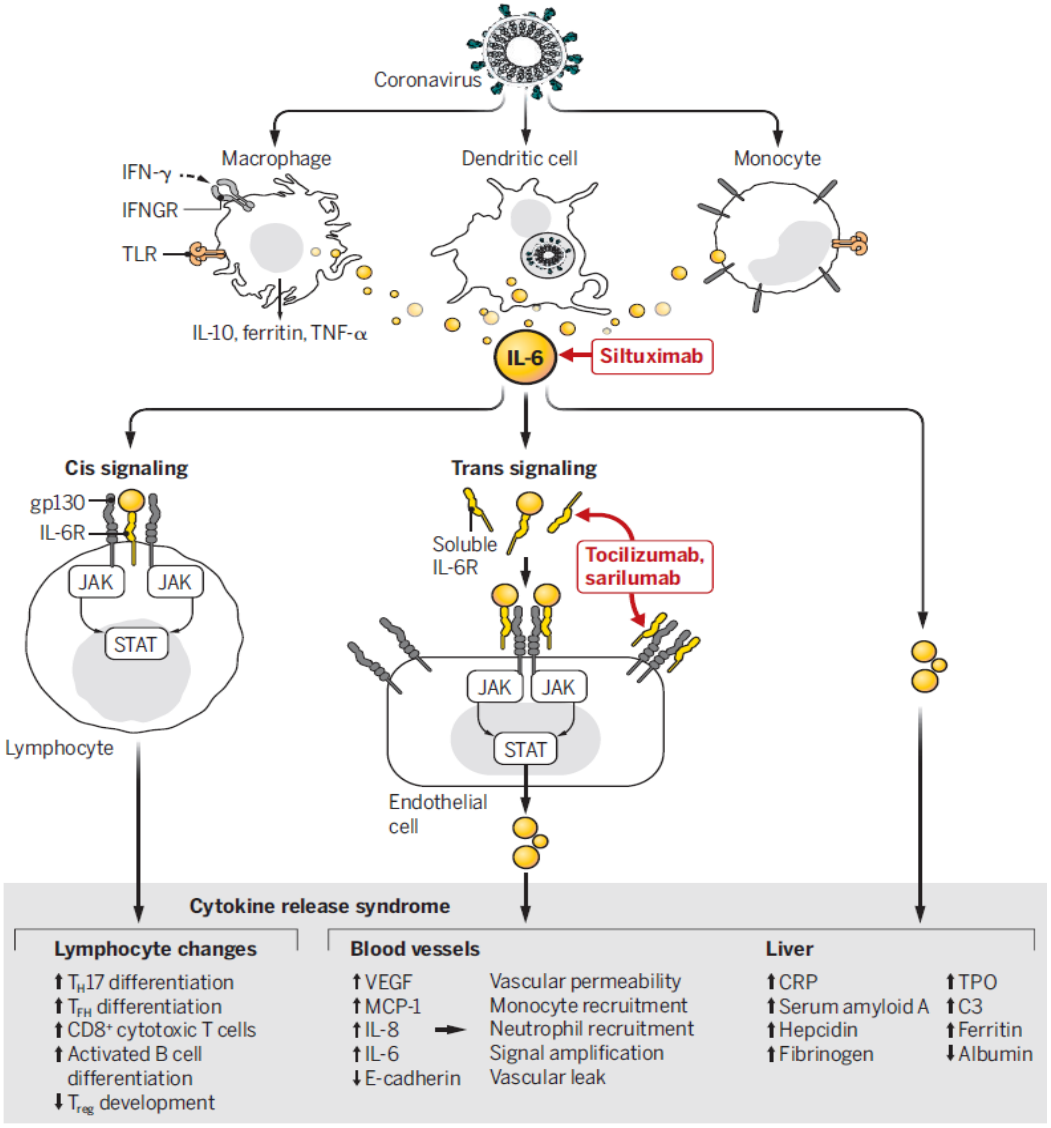


Figure: **Immunological landscape in polymicrobial sepsis (A) and COVID-19 (B)**
Bullet points refer to the symptoms seen throughout disease progression. MOF=multiorgan failure. COVID-19=coronavirus disease 19. MDSC=myeloid-derived suppressor cells. HLA-DR=human leukocyte antigen-DR. sPD-L1=soluble programmed cell death protein 1.

Lancet Respir Med 2020 Published Online April 28, 2020

Cytokine release syndrome in severe COVID-19

Lessons from arthritis and cell therapy in cancer patients point to therapy for severe disease



C3, complement 3; CRP, C reactive protein; IFN-γ, interferon-γ; IFNGR, IFN-γ receptor; IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein–1; STAT3, signal transducer and activator of transcription 3; T_{FH}, T follicular helper cell; T_H17, T helper 17 cell; TNF-α, tumor necrosis factor–α; TLR, Toll-like receptor; TPO, thrombopoietin; T_{reg}, T regulatory cell; VEGF, vascular endothelial growth factor.

Cytokine Release Syndrome in severe COVID-19 (1)

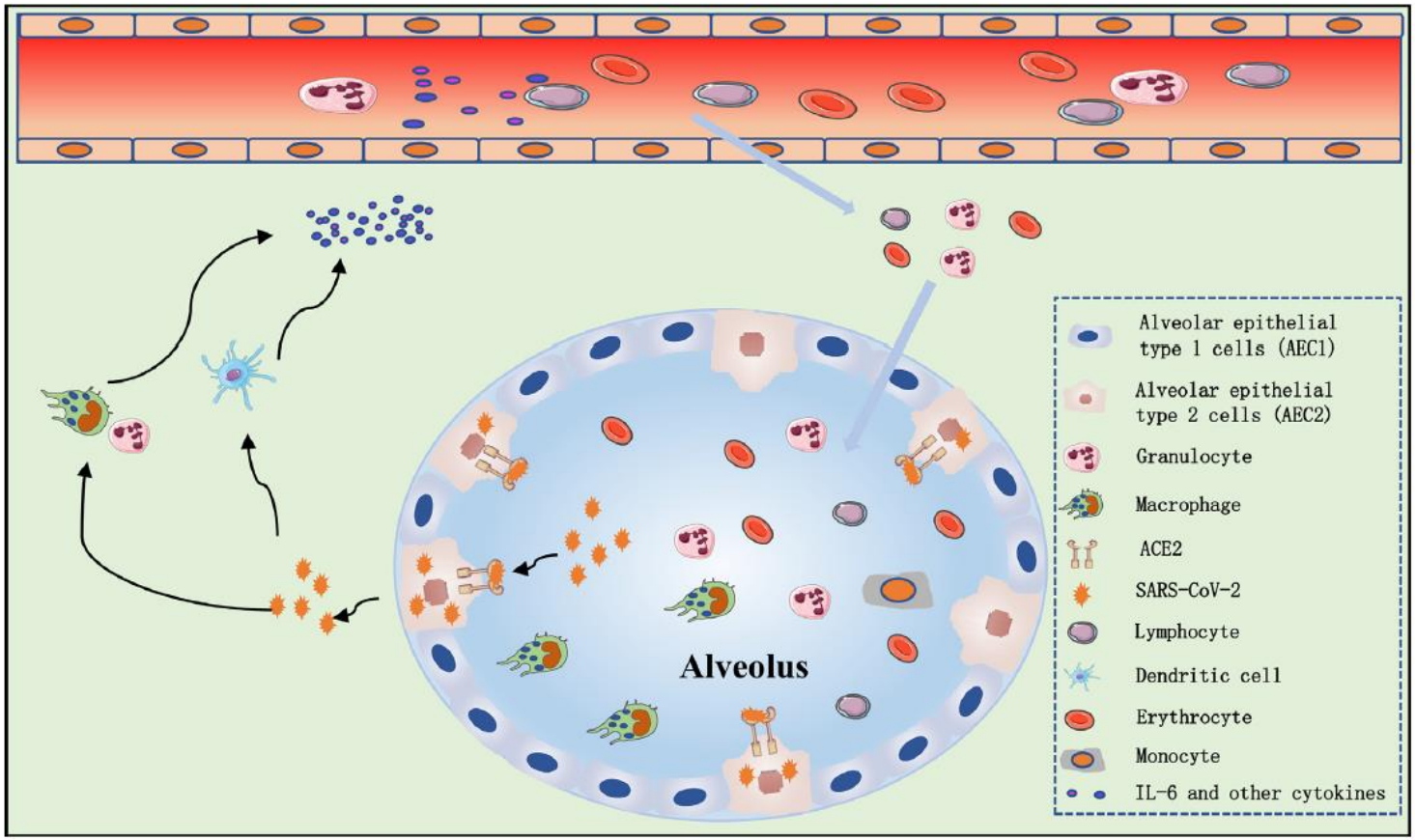


Fig. 1. Possible mechanism of cytokine release syndrome in severe coronavirus disease 2019 (COVID-19) patients. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects alveolar epithelial cells [mainly alveolar epithelial type 2 (AEC2) cells] through the angiotensin-converting enzyme 2 (ACE2) receptor. Destruction of epithelial cells and the increase of cell permeability lead to release of the virus. SARS-CoV-2 activates the innate immune system; macrophages and other innate immune cells not only capture the virus but also release a large number of cytokines and chemokines, including interleukin-6 (IL-6). Adaptive immunity is also activated by antigen-presenting cells (mainly dendritic cells). T- and B-cells not only play an antiviral role but also directly or indirectly promote the secretion of inflammatory cytokines. In addition, under the stimulation of inflammatory factors, a large number of inflammatory exudates and erythrocytes enter the alveoli, resulting in dyspnoea and respiratory failure.

International Journal of Antimicrobial Agents 55 (2020)

Cytokine Release Syndrome in severe COVID-19 (2)

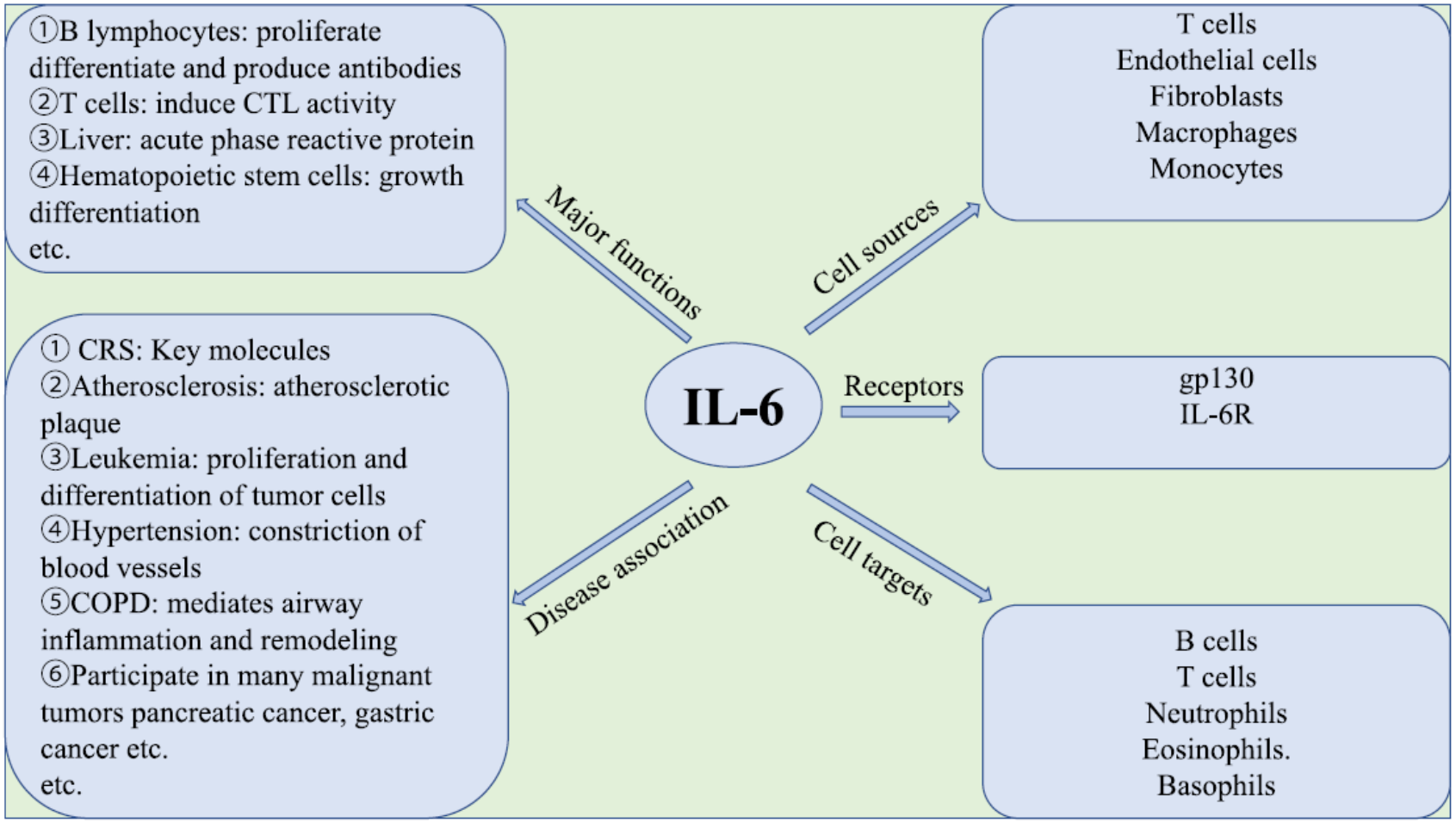


Fig. 2. Brief introduction to interleukin-6 (IL-6). CTL, cytotoxic T lymphocyte; CRS, cytokine release syndrome; COPD, chronic obstructive pulmonary disease; gp130, glycoprotein 130; IL-6R, interleukin-6 receptor.

Selected Candidate Therapies for COVID-19

Antiviral agent

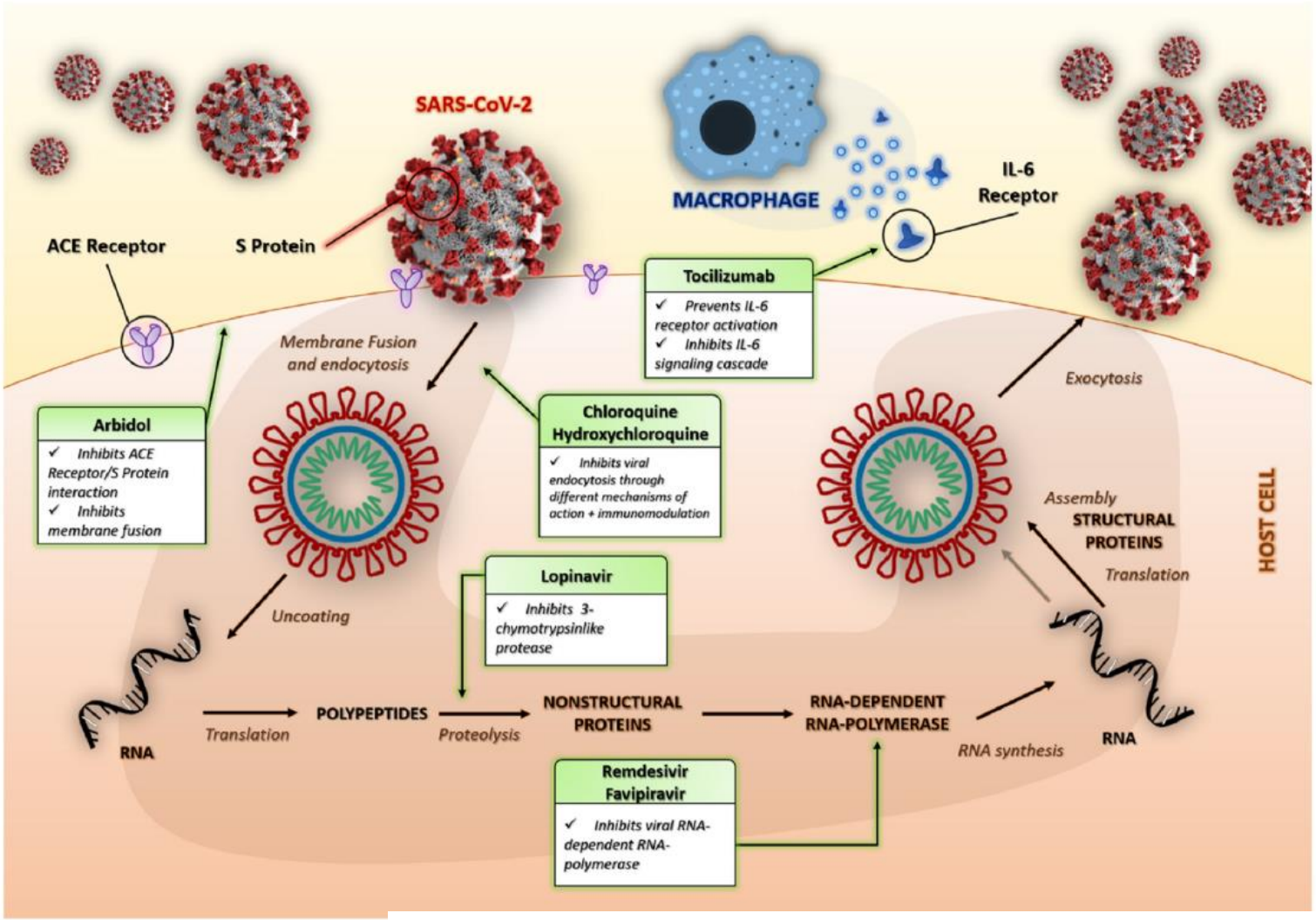
- Chloroquine
- Hydroxychloroquine
- Lopinavir-Ritonavir
- Remdesivir

Immune-based agents

- Convalescent plasma
- Glucocorticoid
- IL-1 inhibitors
- IL-6 inhibitors
- JAK inhibitors

This article was published on May 15, 2020, at NEJM.org.

Main targets of the drug therapies



European Journal of Pharmacology 882 (2020) 173328

Table 1. Selected Candidate Therapies for Coronavirus Disease 2019 (Covid-19).*

Class	Availability	Rationale	Clinical Data
Antiviral agents			
Chloroquine	FDA-approved for extraintestinal amoebiasis, malaria; FDA emergency-use authorization from Strategic National Stockpile for certain hospitalized patients with Covid-19	In vitro activity against SARS-CoV-2[44]	Limited: small randomized trial showed limited benefit[45]; small trial stopped early because of increased mortality with higher dose[46]; randomized, controlled trials in progress
Hydroxychloroquine	FDA-approved for lupus, malaria, rheumatoid arthritis; FDA emergency-use authorization from Strategic National Stockpile for certain hospitalized patients with Covid-19	In vitro activity against SARS-CoV-2[47]	Limited: small randomized trials and retrospective case series with inconsistent results[48-51]; randomized, controlled trials in progress
Lopinavir–ritonavir	FDA-approved for HIV infection	In vitro activity against SARS-CoV-2[52]	Small randomized clinical trial failed to show clinical benefit[53]; other randomized, controlled trials in progress
Remdesivir	Investigational; FDA emergency-use authorization for hospitalized patients with severe Covid-19; compassionate-use program for pregnant women and children with severe Covid-19; expanded-access program for persons unable to participate in clinical trials (ClinicalTrials.gov number, NCT04323761)	In vitro activity against SARS-CoV-2[44]	Small, single-group, uncontrolled study showed clinical benefit in a majority of patients[54]; underenrolled and underpowered randomized, placebo-controlled trial involving hospitalized patients showed no significant differences in clinical or virologic outcomes[55]; randomized, placebo-controlled trial involving hospitalized patients showed faster time to recovery with remdesivir[43]; additional clinical trials in progress
Immune-based agents			
BTK inhibitors (acalabrutinib, ibrutinib, rilzabrutinib)	FDA-approved for some hematologic cancers	Immunomodulation-targeting cytokines	Clinical trials in progress
Convalescent plasma	Investigational; FDA single-patient emergency IND; expanded-access program for persons ineligible for or unable to participate in clinical trials	Use in other viral illnesses, including H1N1 influenza, SARS, and MERS	Limited: small, uncontrolled cohort studies suggested benefit, but confirmation required[56,57]; randomized, controlled trials in progress
Glucocorticoids	FDA-approved for multiple indications	Broad immunomodulation	Limited: retrospective, nonrandomized cohort study showed association with lower mortality among patients with severe Covid-19 and ARDS,[39] but concern for survivor treatment bias; randomized clinical trials involving patients with influenza, MERS, or SARS did not show benefit and suggested possible harm (increased viral shedding and increased mortality)[58-60]
Interleukin-1 inhibitors (anakinra, canakinumab)	FDA-approved for some autoimmune diseases	Immunomodulation; activity in macrophage activation syndrome	Clinical trials in progress
Interleukin-6 inhibitors (sarilumab, siltuximab, tocilizumab)	FDA-approved for some autoimmune diseases and cytokine release syndrome (tocilizumab)	Immunomodulation; activity in cytokine release syndrome	Limited: in a small cohort study, a majority of patients who received siltuximab had an improved or stabilized condition[61]; randomized, controlled trials in progress
JAK inhibitors (baricitinib, ruxolitinib)	FDA-approved for rheumatoid arthritis (baricitinib) and myelofibrosis and polycythemia vera (ruxolitinib)	Broad immunomodulation	Clinical trials in progress

* Selected references are provided for rationale and clinical data. ARDS denotes acute respiratory distress syndrome, BTK Bruton's tyrosine kinase, FDA Food and Drug Administration, HIV human immunodeficiency virus, IND investigational new drug, JAK Janus kinase, MERS Middle East respiratory syndrome, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

This article was published on May 15, 2020, at NEJM.org.

西班牙流感在美國期刊的痕跡！

March 30,2020

新冠肺炎疫情全球肆虐，人們在急需疫苗以及藥物的保護之際，美國總統川普19日宣布，將加速奎寧（quinine）來對抗新冠病毒之研究。奎寧為一種相當有歷史的藥物，過去在拉丁美洲的金雞納樹皮中被發現，數百年來都用於治療瘧疾，但用在治療呼吸道流感疾病上，新冠肺炎可不是首例。 20世紀初的西班牙流感(Spanish Flu)造成全世界5億人感染，1.7千萬至5千萬死亡，為人類歷史上最致命的自然事件之一。根據The Independent ... Devoted to the Consideration of Politics, Social and Economic Tendencies, History, Literature, and the Arts於1918年9月的一篇報導FIGHTING THE SPANISH "FLU"，便指出英國為預防與治療西班牙流感已嘗試使用奎寧。

Gilliams Service

FIGHTING THE SPANISH "FLU"

England, too, is having her troubles with the new contagious fever-and-cold-in-the-head disease that has been spreading thru some of our seaport cities. These workers at a British munitions plant are lined up for the regular dose of quinine that they count on to prevent the "flu"

The Chinese Students' Monthly (1909-1929); New York [New York]01 Jan 1921: 34

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary 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*

This article was published on May 22, 2020, at NEJM.org.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

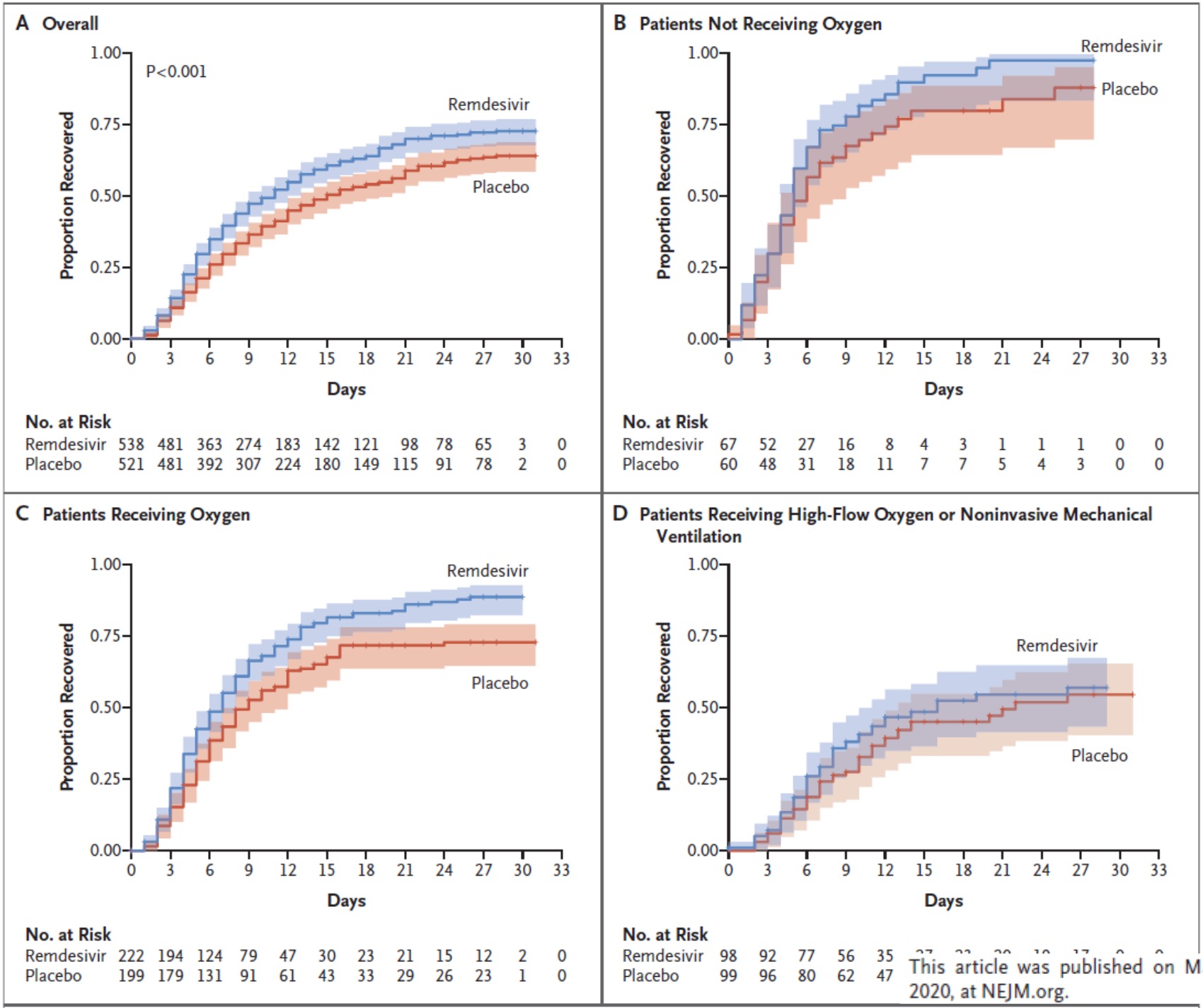
RESULTS

A total of 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; $P<0.001$). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

CONCLUSIONS

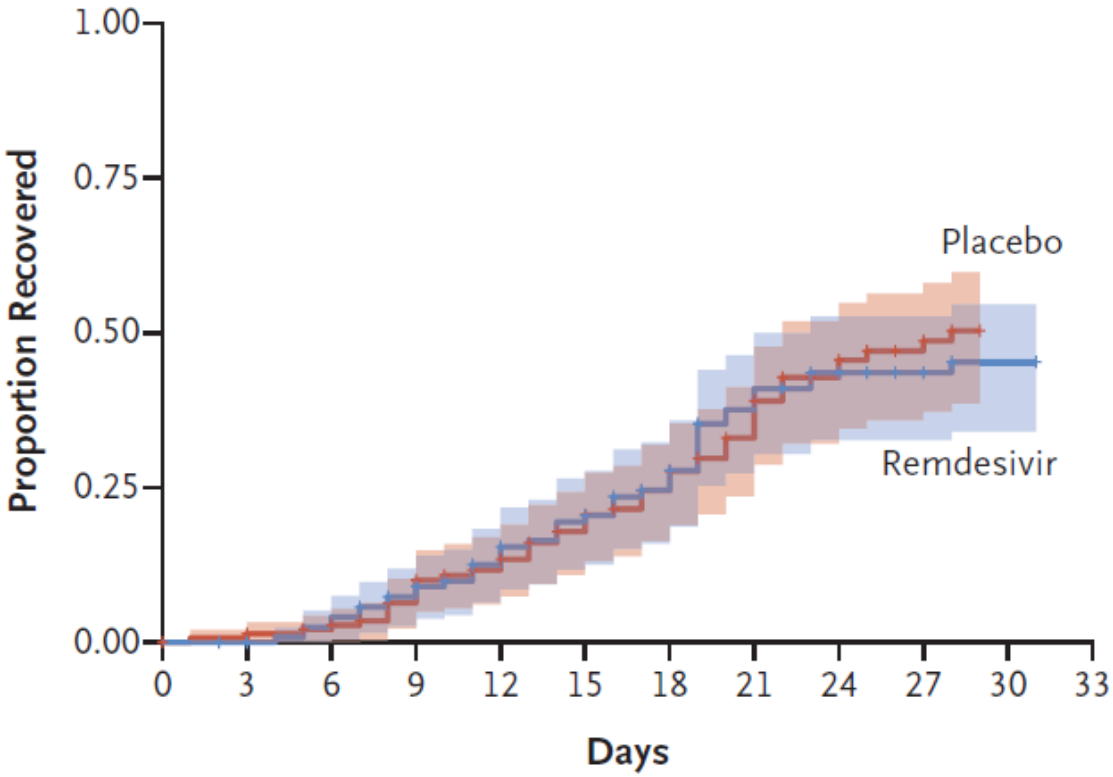
Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACCT-1 ClinicalTrials.gov number, NCT04280705.)

This article was published on May 22, 2020, at NEJM.org.



This article was published on May 22, 2020, at NEJM.org.

E Patients Receiving Mechanical Ventilation or ECMO



No. at Risk

Remdesivir	125	124	120	111	91	80	71	55	42	34	1	0
Placebo	147	145	141	127	102	91	73	56	41	33	0	0

This article was published on May 22, 2020, at NEJM.org.

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

	Overall*		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=538)	Placebo (N=521)	Remdesivir (N=67)	Placebo (N=60)	Remdesivir (N=222)	Placebo (N=199)	Remdesivir (N=98)	Placebo (N=99)	Remdesivir (N=125)	Placebo (N=147)
Recovery										
No. of recoveries	334	273	61	47	177	128	47	43	45	51
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)	5 (4–6)	6 (4–8)	7 (6–8)	9 (7–11)	16 (NE– 10)	22 (NE– 12)	NE–NE	28 (NE– 22)
Rate ratio (95% CI)†	1.32 (1.12–1.55 [P<0.001])		1.38 (0.94–2.03)		1.47 (1.17–1.84)		1.20 (0.79–1.81)		0.95 (0.64–1.42)	
Mortality										
Hazard ratio (95% CI)	0.70 (0.47–1.04)		0.46 (0.04–5.08)		0.22 (0.08–0.58)		1.12 (0.53–2.38)		1.06 (0.59–1.92)	
No. of deaths by day 14	32	54	1	1	4	19	13	13	13	19
Kaplan–Meier estimate — % (95% CI)	7.1 (5.0–9.9)	11.9 (9.2–15.4)	1.5 (0.2–10.1)	2.5 (0.4–16.5)	2.4 (0.9–6.4)	10.9 (7.1–16.7)	15.2 (9.0–25.0)	14.7 (8.7–24.3)	11.3 (6.7–18.8)	14.1 (9.2–21.2)
Ordinal score at day 15 (±2 days) — no. (%)‡										
Patients with baseline and day 15 score data — no.	434	410	60	51	196	161	71	77	101	115
1	99 (22.8)	76 (18.5)	22 (36.7)	15 (29.4)	54 (27.6)	45 (28.0)	13 (18.3)	7 (9.1)	10 (9.9)	8 (7.0)
2	158 (36.4)	127 (31.0)	25 (41.7)	21 (41.2)	95 (48.5)	66 (41.0)	28 (39.4)	27 (35.1)	6 (5.9)	10 (8.7)
3	11 (2.5)	6 (1.5)	7 (11.7)	4 (7.8)	4 (2.0)	2 (1.2)	0	0	0	0
4	23 (5.3)	20 (4.9)	1 (1.7)	3 (5.9)	12 (6.1)	7 (4.3)	4 (5.6)	4 (5.2)	6 (5.9)	6 (5.2)
5	34 (7.8)	40 (9.8)	3 (5.0)	5 (9.8)	14 (7.1)	6 (3.7)	2 (2.8)	7 (9.1)	15 (14.9)	22 (19.1)
6	16 (3.7)	14 (3.4)	1 (1.7)	0 (0)	1 (0.5)	3 (1.9)	6 (8.5)	6 (7.8)	7 (6.9)	5 (4.3)
7	60 (13.8)	72 (17.6)	0 (0)	2 (3.9)	12 (6.1)	12 (7.5)	5 (7.0)	13 (16.9)	43 (42.6)	45 (39.1)
8	33 (7.6)	55 (13.4)	1 (1.7)	1 (2.0)	4 (2.0)	20 (12.4)	13 (18.3)	13 (16.9)	14 (13.9)	19 (16.5)
Odds ratio (95% CI)	1.50 (1.18–1.91 [P=0.001])		1.51 (0.76–3.00)		1.31 (0.89–1.92)		1.60 (0.89–2.86)		1.04 (0.64–1.68)	

This article was published on May 22, 2020, at NEJM.org.

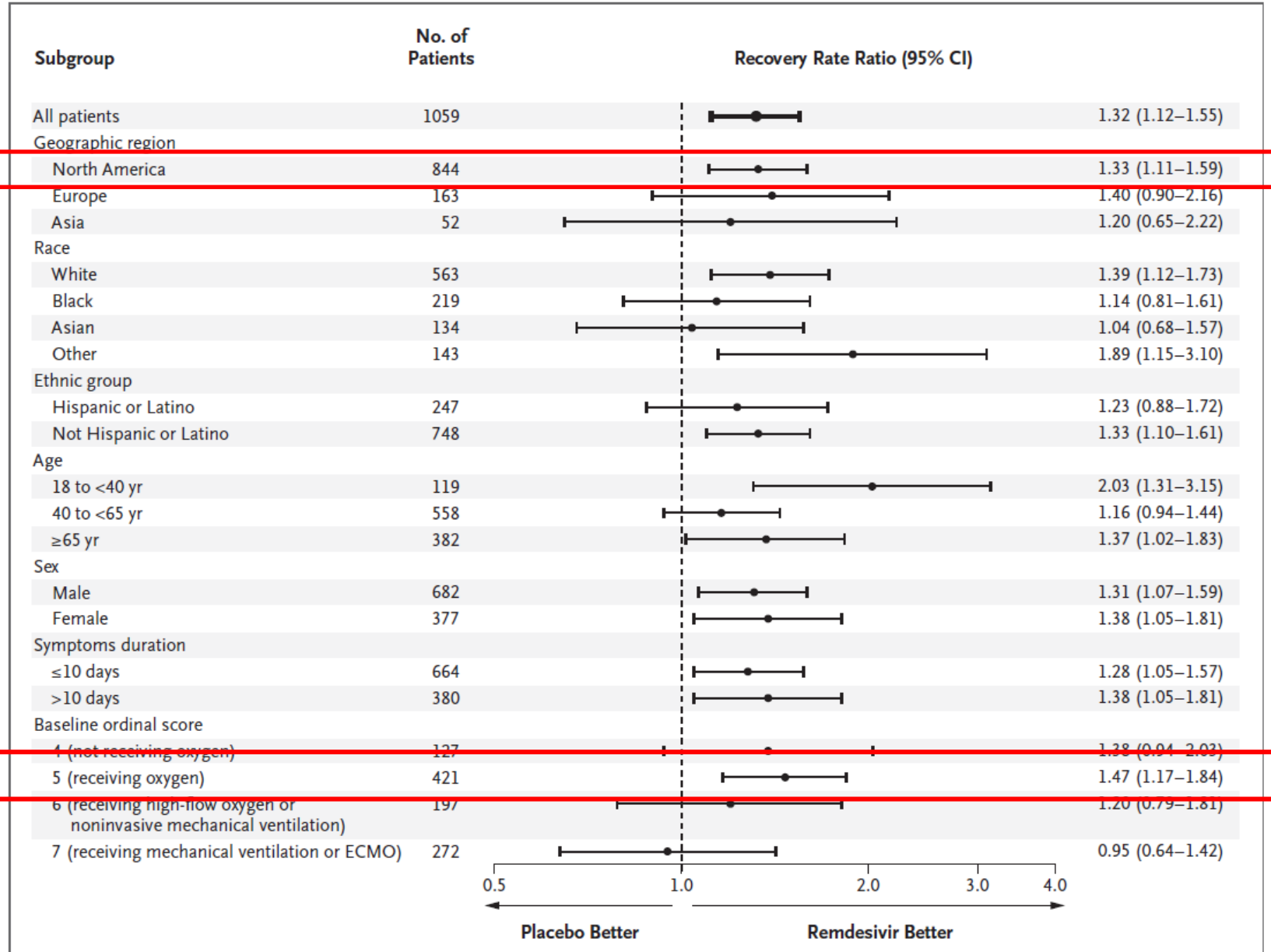


Figure 3. Time to Recovery According to Subgroup.

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

This article was published on May 22, 2020, at NEJM.org.

Conclusions

- Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 patients and evidence of lower respiratory tract infection.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

METHODS

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

This article was published on July 17, 2020, at NEJM.org.

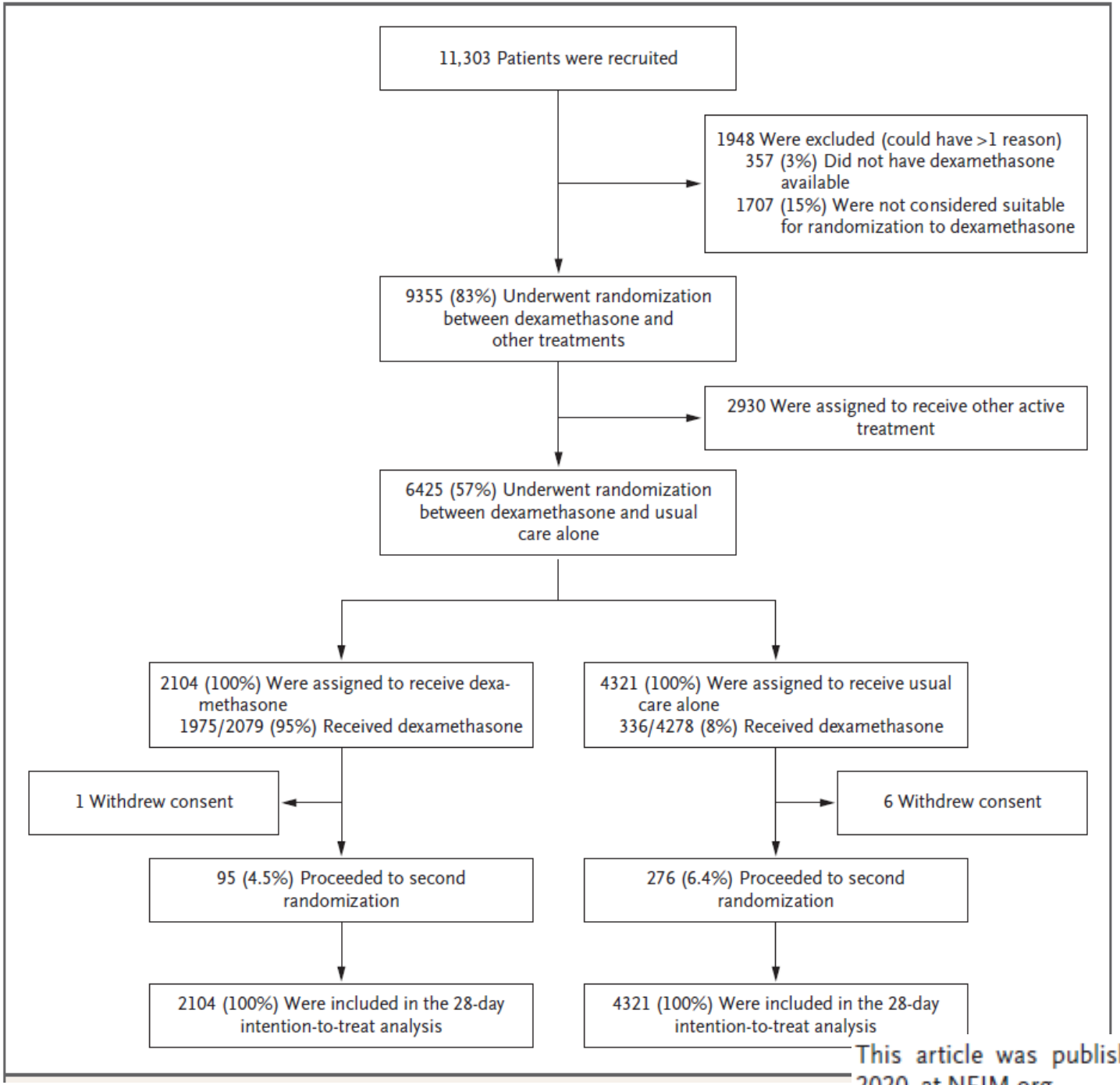

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Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	

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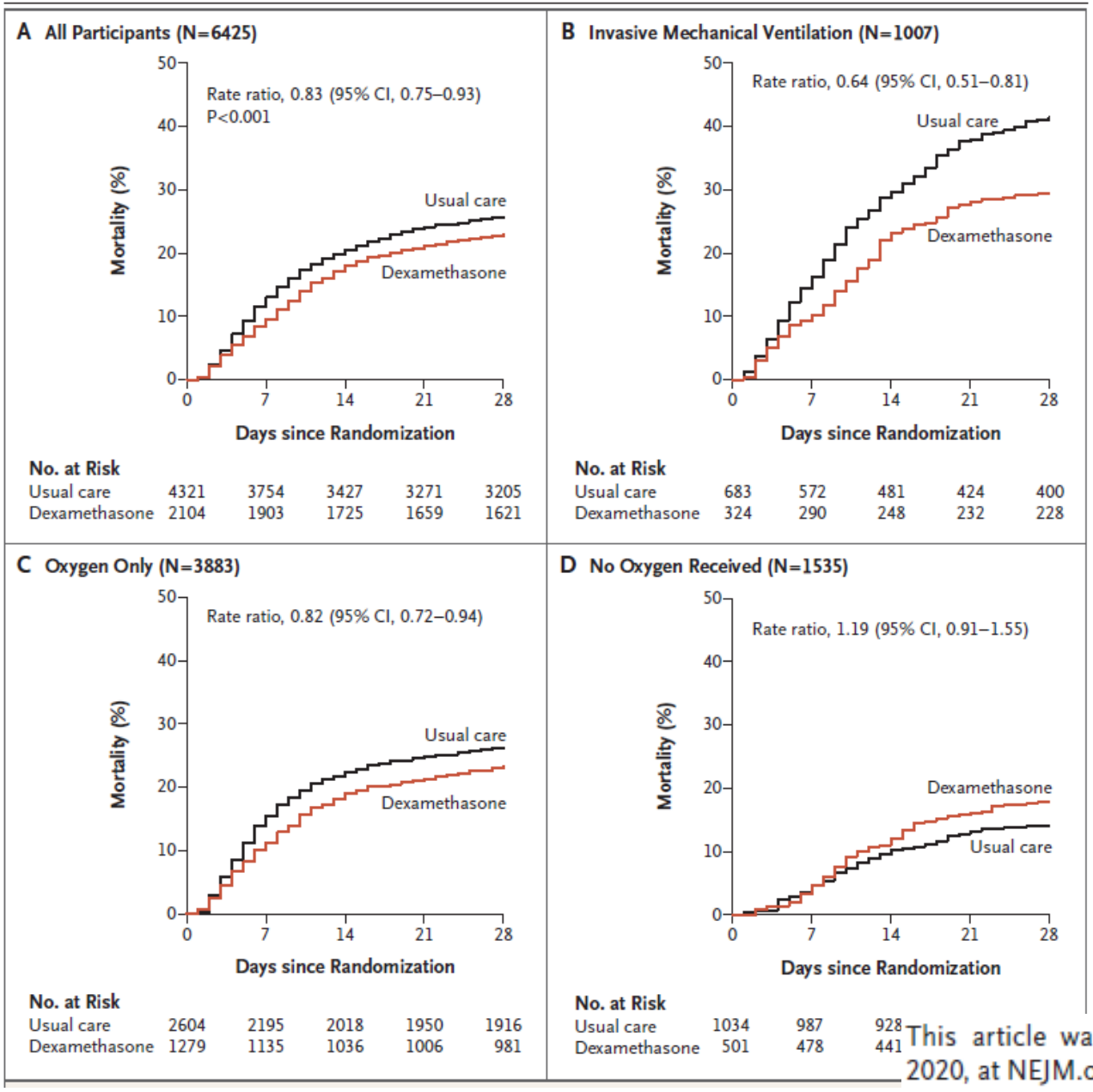
Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.



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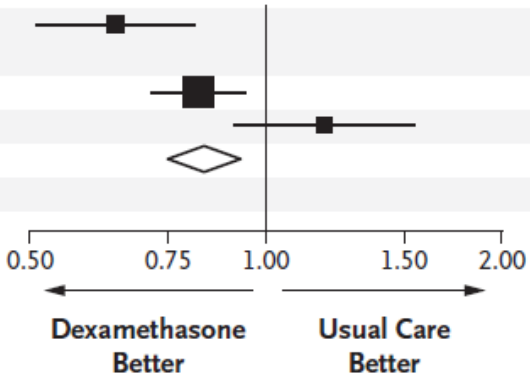
Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

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



Primary and Secondary Outcomes.

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

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Conclusions

- In patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

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The NEW ENGLAND JOURNAL of MEDICINE

Severe Covid-19

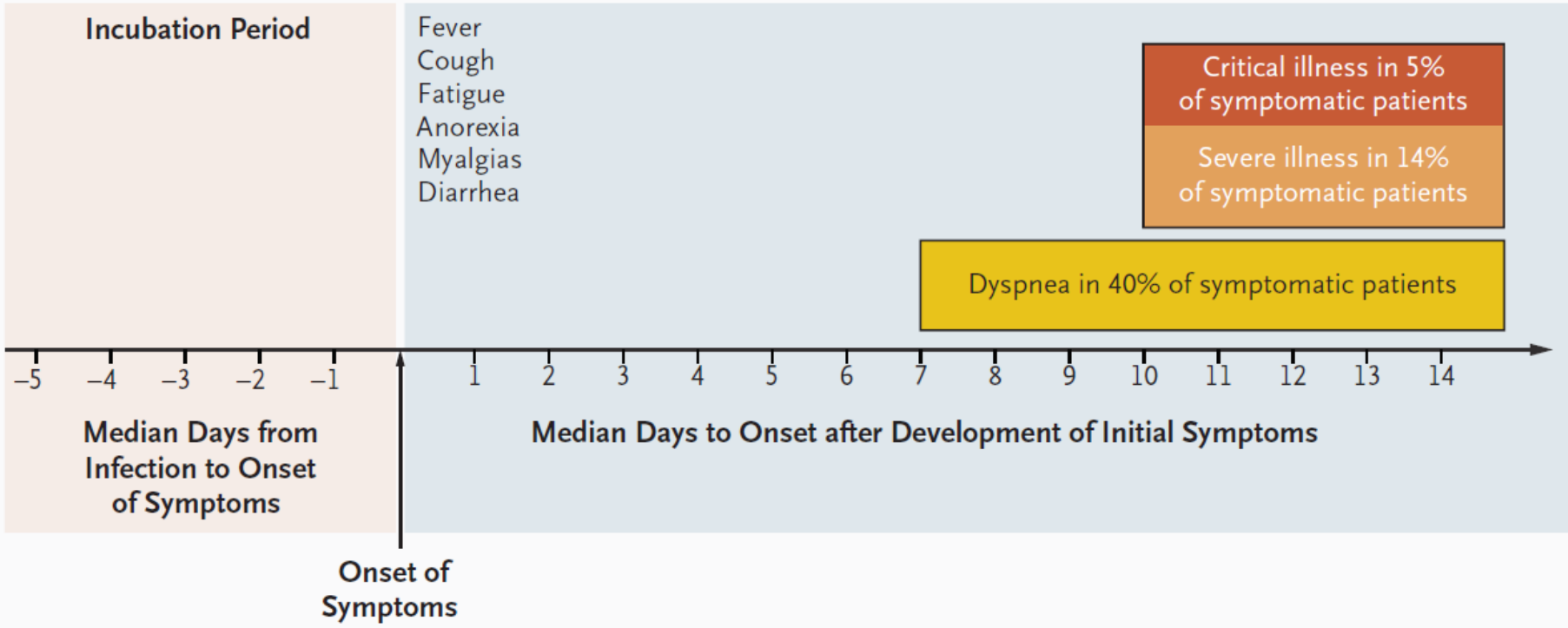

Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

The left border of the colored boxes shows the median time to onset of symptoms and complications. There is wide variation in the duration of symptoms and complications. Adapted from Zhou et al.[2] and the Centers for Disease Control and Prevention.[1]

This article was published on May 15, 2020, at NEJM.org.

KEY CLINICAL POINTS

EVALUATION AND MANAGEMENT OF SEVERE COVID-19

- Patients with severe coronavirus disease 2019 (Covid-19) may become critically ill with acute respiratory distress syndrome that typically begins approximately 1 week after the onset of symptoms.
- Deciding when a patient with severe Covid-19 should receive endotracheal intubation is an essential component of care.
- After intubation, patients should receive lung-protective ventilation with plateau pressure less than or equal to 30 cm of water and with tidal volumes based on the patient's height.
- Prone positioning is a potential treatment strategy for refractory hypoxemia.
- Thrombosis and renal failure are well-recognized complications of severe Covid-19.
- Data are needed from randomized trials to inform the benefits and risks of antiviral or immunomodulatory therapies for severe Covid-19; as of mid-May 2020, no agents had been approved by the Food and Drug Administration for treatment of these patients.
- Preliminary data from a randomized, placebo-controlled trial involving patients with severe Covid-19 suggest that the investigational antiviral remdesivir shortens time to recovery.

This article was published on May 15, 2020, at NEJM.org.

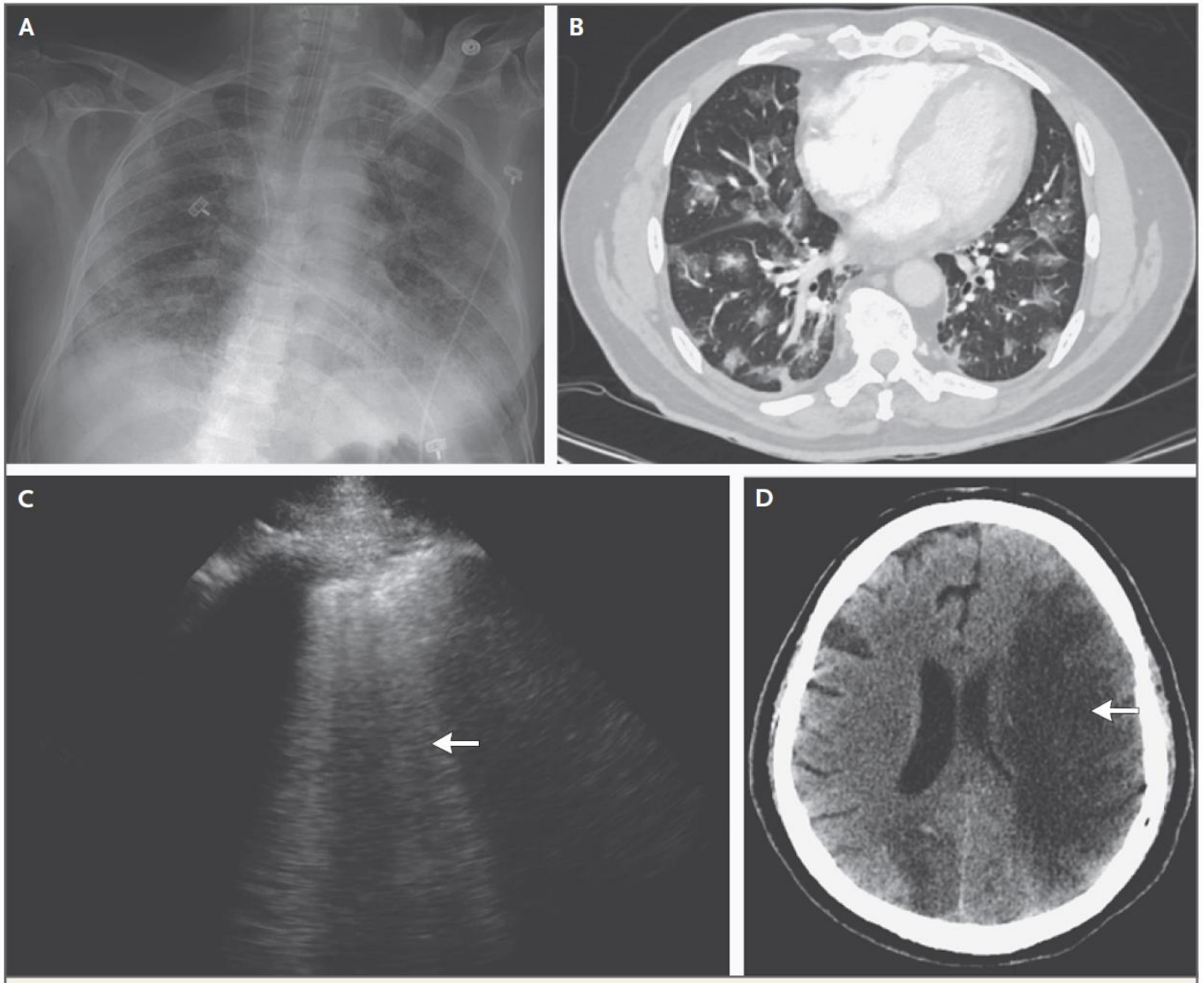

Figure 2. Radiographic and Ultrasonographic Findings of Severe Covid-19.

Chest radiography (Panel A) shows bilateral ground-glass opacities and consolidations. Computed tomography (CT) of the chest (Panel B) shows bilateral ground-glass opacities. Thoracic ultrasonography (Panel C) shows B lines (arrow); this image is courtesy of Dr. Christopher Parkhurst. CT of the head (Panel D) shows left-greater-than-right cerebral infarcts (arrow).

This article was published on May 15, 2020, at NEJM.org.

Figure 3. Invasive Mechanical Ventilation for Covid-19–Related Respiratory Failure.

A Determination of Need for Endotracheal Intubation for Covid-19–Related Respiratory Failure

Possible Clinical Indications for Endotracheal Intubation

- Impending airway obstruction
- Signs of unsustainable work of breathing
- Refractory hypoxemia
- Hypercapnia or acidemia
- Encephalopathy or inadequate airway protection

Additional Considerations

- Does illness trajectory predict deterioration?
- Are difficulties in endotracheal intubation anticipated?
- Is there hemodynamic instability?
- Will intubating now improve the safety of a planned procedure or transportation?
- Will intubating now improve infection control and staff safety?

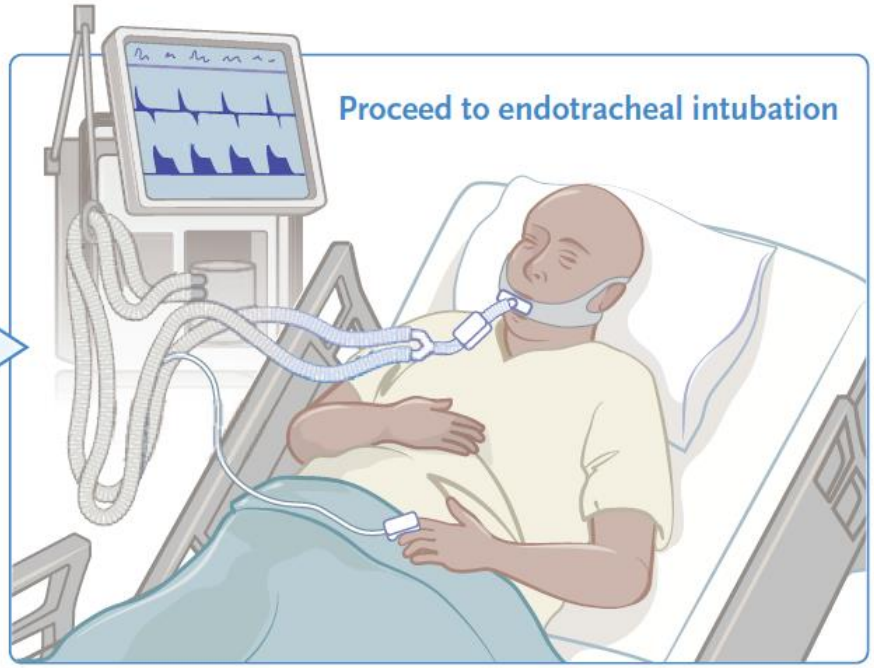

Figure 3. Invasive Mechanical Ventilation for Covid-19–Related Respiratory Failure.

As shown in Panel A, a life-threatening problem in the purple box or a combination of less severe problems in the purple and tan boxes determines the need for endotracheal intubation. In Panel B, "lung derecruitment" refers to the collapse of alveoli. All pressures are measured in the ventilator circuit and referenced to atmospheric pressure. ARDS denotes acute respiratory distress syndrome, and PEEP positive end-expiratory pressure.

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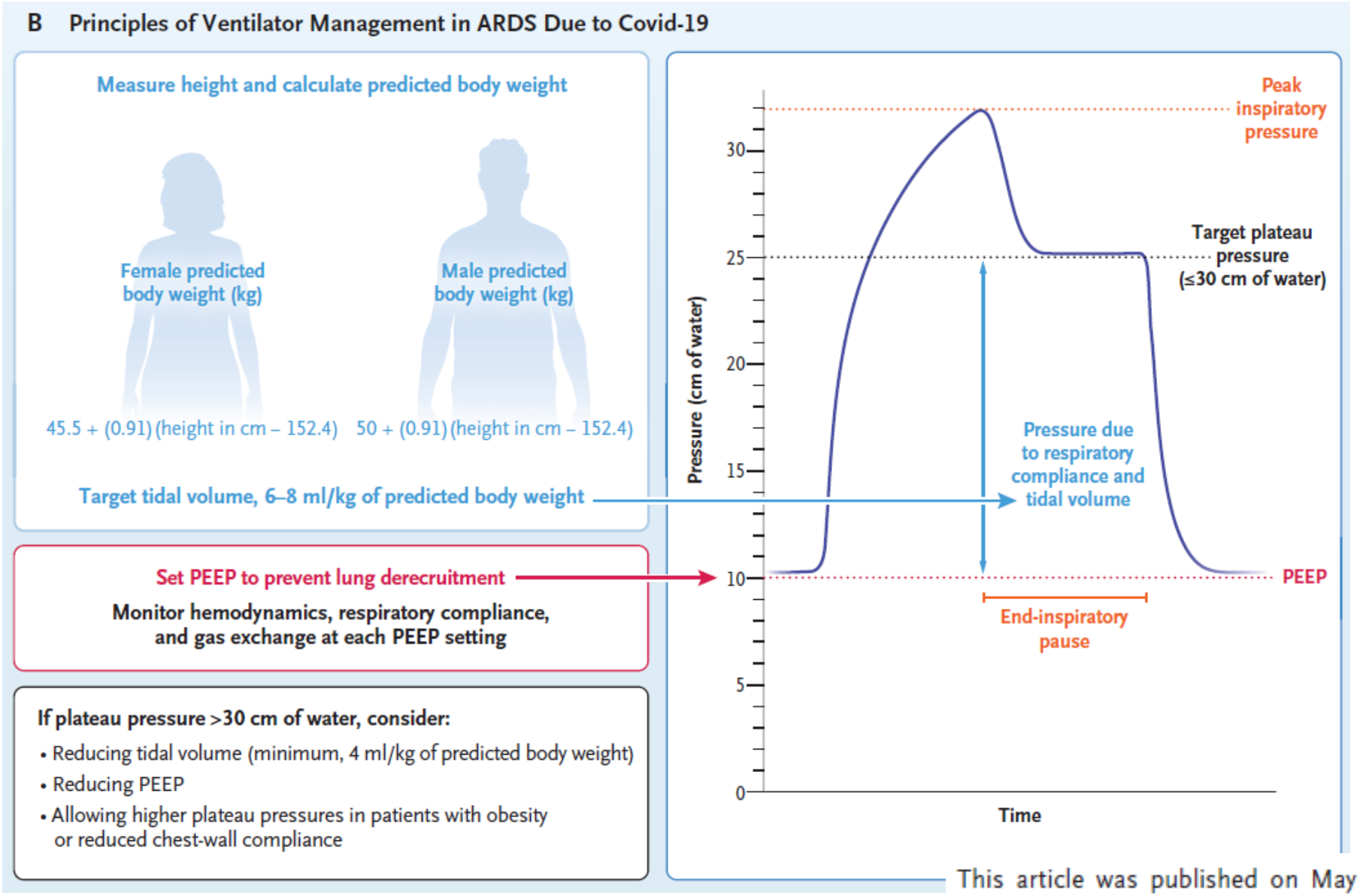
Figure 3. Invasive Mechanical Ventilation for Covid-19–Related Respiratory Failure.



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JAMA Insights | CLINICAL UPDATE

Management of COVID-19 Respiratory Distress

John J. Marini, MD; Luciano Gattinoni, MD

CARDS: COVID-19 related ARDS

JAMA Published online April 24, 2020

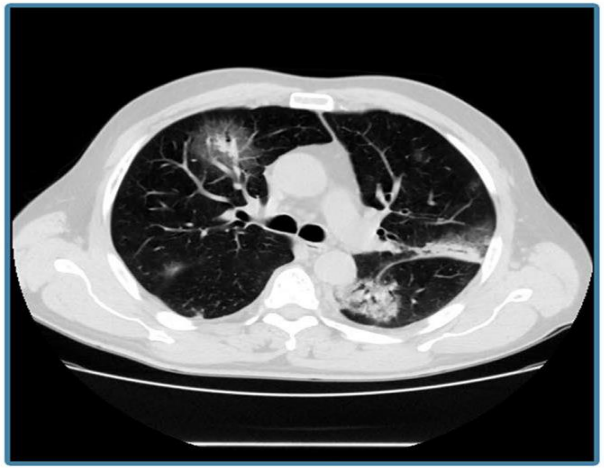
Table. Time Course and Treatment Approach to Ventilation Support for Patients With CARDS

Time period	Objective	Respiratory support options	Rationale
Before intubation	Adequate gas exchange Avoid P-SILI	Supplemental oxygen, CPAP, NIV, HFNC Awake prone positioning, Target nonvigorous breathing	Powerful respiratory effort can cause reinforcing lung and vascular stress, resulting in injury
During mechanical ventilation	Avoid pulmonary deterioration and VILI vortex	Minimize PEEP, frequency and tidal volume Adjust to acceptable gas exchange Maintain fluid balance Reduce O_2 demand Consider ECMO	Minimize transpulmonary and vascular stresses
After intubation	Minimize pulmonary stress Optimize O_2 Avoid VILI vortex	Type L[a]: use lower PEEP (<10 cm H_2O) Use more liberal tidal volume (7-9 mL/kg) as needed Reduce O_2 demand Consider prone positioning	Lower tidal volumes are unnecessary Higher PEEP is ineffective, creates dead space, and adversely redirects blood flow
	Reduce and evenly distribute lung and vascular stresses Optimize O_2 Avoid VILI vortex	Type H[a]: use higher PEEP (<15 cm H_2O) Lower tidal volume (5-7 mL/kg) Reduce O_2 demand Implement prone positioning	More closely behaves and responds like typical ARDS
Weaning phase	Avoid reversion to previously worsened pulmonary state by causing VILI and worsening edema	Make transitions cautiously Avoid abrupt changes Spontaneous trials only at the very end of the weaning process	Strong spontaneous efforts raise O_2 demand, increase edema, and promote P-SILI

COVID-19 pneumonia: different respiratory treatments for different phenotypes?

Luciano Gattinoni[1*], Davide Chiumello[2], Pietro Caironi[3,4], Mattia Busana[1], Federica Romitti[1], Luca Brazzi[5] and Luigi Camporota[6]

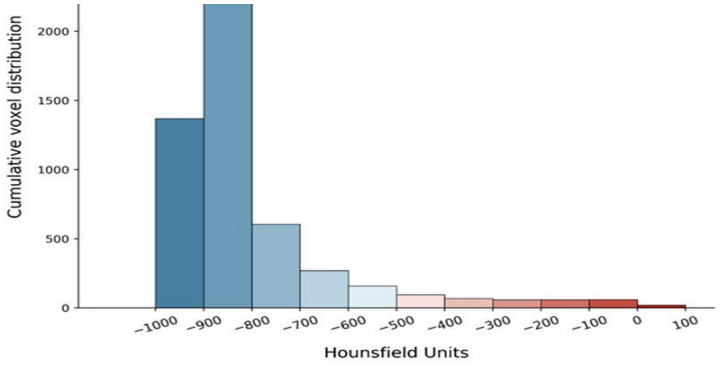
A



COVID-19 pneumonia, Type L

At the beginning, COVID-19 pneumonia presents with the following characteristics:

PaO_2/FiO_2
95 mmHg



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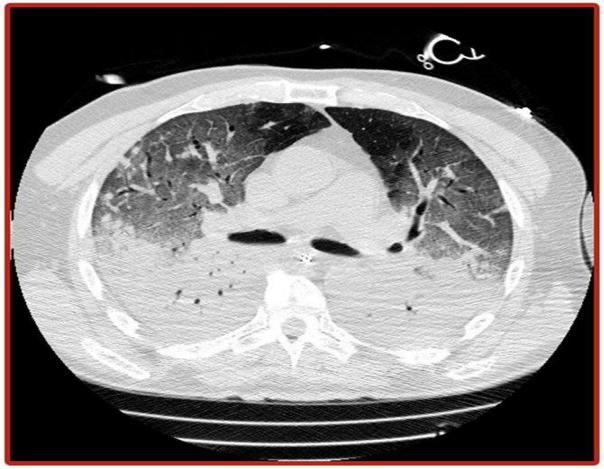
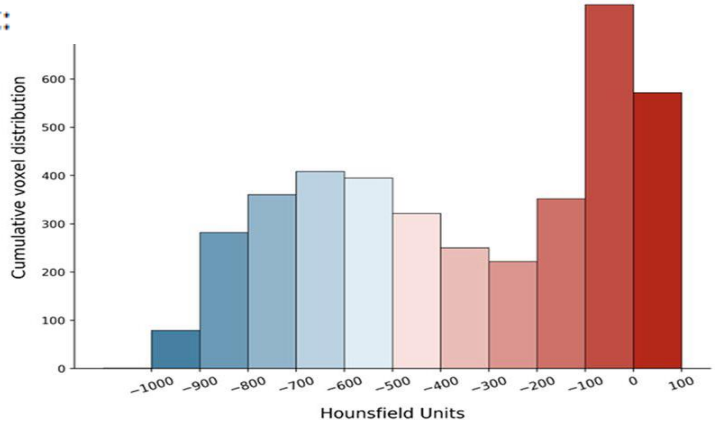


COVID-19 pneumonia, Type H

The Type H patient:

PaO_2/FiO_2
84 mmHg



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COVID-19 pneumonia: ARDS or not?

Luciano Gattinoni[1*], Davide Chiumello[2] and Sandra Rossi[3]

Non ARDS

ARDS

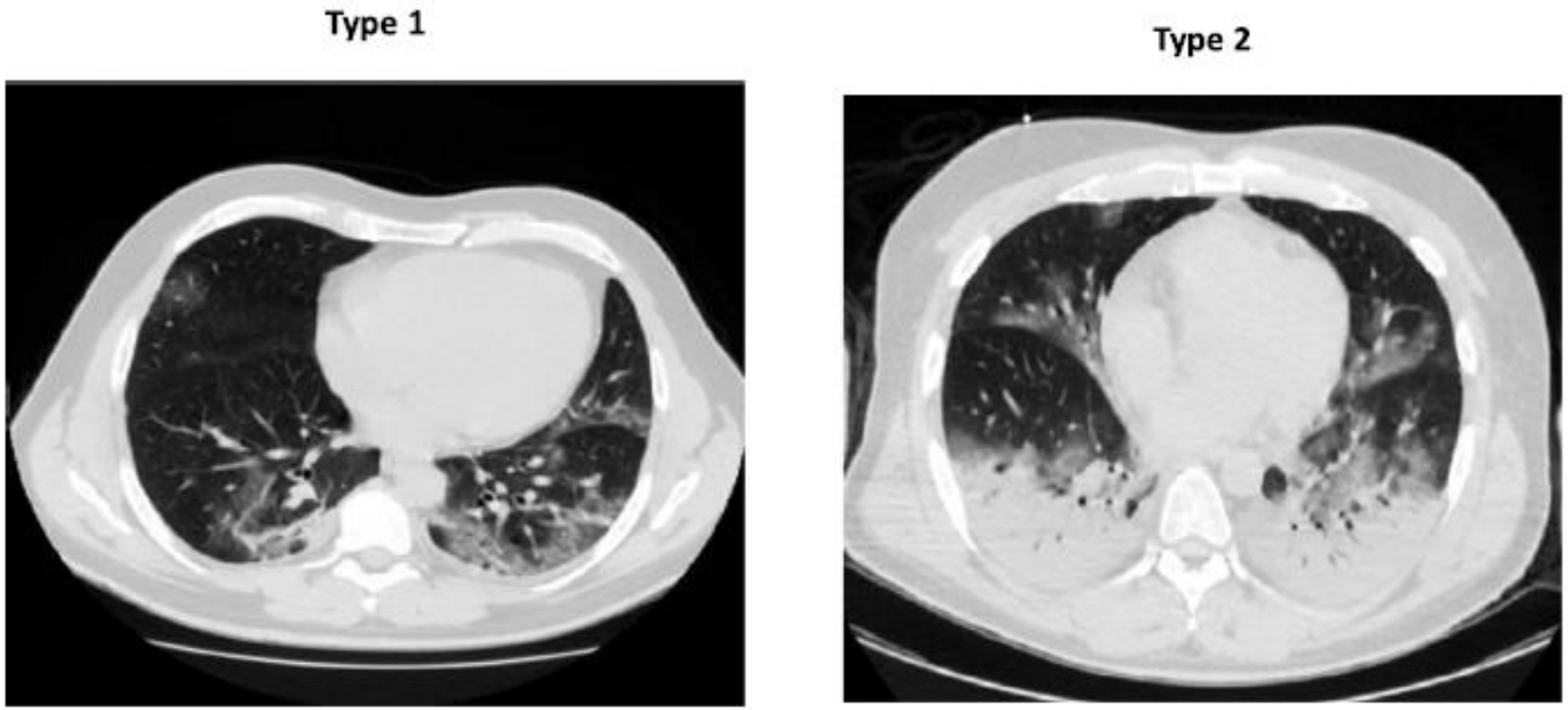


Fig. 1 In these 2 patients were recorded the following variables: type 1 lung weight (1192 g), gas volume (2774 ml), percentage of non-aerated tissue (8.4%), venous admixture (56%), P/F (68), and respiratory system compliance (80 ml/cmH_2O); type 2 lung weight (1441 g), gas volume (1640 ml), percentage of non-aerated tissue (39%), venous admixture (49%), P/F (61), and respiratory system compliance (43 ml/cmH_2O)

COVID-19 pneumonia: different respiratory treatments for different phenotypes?

Luciano Gattinoni[1*], Davide Chiumello[2], Pietro Caironi[3,4], Mattia Busana[1], Federica Romitti[1], Luca Brazzi[5] and Luigi Camporota[6]

L type (type 1)

- Characteristics: vasoplegia (lose of vasoconstriction when hypoxemia)
  - Low elastance (High compliance)
  - Low V/Q
  - Low Lung weight
  - Low Recruitability
  - Poor response to PEEP
- Treatment and Management:
  - Increase FiO2 to improve hypoxemia
  - Early intubation if necessary
- MV setting
  - TV: 7-9 ml/PBW
  - PEEP: 8-10 cmH2O
  - RR =< 20

H type (type 2)

- Characteristics:
  - High elastance (Low compliance)
  - High Shunting
  - High Lung weight
  - High Recruitability
  - Response to PEEP
- Treatment and Management:
  - As severe ARDS
    - Low TV, High PEEP, NMB, RM, iNO, PP, ECMO…

Gattinoni *et al. Critical Care* (2020) 24:154

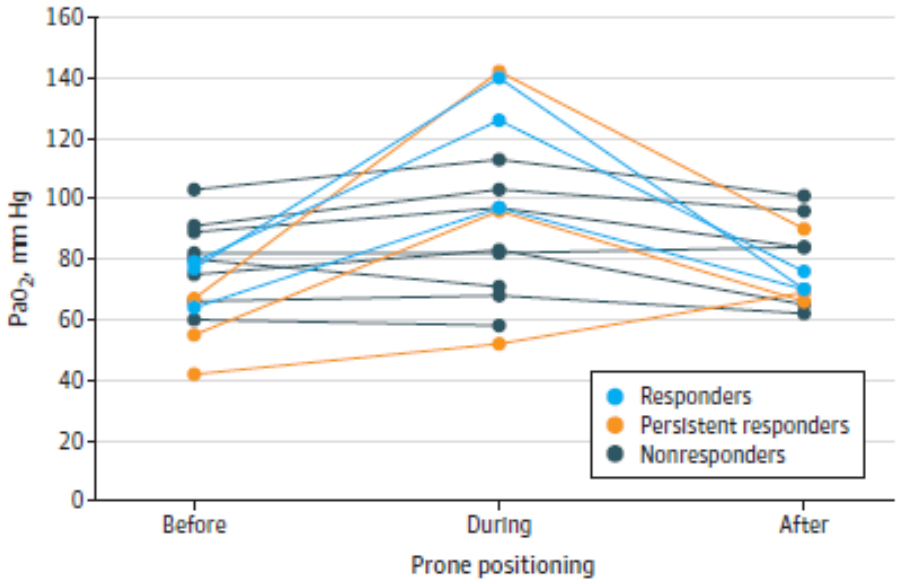
Prone ventilation in COVID-19

Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure

Table. Characteristics of Patients and Main Results

Characteristic	Total (N = 24)[a]	PP subgroups <1 h (n = 4)	1-<3 h (n = 5)	≥3 h (n = 15)
Baseline characteristics				
Age, mean (SD), y	66.1 (10.2)	63.8 (7.8)	61 (7.9)	68.4 (11.1)
Sex, No. (%)				
Women	8 (33)	2 (50)	1 (20)	5 (33)
Men	16 (67)	2 (50)	4 (80)	10 (67)
BMI >30, No. (%)	5 (23)	1 (50)	1 (20)	3 (20)
High blood pressure, No. (%)	6 (26)	1 (25)	2 (50)	3 (20)
SOFA score, mean (SD)	2.8 (0.9)	3.5 (0.7)	2.8 (0.8)	2.7 (1)
Oxygen supplementation, No. (%)				
<4 L/min	16 (67)	2 (50)	3 (60)	11 (73)
≥4 L/min or HFNC	8 (33)	2 (50)	2 (40)	4 (27)
Respiratory rate, mean (SD), breaths/min	18 (2.7)	18.3 (4)	20 (3.6)	17.3 (1.8)
Gas exchange and VAS scores before PP				
Pao_2, mean (SD), mm Hg	72.8 (14.2)	79.7 (11.7)	66.4 (8.9)	73.6 (15.9)
$Paco_2$, mean (SD), mm Hg	34.1 (5.3)	39.7 (4.6)	32.4 (3.9)	33.5 (5.4)
VAS, median (IQR)[b]				
Dyspnea	3 (2-5)	3 (1-3)	5 (3-7)	2 (1-5)
Discomfort	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)
Gas exchange and VAS scores during PP[c]				
Pao_2, mean (SD), mm Hg	91 (27.3)		73 (12.1)	94.9 (28.3)
$Paco_2$, mean (SD), mm Hg	32.8 (4.5)		32 (3)	33 (4.8)
VAS, median (IQR)[b]				
Dyspnea	2 (1-4.5)		7 (2-8)	2 (1-4)
Discomfort	4 (1-5.5)		2 (2-4)	4 (1-6)
Gas exchange and VAS scores after resupination[c]				
Pao_2, mean (SD), mm Hg	77.6 (11.5)		77 (2)	77.8 (13)
$Paco_2$, mean (SD), mm Hg	32.3 (5.1)		28.7 (5.9)	33.3 (4.7)
VAS, median (IQR)[b]				
Dyspnea	2.5 (1-5)		5 (4-7)	2 (1-4)
Discomfort	0 (0-1)		0 (0-1)	0 (0-1)

Figure. Individual Partial Pressure of Arterial Oxygen (Pao_2) Variation for Patients Who Sustained Prone Positioning (PP) for at Least 3 Hours



During PP indicates the 1 to 2 hours after proning and after PP indicates the 6 to 12 hours after resupination. Responders to PP = Pao_2 increase ≥20% between before and during PP. Persistent responders to PP = Pao_2 increase ≥20% between before PP and after resupination. All the persistent responders are also responders. One patient among the 15 refused arterial blood gases during PP and after resupination. For 2 patients, arterial blood gases after resupination were missing.

Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit

Table. Baseline Characteristics of 15 Patients With COVID-19 Who Received Noninvasive Ventilation in the Prone Position Outside the ICU

Characteristics	Value
Age, mean (SD), y	59 (6.5)
BMI, mean (SD)	24 (3.4)
Sex, No. (%)	
Women	2 (13.3)
Men	13 (86.6)
Time, median (IQR), d	
From first symptom appearance	15 (12-21)
From hospitalization	9 (7.5-14)
From NIV start	7 (4-10)
From NIV in the prone position start	5 (3-10)
Pao_2:Fio_2 on first MET call[a]	157 (43.0)

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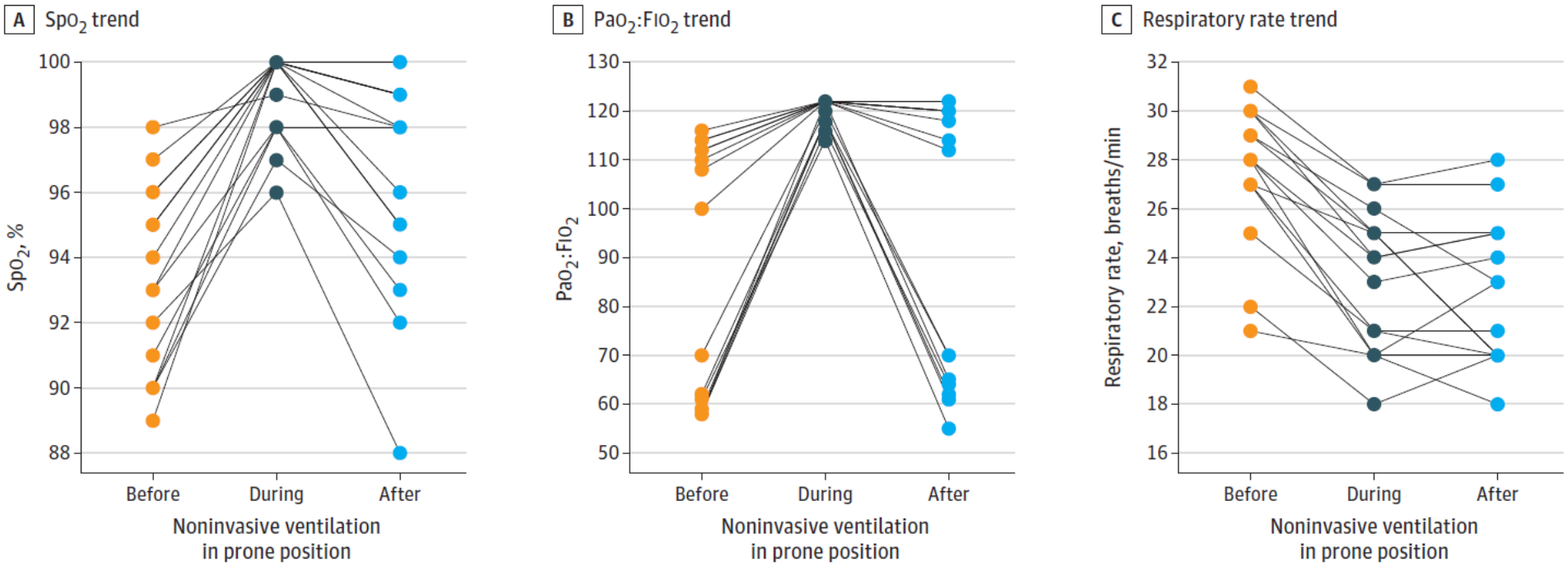
Figure. Respiratory Parameters in the Individual Patients Before, During, and After Noninvasive Ventilation in the Prone Position



The graphs represent trends of respiratory parameters in the individual patient at the 3 time points. Before pronation: immediately before initiating noninvasive ventilation (NIV) while the patient was still in the supine position. During pronation: after 1 hour of receiving NIV treatment while the patient was in the prone position. After pronation: 1 hour after NIV treatment stopped when the patient was in the supine position. A, Peripheral oxygen saturation (Spo_2), $P < .001$ between before and during pronation, $P < .004$ between before and after pronation. B, Arterial partial pressure of oxygen (Pao_2) to inspired oxygen fraction (Fio_2), $P < .001$ between before and during pronation, $P < .004$ between before and after pronation. C, Respiratory rate $P < .001$ between before and during pronation, $P < .001$ between before and after pronation.

Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19?

Irene Telias, MD; Bhushan H. Katira, MD; Laurent Brochard, MD

A substantial proportion of patients with coronavirus disease 19 (COVID-19) develop severe respiratory failure and require mechanical ventilation, most often fulfilling criteria for acute respiratory distress syndrome (ARDS).[1] The characteristics of these patients are heterogeneous, consistent with what is known about ARDS.[1,2] Inflammatory edema leads to varying degrees of lung collapse resulting in ventilation perfusion ratio ($\dot{V}/\dot{Q}$) mismatching, including a significant shunt fraction. Additionally, lung microthrombi are suspected and result in different levels of dead space and inefficient ventilation.[3] In sedated patients, gravitational forces lead to lung atelectasis occurs in the dependent lung regions, and the remaining aerated lung available for gas exchange becomes small. Insufficient hypoxic vasoconstriction, another feature of ARDS that contributes to $\dot{V}/\dot{Q}$ mismatch, is suggested by the finding of hypoxemia with relatively preserved compliance in some patients.[4]

Related articles

Vigorous breathing efforts among patients with moderate and severe ARDS during spontaneous or assisted invasive or noninvasive ventilation (NIV) can worsen lung injury and result in patient self-inflicted lung injury (P-SILI).[5] Strong respiratory efforts lead to large negative swings in pleural pressure generating excessive lung stress and strain and to increased lung edema due to negative transalveolar pressure. Because of atelectasis in the dependent regions, the force generated by diaphragmatic contractions remains predominantly localized in regions close to the muscular portion of the diaphragm and generates a pressure gradient inside the lung, with displacement of gas from nondependent to dependent areas. This phenomenon, called *pendelluft*, increases regional lung stress and strain even in the absence of large tidal volumes.[6]

Strong breathing efforts are controlled by the output of the respiratory centers, the respiratory drive, primarily regulated by the chemoreflex control system.[7] The combination of a high metabolic rate (eg, sepsis, fever) and inefficient ventilation increases respiratory drive. Additionally, lung injury, through J receptors in the lung, and systemic or brainstem inflammation stimulate the respiratory drive. A dissociation between what the brain expects and what the ventilatory system can achieve results in dyspnea that further stimulates the respiratory drive. Excessive drive can then overcome lung-protective reflexes, such as Hering-Breuer inflation reflex, and worsen lung injury.

In the context of worsening oxygenation and increased work of breathing, invasive mechanical ventilation with sedation, paralysis, and positive end-expiratory pressure to control breathing effort ensures lung protective ventilation (ie, low tidal volume) minimizing P-SILI.[5] However, potential adverse consequences are well known including immobilization, disuse diaphragmatic atrophy, associated infections, sleep disturbances, and possibly neurocognitive dysfunction. Helmet NIV and high-flow nasal cannula-delivered oxygen were suggested to be clinically more effective than NIV delivered via facemask and regular oxygen in early hypoxemic respiratory failure.[8] However, monitoring tidal volume and breathing effort in these patients is challenging with the potential risk of direct harm and delayed intubation, as shown during NIV. During the COVID-19 pandemic, high burden of intensive care unit workload and concern for possible ventilator shortage further prompted clinicians to pursue alternative strategies to avoid intubation.

In this issue of *JAMA*, 2 small case series describe the use of the prone position in awake patients with COVID-19 during spontaneous and assisted breathing outside the ICU. The studies have limitations but illustrate interesting points. Elharrar et al[9] reported a single-center before-after study that included 24 patients with acute hypoxemic respiratory failure and infiltrates on chest computed tomographic scans. Prone positioning was started without changing the system for oxygen supply or fraction of inspired oxygen (F_{IO_2}). Four patients did not tolerate the prone position for more than an hour (requiring later intubation); 6 of 15 patients who tolerated prone position showed a mean (SD) increase in Pa_{O_2} of more than 20% from baseline (74 [16] to 95 [28] mm Hg; $P = .006$) but 3 patients returned to baseline Pa_{O_2} after supination.

Sartini et al[10] performed a 1-day cross-sectional before-after study that included 15 awake patients with mild and moderate ARDS. The estimated mean (SD) Pa_{O_2}:F_{IO_2} was 157 (43). Patients received NIV with sessions of prone positioning after poor response to continuous positive airway pressure (CPAP) of 10 cm H_2O. On the day of the study, the patients had a median of 2 sessions (interquartile range [IQR], 1-3) of prone positioning for 3 hours (IQR, 1-6 hours). Compared with before receiving NIV, oxygenation and respiratory rate improved during NIV while prone (estimated Pa_{O_2}:F_{IO_2}, 100 [IQR, 60-112] to 122 [IQR, 118-122] and respiratory rate 28 breaths/min [IQR, 27-30] to 24 [21-25] breaths/min), and remained improved 1 hour after NIV session in prone position in most patients (12 of 15). At 14 days, 1 patient was intubated and another died.

Several conclusions can be drawn cautiously from these case series, although the findings cannot be generalized without confirmation in larger trials. Many but not all patients with hypoxemic respiratory failure tolerate the prone position while awake, breathing spontaneously or while receiving NIV. Among patients who tolerated a session of prone positioning, improvement in oxygenation and decrease in respiratory rate occurred, suggesting a lower power of breathing (respiratory rate is poorly correlated with respiratory drive but in this context, it is potentially associated with lower power). The effects were transient, and respiratory rates and oxygenation often returned to baseline after supination.

Limitations have been listed by the authors, including the small sample size and lack of control groups. Overall, prone sessions during the studies were short, partly because of limited patient tolerance. Important information for interpretation of the results was missing such as baseline severity of hypoxemia[9] and which NIV interface and settings were used during the prone sessions.[10] It is also unclear if the physiological changes while prone were due to the position, the use of NIV, or a synergistic effect of both. The inclusion of patients who initially worsened after a trial of CPAP may suggest that the prone position improved tolerance of NIV.

The prone position can improve oxygenation and can potentially result in less injurious ventilation. Because of a higher density of pulmonary vessels in the dorsal lung region (independently of gravity), the change of ventilation distribution while prone (ie, relative increase in ventilation in the dorsal nondependent areas) results in improved $\dot{V}/\dot{Q}$ matching and oxygenation.[11] This does not necessarily equate to lung protection and better outcome.[12] While prone, the chest wall compliance decreases when the anterior, more flexible part of the chest is facing the bed, explaining in part a more homogeneous distribution of ventilation and regional lung stress and decreasing the risk of ventilation-induced lung injury and possibly pendelluft.[13] It is possible that the contraction of the muscular diaphragm, which faces the open dorsal lung during pronation exerts a more uniform distribution of stress, whereas the muscular diaphragm exerts a more localized stress when facing the collapsed lung during supination. These mechanisms and the effect of prone positioning on respiratory drive and effort need to be investigated in spontaneously breathing patients. In a crossover study involving 14 infants with bronchiolitis, the prone position with nasal CPAP reduced effort and improved neuromechanical coupling.[14]

Prone position during invasive mechanical ventilation improved oxygenation in large randomized clinical trials (RCTs) of patients with ARDS.[15] However, better oxygenation was not associated with improved survival in trials with short duration of prone positioning. In an RCT that included 466 patients with moderate and severe ARDS (Pa_{O_2}:F_{IO_2} <150), prone positioning for at least 16 hours per day with protective mechanical ventilation reduced 90-day mortality.[16] Previously, small case series showed feasibility and improvement in oxygenation in awake patientsplaced in the prone position during spontaneous or assisted breathing while receiving NIV and oxygen through high-flow nasal cannula.

The prone position during spontaneous and assisted breathing in patients with acute hypoxemic respiratory failure may become a therapeutic intervention in the near future. Tolerance is sometimes a limitation of the technique, the physiological effects are not clarified, and the benefits of very short sessions may be questionable. Can the prone position prevent intubation? This question is essential, but intubation is a medical decision, not a physiological state. Improvement in oxygenation during prone positioning may prevent clinicians from making decisions about intubation solely based on hypoxemia. This is potentially a good outcome, but clinical assessment of work of breathing is essential in this context to avoid delayed intubation with eventually poor outcome. A detailed physiological study is ongoing (NCT03095300) and at least 2 RCTs (NCT04347941, NCT04350723) will address some of these questions. In the meantime, clinicians should closely monitor patients for whom prone positioning is used for tolerance and response and aim to prevent delayed intubation and controlled mechanical ventilation when necessary.

Clinical management of COVID-19

Interim guidance
27 May 2020

World Health Organization

Contents

Table 2. COVID-19 disease severity

Mild disease		Symptomatic patients (Table 1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. See the WHO website for most up-to-date case definitions *(1)*.
Moderate disease	**Pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 90% on room air *(54)*. **Child** with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(55)*.
		While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe disease	**Severe pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 < 90% on room air *(54)*. **Child** with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: • Central cyanosis or SpO_2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions *(55,56)*. • Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(55)*. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

Critical disease	**Acute respiratory distress syndrome (ARDS)** ***(57-59)***	**Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging:** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. **Oxygenation impairment in adults** *(57, 59)*: • Mild ARDS: 200 mmHg < PaO_2/FiO_2[a] ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O).[b] • Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O).[b] • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O).[b] **Oxygenation impairment in children:** note OI and OSI.[c] Use OI when available. If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SpO_2/FiO_2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤ 264. • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5. • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3. • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.

Critical disease	**Sepsis** *(3,4)*	**Adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output *(3)*, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia. **Children:** suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria,[e] of which one must be abnormal temperature or white blood cell count.
	Septic shock *(3,4)*	**Adults:** persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children:** any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia *(60, 61)*.

Other complications that have been described in COVID-19 patients include acute, life-threatening conditions such as: acute pulmonary embolism, acute coronary syndrome, acute stroke and delirium. Clinical suspicion for these complications should be heightened when caring for COVID-19 patients, and appropriate diagnostic and treatment protocols available.

Complications: Acute Pulmonary Embolism, Acute Coronary Syndrome, Acute Stroke, Delirium

8. Management of severe COVID-19: severe pneumonia treatment

- All areas where severe patients may be cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask, and mask with reservoir bag).

- We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs and to any patient without emergency signs and $SpO_2 < 90\%$.

- Closely monitor patients for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock and respond immediately with supportive care interventions.

- Use cautious fluid management in patients with COVID-19 without tissue hypoperfusion and fluid responsiveness.

9. Management of critical COVID-19: acute respiratory distress syndrome (ARDS)

The following recommendations pertain to adult and paediatric patients with mild ARDS who are treated with non-invasive or high-flow nasal oxygen (HFNO) systems.

In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used. Refer to Table 2 for definitions of mild, moderate and severe ARDS.

The following recommendations pertain to adult and paediatric patients with ARDS who need intubation and invasive mechanical ventilation.

We recommend prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support.

We recommend that endotracheal intubation be performed by a trained and experienced provider using airborne precautions.

The following recommendations pertain to mechanically ventilated adult and paediatric patients with ARDS *(3, 92)*.

- **We recommend implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH_2O).**

- **In adult patients with severe ARDS (PaO_2/FiO_2 < 150) prone ventilation for 12–16 hours per day is recommended.**

- **Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness.**

- **In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where during titration the patient is monitored for effects (beneficial or harmful) and driving pressure.**

In patients with moderate-severe ARDS (PaO_2/FiO_2 < 150), neuromuscular blockade by continuous infusion should not be routinely used.

Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis and increased risk of infection of health care workers.

In patients with excessive secretions, or difficulty clearing secretions, consider application of airway clearance techniques. These should be performed only if deemed medically appropriate *(81)*.

The following recommendations pertain to adult and paediatric patients with ARDS in whom lung protective ventilation strategy fails to achieve adequate oxygenation and ventilation.

In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxaemia (e.g. including a ratio of partial pressure of arterial oxygen [PaO_2] to the fraction of inspired oxygen [FiO_2] of < 50 mmHg for 3 hours, a PaO_2:FiO_2 of < 80 mmHg for > 6 hours) despite lung protective ventilation.

12. Antivirals, immunomodulators and other adjunctive therapies for COVID-19

We recommend that the following drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials:

- Chloroquine and hydroxychloroquine (+/- azithromycin), including but not limited to:
- Antivirals, including but not limited to:
  - Lopinavir/ritonavir
  - Remdesivir
  - Umifenovir
  - Favipiravir
- Immunomodulators, including but not limited to:
  - Tocilizumab
  - Interferon-β-1a
- Plasma therapy.

13. Corticosteroid therapy and COVID-19

We recommend against the routine use of systemic corticosteroids for treatment of viral pneumonia.

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

(1) Infection control

(2) Lab. Diagnosis

(3) Hemodynamic support

(4) Ventilatory support

(5) COVID-19 therapy

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Ventilation:

23	In adults with COVID-19, we ***suggest*** starting supplemental oxygen if the peripheral oxygen saturation (Spo_2) is < 92%, and ***recommend*** starting supplemental oxygen if Spo_2 is < 90%	Weak Strong
24	In adults with COVID-19 and **acute hypoxemic respiratory failure on oxygen**, we ***recommend*** that Spo_2 be maintained no higher than 96%.	Strong
25	For adults with COVID-19 and **acute hypoxemic respiratory failure** despite conventional oxygen therapy, we ***suggest*** using HFNC over conventional oxygen therapy.	Weak
26	In adults with COVID-19 and **acute hypoxemic respiratory failure**, we ***suggest*** using HFNC over NIPPV.	Weak
27	In adults with COVID-19 and **acute hypoxemic respiratory failure**, if HFNC is not available and there is no urgent indication for endotracheal intubation, we ***suggest*** a trial of NIPPV with close monitoring and short-interval assessment for worsening of respiratory failure.	Weak
28	**We were not able to make a recommendation** regarding the use of helmet NIPPV compared with mask NIPPV. It is an option, but we are not certain about its safety or efficacy in COVID-19.	No recommendation
29	In adults with COVID-19 receiving NIPPV or HFNC, we ***recommend*** close monitoring for worsening of respiratory status, and early intubation in a controlled setting if worsening occurs.	Best practice statement
30	In mechanically ventilated adults with COVID-19 and ARDS, we ***recommend*** using low tidal volume (Vt) ventilation (Vt 4-8 mL/kg of predicted body weight), over higher tidal volumes (Vt>8 mL/kg).	Strong
31	For mechanically ventilated adults with COVID-19 and **ARDS**, we ***recommend*** targeting plateau pressures (Pplat) of < 30 cm H_2O.	Strong
32	For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, we ***suggest*** using a higher PEEP strategy, over a lower PEEP strategy. **Remarks**: If using a higher PEEP strategy (i.e., PEEP > 10 cm H_2O), clinicians should monitor patients for barotrauma.	Strong
33	For mechanically ventilated adults with COVID-19 and ARDS, we ***suggest*** using a conservative fluid strategy over a liberal fluid strategy.	Weak
34	For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**, we ***suggest*** prone ventilation for **12 to 16 hours**, over no prone ventilation.	Weak

35.1	For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**, we ***suggest*** using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA), over continuous NMBA infusion, to facilitate protective lung ventilation.	Weak
35.2	In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, we ***suggest*** using a continuous NMBA infusion for up to 48 hours.	Weak
36	In mechanically ventilated adults with COVID-19 ARDS, we ***recommend against*** the routine use of inhaled nitric oxide.	Weak
37	In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, we ***suggest*** a trial of inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off.	Weak
38	For mechanically ventilated adults with COVID-19 and hypoxemia despite optimizing ventilation, we ***suggest*** using recruitment maneuvers, over not using recruitment maneuvers.	Weak
39	If recruitment maneuvers are used, we ***recommend against*** using staircase (incremental PEEP) recruitment maneuvers.	Strong
40	In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, we ***suggest*** using venovenous (VV) ECMO if available, or referring the patient to an ECMO center. **Remark**: Due to the resource-intensive nature of ECMO, and the need for experienced centers and healthcare workers, and infrastructure, ECMO should only be considered in carefully selected patients with COVID-19 and severe ARDS.	Weak

Summary of recommendations on the management of patients with COVID-19 and ARDS

COVID-19 with mild ARDS

DO:
Vt 4-8 ml/kg and P_{plat} <30 cm H_2O

DO:
Investigate for bacterial infection

DO:
Target SpO2 92% - 96%

CONSIDER:
Conservative fluid strategy

CONSIDER:
Empiric antibiotics

UNCERTAIN:
Systemic corticosteroids

COVID-19 with mod to severe ARDS

CONSIDER:
Higher PEEP

CONSIDER:
NMBA boluses to facilitate ventilation targets

CONSIDER: if PEEP responsive
Traditional recruitment maneuvers

CONSIDER:
Prone ventilation 12 -16 h

CONSIDER: if proning, high P_{plt}, asynchrony
NMBA infusion for 24 h

DON'T DO:
Staircase recruitment maneuvers

CONSIDER:
Short course of systemic corticosteroids

UNCERTAIN:
Antivirals, chloroquine, anti-IL6

Rescue/adjunctive therapy

UNCERTAIN:
Antivirals, chloroquine, anti-IL6

CONSIDER: if proning, high P_{plt}, asynchrony
NMBA infusion for 24 h

CONSIDER:
Prone ventilation 12 -16 h

CONSIDER: STOP if no quick response
A trial of inhaled nitric oxide

CONSIDER: follow local criteria for ECMO
V-V ECMO or referral to ECMO center

Mod = moderate
ARDS = adult respiratory distress syndrome
P_{plat} = plateau pressure
SpO2 = peripheral capillary oxygen saturation
PEEP = positive end-expiratory pressure
NMBA = neuromuscular blocking agents
ECMO = extracorporeal membrane oxygenation

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Summary

COVID-19 pneumonia: different respiratory treatments for different phenotypes?

Luciano Gattinoni[1*], Davide Chiumello[2], Pietro Caironi[3,4], Mattia Busana[1], Federica Romitti[1], Luca Brazzi[5] and Luigi Camporota[6]

L type (type 1)

- Characteristics: vasoplegia (lose of vasoconstriction when hypoxemia)
  - Low elastance (High compliance)
  - Low V/Q
  - Low Lung weight
  - Low Recruitability
  - Poor response to PEEP
- Treatment and Management:
  - Increase FiO2 to improve hypoxemia
  - Early intubation if necessary
- MV setting
  - TV: 7-9 ml/PBW
  - PEEP: 8-10 cmH2O
  - RR =< 20

H type (type 2)

- Characteristics:
  - High elastance (Low compliance)
  - High Shunting
  - High Lung weight
  - High Recruitability
  - Response to PEEP
- Treatment and Management:
  - As severe ARDS
    - Low TV, High PEEP, NMB, RM, iNO, PP, ECMO…

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Thank you for your attention !

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