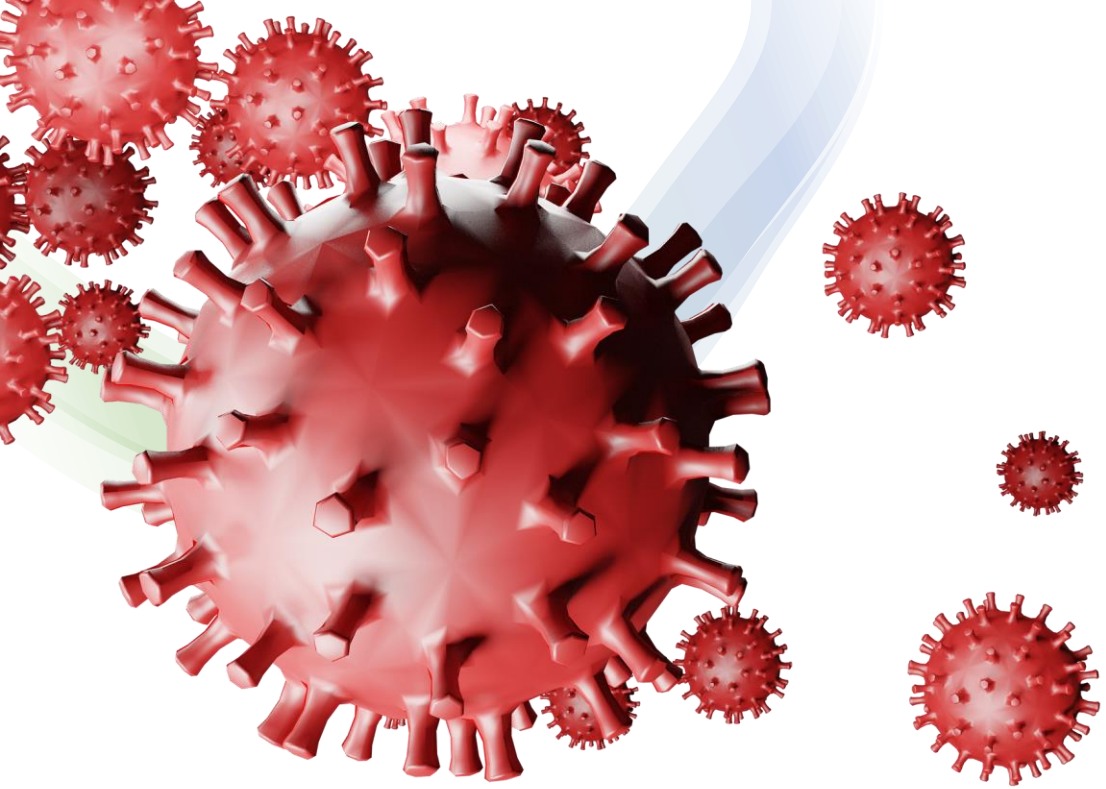

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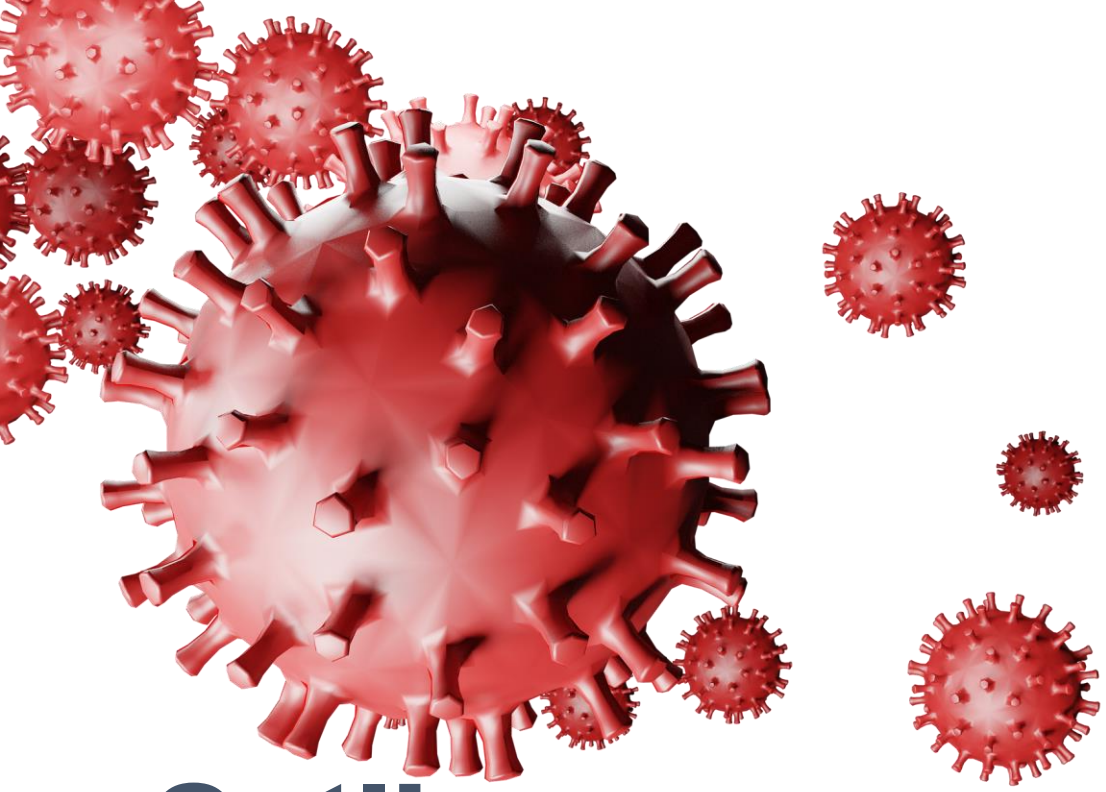
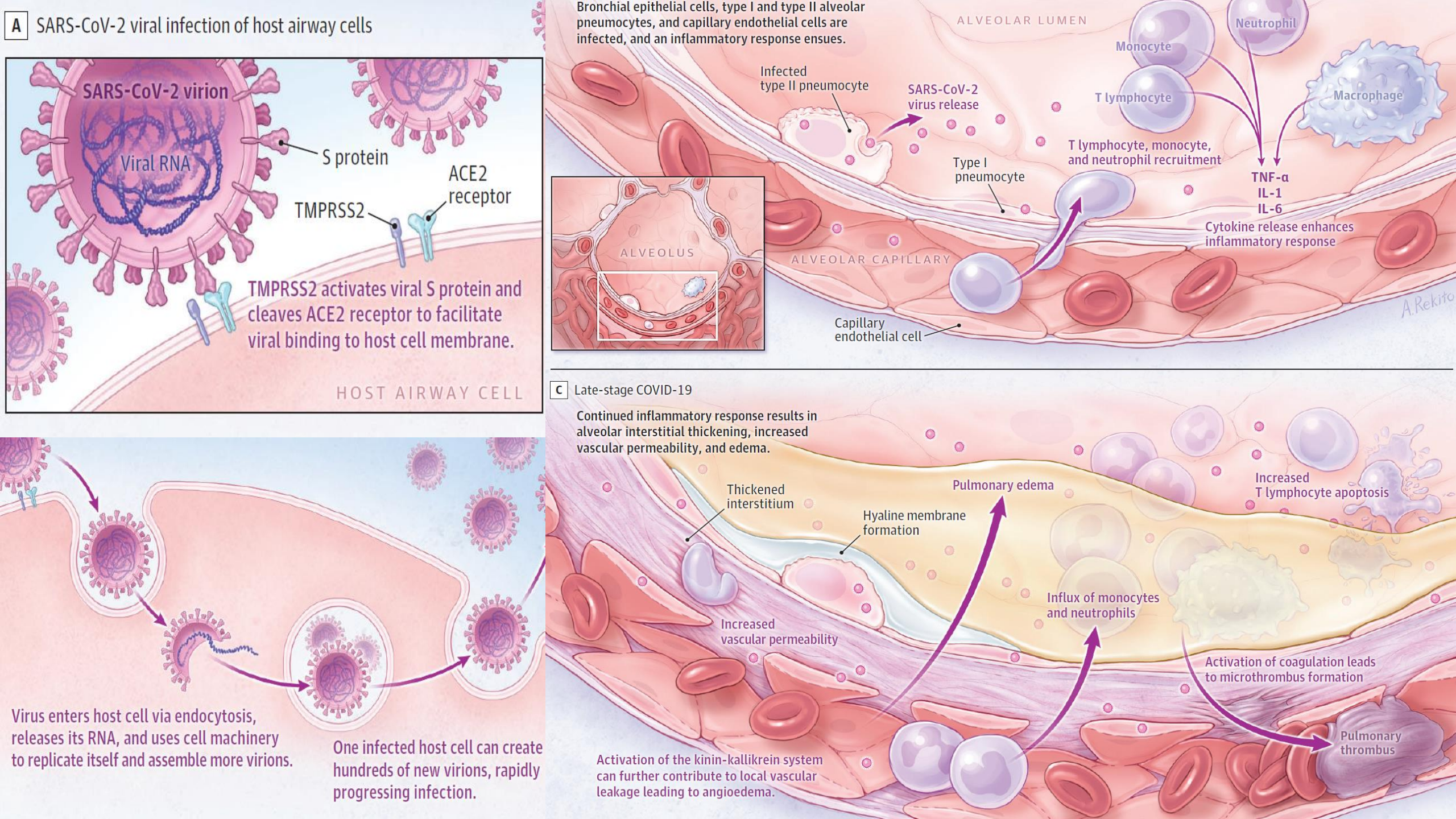
Management of COVID-19: Diagnosis and Treatment

OPASS PUTCHAROEN M.D.

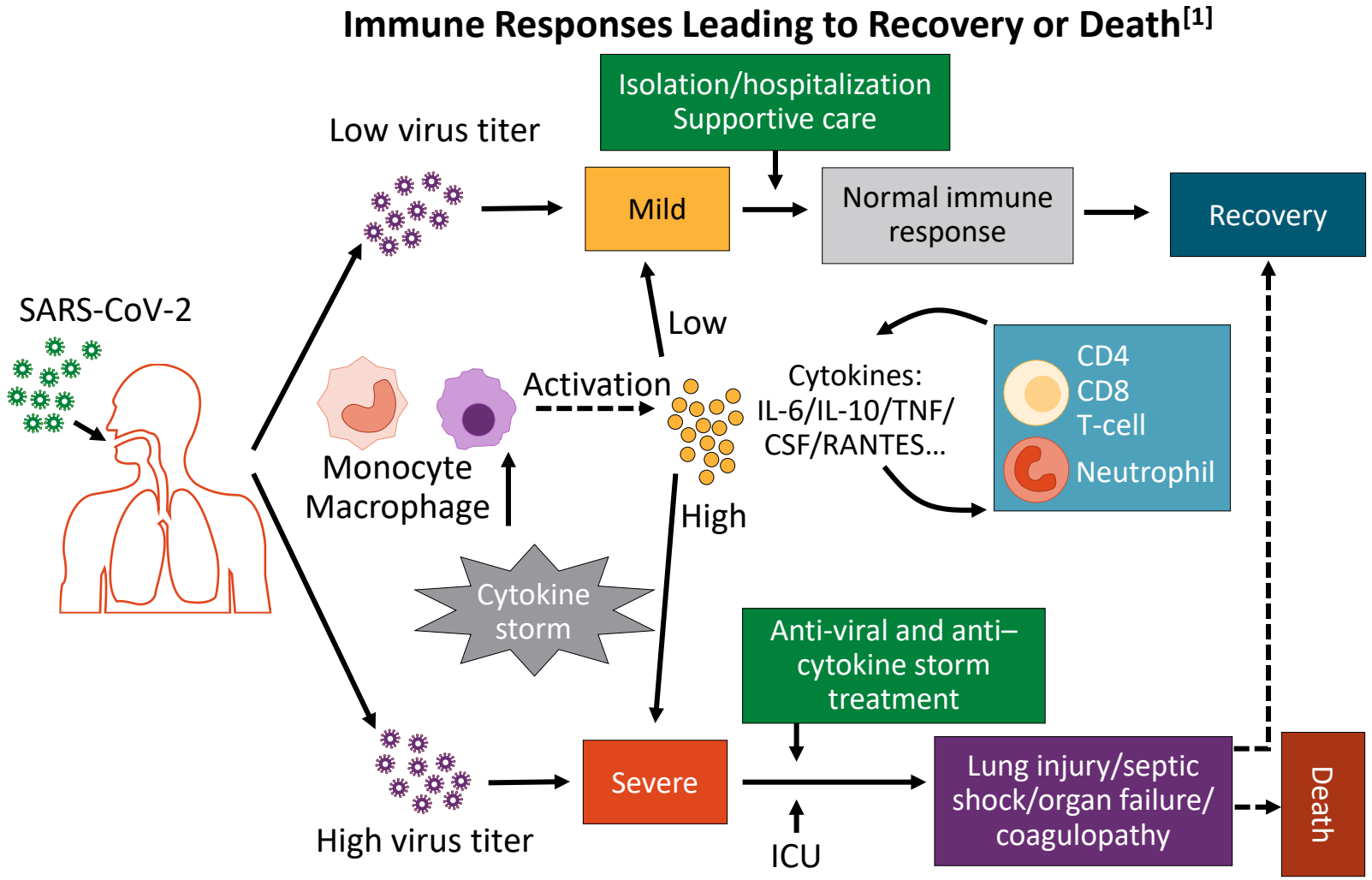


Outline:

- ❑ Diagnosis
- ❑ Review of treatment
- ❑ Pharmacologic options


A SARS-CoV-2 viral infection of host airway cells
SARS-CoV-2 virion
Viral RNA
S protein
ACE2 receptor
TMPRSS2
TMPRSS2 activates viral S protein and cleaves ACE2 receptor to facilitate viral binding to host cell membrane.
HOST AIRWAY CELL
Virus enters host cell via endocytosis, releases its RNA, and uses cell machinery to replicate itself and assemble more virions.
One infected host cell can create hundreds of new virions, rapidly progressing infection.
Bronchial epithelial cells, type I and type II alveolar pneumocytes, and capillary endothelial cells are infected, and an inflammatory response ensues.
ALVEOLAR LUMEN
Neutrophil
Monocyte
T lymphocyte
Macrophage
Infected type II pneumocyte
SARS-CoV-2 virus release
T lymphocyte, monocyte, and neutrophil recruitment
Type I pneumocyte
TNF-α
IL-1
IL-6
Cytokine release enhances inflammatory response
ALVEOLUS
ALVEOLAR CAPILLARY
Capillary endothelial cell
A.Rekito
C Late-stage COVID-19
Continued inflammatory response results in alveolar interstitial thickening, increased vascular permeability, and edema.
Thickened interstitium
Hyaline membrane formation
Pulmonary edema
Increased T lymphocyte apoptosis
Increased vascular permeability
Influx of monocytes and neutrophils
Activation of coagulation leads to microthrombus formation
Pulmonary thrombus
Activation of the kinin-kallikrein system can further contribute to local vascular leakage leading to angioedema.

COVID-19: infection and immunity



Adequate immune responses[2]

- Timely innate/adaptive responses
- **Quick type 1 IFN response**
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

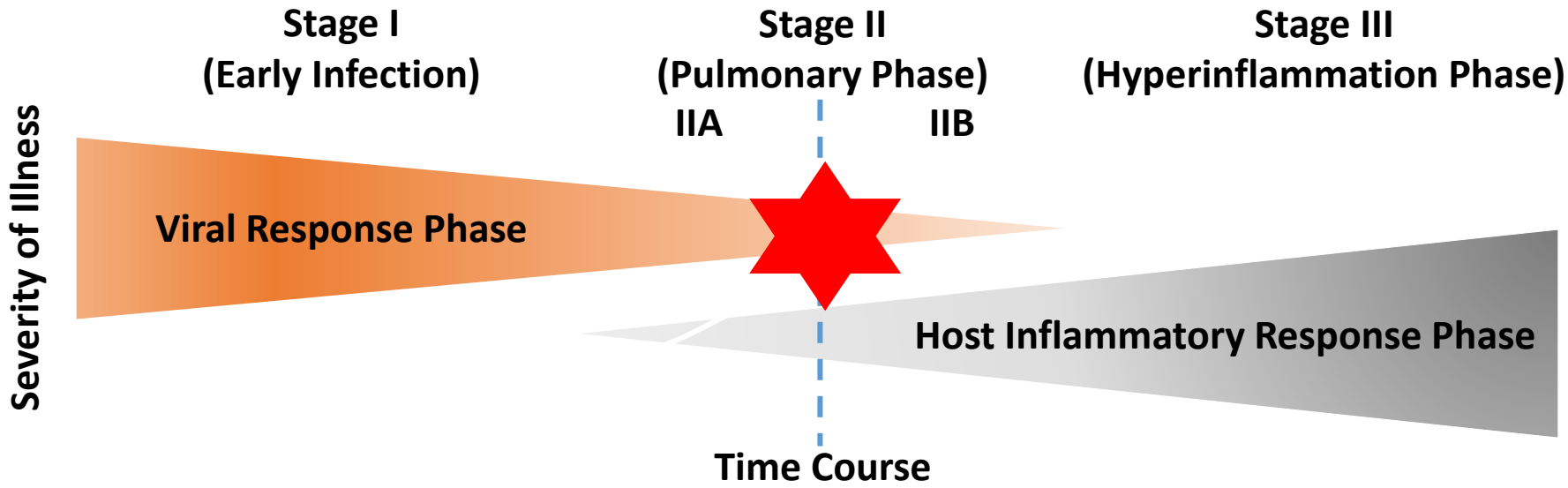
Inadequate immune responses[2]

- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

1. Wang. J Leukoc Biol. 2020;108:17. 2. Sokolowska. Allergy. 2020;75:2445.

Slide credit: clinicaloptions.com

COVID-19 at Different Stages



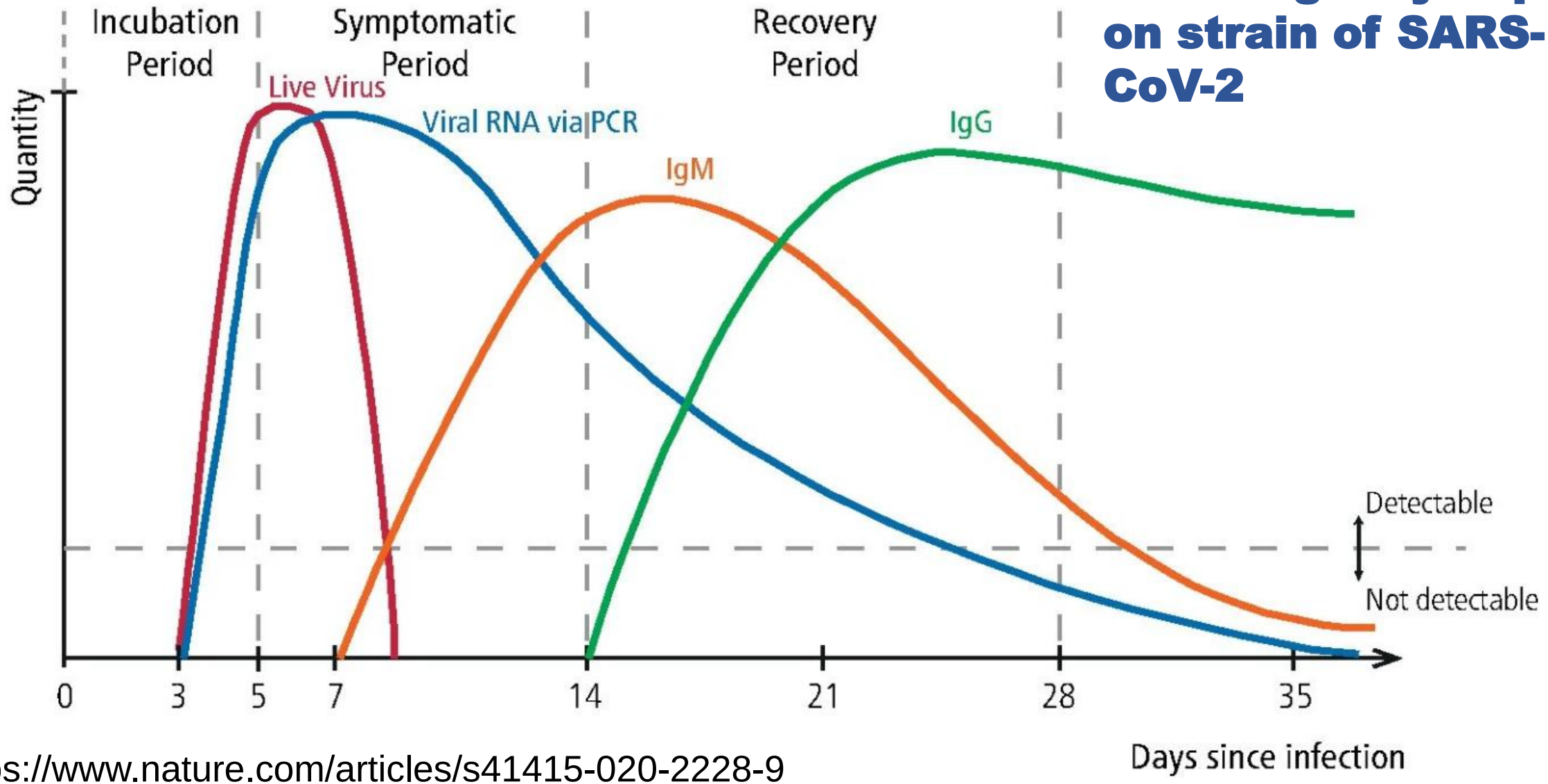
Clinical symptoms	Mild constitutional symptoms Fever > 99.6°F Dry cough	Shortness of breath without (IIA) and with hypoxia (IIB) ($PaO_2/FiO_2 \leq 300$ mm Hg)	ARDS SIRS/shock Cardiac failure
Clinical signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory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

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

Diagnosis

What Test

****Duration of viral shedding may depend on strain of SARS-CoV-2**



https://www.nature.com/articles/s41415-020-2228-9

Diagnosis

What Test

- **Nucleic acid amplification testing (NAAT),** most commonly with a **reverse-transcription polymerase chain reaction (RT-PCR) assay**, to detect SARS-CoV-2 RNA from the upper respiratory tract is the preferred initial diagnostic test for COVID-19
- **Preferred types of specimens**
  - Nasopharyngeal swab specimen
  - Oropharyngeal swab specimen
  - Saliva specimen
  - Sputum

Consideration:

- High analytic sensitivity and specificity in ideal settings.
- Clinical performance depends on the type and quality of the specimen and the duration of illness at the time of testing.
- Reported false-negative rate ranges from <5 to 40%, depending on the test used

MMWR Morb Mortal Wkly Rep. 2020;69(5):140. Epub 2020 Feb 7

Diagnosis

Nucleic acid amplification testing (NAAT)-RT-PCR

Consideration: Test sensitivity

- **Type of specimen:** Lower respiratory tract specimens may have higher viral loads and be more likely to yield positive tests than upper respiratory tract specimens
- **Duration of illness:** Too early infection may cause false negative
- **NAAT assays**: There are differences in the limit of detection among **the major commercial** and retesting samples on different platforms may yield conflicting results

Cautions:
Negative RT-PCR may be false negative --
In patient with high suspicion of COVID-19, repeated test is recommended

MMWR Morb Mortal Wkly Rep. 2020;69(5):140. Epub 2020 Feb 7

Diagnosis

Nucleic acid amplification testing (NAAT)

Cycle threshold — The cycle threshold (Ct)

- Refers to the number of cycles in an RT-PCR assay needed to amplify viral RNA to reach a detectable level.

  The Ct value can thus indicate the relative viral RNA level in a specimen (with lower Ct values reflective of higher viral levels

- Laboratories generally do not provide the Ct value with the qualitative NAAT result, although it can be obtained upon request for some testing platforms.

Diagnosis

Serology

- Serologic tests detect antibodies to SARS-CoV-2 in the blood, and those that have been adequately validated can help **identify patients who previously had SARS-CoV-2 infection as well as patients with current infection who have had symptoms for three to four weeks**
- Detectable antibodies generally take several days to weeks to develop; **IgG usually develops by 14 days after onset of symptoms**
- **They have very limited utility for diagnosis in the acute setting**
- Individual results should be interpreted with caution in settings of low seroprevalence; serologic tests that have high specificity still have a low positive predictive value

MMWR Morb Mortal Wkly Rep. 2020;69(5):140. Epub 2020 Feb 7

Diagnosis

Antigen testing as an alternative to NAAT

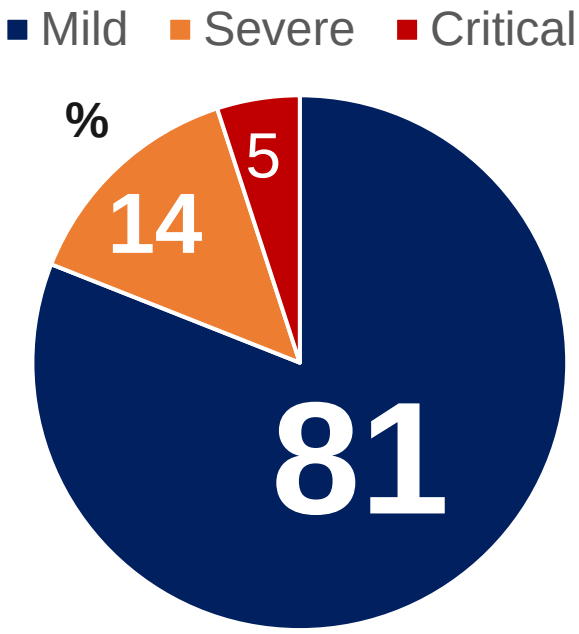
- Tests that detect SARS-CoV-2 antigen can be performed rapidly and at the point of care and thus may be more accessible with a faster time to results than some NAATs.
- Antigen tests are typically **less sensitive than NAATs**
- Antigen tests may be useful **alternatives to NAAT** for diagnosis of SARS-CoV-2 symptomatic individuals who are thought to be in the early stages of infection
- Other situations: Asymptomatic individual with exposure or serial screening in congregate settings

https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays (Accessed on September 21, 2020)
https://www.cdc.gov/coronavirus/2019-ncov/php/testing/expanded-screening-testing.html (Accessed on February 25, 2021).

Practical points on diagnosis

- Do not use serology for identification of acute infection
- **Negative test from RT-PCR or antigen test does not mean no infection**
- **Repeated test may be needed on some individuals**
- Previous infection of SARS-CoV-2 may cause persistent positive RT-PCR for weeks
- **Symptomatic/severe COVOD-19 may cause prolonged shedding with high probability of transmission**

Clinical Management: Clinical parameters for prediction of severe COVID-19



Who is at risk for severe COVID-19

- Elderly
- **chronic health conditions** such as cardiovascular disease, DM, immunosuppression and obesity
- Men>> Women
- Some racial and ethnic groups such as Black and Hispanic

The mortality in the critically ill group was 49%.

Definition of severe COVID-19

- RR of 30 or more breaths per minute
- Blood oxygen saturation of 93% or less
- A ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao2:Fio2) of less than 300 mm Hg
- Pulmonary infiltrates in more than 50%

Key clinical manifestations of COVID-19

- Pathogenesis: infection and inflammation (early and late phase)
- Asymptomatic and presymptomatic transmission
- Most cases: asymptomatic and mild symptomatic infection
- Clinical course is dynamic with progression to severe disease in high-risk group
- Most of severe disease occurs after 1st week after symptoms

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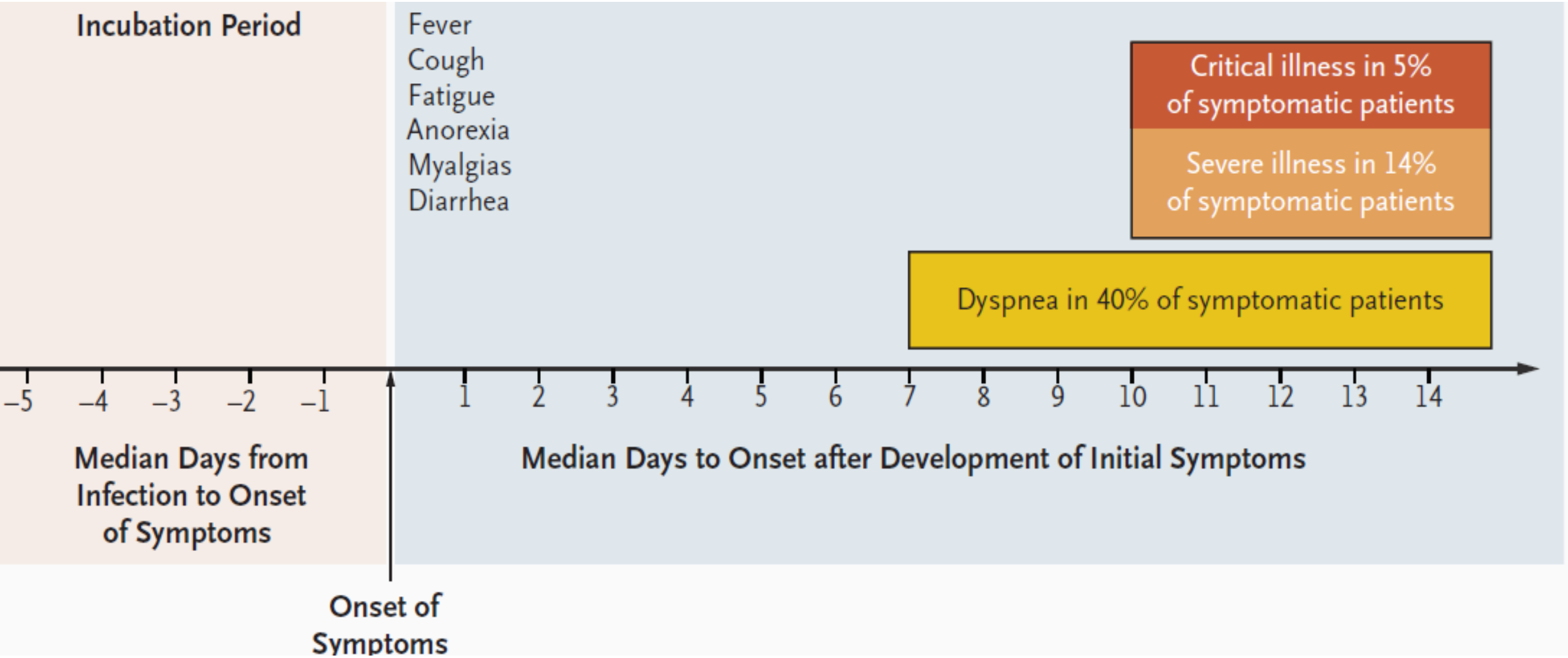
When the patient progress to severe COVID



www.nejm.org

Management in severe COVID

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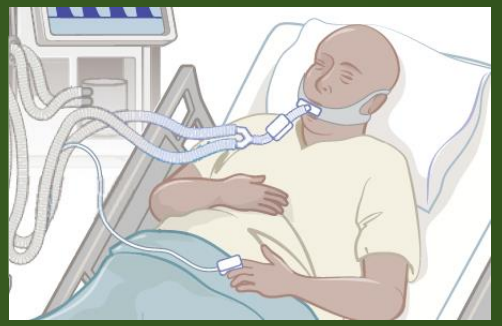

Respiratory

- Oxygen supplement therapy
- Mechanical ventilation

Pharmacologic treatment

- Antivirals
- Anti-inflammatory agents

Supportive care

- Adequate fluid management
- Renal replacement therapy
- Thromboprophylactic therapy

Management of COVID-19 pneumonia:

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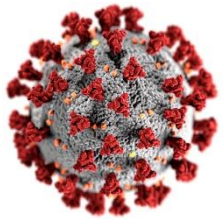
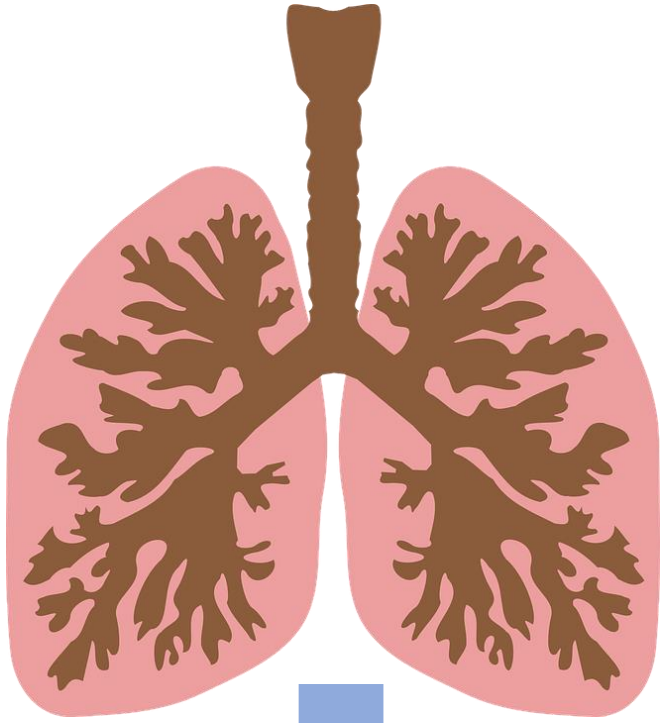


Virus

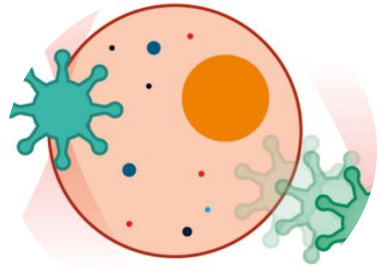
Antiviral agents:

- **Remdesivir**
- **Favipiravir**
- **HCQ&CQ**
- **IVIG**
- **Protease inhibitors**
- **Ribavirin**
- **IFN**
- **Convalescent plasma**



Respiratory support

- **Mechanical ventilation**
- **ECMO**

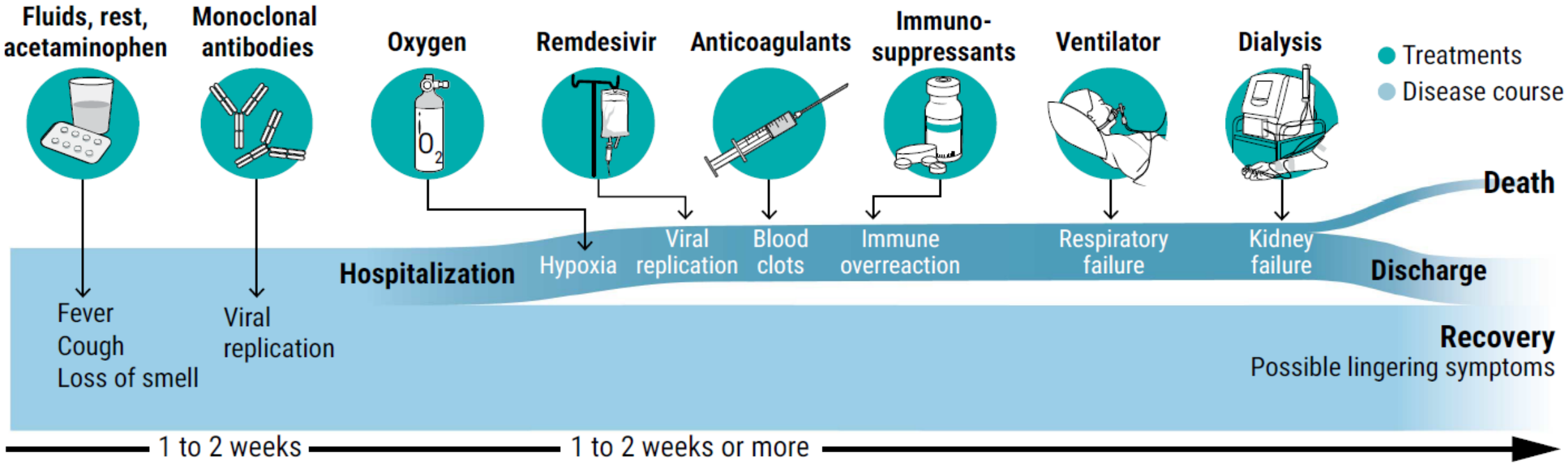


Immune overactivity

Cytokine release syndrome:

- **Anti IL-6 monoclonal Ab: tocilizumab**
- **Extracorporeal therapies**
- **Corticosteroid**

Timing and interventions



Monoclonal antibodies appear to reduce risk of hospitalization in outpatients at high risk of severe disease—provided patients can access them.

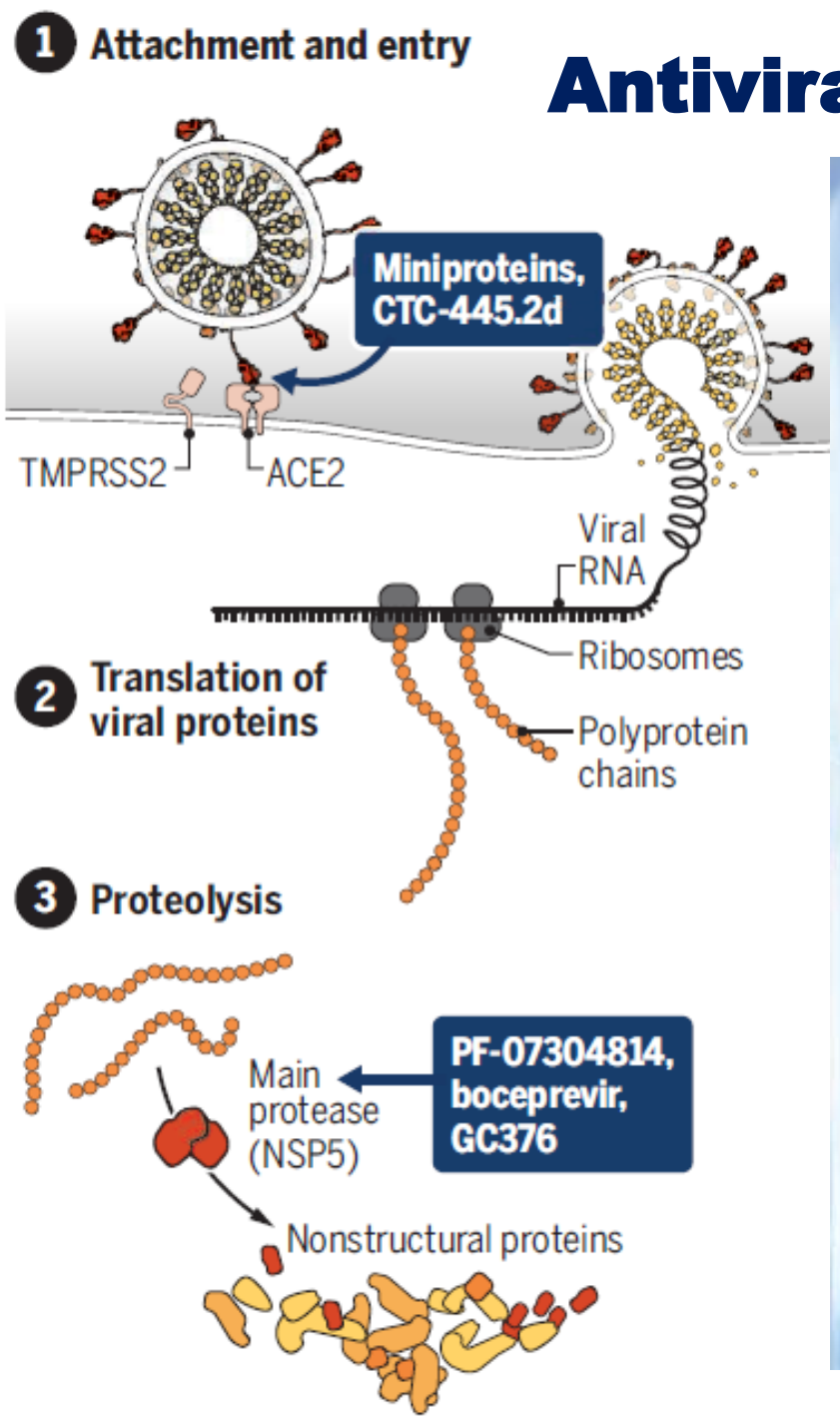
Oxygen, delivered through nasal prongs, a mask, or an invasive breathing tube, is crucial to COVID-19 care. But how it's administered varies among hospitals.

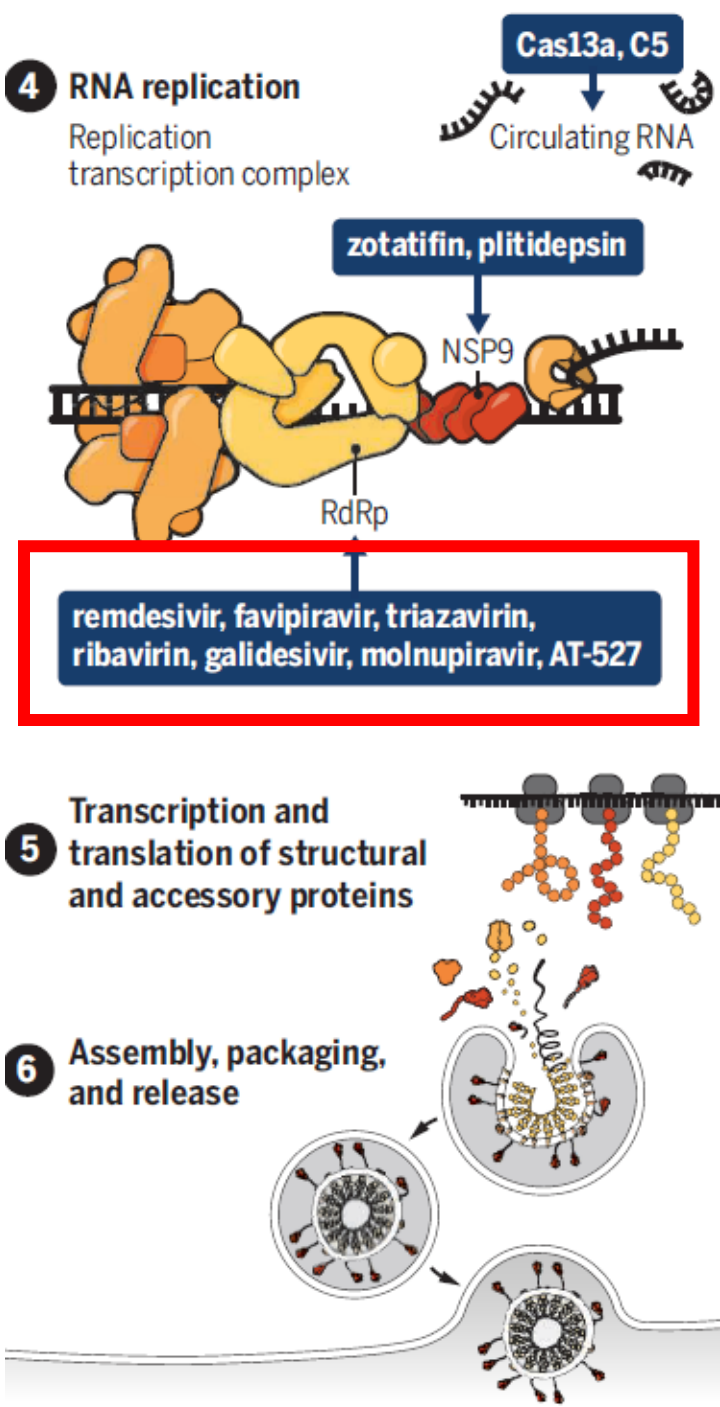
The antiviral remdesivir is widely used in hospitalized patients, but evidence is mixed on its ability to shorten hospital stays; it hasn't been shown to improve survival.

Anticoagulants can prevent blood clots that are common in COVID-19 patients, but physicians must weigh the risk of bleeding when deciding the right dose.

The immunosuppressant drugs dexamethasone and tocilizumab have both reduced mortality in large clinical trials of hospitalized patients, showing that it's possible to tame the potentially deadly inflammation that characterizes severe disease.

Antiviral therapy for COVID-19

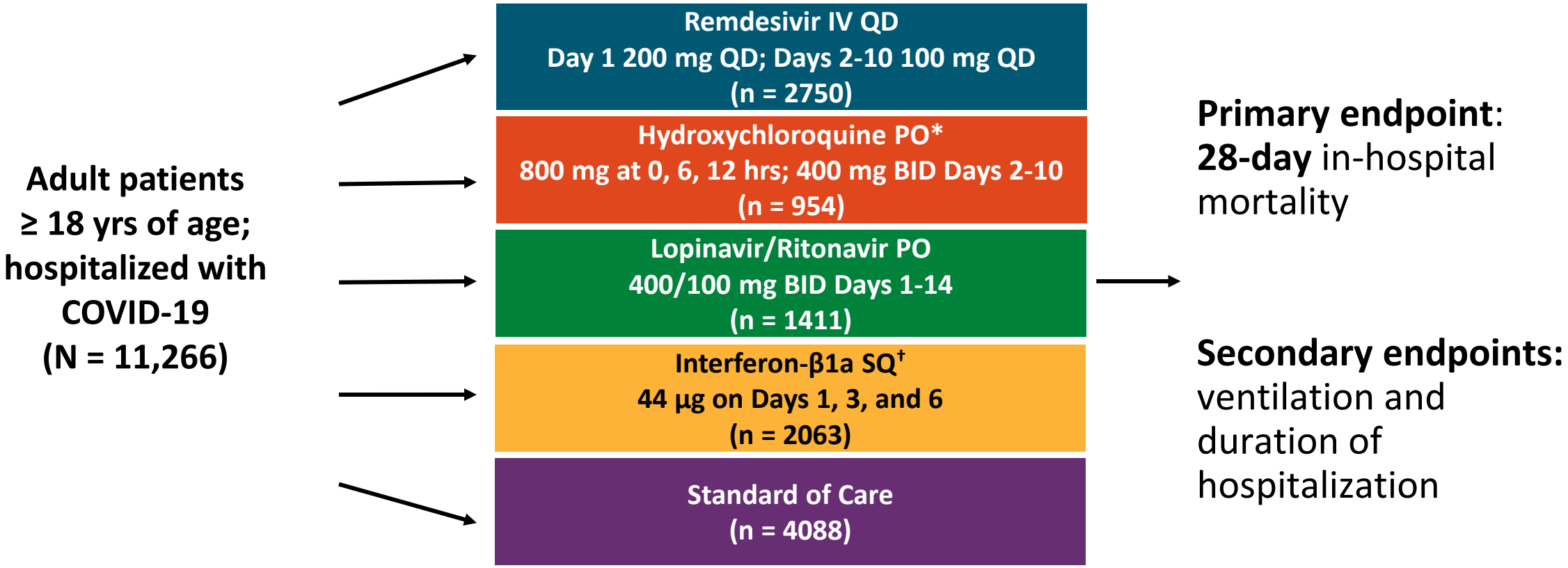




WHO SOLIDARITY Trial: Antiviral Drugs to Treat Hospitalized Patients With COVID-19

See the investigational treatments section for these data

- Adaptive, open-label, randomized phase III trial conducted in 405 hospitals in 30 countries



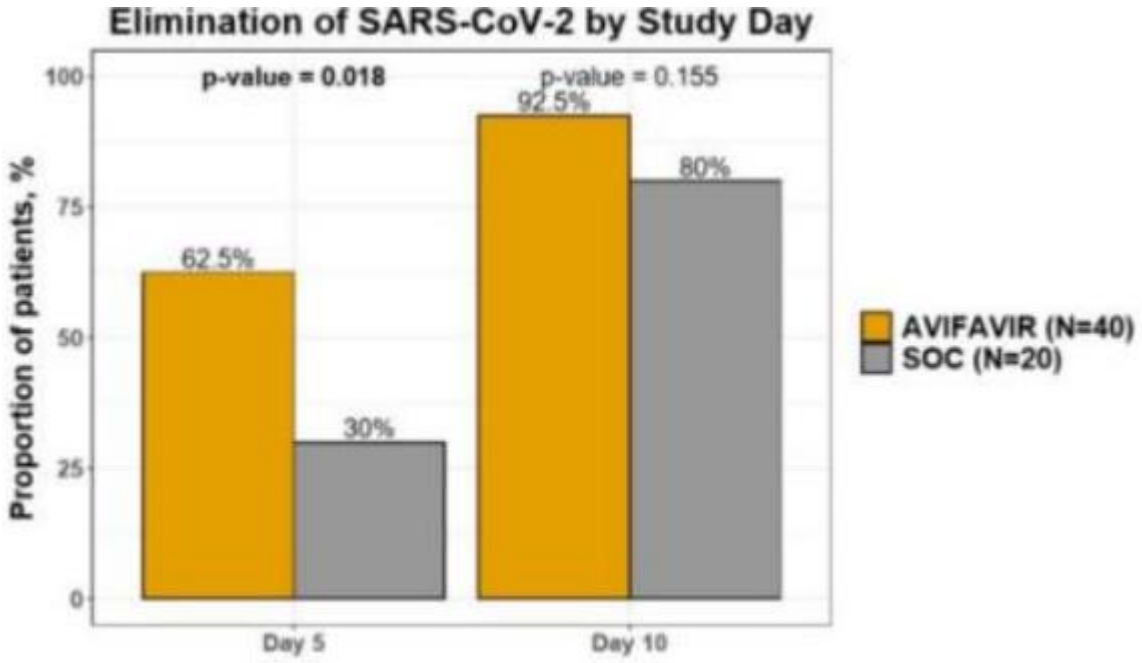
*If administered through nasogastric tube, loading dose of 600 mg BID followed by 400 mg QD for 9 days.

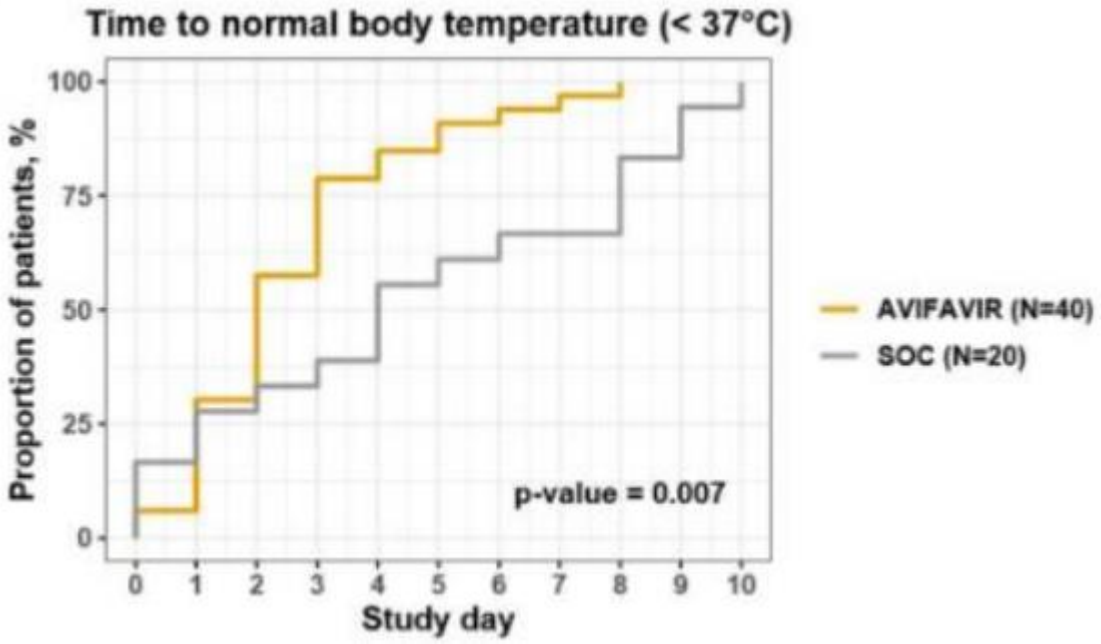
†Given with LPV/RTV until July 4, 2020 (n = 651). Patients on high-flow oxygen, ventilators, or ECMO were given 10 **µg IV daily for 6 days.**

Pan. MedRxiv. 2020;[Preprint]. Note: this publication has not been peer reviewed. NCT04280705.

Favipiravir

- **In May 2020 the Russian Ministry of Health granted fast-track marketing authorization to RNA polymerase inhibitor AVIFAVIR (favipiravir) for the treatment of COVID-19 patients.**
- **In the pilot stage of Phase II/III clinical trial, AVIFAVIR enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days, and was safe and well-tolerated.**





SOC=hydroxychloroquine or chloroquine

Clin Infect Dis. 2020 Aug 9;ciaa1176. doi: 10.1093/cid/ciaa1176. Online ahead of print.

Favipiravir is indicated for high risk patients with mild infection or mild pneumonia

กรมการแพทย์
DEPARTMENT OF MEDICAL SERVICES

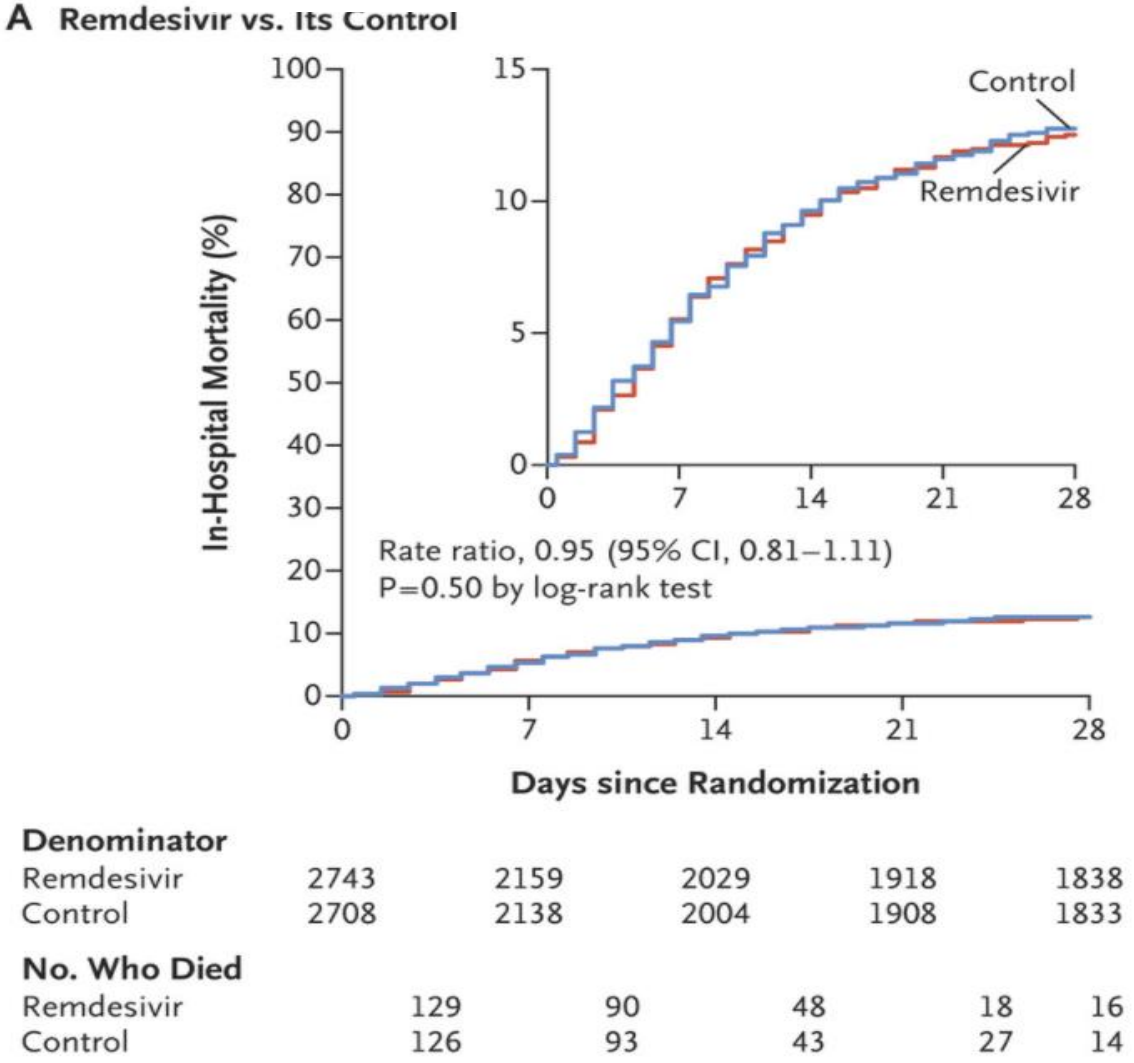
ผู้ป่วยที่ไม่มีอาการ หรือมีอาการไม่รุนแรง แต่มีปัจจัยเสี่ยงต่อการเป็นโรครุนแรง หรือมีโรคร่วมสำคัญ หรือผู้ป่วยที่มีปอดบวม (pneumonia) เล็กน้อย (COVID-19 with risk factors for severe disease or having co-morbidity or mild pneumonia) ปัจจัยเสี่ยงข้อใดข้อหนึ่งต่อไปนี้ ได้แก่ อายุ >60 ปี โรคปอดอุดกั้นเรื้อรัง (COPD) รวมโรคปอดเรื้อรังอื่น ๆ โรคไตเรื้อรัง (CKD) โรคหัวใจและหลอดเลือด รวมโรคหัวใจแต่กำเนิด โรคหลอดเลือดสมอง เบาหวานที่ควบคุมไม่ได้ ภาวะอ้วน (น้ำหนักมากกว่า 90 กก.) ตับแข็ง ภาวะภูมิคุ้มกันต่ำ และ lymphocyte น้อยกว่า 1,000 เซลล์/ลบ.มม. หรือผู้ป่วยที่ไม่มีปัจจัยเสี่ยงแต่มีแนวโน้มที่จะมีความรุนแรงของโรคมากขึ้น

- แนะนำให้นอนโรงพยาบาล อย่างน้อย 14 วัน นับจากวันที่เริ่มมีอาการ หรือจนกว่าอาการจะดีขึ้น
- แนะนำให้ favipiravir โดยเริ่มให้ยาเร็วที่สุด ให้ยานาน 5 วัน หรือ มากกว่า ขึ้นกับอาการทางคลินิกตามความเหมาะสม หรือปรึกษาผู้เชี่ยวชาญ
- อาจพิจารณาให้ corticosteroid ร่วมกับ favipiravir ในกรณีที่มีผู้ป่วยมีอาการและภาพถ่ายรังสีปอดที่แย่ลง คือ มี progression of infiltrates หรือค่า room air SpO_2 ≤96% หรือพบว่ามี SpO_2 ขณะออกแรงลดลง ≥3% ของค่าที่วัดได้ครั้งแรก (exercise-induced hypoxia)

SOLIDARITY

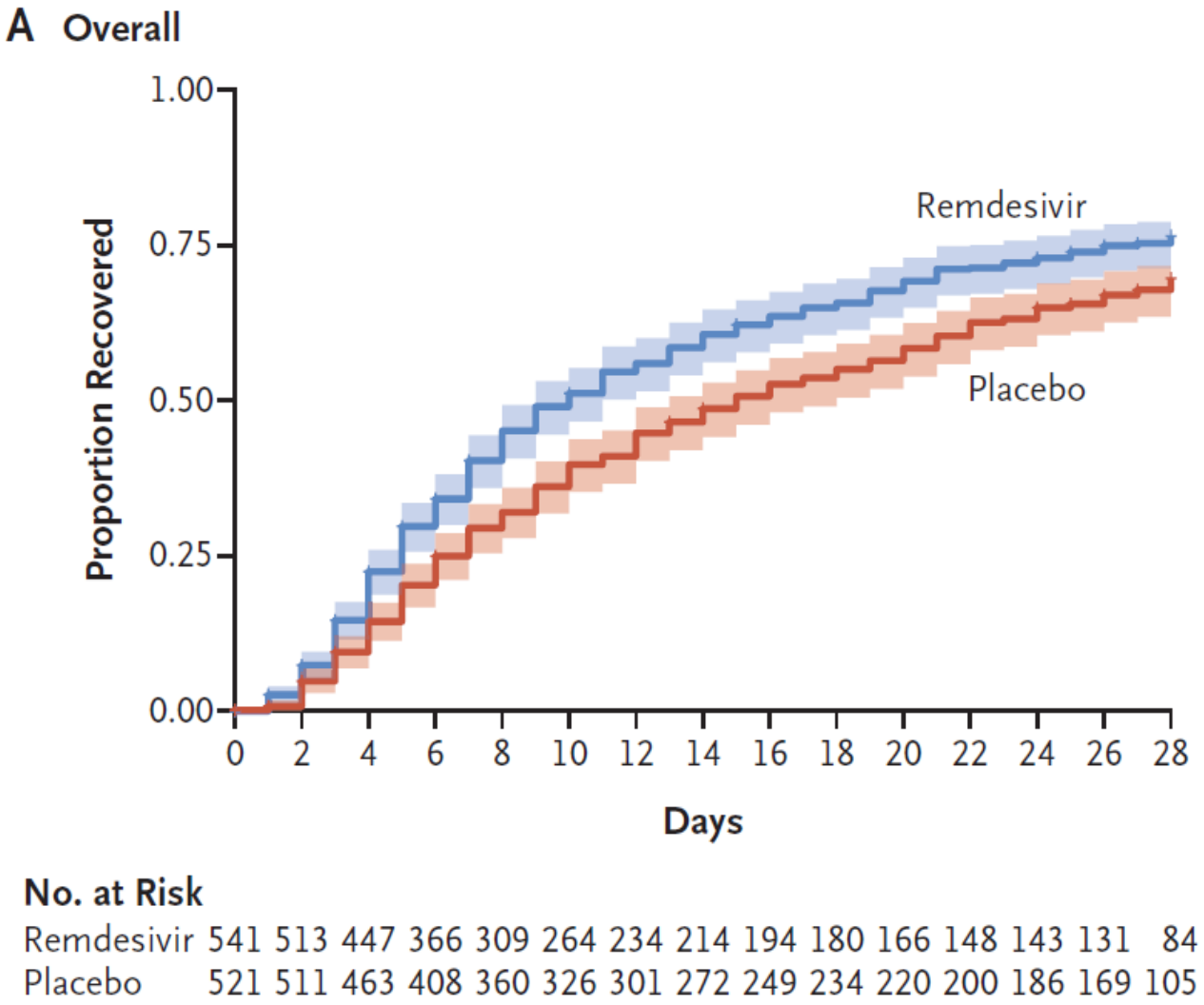
Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*



- **Multinational, randomized open-label trial**
- At 405 hospitals in 30 countries, N=11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to HCQ, 1411 to LPV (without interferon), 2063 to IFN (including 651 to IFN plus LPV)
- 4088 to no trial drug
- Death occurred in 301 of 2743 patients receiving remdesivir and in 303 of 2708 receiving its control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P=0.50)
- Remdesivir, HCQ, LPV, and IFN regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.

N Engl J Med 2021; 384:497-511



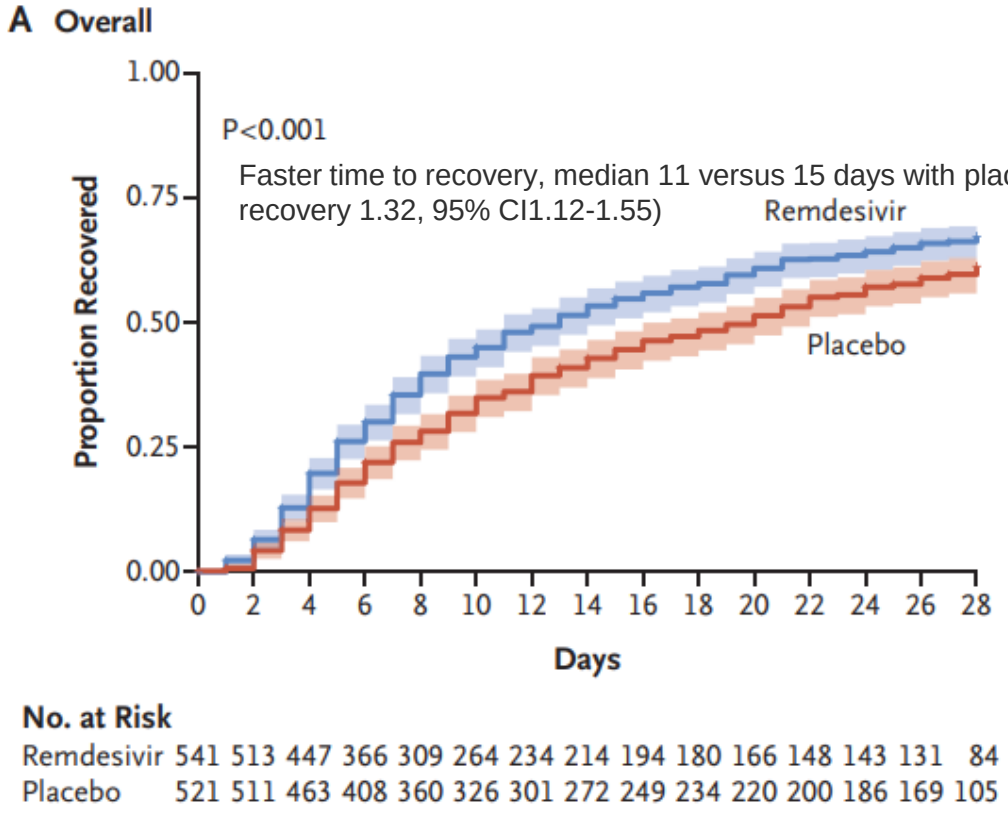
- **Overall, there was a trend towards lower 29-day mortality that was not statistically significant (11.4 versus 15.2 percent with placebo, HR 0.73, 95% CI 0.52-1.03).**
- Among the subset of patients who were on oxygen supplementation but did not require high-flow oxygen or ventilatory support (either noninvasive or invasive), there was a statistically significant mortality benefit at that time point (4.0 versus 12.7 percent, HR 0.30, 95% CI 0.14-0.64).

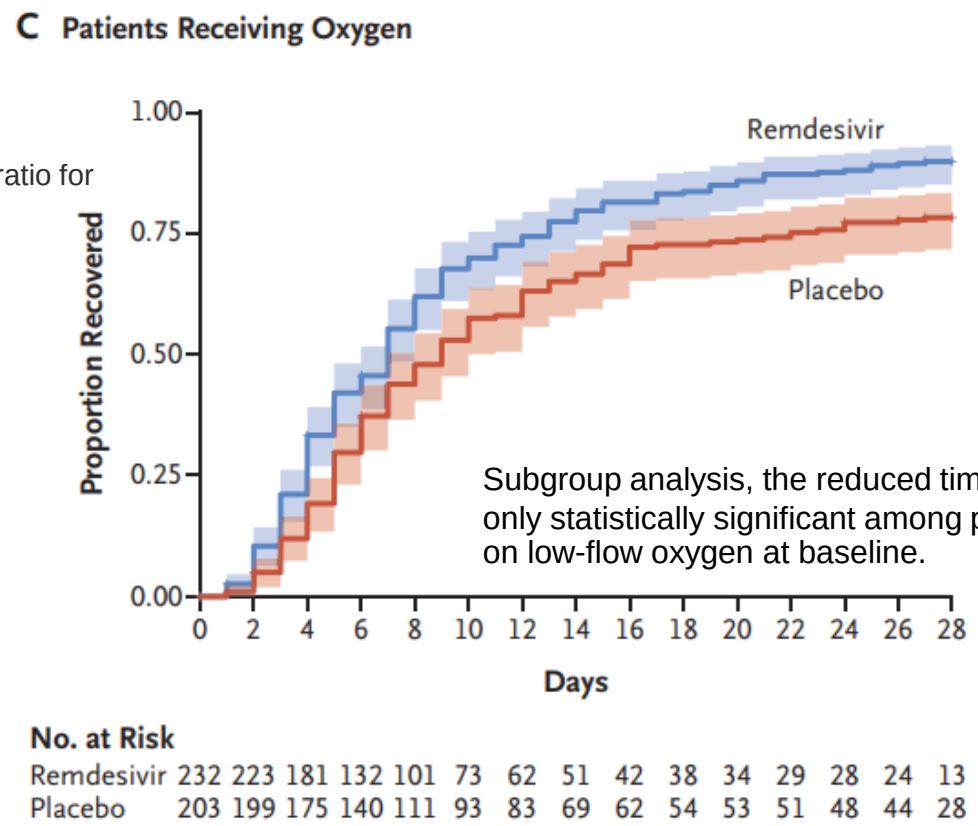
Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19

N Engl J Med. 2020;383(19):1813. Epub 2020 Oct 8.

Remdesivir in severe disease

Evidence for a clinical benefit of remdesivir is strongest for patients with severe disease who do not require high-flow supplemental oxygen or ventilatory support





Subgroup analysis, the reduced time to recovery was only statistically significant among patients who were on low-flow oxygen at baseline.

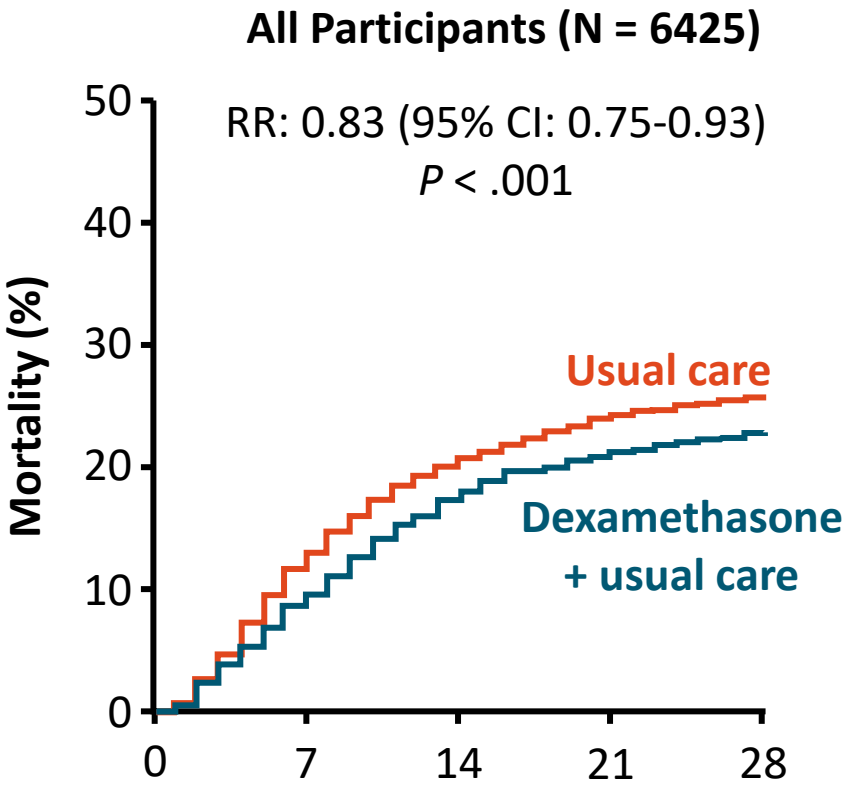
Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection.

A preliminary version of this article was published on May 22, 2020, at NEJM.org. This article was published on October 8, 2020, at NEJM.org

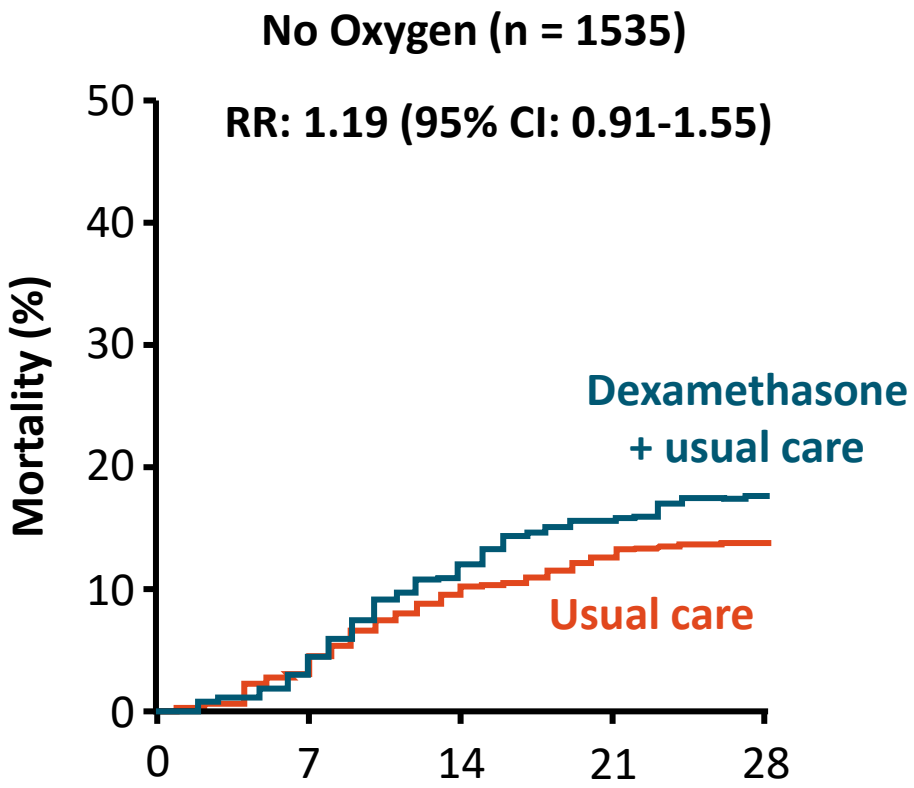
อาจพิจารณาให้ Remdesivir แทน Favipiravir กรณีที่

- ผู้ป่วยมีอาการปอดอักเสบอย่างรุนแรง (SpO2 ที่ room air $\leq$ 94%) หรือ กรณีที่ต้องใช้อุปกรณ์ non-invasive หรือ invasive ventilation รวมทั้ง extracorporeal membrane oxygenation (ECMO) ตามแนวทางของสมาคมโรคติดเชื้อสหรัฐอเมริกา (Infectious Disease Society of America, IDSA) และสถาบันสุขภาพแห่งชาติ สหรัฐอเมริกา (National Institute of Health, NIH)
- มีข้อห้ามบริหารยาทางปาก หรือ มีปัญหาการดูดซึม เป็นต้น
- **ไม่ตอบสนองต่อการยาอื่นในระยะเวลาหลังให้ยา 72 ชั่วโมง**
- ทั้งนี้การศึกษาขององค์การอนามัยโลก พบว่า Remdesivir ไม่ได้ช่วยลดอัตราตาย

RECOVERY Trial: Mortality With Dexamethasone + Usual Care vs Usual Care Alone



Patients at Risk, n					
Dexamethasone	2104	1903	1725	1659	1621
Usual care	4321	3754	3427	3271	3205

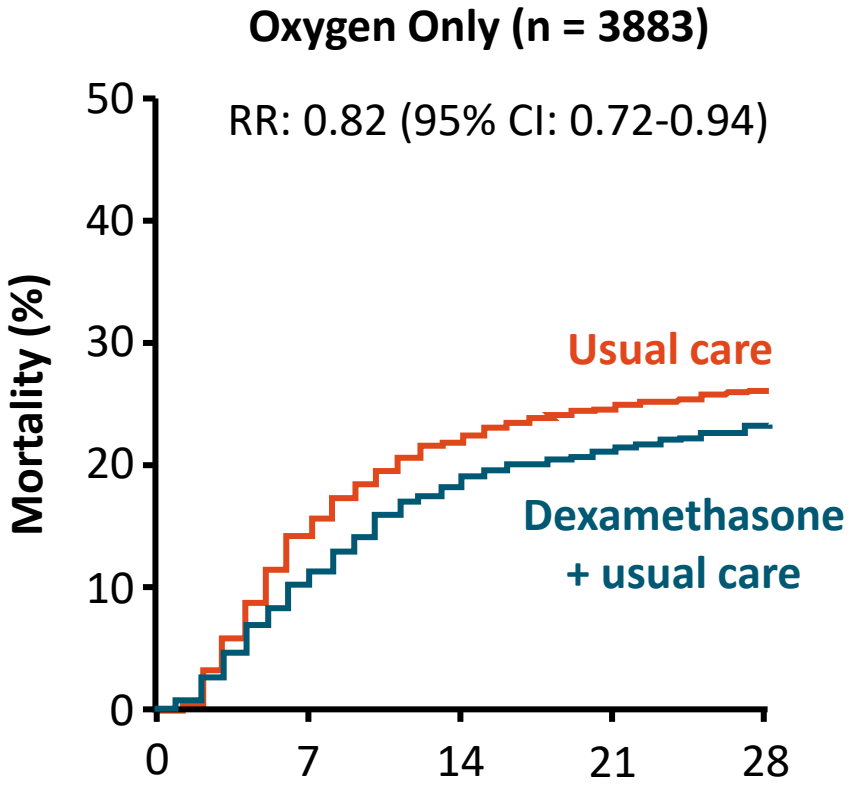


Patients at Risk, n					
Dexamethasone	501	478	441	421	412
Usual care	1034	987	928	897	889

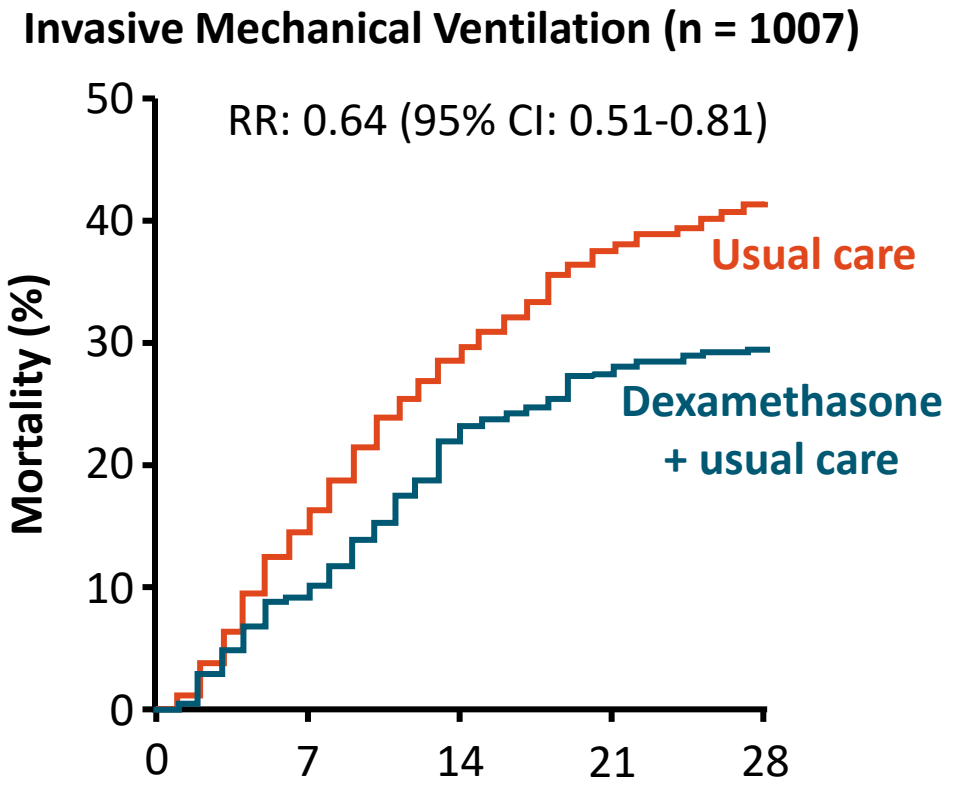
RECOVERY Collaborative Group. NEJM. 2020;[Epub].

Steroid and other anti-inflammatory agents

RECOVERY Trial: Mortality in Patients on Oxygen or Mechanical Ventilation ± Dexamethasone



Patients at Risk, n					
Dexamethasone	1279	1135	1036	1006	981
Usual care	2604	2195	2018	1950	1916



Patients at Risk, n					
Dexamethasone	324	290	248	232	228
Usual care	683	572	481	424	400

RECOVERY Collaborative Group. NEJM. 2020;[Epub].

WHO Living Guidance: Corticosteroids for COVID-19

Categories of Illness	Definition	Recommendation
Critical COVID-19	▪ ARDS, sepsis, septic shock ▪ Other conditions that would normally require life-sustaining therapies (mechanical ventilation) or vasopressor therapy	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Severe COVID-19	Any of the following: ▪ $0_2 < 90\%$ on room air* ▪ RR > 30 breaths/min in adults and children aged > 5 yrs; RR ≥ 40 in children aged 1-5 yrs; RR ≥ 50 in children aged 2-11 mos ▪ Signs of respiratory distress (accessory muscle use, inability to complete full sentences; in children very severe chest wall indrawing, grunting, central cyanosis, etc)	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Non-severe COVID-19	▪ Absence of any signs of severe or critical COVID-19	▪ Suggest no corticosteroids

*Note that this threshold to define severe COVID-19 is arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. Clinicians must use their judgement, and the panel suggests erring on the side of considering the illness as severe if there is any doubt.

WHO Living Guidance. Corticosteroids for COVID-19. September 2, 2020.

IDSA Recommendations FOR Treatment of Patients With COVID-19

- Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

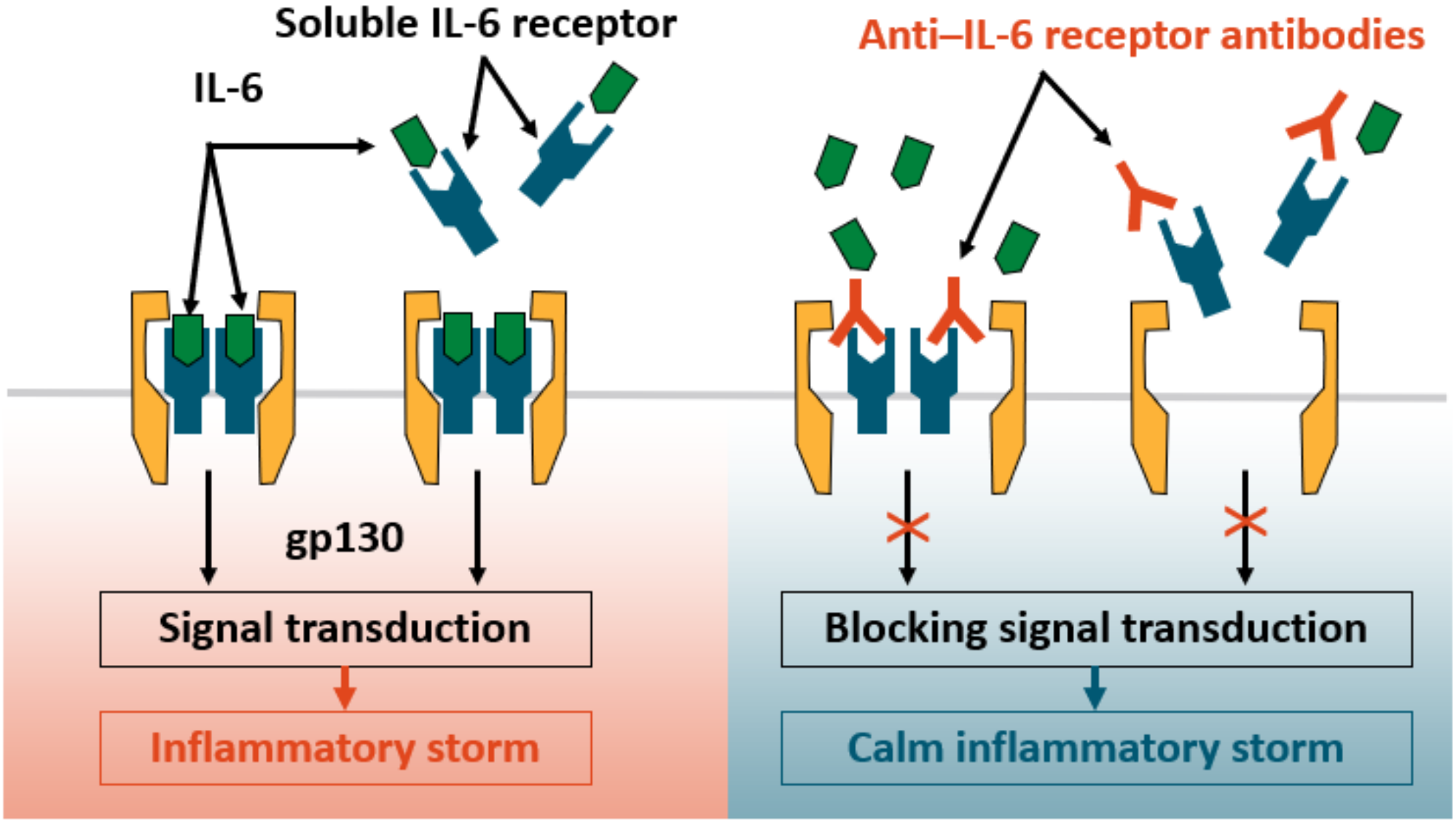
IDSA Guidance	Patient Population	Treatment
Recommends	▪ Hospitalized with critical* COVID-19	▪ Dexamethasone† vs none
Suggests	▪ Hospitalized with severe‡ COVID-19 ▪ Hospitalized with severe*‡ COVID-19 ▪ Hospitalized with severe‡ COVID-19 and corticosteroids contraindicated	▪ Dexamethasone† vs none ▪ Remdesivir§ vs no antiviral ▪ Baricitinib + remdesivir vs remdesivir alone
Recommends only in clinical trial	▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19	▪ Convalescent plasma ▪ Baricitinib + remdesivir + corticosteroids

*Mechanical ventilation or ECMO. Includes end organ dysfunction (eg, ARDS). †If unavailable, methylprednisolone and prednisone acceptable at equivalent total daily doses. ‡SpO_2 ≤ 94% on room air, including those on supplemental oxygen. §For patients on supplemental oxygen, 5 days suggested; for patients on mechanical ventilation or ECMO, 10 days.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 3.6.0.

Slide credit: clinicaloptions.com

Anti–IL-6 Receptor Antibodies

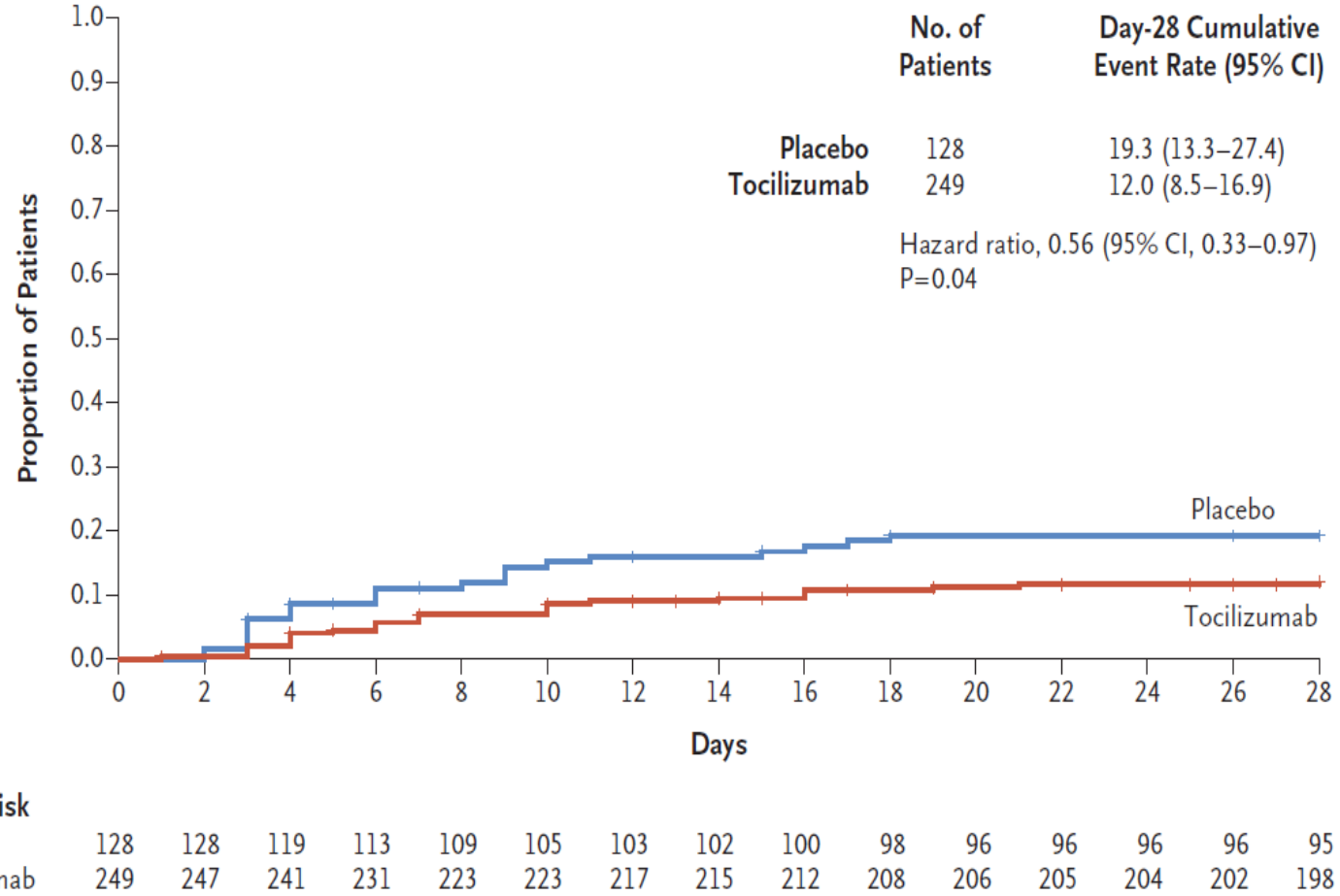


Fu. J Translational Medicine. 2020;18:164.

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

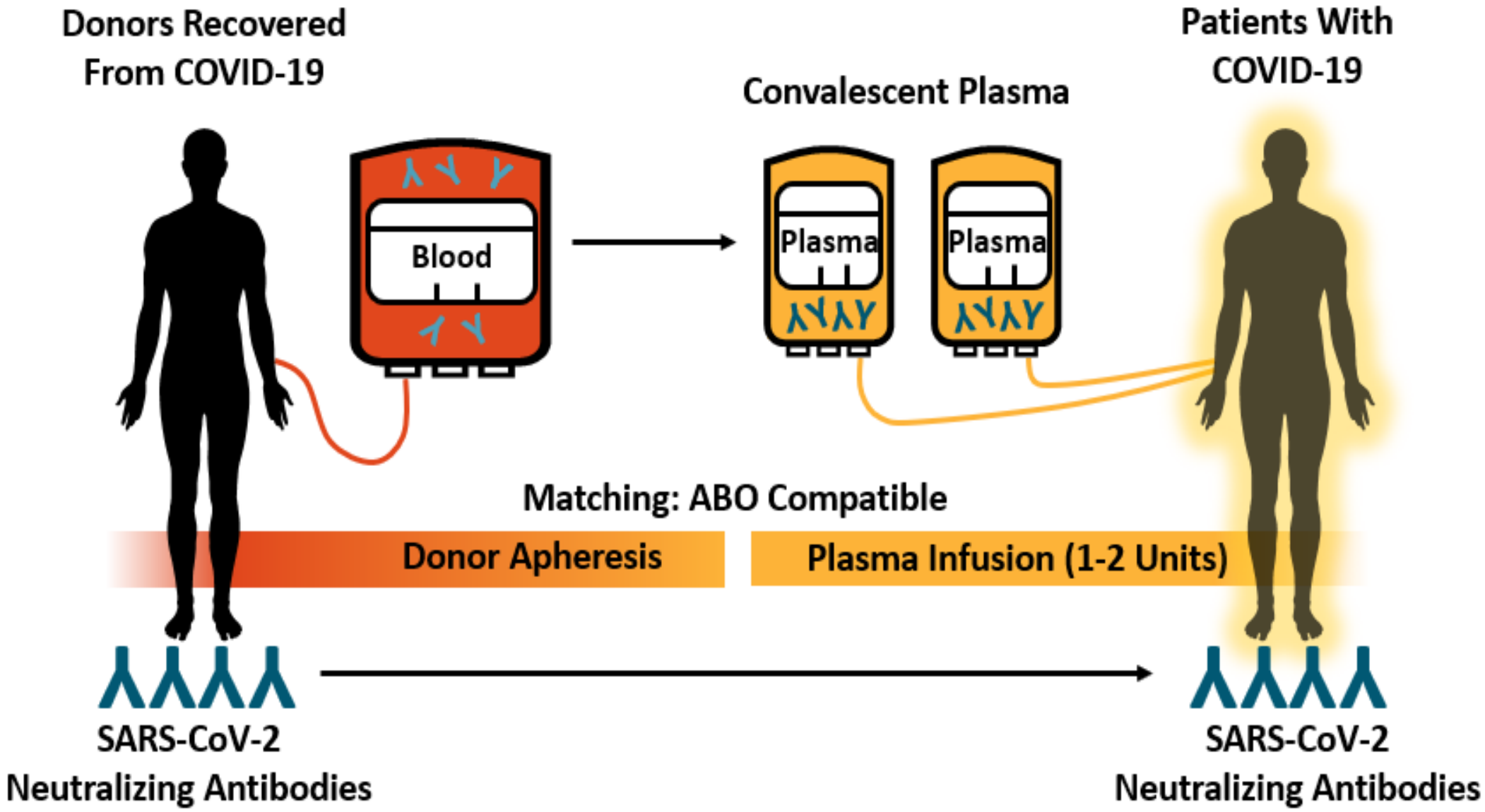
N Engl J Med 2021;384:20-30.

- **N=389 hospitalized patients with COVID-19 who were not on ventilatory support**
- Tocilizumab reduced progression to mechanical ventilation or death at 28 days (12 versus 19 percent; HR 0.556, 95% CI 0.33-0.97)
- Tocilizumab did not reduce overall 28-day mortality (10.4 versus 8.6 percent)



In hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival

How convalescent plasma works



The NEW ENGLAND JOURNAL of MEDICINE

Early High-Titer Plasma to Prevent Severe Covid-19

DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

160

Older adults with confirmed Covid-19 (≥75 yr of age or 65–74 yr with ≥1 coexisting condition)

	Convalescent plasma (IgG titer >1:1000)	Placebo (0.9% normal saline)
		
	N=80	N=80
Severe respiratory disease (≥30 breaths per min, oxygen saturation <93% while breathing ambient air, or both)	**13 patients (16%)**	**25 patients (31%)**

Relative risk, 0.52; 95% CI, 0.29 to 0.94; P=0.03

High-titer convalescent plasma administered to older adults within 72 hours after the onset of mild Covid-19 reduced progression to severe disease.

R. Libster et al. 10.1056/NEJMoa2033700

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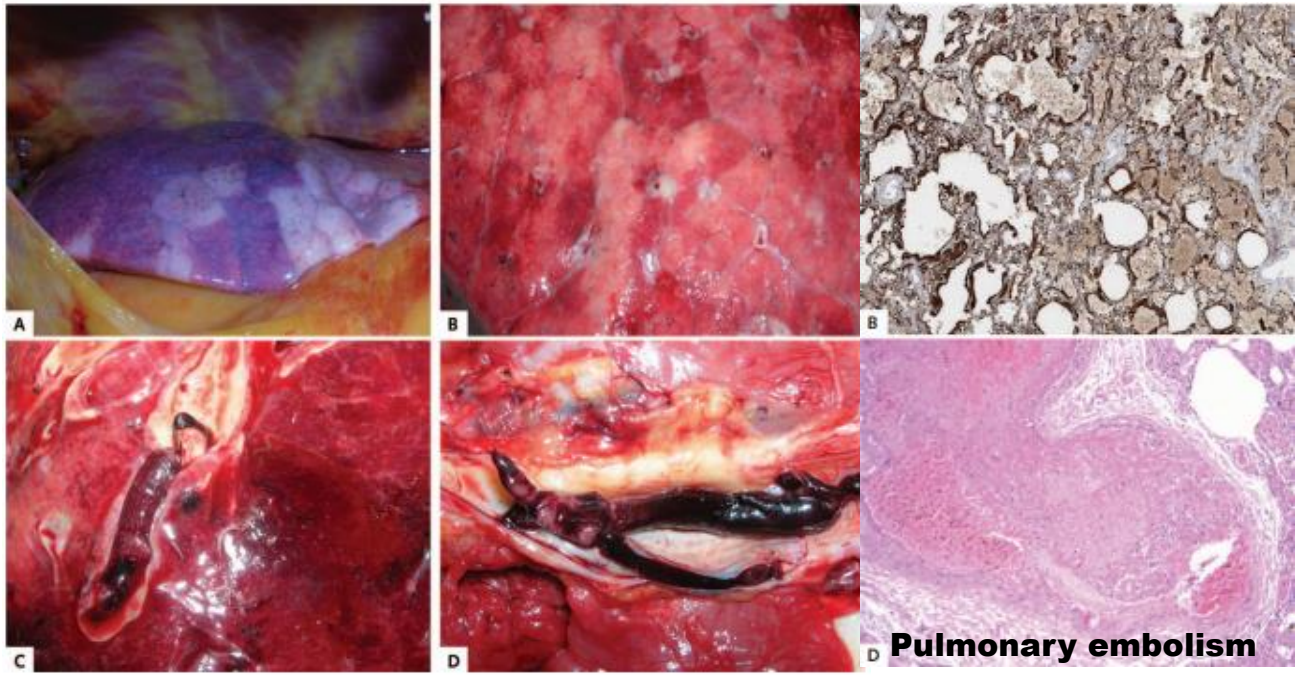
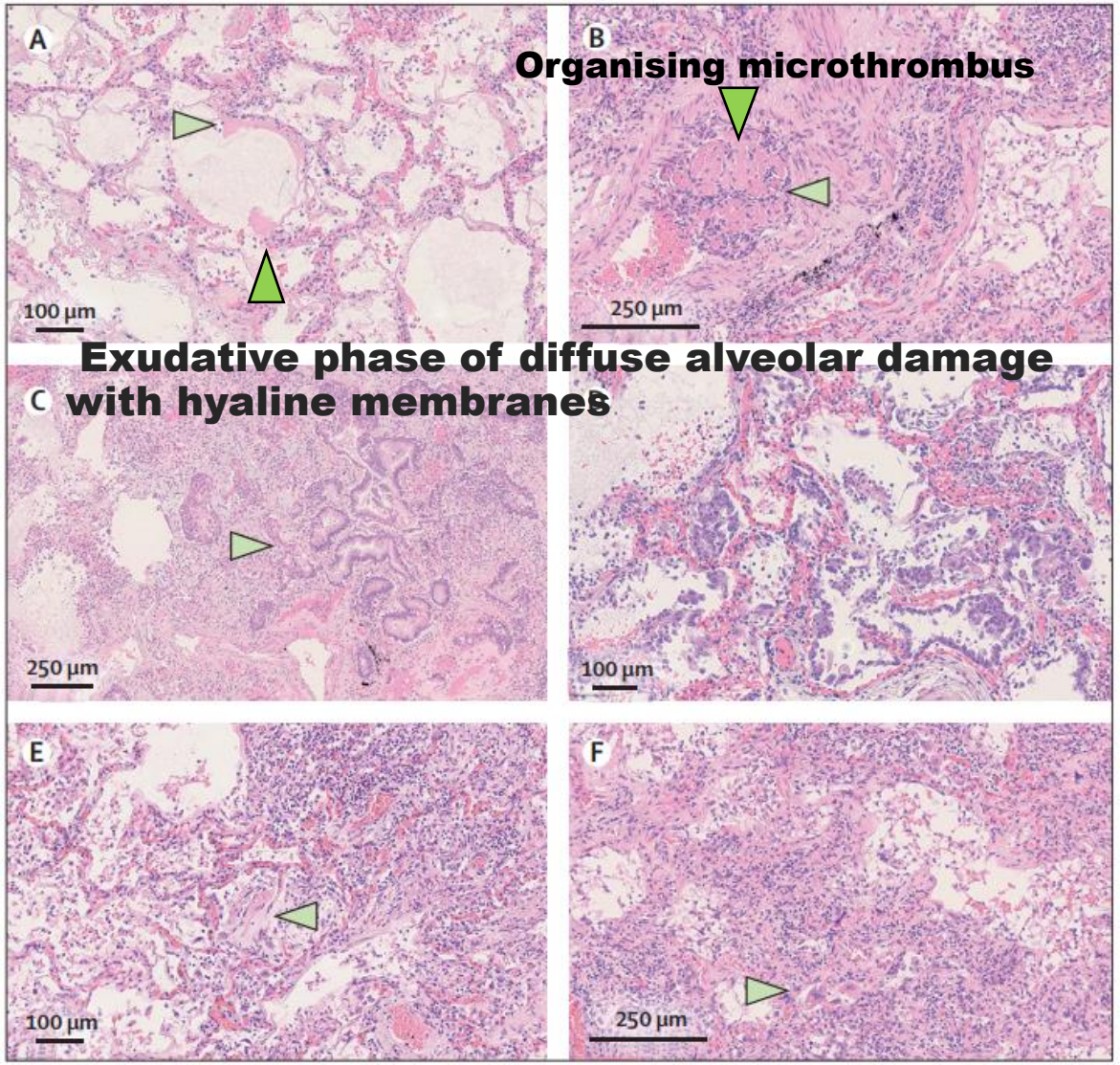
Pulmonary post-mortem findings in a series of COVID-19 cases



Ann Intern Med. doi:10.7326/M20-2003



Lancet Infect Dis 2020;20: 1135–40

- Capillary congestion (in all 38cases)
- Necrosis of pneumocytes (in all 38 cases)
- Hyaline membranes (in 33 cases)
- Interstitialintra-alveolar oedema (in 37 cases)
- Type 2 pneumocyte hyperplasia (in all 38 cases)
- Squamous metaplasia with atypia (in 21 cases)
- Platelet–fibrin thrombi (in 33 cases)

Guidance on Thromboprophylaxis

Recommending Organization*

NIH[1]	ASH[2]
▪ **Hospitalized adults with COVID-19 should receive VTE prophylaxis per the SoC for other hospitalized adults** ▪ Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual SoC for patients without COVID-19 ▪ Currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside of clinical trial ▪ Hospitalized patients should not be routinely discharged on VTE prophylaxis (extended VTE prophylaxis can be considered in patients with low bleeding risk and high VTE risk)	▪ **All hospitalized adults with COVID-19 should receive thromboprophylaxis with low-molecular-weight heparin over unfractionated heparin, unless bleeding risk outweighs thrombosis risk** ▪ Fondaparinux is recommended in the setting of heparin-induced thrombocytopenia ▪ In patients in whom anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (eg, pneumatic compression devices) ▪ Encourage participation on clinical trials rather than empiric use of therapeutic-dose heparin in COVID-19 patients with no other indication for therapeutic dose anticoagulation

*Additional recommendations available from the International Society on Thrombosis and Haemostasis[3], and CHEST.[4]

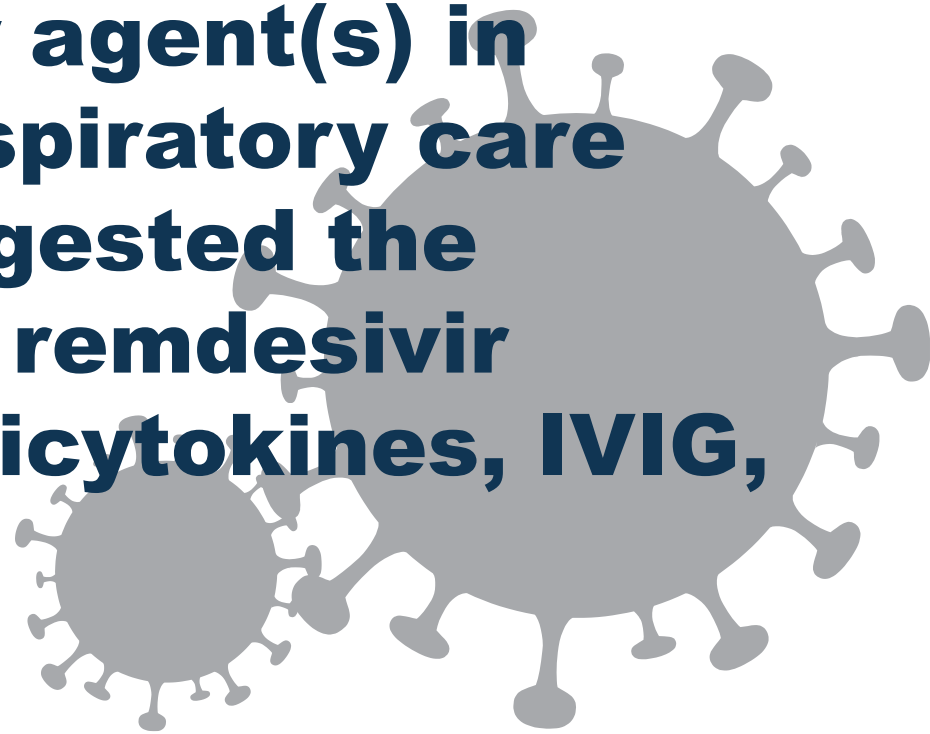
1. NIH. COVID-19 Treatment Guidelines. Updated: May 12, 2020. 2. American Society of Hematology. COVID-19 and VTE/ Anticoagulation: Frequently Asked Questions. 3. Spyropoulos. J Thromb Haemost. 2020;[Epub]. 4. Moores. CHEST. 2020;[Epub].

Slide credit: clinicaloptions.com

Summary: Treatment for COVID-19

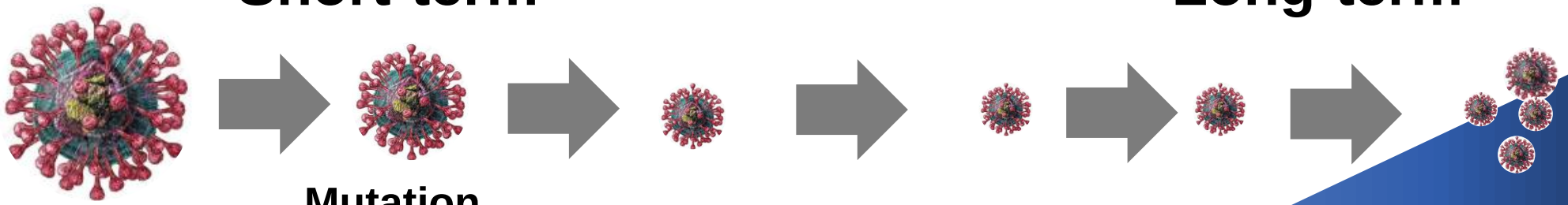
"COVID-19 always keeps us surprised"

- COVID-19 is a systemic disease caused by viral invasion and immune response to virus
- Treatment: supportive treatment in mild case, antiviral and antiinflammatory agent(s) in moderate/severe case plus respiratory care
- Data from clinical studies suggested the benefits of corticosteroid and remdesivir
- Other potential treatment: anticytokines, IVIG, convalescent plasma



Future of pandemic

TRC EIDCC
Thai Red Cross Emerging Infectious Diseases Clinical Center



Short-term

Long-term

Mutation

Transition phase to mild endemic virus

Milder form of infection

Herd immunity

- Infection-reinfection
- Vaccination & booster

Crisis phase