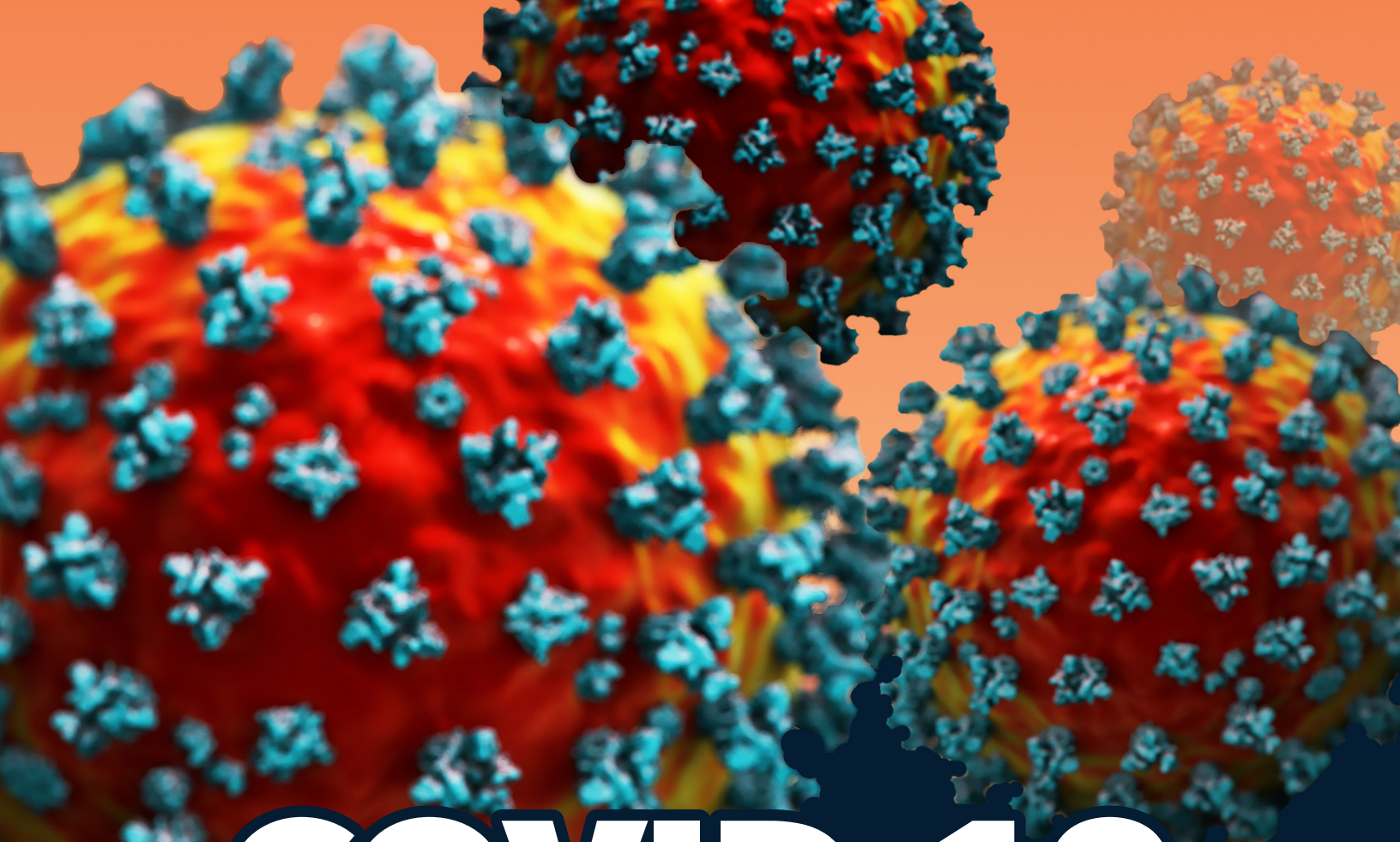

COVID-19 FRONTLINE:

Evolving Strategies in the Management and Prevention of **COVID-19**

Michael Niederman MD, MACP, FCCP, FCCM, FERS

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This activity is supported by educational grants from AbbVie, Astellas, Genentech, Merck & Co., Inc., and Pfizer.

Agenda

I. COVID-19: An Overview

a. Pathophysiology of the SARS-CoV-2 virus and COVID-19
b. Clinical presentation of COVID-19
c. Epidemiology of COVID-19
d. Risk factors for severe disease
e. Potential role of hyperinflammation in COVID-19

II. Treatment of COVID-19

a. Medical management of:
    i. Severe and critical COVID-19
    ii. Acute respiratory distress syndrome in COVID-19
    iii. Septic shock in critically ill patients
    iv. Extrapulmonary manifestations
b. Prevention of complications in critically ill patients
c. Persistent symptoms after COVID-19 infection

III. Emerging Therapies

a. Incorporating recommended treatment options into clinical care
b. Clinical trial data on the efficacy and safety of:
    i. Recommended treatment options
    ii. Emerging and off-label treatment options
    iii. Emerging vaccines

IV. Case Studies

COVID-19 Frontline TeleECHO Series: Evolving Strategies in the Management and Prevention of COVID-19

FACULTY

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PROGRAM OVERVIEW

The COVID-19 FRONTLINE TeleECHO series provides a comprehensive and up-to-date perspective on the ever-changing management of patients with COVID-19. Each TeleECHO session features in-depth case studies to encourage retention of the lessons and provide new perspectives on the management of patients during the COVID-19 pandemic. The case studies will focus on different issues facing clinicians, such as the management of severe and critically ill patients, the treatment of pulmonary and extrapulmonary manifestations, and the impact of comorbidities on treatment.

TARGET AUDIENCE

This activity is designed to meet the educational needs of a variety of specialties, including infectious disease specialists, pulmonary medicine specialists, emergency room practitioners, advanced practitioners, nurses, and other healthcare professionals to help support them in their effort to optimize care of patients with COVID-19.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Identify clinical predictors of disease severity and discuss the pathophysiology of COVID-19
- Evaluate clinical trial data on the efficacy and safety of emerging therapies and vaccines for the management of COVID-19
- Apply current treatment guidelines, clinical trial data, and patient-specific factors to the management of patients with COVID-19

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the treatment of patients with COVID-19.

Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

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METHOD OF PARTICIPATION

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1. Read the CME/CNE information and faculty disclosures.
2. Participate in the web-based live activity.
3. Submit the evaluation form to Med Learning Group.

You will receive your certificate upon completion.

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COVID-19 Front Line: Evolving Strategies in the Management and Prevention of COVID-19

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1

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2

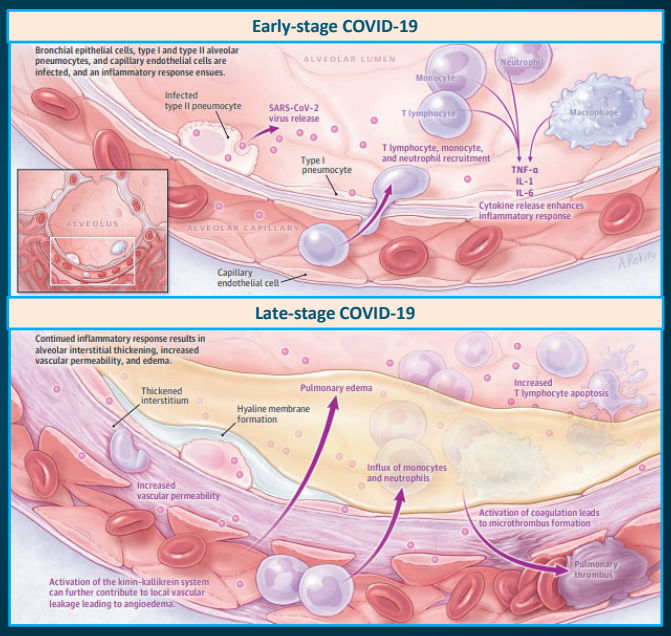
Learning Objectives

- Identify clinical predictors of disease severity and discuss the pathophysiology of COVID-19
- Evaluate clinical trial data on the efficacy and safety of emerging therapies and vaccines for managing COVID-19
- Apply current treatment guidelines, clinical trial data, and patient-specific factors to managing patients with COVID-19

3

Pathophysiology of COVID-19

- COVID-19 is caused by the SARS-CoV-2 virus
- The virus is spread primarily via respiratory droplets during face-to-face contact
- Average time from exposure to symptom onset is 5 days
- Symptoms develop within 11.5 days in 97.5% of patients with symptoms



COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

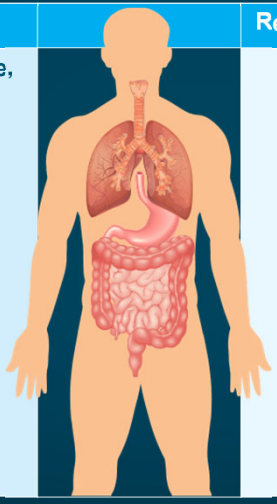
Wiersinga WJ, et al. *JAMA*. 2020;324:782-793.

4

Clinical Presentation of COVID-19

Systemic and respiratory disorders caused by COVID-19

Systemic Disorders	Respiratory Disorders
Fever, cough, fatigue, sputum production, headache	Rhinorrhea, sneezing, sore throat
Hemoptysis, acute cardiac injury	Pneumonia
Hypoxemia	Ground-glass opacities
Dyspnea, Lymphopenia	RNAemia, acute respiratory distress syndrome
Diarrhea	



Most common symptoms of COVID-19 at presentation

Symptom	Patients Presenting with Symptom (N = 1420)
Headache	70.3%
Loss of smell	70.2%
Nasal obstruction	67.8%
Asthenia	63.3%
Cough	63.2%
Myalgia	62.5%
Rhinorrhea	60.1%
Taste dysfunction	54.2%
Sore throat	52.9%
Fever (>38°C)	45.4%

RNA = ribonucleic acid; C = Celsius.

Guan WJ, et al. *N Engl J Med*. 2020;382:1708-1720. Rothan HA, et al. *J Autoimmun*. 2020;109:102433. Lechien JR , et al. *J Intern Med*. 2020;288:335-344. Wang WW, et al. *J Med Virol*. 2020;92:441-447.

5

COVID-19 Disease Severity

A large study of 44,672 confirmed COVID-19 cases identified by the Chinese Centers for Disease Control and Prevention found that:

- 14% of cases were severe
- 5% of cases were critical, with a case-fatality rate of 49%

	Disease Characteristics
Mild illness	Various symptoms (eg, fever, cough, sore throat, headache, malaise, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	SpO_2 ≥94% on room air and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	SpO_2 <94% on room air, PaO_2/FiO_2 <300, respiratory rate >30 breaths/min, or lung infiltrates >50%
Critical illness	Respiratory failure, septic shock, and/or multiorgan dysfunction

SpO_2 = oxygen saturation; PaO_2 = arterial partial pressure of oxygen; FiO_2 = fraction of inspired oxygen.

Wu Z, et al. *JAMA*. 2020;323:1239-1242. National Institutes of Health (NIH). Management of persons with COVID-19 (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/). Accessed 10/30/2020.

6

Risk Factors for Severe Disease

Case series of 5700 hospitalized patients in NYC, Long Island, and Westchester County, NY found:

- Median number of total comorbidities at admission: 4 (IQR: 2–8)
- 87.6% of patients had more than one comorbidity
- Most common comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%)

Case-fatality rate in observational study of COVID-19 cases in China (n = 72,314)

Characteristics	Case-fatality rate
All confirmed cases	2.3%
Critical cases	49.0%
≥80 years of age	14.8%
Cardiovascular disease	10.5%
70–79 years of age	8.0%
Diabetes	7.3%
Chronic respiratory disease	6.3%
Hypertension	6.0%
Cancer	5.6%

IQR = interquartile range.

Richardson S, et al. *JAMA*. 2020;323:2052-2059. Wu Z, et al. *JAMA*. 2020:323:1239-1242.

7

Clinical Predictors of Disease Severity

- A study comparing severe and critically ill COVID-19 patients with those with mild or moderate disease found significant changes in several laboratory parameters
- Specific IgG to SARS-CoV-2 in severe and critically ill patients was significantly lower than in other COVID-19 patients (P <.05)

Commonly altered laboratory parameters in patients with severe or critical COVID-19	
↑ D-dimer	↓ lymphocyte count
↑ fibrinogen	↓ red blood cells
↑ white blood cell count	↓ hemoglobin
↑ neutrophil count	
↑ IL-6	
↑ c-reactive protein	
↑ procalcitonin	
↑ ESR	
↑ ferritin	
↑ lactate dehydrogenase	

IgG = immunoglobulin G; IL = interleukin; ESR = erythrocyte sedimentation rate.

Yuan X, et al. *Int J Hematol*. 2020;112:553-559.

8

Management of COVID-19

9

Medical Management of Severe COVID-19

- Provide immediate supplemental O_2, targeting SpO_2 >94%, to patients with severe acute respiratory illness (SARI) and respiratory distress, hypoxemia, or shock
- Monitor for clinical deterioration (eg, rapidly progressive respiratory failure, sepsis) and provide immediate supportive care
- Review comorbidities, assess current chronic therapies, and monitor for drug-drug interactions
  - ACE inhibitors and ARBs may be continued as they do not affect mortality or risk of infection
- Practice conservative fluid management in patients with SARI if no shock
- Consider administration of remdesivir or dexamethasone
- Administer empiric antimicrobials within 1 hour of sepsis identification
- De-escalate empiric therapy based on microbiology results and clinical judgment

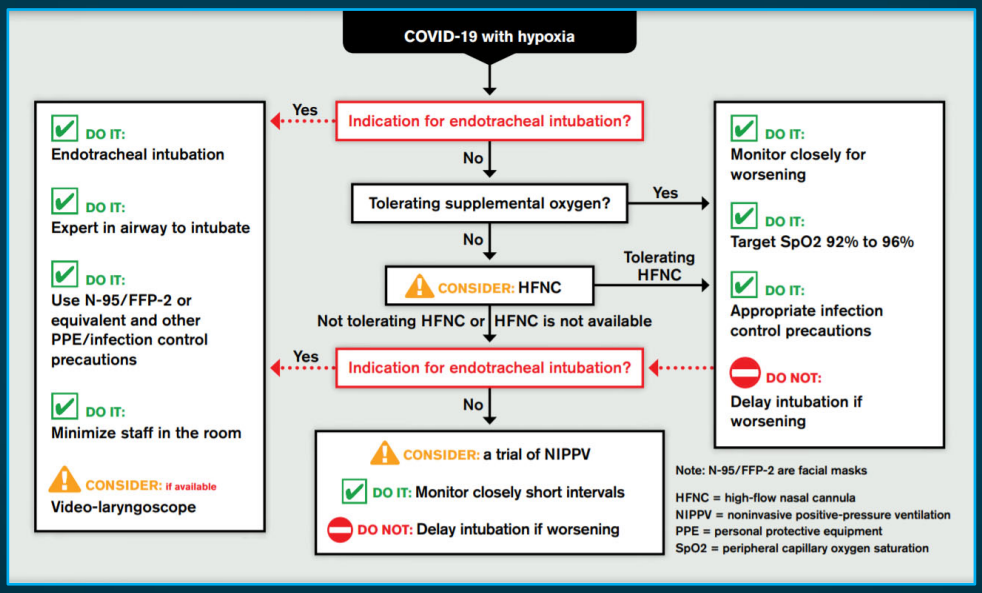
O_2 = oxygen; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

WHO. Clinical Management of COVID-19. Version 1.3. 9. Fosbol EL, et al. *JAMA*. 2020;324:168-177. Bhimraj A, et al. *IDSA Guidelines*. V3.3.0 (www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v3.3.0.pdf). Accessed 10/31/2020.

10

Surviving Sepsis Campaign

Initial Management of Hypoxic COVID-19 Patients



Alhazzani W, et al. *Intensive Care Med*. 2020;46:854-887.

11

Medical Management of ARDS in Critically Ill COVID-19 Patients

All patients with ARDS	• Provide advanced oxygen/ventilatory support if patient in respiratory distress does not respond to standard oxygen therapy and develops severe hypoxemic respiratory failure • Reserve performance of endotracheal intubation with airborne precautions for trained and experienced providers
Mechanically ventilated patients	• Use lower tidal volumes (4–8 mL/kg), inspiratory pressures (plateau pressure <30 cmH_2O) • Apply prone ventilation 12–16 hours/day in adults with severe ARDS • Practice conservative fluid management if no tissue hypoperfusion • In case of moderate to severe ARDS, higher vs lower PEEP suggested; avoid neuromuscular blockade by continuous infusion • Avoid disconnecting ventilator; clamp endotracheal tube if transferring to transport ventilator • Use inline catheters for airway suctioning • Consider ECMO referral if refractory hypoxemia persists despite lung-protective ventilation
Patients receiving noninvasive or high-flow oxygen	• Reserve high-flow nasal cannula (HFNO) and noninvasive ventilation (NIV) for select patients with hypoxemic respiratory failure • Monitor patients receiving HFNO or NIV for clinical deterioration

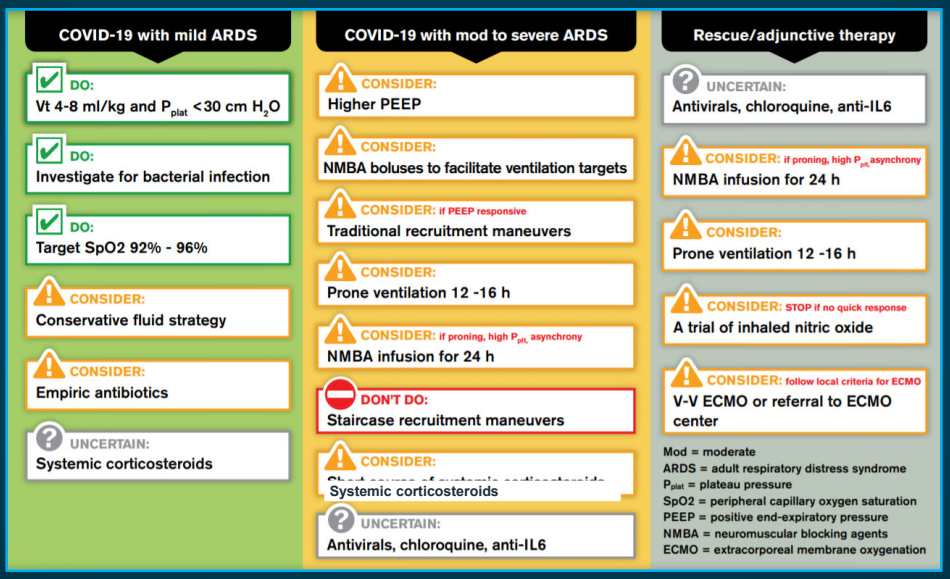
ARDS = acute respiratory distress syndrome; PBW = predicted body weight; PEEP = positive end-expiratory pressure; ECMO = extracorporeal membrane oxygenation.

WHO. Clinical management of COVID-19 (www.who.int/publications-detail/clinical-management-of-covid-19. Accessed 10/31/2020.

12

Surviving Sepsis Campaign

Recommendations on the Management of Patients with COVID-19 and ARDS



Alhazzani W, et al. *Intensive Care Med*. 2020;46:854-887.

13

Prevention of Complications in Critically Ill COVID-19 Patients

Days of invasive mechanical ventilation	• Assess daily for readiness to breathe spontaneously • Minimize sedation (continuous or intermittent) with specific titration targets in mind
Ventilator-associated pneumonia	• Use oral vs nasal intubation in adolescents/adults • Maintain semirecumbent patient positioning (ie, head of bed elevation 30–45°) • Use closed suctioning system; drain condensate periodically • Use new ventilator circuit per patient; exchange for same patient only if soiled/damaged • Replace heat moisture exchanger if malfunctioning or soiled, or every 5–7 days
Catheter-related bloodstream infection	• Use checklist and real-time observer to confirm steps for sterile insertion, as daily reminder to remove catheter if unneeded
Pressure ulcers	• Turn patient every 2 hours
Stress ulcers and GI bleeds	• Administer enteral nutrition within 24–48 hr of admission, H2RAs or PPIs if risk for GI bleed
Side effects and DDIs	• Consider pharmacokinetic and pharmacodynamic effects of all medications

GI = gastrointestinal; H2RA = histamine H-2 receptor antagonist; PPI = proton-pump inhibitor; DDI = drug-drug interaction.

WHO. Clinical management of COVID-19 (www.who.int/publications-detail/clinical-management-of-covid-19. Accessed 10/31/2020.

14

Extrapulmonary Manifestations

Renal dysfunction	• When renal replacement therapy is indicated, continuous renal replacement therapy (CRRT) is recommended, if available • If CRRT is unavailable or not possible, prolonged intermittent renal replacement therapy rather than intermittent hemodialysis is recommended
Hematological	• Anticoagulant thromboprophylaxis is recommended for critically ill patients with COVID-19 – LMWH is preferred – Use of LMWH or UFH is recommended over fondaparinux or direct oral anticoagulants (DOACs) • In acutely ill hospitalized patients with COVID-19, prophylaxis with LMWH or fondaparinux is recommended over UFH; prophylaxis with LMWH, fondaparinux or UFH is recommended over DOACs • COVID-19 diagnosis should not influence the recommendation for VTE prophylaxis in hospitalized children • Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care (SoC)

LMWH = low molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism

NIH COVID-19 Treatment Guidelines (https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf/). Last updated 10/22/2020. Accessed 10/31/2020. Moores LK, et al. *Chest*. 2020;158:1143-1163.

15

Clinical Trial Data on Emerging Treatment Options

16

IDSA: Recommended Treatment Options

Treatment Option	Guidance
Remdesivir	• Recommended for hospitalized patients with severe COVID-19 • Most benefit seen in those with severe COVID-19 on supplemental oxygen rather than patients on mechanical ventilation or ECMO • 5 days of treatment recommended for patients on supplemental oxygen • 10 days of treatment recommended for patients on mechanical ventilation or ECMO
Glucocorticoids	• Recommended for hospitalized patients with severe COVID-19 • Dexamethasone 6 mg IV or PO for 10 days or equivalent • Not recommended for hospitalized patients without hypoxemia requiring supplemental oxygen

IDSA = Infectious Diseases Society of America; PO = by mouth.

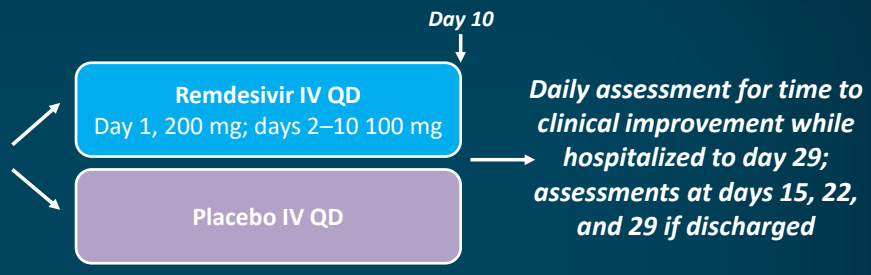
Bhimraj A, et al. IDSA Guidelines. V3.3.0 (www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v3.3.0.pdf). Accessed 10/31/2020.

17

Adaptive COVID-19 Treatment Trial (NIAID ACTT-1): Trial Design

- Multicenter, adaptive, randomized, double-blind, placebo-controlled phase 3 trial

Inclusion criteria (N = 1063)
- Adult patients ≥18 years of age
- Hospitalized with symptoms of COVID-19/SARS-CoV-2 infection and ≥1 of following:
  - Radiographic infiltrates by imaging
  - SpO_2 ≤94% on room air
  - Requiring supplemental oxygen
  - Requiring mechanical ventilation



- Primary endpoint: time to recovery by day 29 according to 8-point ordinal scale
- Secondary endpoints: treatment-related improvements in ordinal scale at day 15

QD = each day.

Beigel JH, et al. *N Engl J Med*. 2020;May 22: Epub ahead of print. NCT04280705.

18

COVID-19 Clinical Status Ordinal Scale

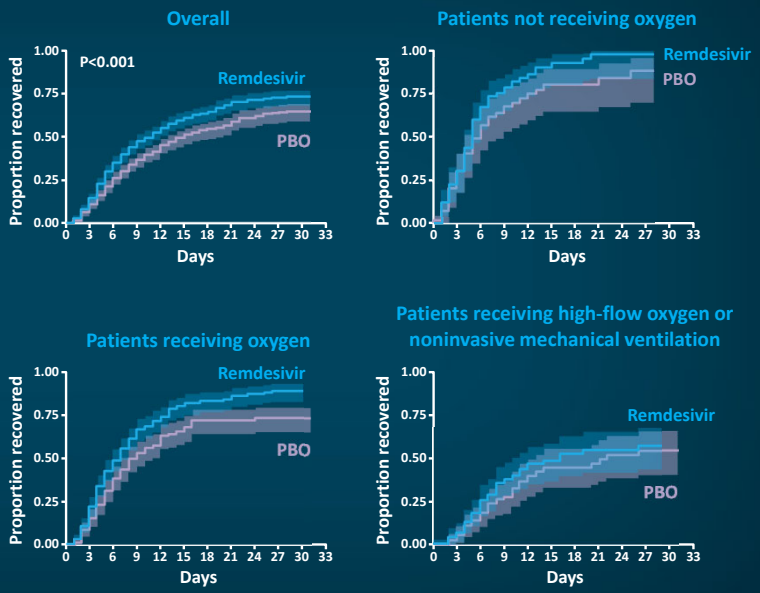
Clinical Status Ordinal Scale	Clinical Status Description for Assessment
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities, and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen, and no longer requires ongoing medical care (if hospitalization extended for infection-control purposes)
4	Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on noninvasive ventilation or high-flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

Beigel JH, et al. *N Engl J Med.* 2020;May 22: Epub ahead of print.

19

NIAID ACTT-1 Results

- Faster median recovery with remdesivir (11 days vs 15 days; *P* <.001)
- Kaplan-Meier estimates of mortality by 14 days:
  - 7.1% with remdesivir
  - 11.9% with placebo
  - HR = 0.70; 95% CI, 0.47–1.04



HR = hazard ratio; CI = confidence interval; PBO = placebo.

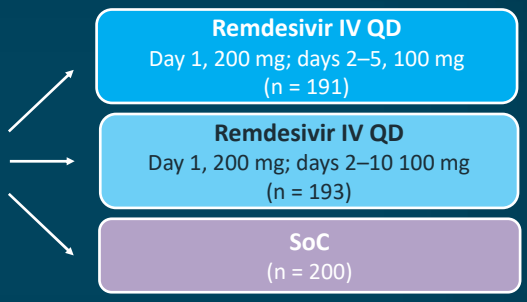
Beigel JH, et al. *N Engl J Med.* 2020;May 22: Epub ahead of print.

20

SIMPLE-Moderate Study: Trial Design

- Multicenter, randomized, open-label phase 3 trial of remdesivir in patients with moderate COVID-19

Inclusion criteria (N = 584)
- Patients ≥12 years of age
- Hospitalized with SARS-CoV-2 infection confirmed by RT-PCR
- Radiographic infiltrates by imaging
- SpO_2 >94% on room air



- Primary endpoint: improvement on 7-point ordinal scale on day 11
- Secondary endpoint: treatment-emergent adverse events

RT-PCR = reverse transcriptase-polymerase chain reaction.

NCT04292730.

21

SIMPLE-Moderate Study: Efficacy

Patients receiving 5-day remdesivir were 65% more likely to have clinical improvement at day 11 vs SoC (OR = 1.65; 95% CI: 1.09–2.48; *P* = .017)

- No significant improvement noted with 10-day remdesivir vs SoC; OR = 1.31; 95% CI, 0.88–1.95; *P*= .18)

Clinical efficacy at day 11	Remdesivir 5-Day (n = 191) n (%)	Remdesivir 10-Day (n = 193) n (%)	SoC (n = 200) n (%)
≥2-point improvement on ordinal scale	134 (70)	126 (65)	121 (61)
≥1-point improvement on ordinal scale	146 (76)	135 (70)	132 (66)
Requiring any oxygen support	12 (6)	13 (7)	22 (11)
≥1-point worsening in ordinal scale	6 (3)	12 (6)	22 (11)
Death	0	2 (1)	4 (2)

OR = odds ratio.

Gilead press release (PR). 6/1/2020 (www.gilead.com/news-and-press/press-room/press-releases/2020/6/gilead-announces-results-from-phase-3-trial-of-remdesivir-in-patients-with-moderate-covid-19). Accessed 10/31/2020.

22

Remdesivir Safety Information and Warnings

- Most common AEs are nausea, diarrhea, and headache
- Recommended daily monitoring: serum chemistries, hematology, ALT, AST, renal function tests, bilirubin, ALP
- Infusion-related reactions have occurred in patients receiving remdesivir; immediately discontinue if signs of clinically significant infusion reaction occur
- Transaminase elevations have occurred in healthy controls and patients with COVID-19 receiving remdesivir
  - Do not administer if ALT ≥5 x ULN at baseline
  - Discontinue if ALT ≥5 x ULN; resume treatment when ALT elevation resolves

Adverse Events	Remdesivir 5 Days (n = 200)	Remdesivir 10 Days (n = 197)
Any	71%	74%
Serious	21%	35%
Grade ≥3	31%	43%
Discontinued due to AE	5%	10%
All-cause mortality at day 28	10%	13%

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ULN = upper limit normal

Remdesivir EUA Provider Fact Sheet.

23

RECOVERY Trial Design

- Eligible patients (hospitalized with clinically suspected or laboratory-confirmed SARS-CoV-2 infection) were randomized to:

No additional treatment | **Dexamethasone** | **Hydroxychloroquine** | **Lopinavir/ritonavir** | **Azithromycin**

- Factorial design with simultaneous randomization to no additional therapy or **convalescent plasma**
- Patients with progressive disease (hypoxia and an inflammatory state) may undergo second randomization to no additional treatment or **tocilizumab**
- Primary endpoint: 28-day mortality

Randomized Evaluation of COVID-19 Therapy—RECOVERY (www.recoverytrial.net/files/recovery-protocol-v7-0-2020-06-18.pdf). Accessed 10/31/2020.

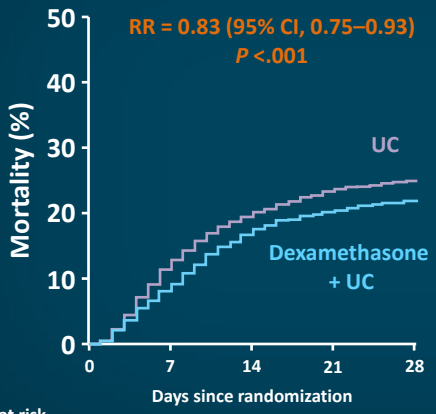
24

RECOVERY Trial

Mortality With Dexamethasone + Usual Care (UC) vs UC Alone

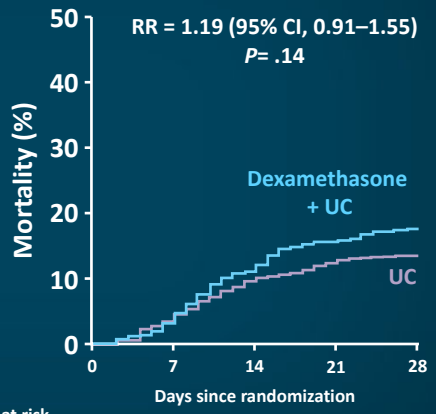
2104 patients randomized to dexamethasone 6 mg QD for up to 10 days; 4321 patients received UC alone

All participants (n = 6425)



No. at risk					
UC	4321	3754	3427	3271	3205
Dexamethasone/UC	2104	1903	1725	1659	1621

No oxygen (n = 1535)



No. at risk					
UC	501	463	420	394	383
Dexamethasone/UC	1034	969	890	856	832

RR = relative risk.

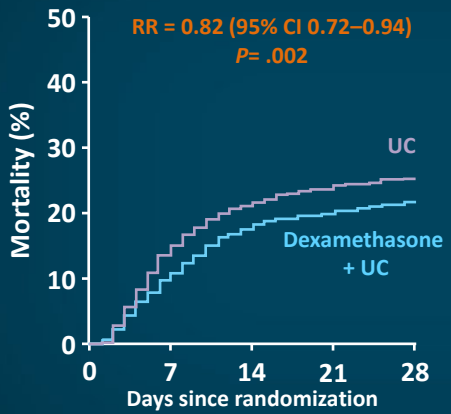
Horby P, et al; RECOVERY Collaborative Group. *N Engl J Med.* 2020;Jul 17:Epub ahead of print.

25

RECOVERY Trial

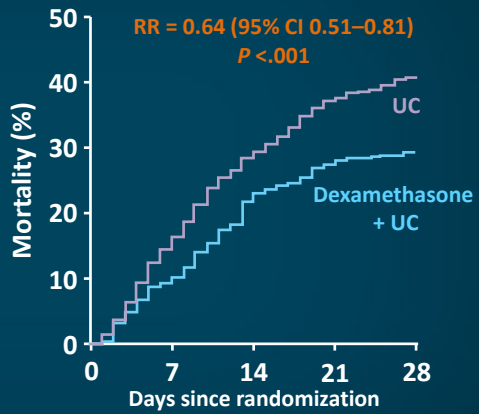
Mortality in Patients On Oxygen or Mechanical Ventilation ± Dexamethasone

Oxygen only (n = 3883)



No. at risk					
Dexamethasone/UC	1279	1135	1036	1006	981
UC	2604	2195	2018	1950	1916

Invasive mechanical ventilation (n = 1007)



No. at Risk					
Dexamethasone/UC	324	290	248	232	228
UC	683	572	481	424	400

Horby P, et al; RECOVERY Collaborative Group. *N Engl J Med.* 2020;Jul 17:Epub ahead of print.

26

RECOVERY Trial: Secondary Outcomes

Outcome	Dexamethasone + UC	UC Only	RR (95% CI)
Discharged from hospital within 28 days	67.2%	63.5%	1.10 (1.03–1.17)
Receipt of invasive mechanical ventilation or death	25.6%	27.3%	0.92 (0.84–1.01)
Invasive mechanical ventilation	5.7%	7.8%	0.77 (0.62–0.95)
Death	21.7%	22.7%	0.93 (0.84–1.03)

Horby P, et al; RECOVERY Collaborative Group. *N Engl J Med.* 2020;Jul 17: Epub ahead of print.

27

Hydroxychloroquine*

- Randomized RECOVERY trial:
  - 1542 patients randomized to hydroxychloroquine and 3132 patients to usual care alone
  - No significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs 23.5% usual care; HR = 1.11; *P*= .10)
  - No beneficial effect on hospital stay duration or other outcomes
- Observational study:
  - No benefit with hydroxychloroquine in 1376 hospitalized patients
  - 45.8% received hydroxychloroquine within 24 hours of presentation and 85.9% within 48 hours

Associations between Hydroxychloroquine Use and Composite Endpoint of Intubation or Death	
Analysis	**Intubation or Death**
No. of events/no. of patients at risk (%)	
Hydroxychloroquine	262/811 (32.3)
No hydroxychloroquine	84/565 (14.9)
Crude analysis, HR (95% CI)	2.37 (1.84–3.02)
Multivariable analysis, HR (95% CI)	1.00 (0.76–1.32)
Propensity-score analyses, HR (95% CI)	
With inverse probability weighting	1.04 (0.82–1.32)
With matching	0.98 (0.73–1.31)
Adjusted for propensity score	0.97 (0.74–1.28)

*Not an FDA-approved treatment.

Geleris J, et al. *N Engl J Med*. 2020;382:2411-2418.

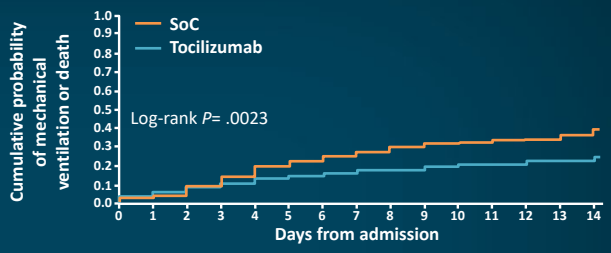
28

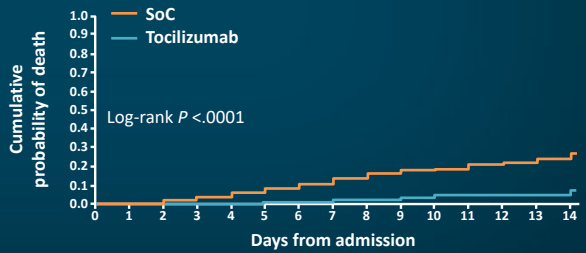
COVID-19 Animation

29

Tocilizumab*

- Retrospective, observational cohort study of 544 patients with severe COVID-19 pneumonia
- 20% of patients in standard care group died, compared with 7% in tocilizumab group (*P* <.0001)
- Tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (aHR = 0.61; 95% CI, 0.40–0.92; *P*= .02)





*Not an FDA-approved treatment.

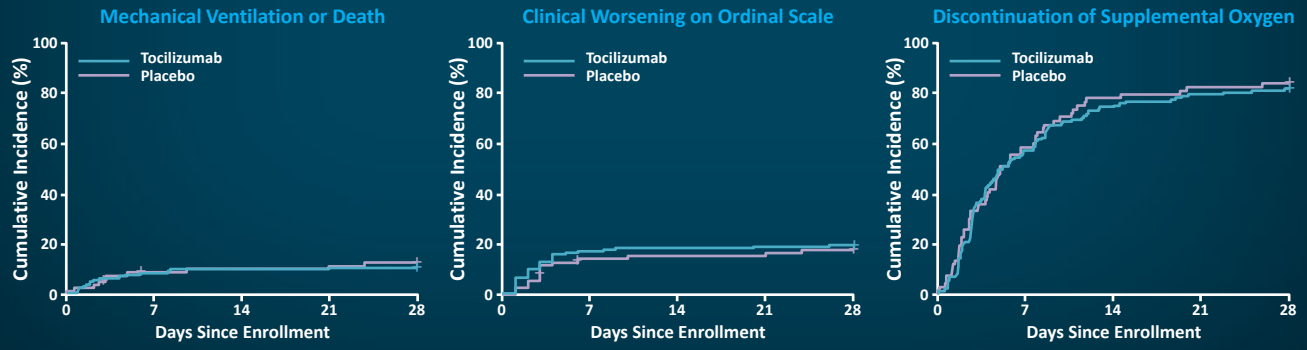
aHR = adjusted HR.

Guaraldi G, et al. *Lancet Rheumatol*. 2020;2:e474-e484.

30

Tocilizumab in Patients Hospitalized with COVID-19

- Randomized, double-blind, placebo-controlled trial of 243 patients with confirmed SARS-CoV-2 infection, hyperinflammatory states, and ≥2 or more of the following:
  - Fever
  - Pulmonary infiltrates
  - Need for supplemental O2 to maintain O2 saturation >92%

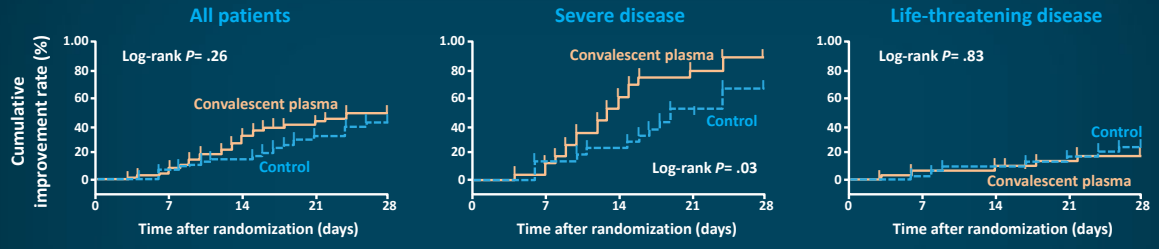


Stone JH, et al. *N Engl J Med*. 2020;Epub ahead of print.

31

Convalescent Plasma

- Open-label, randomized trial of 103 patients with severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or mechanical ventilation) disease



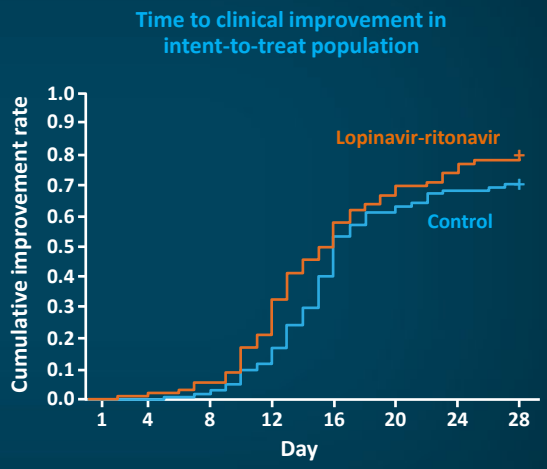
- Clinical improvement occurred within 28 days in 51.9% of the convalescent plasma group vs 43.1% in the control group (HR = 1.40; 95%, 0.79–2.49; *P*= .26)
- No significant difference between groups in 28-day mortality or time from randomization to discharge

Li L, et al. *JAMA*. 2020;324:460-470.

32

Lopinavir/Ritonavir*

- 199 hospitalized COVID-19 patients with O_2 sat ≤94% on room air or PaO_2/FiO_2 <300 mmHg
- Primary endpoint: time to clinical improvement
  - No differences in time to clinical improvement between treatment groups
- 28-day mortality was numerically lower in lopinavir/ritonavir group (19.2% vs 25.0%)
- Patients in lopinavir/ritonavir group had shorter stay in ICU (6 days vs 11 days)



*Not an FDA-approved treatment.

ICU = intensive care unit.

Cao B, et al. *N Engl J Med*. 2020;382:1787-1799.

33

Other Randomized Clinical Trials for COVID-19

Agent	N	Population	Comparator	Primary Outcome
Lopinavir/ritonavir/ interferon β-1b/ ribavirin	127	Adults, mild to moderate	Lopinavir/ritonavir	Patients in combination group showed faster viral clearance and more rapid clinical improvement
Sofosbuvir/ daclatasvir	66	Adults, severe	Lopinavir/ritonavir	88% achieved clinical recovery ≤14 days vs 67% with control (*P*= .076)
Hydroxychloroquine	150	Adults, mild to moderate	SoC alone	No difference in negative conversion of SARS-CoV-2 by day 28
Tocilizumab	129	Moderate or severe pneumonia	SoC alone	Improvement in composite endpoint of death or need for ventilation at day 14 with tocilizumab vs standard care
Sarilumab (200 or 400 mg)	457	Severe or critical	Placebo	CRP decline: 77% and 79% vs 21% Recommended continuing phase 3 only in critical subgroup with 400 mg sarilumab vs placebo

CRP = C-reactive protein.

Hung IFN, et al. *Lancet*. 2020;395:1695-1704. Li L, et al. Med. 2020; Epub. Wang Y, et al. *Lancet*. 2020;395:1569-1578. Goldman JD, et al. *N Engl J Med*. 2020;May 27; Epub ahead of print. Chen C, et al. MedRxiv. 2020 April 15. Tang W, et al. MedRxiv. 2020 May 7. Assistance Publique - Hôpitaux de Paris/Universities/INSERM-REACTing COVID-19 academic research collaboration. PR 2020 April 27. NCT04331808. NCT04315298. Regeneron PR. 2020 April 27. Sadeghi A, et al. IAS 2020: abstract 11125.

34

Vaccine Candidates

Vaccine Candidate	Vaccine Type	Key Data from Clinical Trials
BNT162b2	Lipid nanoparticle-encapsulated mRNA vaccine	90% effective in preventing COVID-19 after 2 doses in subjects without evidence of prior SARS-CoV-2 infection
AZD1222/ ChAdOx1	Simian adenovirus vector containing DNA coding for spike glycoprotein	Neutralizing antibodies were detected in 91–100% of participants after a single dose (depending on assay used) and in 100% after a booster dose
Ad5	Non-replicating adenovirus type-5 vector containing spike DNA	Phase 1 study showed humoral responses peaked at day 28 post-vaccination, and rapid specific T-cell responses were noted from day 14 post-vaccination
NVX-CoV2373	Recombinant nanoparticle vaccine composed of trimeric full-length spike and Matrix-M1 adjuvant	Two-dose adjuvanted regimen induced geometric mean anti-spike IgG and neutralization responses that exceeded convalescent serum

RBD = receptor binding domain

Walsh EE, et al. N Engl J Med. 2020;Oct 14: Epub ahead of print. Pfizer press release (www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against). Accessed 11/11/2020. Folegatti PM, et al. *Lancet*. 2020;396:467-478. Zhu FC, et al. *Lancet*. 2020;395:1845-1854. Keech C, et al. *N Engl J Med*. 2020;Sep 2: Epub ahead of print.

35

Emerging Vaccines
BNT162b2

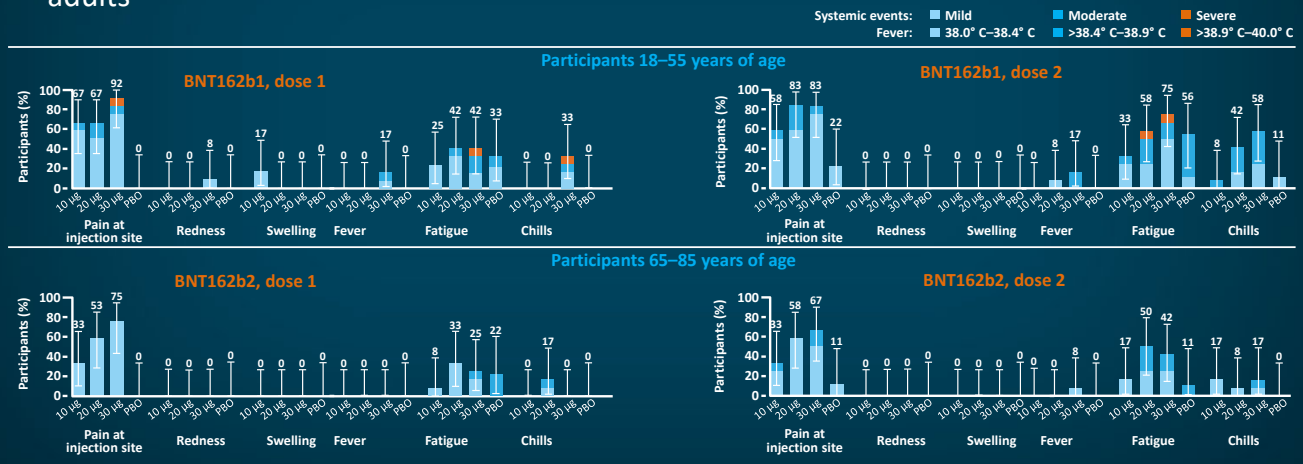
- Interim results from a phase 3 trial found BNT162b2 was more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection
  - Study enrolled 43,538 participants
  - No serious safety concerns have been observed
  - Interim analysis evaluated 94 confirmed cases of COVID-19 in trial participants
- BNT162b2 is an mRNA vaccine with a 2-dose schedule
  - Second injection given 3 weeks after the first
  - Vaccine efficacy rate >90% at 7 days after the second dose
  - Protection is achieved 28 days after the initiation of the vaccination in majority of patients

Pfizer press release (www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against). Accessed 11/11/2020.

36

Emerging Vaccines: BNT162b2 Results

- Phase 1 trial of 195 patients randomized according to age, vaccine dose, and vaccine candidate (BNT162b1 or BNT162b2)
- Lower incidence and severity of systemic reactions with BNT162b2, particularly in older adults

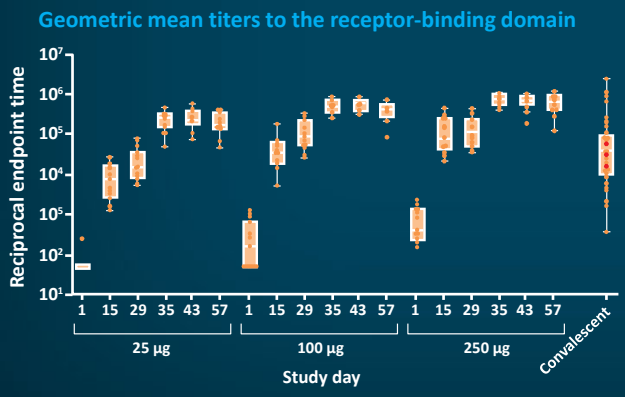


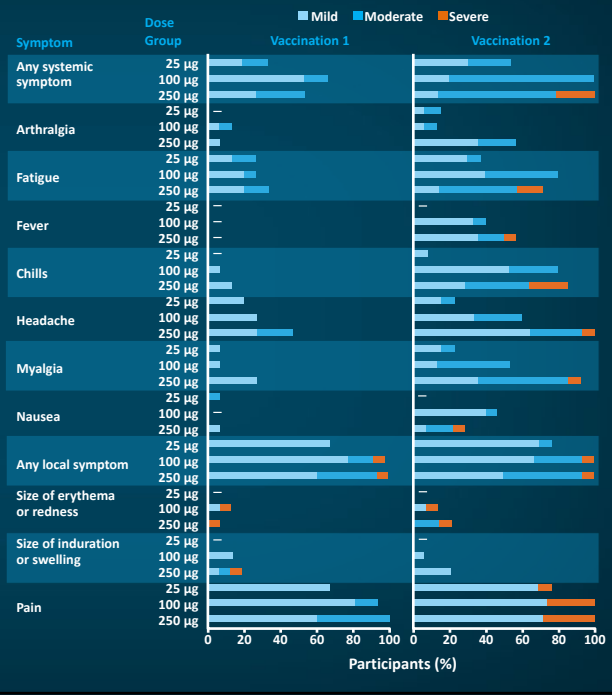
Walsh EE, et al. *N Engl J Med*. 2020;Oct 14: Epub ahead of print.

37

Emerging Vaccines: mRNA-1273

- Phase 1, dose-escalation trial in 45 healthy adults aged 18–55 years
- Participants received 2 doses, 28 days apart, of 25, 100, or 250 µg





Jackson LA, et al. *N Engl J Med*. 2020;Jul 14: Epub ahead of print.

38

Monoclonal Antibodies

Candidate	Patient Population	Results
Bamlanivimab (LY-CoV555)	• Mild-to-moderate COVID-19 patients in outpatient setting • Recently diagnosed: positive test ≤3 days prior to infusion	• **Emergency use authorization issued for patients 12 years and older with mild-to-moderate COVID-19 who are at high risk for progressing to severe COVID-19 or hospitalization** • Bamlanivimab should be administered as soon as possible and within 10 days of symptom onset • Hospitalizations and ER visits occurred in 3% of bamlanivimab-treated patients and 10% of placebo-treated patients
REGN-COV2	• Non-hospitalized patients with COVID-19 • 45% were seropositive (measurable antiviral antibodies) • 41% were seronegative (no measurable antiviral antibodies)	• REGN-COV2 reduced viral load through day 7 in seronegative COVID-19 patients • Among seronegative patients, median time to symptom alleviation was 13 days with placebo, 8 days with high dose, and 6 days with low dose • Medical visits for COVID-19 were needed for 15.2% of placebo-treated patients, 7.7% of high-dose patients, and 4.9% of low-dose patients

FDA (www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19). Lilly Press Release. (https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-receives-fda). Regeneron PR (https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and). Accessed 11/11/2020.

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Persistent Symptoms After COVID-19 Infection

- Recovered COVID-19 patients discharged from acute care may need continued monitoring for long-lasting effects
- In a study of 143 previously hospitalized patients in Rome, Italy:
  - 87.4% had at least one persistent symptom 2 months or longer after initial onset and at more than a month after discharge
  - 32% of patients had 1 or 2 symptoms and 55% had 3 or more
  - None had fever or signs and symptoms of acute illness
  - Most commonly reported persistent symptoms included fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (21%)

Carfi A, et al. *JAMA*. 2020;324:603-605.

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Case Study 1

COVID-19 During Pregnancy

41

COVID-19 During Pregnancy

- 29-year old female, 31 weeks gestation, G2P1
- She reports to the ED following a positive nasal swab for COVID-19 and progressive worsening of dyspnea
- She reports 7 days of dyspnea, fever, and nonproductive cough
- Mild gestational diabetes controlled by diet and exercise
- Social history: Never smoked, no alcohol, no elicit drug use, HIV negative, no occupational exposures

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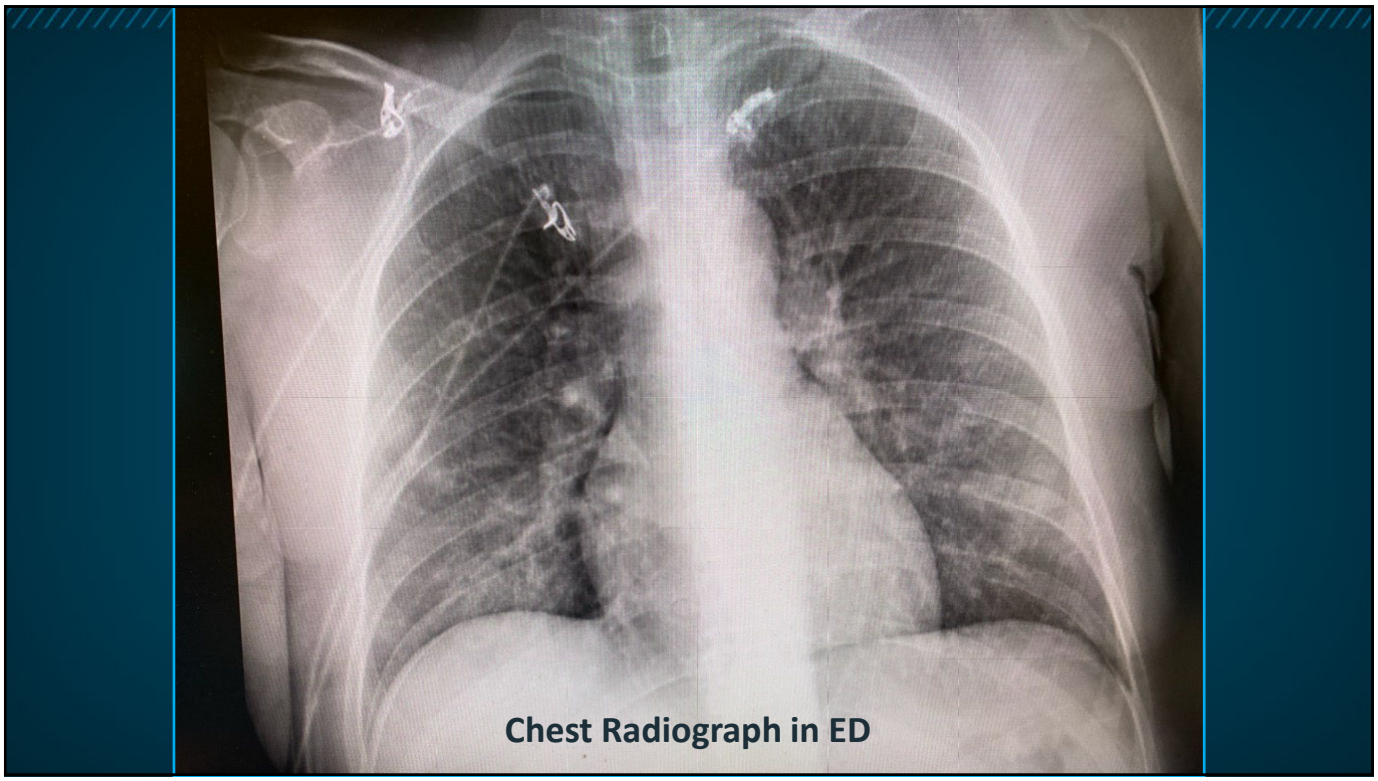

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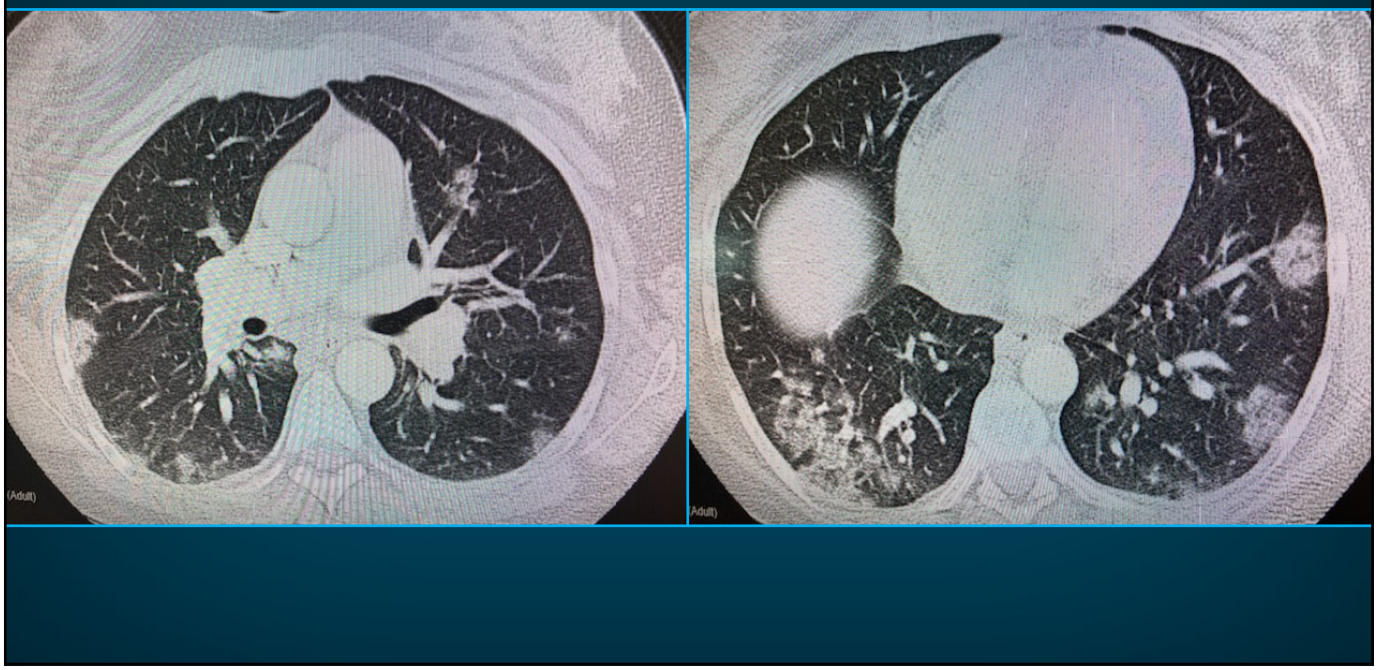
CT Performed in ED to Exclude PE



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How would you manage this patient's COVID-19?

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Would you recommend VTE prophylaxis for this patient?
If so, what medications would you recommend?

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Patient Management Plan

- The patient was admitted to the ICU and placed on supplemental oxygen
- Lateral position recommended as patient was unable to self-prone
- Fetal monitoring by OB
- O_2 saturation was 90% on supplemental oxygen and patient was placed on HFNC
  - Order to start epoprostenol for O_2 saturation persistently <95% on HFNC
- Patient received convalescent plasma and dexamethasone for COVID-19 and fetal lung maturity
- Enoxaparin given for VTE prophylaxis

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Managing COVID-19 During Pregnancy

- Pregnant women may be at increased risk of mechanical ventilation and ICU admission compared to non-pregnant peers
- Corticosteroids may be used to manage COVID-19 in pregnant patients
  - Use caution in patients with preexisting diabetes or gestational diabetes, particularly if under insulin therapy
- Increased risk of thromboembolic events in COVID-19 and pregnancy
  - VTE prophylaxis recommended for all hospitalized patients with COVID-19 and pregnant women with COVID-19 unless contraindicated
  - Unfractionated heparin is preferred in patients who deliver within several days as it is readily reversed
  - Low molecular weight heparin is reasonable in pregnant women who are unlikely to deliver soon

Favilli A, et al. *J Matern Fetal Neonatal Med*. 2020;1-14

48

Case Study 2

Bacterial Pneumonia in a Patient with COVID-19

49

Initial Presentation

- 53-year old man presents to the ED with progressive shortness of breath and headache persisting for 3 weeks
  - Patient reports close contact with a family member with COVID-19 one month ago
  - He was found to be positive for SARS-CoV-2 on nasal PCR testing and admitted
- Prior medical history significant for hypertension, type 2 diabetes, and asthma
- Medications: lisinopril, fluticasone/salmeterol, metformin, liraglutide

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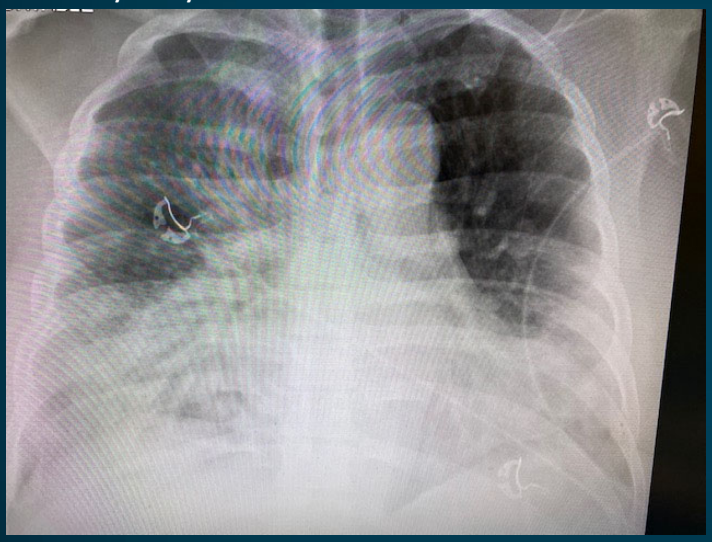
Worsening of Symptoms

Chest x-ray on day 1



- Nasal swab is positive for MRSA
- Patient experienced acute hypoxemic respiratory failure on day 3

How would you manage this patient?

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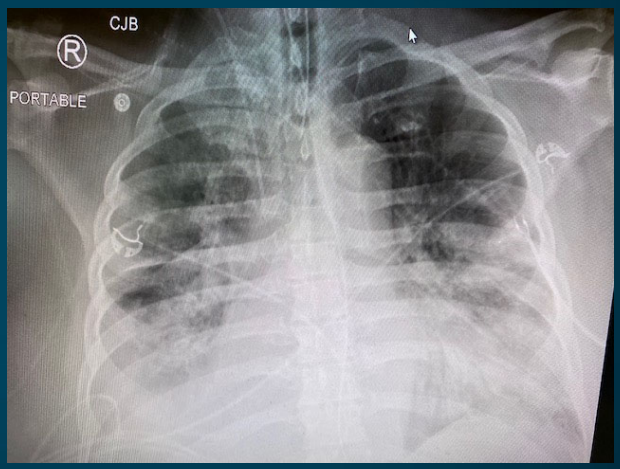
Day 3: ICU Admission

- He was admitted to the ICU and was intubated
  - Patient was treated with oxygen, steroids, BiPAP, and bronchodilators
- Tracheal aspirate cultures positive for MRSA >10^4 cfu/mL
- Patient found to have blood pressure of 180/120 mmHg on day 3 with AKI on CKD



How would you manage this patient?

BiPAP = bilevel positive airway pressure; MRSA = methicillin-resistant staphylococcus aureus; AKI = acute kidney injury; CKD = chronic kidney disease

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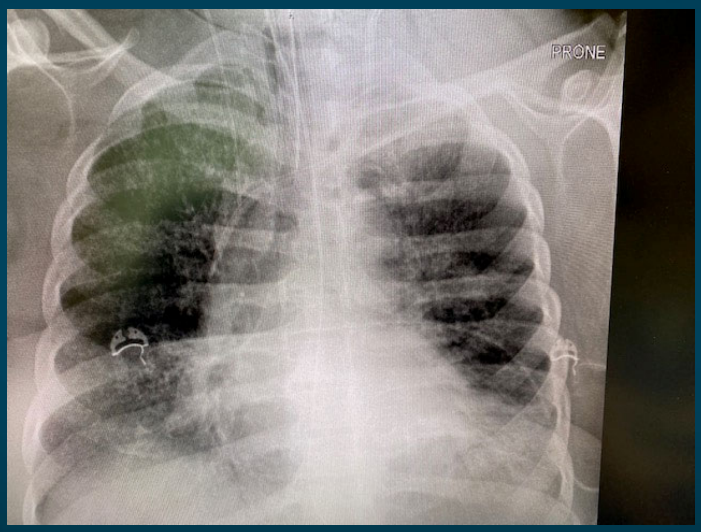
Day 15
Patient was extubated on day 16



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Case Summary

- ~8% of patients with COVID-19 experience bacterial/fungal co-infection during hospital admission, yet ~70% of COVID-19 patients receive antimicrobials
  - Difficult to distinguish between COVID-19 and bacterial pneumonia
- Empiric coverage for bacterial pathogens is recommended for patients with CAP without confirmed COVID-19 but is not required in all patients with confirmed COVID-19-related pneumonia
  - Rapid de-escalation of antimicrobials recommended once SARS-CoV-2 confirmed
  - Bacterial pathogens are likely similar in patients with CAP without COVID-19 and those with COVID-19; no changes to empiric therapy required
  - Procalcitonin could be helpful in limiting overuse of antibiotics in patients with COVID-19-related pneumonia
- For patients with hypertensive emergency, gradually lower BP by approximately 10-20% in the first hour and another 5-15% over the next 23 hours, unless ischemic stroke or acute aortic dissection

Metlay JP, et al. *Ann Intern Med*. 2020;M20-2189. Rawson TM, et al. *Clin Infect Dis*. 2020;Epub.

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COVID-19 Frontline website

https://covid-frontline.com

55

COVID-19 Frontline: Evolving Strategies in the Management and Prevention of COVID-19

Resource	Address
Joost Wiersinga W, et al. **Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review.** *JAMA.* 2020;10.1001/jama.2020.12839.	https://pubmed.ncbi.nlm.nih.gov/32648899/
Guan WJ, et al. **Clinical characteristics of coronavirus disease 2019 in China.** *N Engl J Med*. 2020;382:1708-1720.	https://pubmed.ncbi.nlm.nih.gov/32109013/
Rothan HA, et al. **The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak.** *J Autoimmun*. 2020;109:102433.	https://pubmed.ncbi.nlm.nih.gov/32113704/
Lechien JR, et al. **Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019.** [published online ahead of print, 2020 Apr 30]. *J Intern Med*. 2020; 10.1111/joim.13089.	https://pubmed.ncbi.nlm.nih.gov/32352202/
Wang W, et al. **Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China.** *J Med Virol*. 2020;92:441-447.	https://pubmed.ncbi.nlm.nih.gov/31994742/
Wu Z, et al. **Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention.** *JAMA*. 2020;323:1239-1242.	https://jamanetwork.com/journals/jama/fullarticle/2762130
Richardson S, et al. **Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area.** *JAMA*. 2020 May 26;323:2052–2059.	https://pubmed.ncbi.nlm.nih.gov/32320003/
Yuan X, et al. **Changes of hematological and immunological parameters in COVID-19 patients.** [published online ahead of print, 2020 Jul 12]. *Int J Hematol*. 2020;1-7.	https://pubmed.ncbi.nlm.nih.gov/32656638/
Fosbøl EL, et al. **Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality.** *JAMA*. 2020;324:168-177.	https://pubmed.ncbi.nlm.nih.gov/32558877/
Bhimraj A, et al. **Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19**. *IDSA Guidelines*. V2.1.0.	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
Alhazzani W, et al. **Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19).** *Intensive Care Med*. 2020;46:854-887.	https://pubmed.ncbi.nlm.nih.gov/32222812/
World Health Organization (WHO). **Clinical management of COVID-19.** Interim Guidance. 2020 May 27.	https://www.who.int/publications/i/item/clinical-management-of-covid-19

National Institutes of Health (NIH). **COVID-19 Treatment Guidelines.**	https://www.covid19treatmentguidelines.nih.gov/
Beigel JH, et al. **Remdesivir for the treatment of Covid-19 - Preliminary report.** [published online ahead of print, 2020 May 22].*N Engl J Med*. 2020;NEJMoa2007764.	https://pubmed.ncbi.nlm.nih.gov/32445440/
Campochiaro C, et al. **Efficacy and safety of tocilizumab in severe COVID-19 patients: A single-centre retrospective cohort study.** *Eur J Intern Med. 2020;76:43-49*	https://pubmed.ncbi.nlm.nih.gov/32482597/
Li L, et al. **Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial.** [published online ahead of print, 2020 Jun 3].*JAMA*. 2020;e2010044..	https://pubmed.ncbi.nlm.nih.gov/32492084/
Geleris J, et al. **Observational study of hydroxychloroquine in hospitalized patients with Covid-19.** *N Engl J Med*. 2020;382:2411-2418.	https://pubmed.ncbi.nlm.nih.gov/32379955/
Cao B, et al. **A Trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19.** *N Engl J Med*. 2020;382:1787-1799.	https://pubmed.ncbi.nlm.nih.gov/32187464/
Folegatti PM, et al. **Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial.** *Lancet.* 2020 Jul 20;Epub. doi:10.1016/S0140-6736(20)31604-4	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31604-4/fulltext
Jackson LA, et al. **An mRNA Vaccine against SARS-CoV-2 - Preliminary Report**. [published online ahead of print, 2020 Jul 14].*N Engl J Med*. 2020;10.1056/NEJMoa2022483..	https://pubmed.ncbi.nlm.nih.gov/32663912/