Weill Cornell Medicine

Treatment and Prevention of COVID-19

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Disclosures Related To This Presentation

- Michael S. Niederman, M.D.
  - Commercial disclosures:
    - Consultant and Lecture fees from Fisher Diagnostics
    - Consultant to : Abbvie, Pfizer, Merck, Shionogi, Gilead
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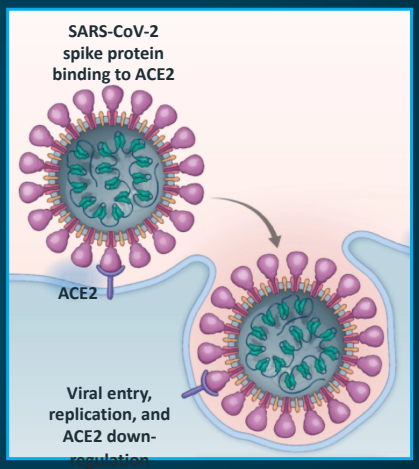
- All relevant financial relationships have been mitigated.

Learning Objectives

- Describe the best therapy for mild COVID-19 treated out of the hospital
- Identify appropriatedecision-making about when to use corticosteroids and new biologic modifiers for patients hospitalized with COVID-19
- Apply current guidelines for patients managed out of the hospital admitted to the hospital and ICU
- Describe current vaccine options

SARS-CoV-2 Virus

- COVID-19 is caused by the SARS-CoV-2 virus[1–3]
- The virus is spread primarily via respiratory droplets during face-to-face contact[2]
- Spike protein on viral surface binds to ACE2 receptor on target cells, facilitating viral entry into host cells[2,3]

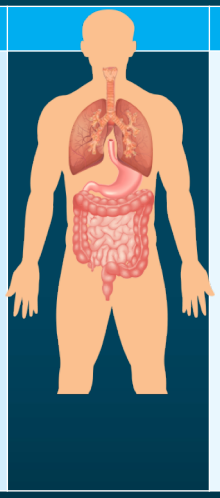


SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; COVID-19 = coronavirus disease 2019; ACE = angiotensin-converting enzyme.

1. Adapted from Vaduganathan M, et al. *N Engl J Med*. 2020;382:1653-1659. 2. Wiersinga WJ, et al. *JAMA*. 324:782-793. 3. Baum A, et al. *Science*. 2020;369:1014-1018.

Clinical Presentation of COVID-19

Systemic and respiratory disorders caused by COVID-19

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

RNA = ribonucleic acid.

Rothan HA, Byrareddy SN. *J Autoimmun*. 2020;109:102433. Guan WJ, et al. *N Engl J Med*. 2020;382:1708-1720.

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 81% of cases were mild

	Disease Characteristics—NIH
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; NIH = National Institutes of Health.

Wu Z, McGoogan JM. *JAMA*. 2020;323:1239-1242. NIH. COVID-19 treatment guidelines (https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf). Accessed 12/2/2020.

Risk Factors for Severe Disease

Gandhi RT et al. NEJM 2020; 383:1757-66

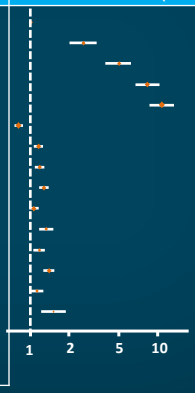
Table 1. Risk Factors for Severe Covid-19.*

Older age
Chronic obstructive pulmonary disease
Cardiovascular disease (e.g., heart failure, coronary artery disease, or cardiomyopathy)
Type 2 diabetes mellitus
Obesity (body-mass index, ≥30)
Sickle cell disease
Chronic kidney disease
Immunocompromised state from solid-organ transplantation
Cancer

Association Between Pre-existing Characteristics and COVID-19 Survival

- Prospective cohort study of 20,133 patients in UK hospitalized with COVID-19
- Increasing age, male sex, and chronic comorbidities, including obesity, were identified as independent risk factors for mortality

		HR (95% CI)	*P*- value
Age on admission (years)	<50		
	50–59	2.63 (2.06–3.35)	<.001
	60–69	4.99 (3.99–6.25)	<.001
	70–79	8.51 (6.85–10.57)	<.001
	≥80	11.09 (8.93–13.77)	<.001
Sex at birth	Female	0.81 (0.75–0.86)	<.001
Chronic cardiac disease	Yes	1.16 (1.08–1.24)	<.001
Chronic pulmonary disease	Yes	1.17 (1.09–1.27)	<.001
Chronic kidney disease	Yes	1.28 (1.18–1.39)	<.001
Diabetes	Yes	1.06 (0.99–1.14)	.087
Obesity	Yes	1.33 (1.19–1.49)	<.001
Chronic neurological disorder	Yes	1.17 (1.06–1.29)	.001
Dementia	Yes	1.40 (1.28–1.52)	<.001
Malignancy	Yes	1.13 (1.02–1.24)	.017
Moderate/severe liver disease	Yes	1.51 (1.21–1.88)	<.001



UK = United Kingdom; HR = hazard ratio; CI = confidence interval.

Docherty AB, et al. *BMJ*. 2020;369:m1985.

Variability in COVID Mortality in ICU

ORIGINAL ARTICLE

Hospital-Level Variation in Death for Critically Ill Patients with COVID-19

Matthew M. Churpek[1], Shruti Gupta[2], Alexandra B. Spicer[1], William F. Parker[3], John Fahrenbach[3], Samantha K. Brenner[4,5], and David E. Leaf[2]; for the STOP-COVID Investigators

[1]Division of Allergy, Pulmonary and Critical Care Medicine, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin; [2]Division of Renal Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [3]Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, Chicago, Illinois; [4]Department of Internal Medicine, Hackensack Meridian School of Medicine, Seton Hall, New Jersey; and [5]Heart and Vascular Hospital, Hackensack University Medical Center, Hackensack Meridian Health, Hackensack, New Jersey

ORCID ID: 0000-0002-5747-2151 (S.G.).

- 70 US hospitals , March-June 2020
- 4019 patients, 38% mortality at 28 days . 66.7% on mech vent
- Mortality related to : acute physiology (49% contribution), demographics and comorbidities (20%), socioeconomic factors (12%), strain (95), hospital quality (8%), treatment (3%)
- Individual mortality depends on patient factors
- AJRCCM 2021; 204: 403-11

Variability in COVID Mortality in ICU

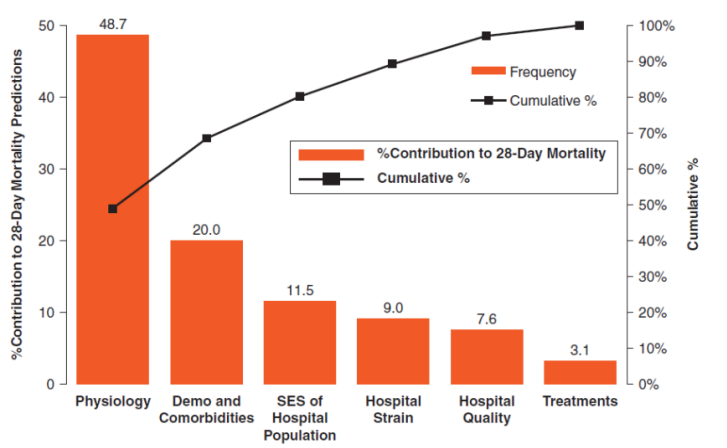


Figure 2. Contributions to 28-day mortality risk based on Shapley values. The figure illustrates the relative contribution of all variables in each domain based on Shapley values calculated from the XGBoost machine learning model (red bars; left *y*-axis). The cumulative contribution of the domains, moving from left to right in the figure, is shown with the line plot (right *y*-axis). Demo = demographics; SES = socioeconomic status.

Disease Pathogenesis: Different Therapies for Different Stages

	Asymptomatic or presymptomatic	Mild illness	Moderate illness	Severe illness	Critical illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (eg, fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94% respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed disease pathogenesis	Viral replication	Viral replication	Viral replication / Inflammation	Inflammation	Inflammation
Potential treatment	Antiviral therapy	Antiviral therapy / Antibody therapy	Antiviral therapy / Antibody therapy	Antiinflammatory therapy	Antiinflammatory therapy
Management considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

According to the Centers for Disease Control and Prevention (CDC), diagnostic testing for SARS-CoV-2 is intended to identify current infection in individuals and is performed when a person has signs or symptoms consistent with Covid-19 or when a person is asymptomatic but has recent known or suspected exposure to SARS-CoV-2. Screening testing for SARS-CoV-2 is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2. Screening testing is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission.

Adapted from Gandhi RT, et al. *N Engl J Med*. 2020;383:1757-1766

NIH Guidelines for Outpatients

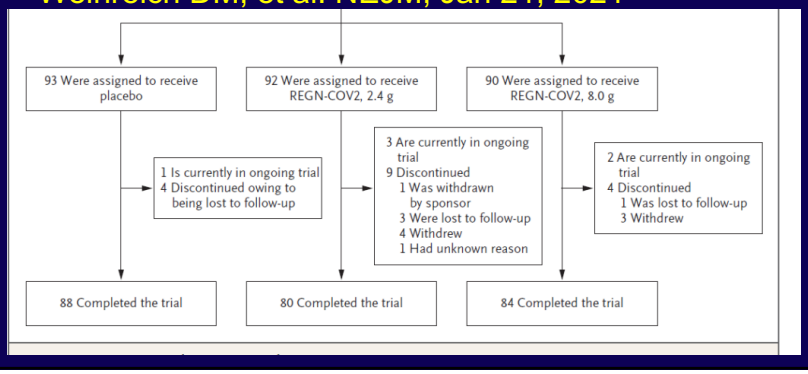
PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Bamlanivimab plus etesevimab**; *or* • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]

Convalescent Serum Antibodies in Severe COVID Not Highly Effective

- No impact on survival at 30 days in severe COVID in hospitalized patients.
  - 334 randomized: 228 antibody, 106 placebo
  - Median of 8 days of sx
  - > 95% with oxygen sat <93% on room air
  - 25% in ICU
  - >90% given steroids
  - Simonovich VA, et al. NEJM 2020;
  - ? Not focused with enough anti-viral activity

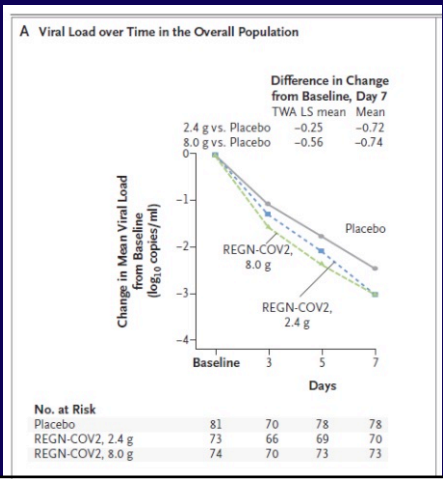
Casirivimab/Indevimab

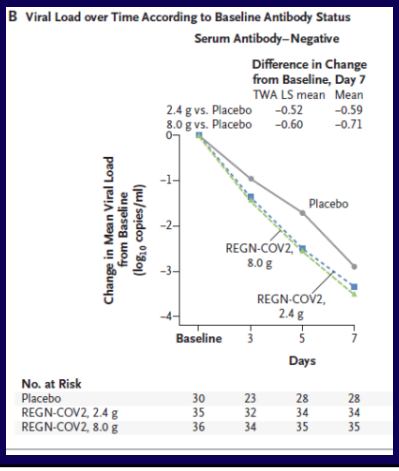
- Double blind phase 1-3 study
- 2 antibodies vs. spike protein, dose ranging study vs. placebo
- 275 outpatients : serial viral load and need for COVID medical visit
  - Weinreich DM, et al. NEJM; Jan 21, 2021



Casirivimab/Indevimab

- Weinreich DM, et al. NEJM; Jan 21, 2021
- Best effect if baseline antibodies negative (41%)





Other Agents Being Evaluated in Outpatients

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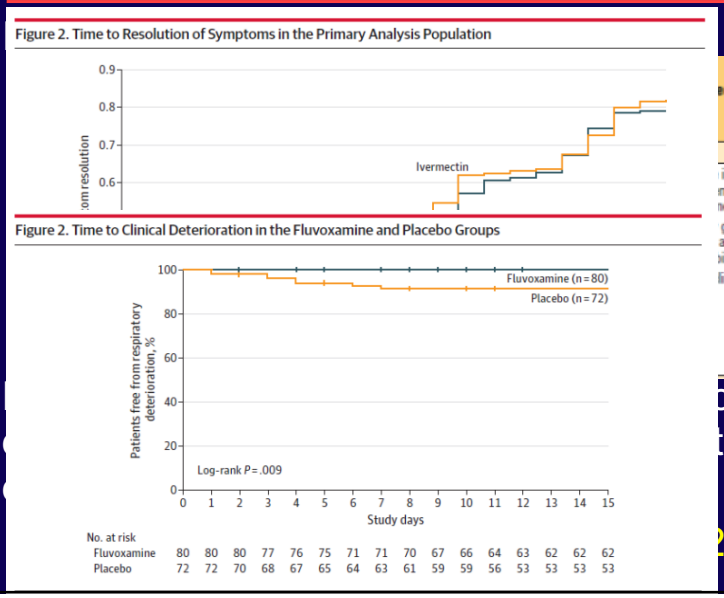

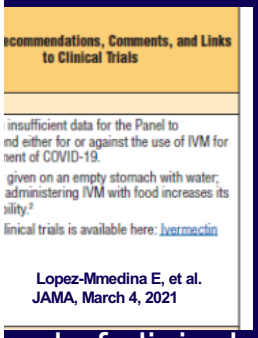

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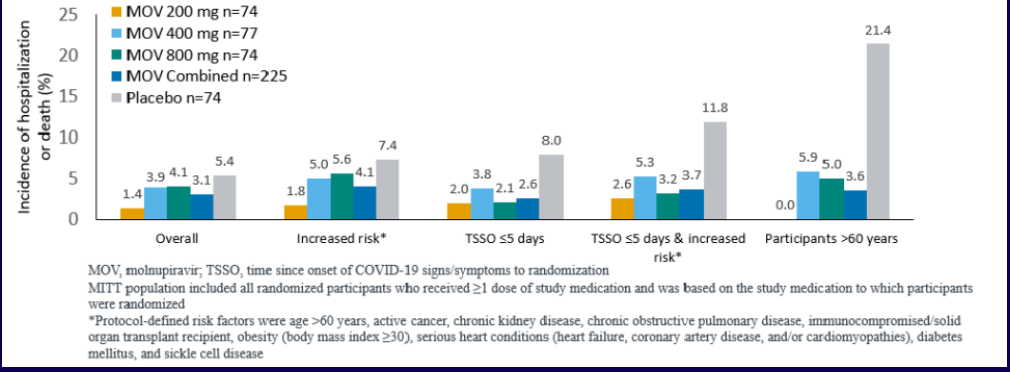
A New Oral Antiviral: Molnupiravir

- Merck's new oral antiviral, undergoing EUA for COVID-19 therapy
  - Ribonucleoside analog orally bioavailable, active vs. RNA viruses such as influenza, Ebola and Coronavirus



MOV, molnupiravir; TSSO, time since onset of COVID-19 signs/symptoms to randomization
MITT population included all randomized participants who received ≥1 dose of study medication and was based on the study medication to which participants were randomized
*Protocol-defined risk factors were age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised/solid organ transplant recipient, obesity (body mass index ≥30), serious heart conditions (heart failure, coronary artery disease, and/or cardiomyopathies), diabetes mellitus, and sickle cell disease

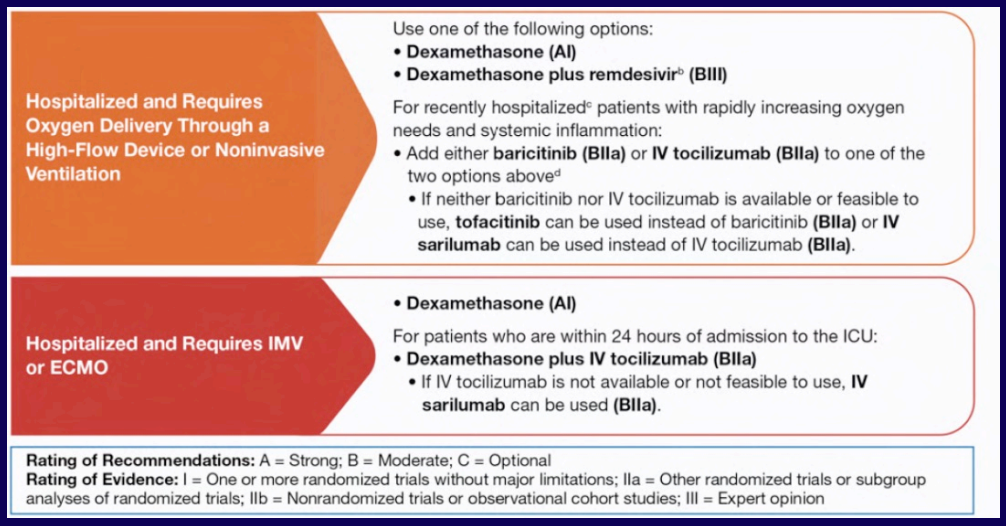
Overview of NIH Guidelines for Inpatients October 2021

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

Dosing regimens and duration of therapy for the drugs recommended in this figure are listed in Table A below.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**

Overview of NIH Guidelines October 2021

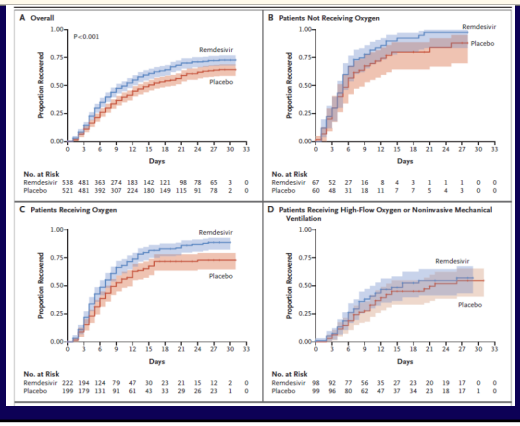


NIH Updates

- Tocilizumab (anti IL-6) , single 800 mg dose with dexamethasone in hospitalized patients with rapid respiratory deterioration
- Bamlinivimab +etesivimab for outpatients with mild-moderate COVID and risk of progression.
  - Not for inpatients
- Casirivimab/indevimab: outpatients at risk for progression
- Monoclonal antibodies for post-exposure prophylaxis in high-risk pts
- Can use baricitinib with remdesivir for patients who cannot take steroids in hospitalized patients, not intubated, on supplemental oxygen.
  - Not without remdesivir and ? If with steroids
- Ivermectin: may prevent viral entry into cells and binding to spike protein and viral replication, but data insufficient to recommend.

Remdesivier for Severe COVID-19

Score on ordinal scale — no. (%)	ALL	REMSESIVIR	PLACEBO
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)
Baseline score missing	46 (4.3)	29 (5.4)	17 (3.3)

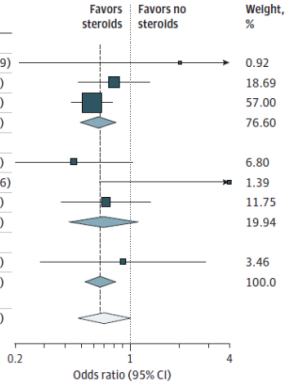


Beigel JH, et al. *N Engl J Med.* 2020;May 22
No mortality effect
Benefit in proportion who recovered

Steroids and COVID-19

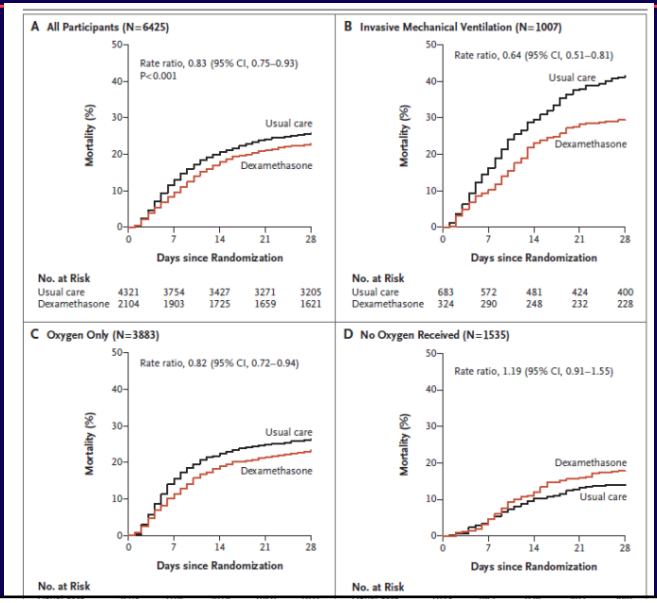
Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov Identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)
Dexamethasone					
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)
Hydrocortisone					
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)
Methylprednisolone					
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)



***JAMA*. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023**
Published online September 2, 2020

RECOVERY Study : NEJM 2020 ; DOI: 10.1056



In Spite of Role in COVID-19, No Steroids for Proven Influenza

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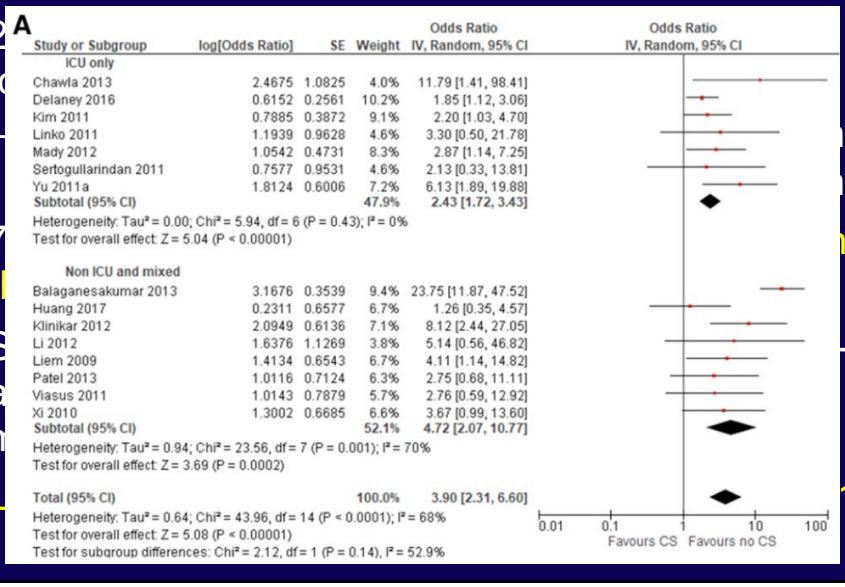
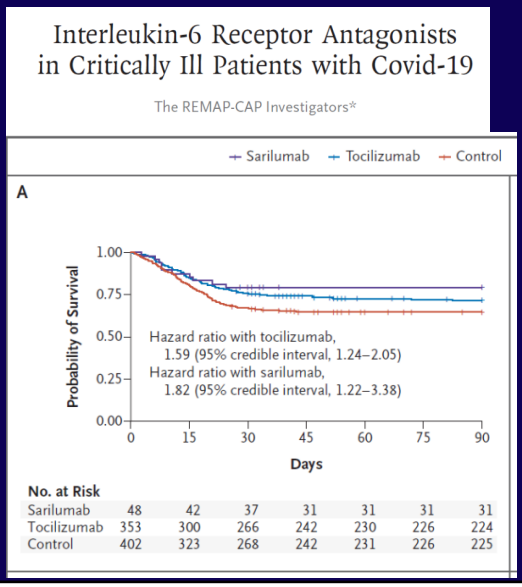


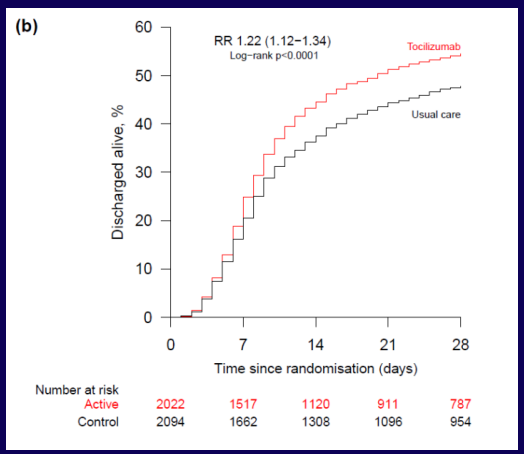
Tocilizumab: REMAP CAP



- REMAP CAP: Randomized platform trial
- All in ICU w/i 24 hours organ support
- 29% MV
- Most got dexamethasone
- IMPROVED SURVIVAL
- NEJM ; Feb 25, 2021

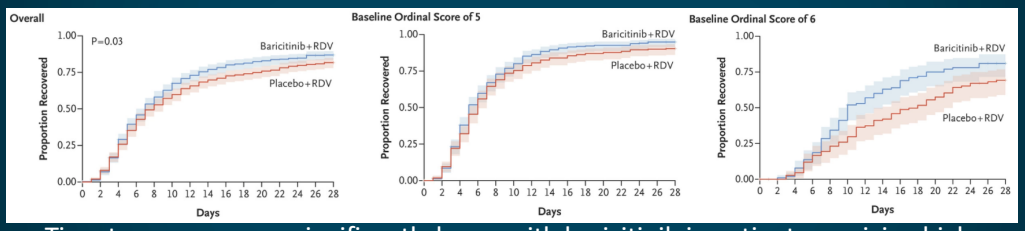
Tocilizumab : RECOVERY Trial : Preliminary Report

- Randomized, controlled, open label platform trial with saturation < 92% of RA and CRP ≥ 75 mg/L
- 4116 patients: 14% MV, 41% NIV, 45% oxygen only
- 82% on steroids
- Improved survival in addition to the effect of steroids
- https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1



Baricitinib Plus Remdesivir: Recovery Time

- Recovery time was reduced with baricitinib vs placebo (7 days vs 8 days; rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; *P*= .03)



- Time to recovery was significantly lower with baricitinib in patients receiving high-flow oxygen or noninvasive ventilation at enrollment (10 days vs 18 days; rate ratio for recovery, 1.51)

Kalil AC, et al. *N Engl J Med.* 2020;Epub ahead of print.

Baricitinib Plus Remdesivir: Results

- Baricitinib was associated with a 30% higher odds of improvement in clinical status at day 15 (OR, 1.3)
- 28-day mortality was 5.1% in the combination group and 7.8% in the control group (HR for death, 0.65)

Outcome	Overall	
	Baricitinib (N=515)	Placebo (N=518)
Recovery		
No. of recoveries	433	406
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03])	
Mortality over first 14 days‡		
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)	
No. of deaths by day 14	8	15
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)
Mortality over entire trial period‡		
Hazard ratio (95% CI)	0.65 (0.39–1.09)	
No. of deaths by day 28	24	37
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)

Kalil AC, et al. *N Engl J Med.* 2020;Epub ahead of print.

Baricitinib ACCT-2: Adverse Events

	Baricitinib Plus Remdesivir (n = 508) No. (%)	Placebo Plus Remdesivir (n = 509) No. (%)
Grade 3 or 4 Aes	207 (40.7)	238 (46.8)
Hyperglycemia	25 (4.9)	40 (7.9)
Anemia	25 (4.9)	33 (6.5)
Decreased lymphocyte count	24 (4.7)	35 (6.9)
Acute kidney injury	20 (3.9)	36 (7.1)
Venous thromboembolism	21 (4.1)	16 (3.1)

Kalil AC, et al. *N Engl J Med.* 2020;Epub ahead of print.

Severe COVID-19 in the ICU

- What is severe COVID?
- When should patients be admitted to the ICU?
- Respiratory failure care
  - High flow oxygen and NIV
  - Intubation : when?
  - How we mechanically ventilate
- Treatment of COVID pneumonia
  - Remdesivir, steroids
  - Other therapies: anti-cytokine, antibody therapy
- Complications: bacterial infection, clotting, renal failure

Therapy Issues in ICU

- Ventilator Management
- ARDS and lung compliance
- Role of medications for severe COVID
- VAP as a complication of respiratory failure

Experiences with Ventilatory Support

	Italy[9]	Seattle, WA, USA[33]	Italy[34]	Boston, MA, USA[2]	Amsterdam[3]	New York City, NY, USA[5]	New York City, NY, USA[4]
Number of patients	16	24	1300	66	38	257	267
Respiratory support*							
Invasive mechanical ventilation	16 (100%)	18 (75%)	1150 (88%)	66 (100%)	38 (100%)	203 (79%)	267 (100%)
Non-invasive ventilation	0	0	137 (11%)	1 (2%)	0	3 (1%)	51 (19%)
HFNC	0	10 (42%)	0	1 (2%)	0	12 (5%)	0
PaO_2/FiO_2 ratio	..	142 (94–177)	160 (114–220)	182 (135–245)	132 (48)†	129 (80–203)	103 (82–134)
Compliance, mL/cm H_2O	50 (14·3)†	29 (25–36)	..	35 (30–43)	49 (24)†	26 (21–38)	28 (23–38)
Plateau pressure, cm H_2O	..	25 (20–28)	..	21 (19–26)	21 (7–23)	27 (22–31)	25 (21–29)
PEEP, cm H_2O	..	..	14 (12–16)	10 (8–12)	10 (9–12)	15 (12–18)	10 (8–12)
Tidal volume, mL/kg PBW	..	..	..	..	..	6·2 (5·9–7·2)	7·0 (6·1–8·1)
FiO_2	..	90% (70–100)	70% (50–80)	..	..	100% (80–100)	..
Prone positioning	Not reported	5/18‡ (28%)	240/875§ (27%)	31 (47%)	Not reported	35 (17%)	108 (40%)
ECMO	Not reported	0	5/498§ (1%)	3 (5%)	Not reported	7 (3%)	Not reported

Data are n (%) or median (IQR), unless otherwise indicated. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. HFNC=high-flow nasal cannula. PaO_2=partial pressure of arterial oxygen. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure. *Some patients received more than one type of respiratory support. †Mean (SD). ‡Denominator is 18 for the group that had invasive mechanical ventilation. §It is not explicitly stated in the manuscript why the denominators are different, although they might represent the group of patients for which these data were collected and available at the time of analysis.

Table 1: **Selected ventilatory characteristics of critically ill patients with COVID-19**

NIH Therapy Recommendations for Ventilated Patients

- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):
  - The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) **(AI)**.
  - The Panel recommends targeting plateau pressures of <30 cm H_2O **(AIIa)**.
  - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BIIa)**.
  - The Panel **recommends against** the routine use of **inhaled nitric oxide (AIIa)**.
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
  - The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy **(BIIa)**.
  - For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BIIa)**.
  - The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation **(BIIa)**.
  - In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled **(BIII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:
  - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers **(CIIa)**.
  - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AIIa)**.
  - The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off **(CIII)**.

Bacterial Lung Infection During COVID-19

- Bacterial lung infection complicating COVID-19
  - Antibiotics used broadly and empirically on admission and throughout the hospital course
  - initial respiratory co-infection with bacteria: How common?
  - Nosocomial superinfection/ pneumonia: How often?
  - How can we safely use less antibiotics?

Meta-analysis of Co-Infection in COVID-19

- 30 studies, 3834 patients, Jan 1-April 17, 2020.
- 14% in ICU with co-infection vs. 4% in mixed ward/ICU.
  - **Most initially got antibiotics**
    - **For >90% in the 10/17 studies with data**
  - Common bacteria: M. pneumoniae, P aeruginosa, H. influenzae
    - Did not distinguish CAP from VAP in the study
  - 3% had viral co-infection: Influenza A and RSV
  - Some with fungus: Aspergillus (CAPA)
- Co-infection with OR of death of 5.8
- Lansbury, L, et al. J of Infection 2020; 81266-75

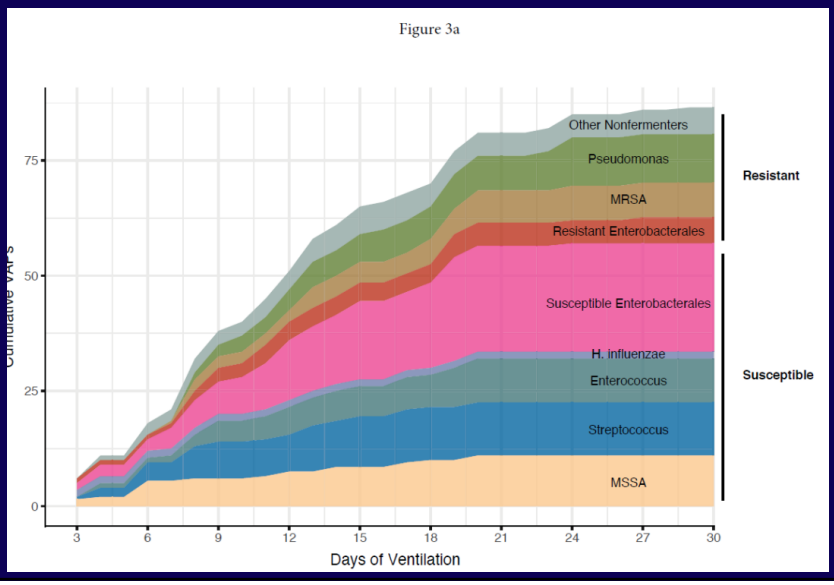
Hospital-Acquired Bacterial Infection in ICU Patients with COVID-19

- 774 with severe COVID, 359(46%) with bacterial HAI
  - 35% with MDR pathogens
  - 50% with VAP , then BSI and CR-BSI
- 31% with no antibiotics on admission, 69% with antibiotics on admit (31% broad-spectrum)
  - 36% with no initial antibiotics got HAI
  - Broad-spectrum therapy more common in those without HAI than with (p=0.002). Did they mask infection?
  - Use of broad-spectrum antibiotics on admit was a risk for HAI in multivariate analysis.
  - Grasselli G, et al. Chest 2021; 160: 454-65

Bacterial Infection with BAL Diagnosis in COVID-19: Impact on Antibiotic Use

- 386 BAL samples (using Biofire and cultures) from 179 COVID-19 patients with SARS-C0V2 and mechanical ventilation
- Only 32% in hospital > 2 days at time of intubation.
- Bacterial superinfection in 21% w/I 48 h intubation
- 44% with at least one VAP. 20.8% with difficult to treat pathogens.
- Antibiotics before BAL in 20% with superinfection 36% without (NS)
  - Not excessive use, and ? If likely antibiotics caused false (-)
  - More narrow spectrum or stopped therapy with negative BAL than with guideline directed use ($p<0.001$); same spectrum in positive BAL.
- BAL guidance can reduce antibiotic use, compared to guideline-based antibiotic use.
  - CRP and PCT did not distinguish superinfection from not.
- Pickens CO, et al. Am J Respir Crit Care 2021; in press.

VAP Bacteriology Over Time During COVID-19: From Pickens et al.



Can PCT Identify Bacterial Infection in COVID-19?

- Retrospective study of 2443 with COVID-19 and

TABLE 2 Mean procalcitonin levels in community-associated bacterial infections and sensitivity and specificity of initial procalcitonin values of 0.25 and 0.50 ng/ml for identifying community-associated bacterial infections

	Procalcitonin level (ng/ml)				Procalcitonin cutoff (ng/ml) of: 0.25				0.50			
Infection type	Mean	SD	*n*	*P* value[a]	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
All community-associated infections	13.16	51.19	148	0.0091	0.601	0.532	0.076	0.954	0.426	0.715	0.088	0.951
Bacteriuria	5.15	22.98	88	0.1428	0.568	0.527	0.043	0.970	0.363	0.710	0.045	0.967
Bacteremia	34.25	85.01	47	0.0125	0.681	0.528	0.027	0.988	0.553	0.712	0.036	0.988
Bacterial pneumonia	16.42	57.81	24	0.2345	0.708	0.526	0.015	0.995	0.500	0.709	0.017	0.993
No infection	2.00	15.26	2,295									

[a]Compared to noninfected patients' initial procalcitonin using 2-sided *t* test.

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high NPV if < 0.25 ng/. Use to withhold antibiotics

- May M, et al. AAC 2021; 65:e02167-20

Use of PCT For Antimicrobial Stewardship With COVID-19 in the ICU

- Prospective cohort study after introduction of PCT to the ICU in Southampton , UK
- All PCR positive for COVID
- 52 with PCT on ICU admit
- Fewer days of antibiotic use in the first 7 days, in low PCT (<0.5 mcg/L) vs high PCT (> 0.5 mcg/L)
  - BUT mean of 5 vs. 7 days. (p<0.001)
  - Shorter duration of ICU stay (5 vs. 15 days, p=0.03)
  - Heesom L, et al. J of Antimicrobial Resistance 2020; 22:782-84

How Should CAP Management Change with COVID?

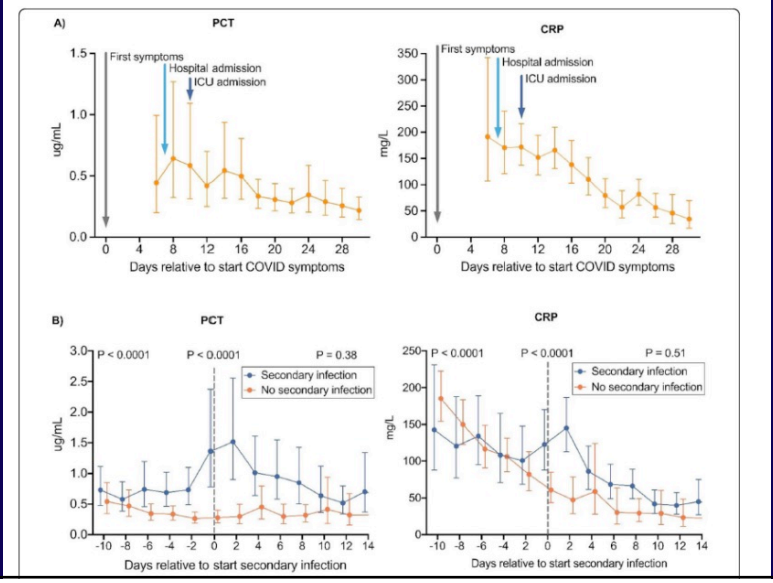
Table. Principles for Management of Pneumonia in Patients With COVID-19

Empirical coverage for bacterial pathogens is recommended in patients with CAP without confirmed COVID-19 but is not required in all patients with confirmed COVID-19–related pneumonia.
The relevant bacterial pathogens in patients with pneumonia and COVID-19 are likely the same as in other patients with pneumonia, and therefore empirical antibiotic recommendations should be the same.
Testing for bacterial pathogens with sputum and blood cultures is most useful when there is concern for multidrug-resistant pathogens.
Procalcitonin could be helpful in limiting overuse of antibiotics in patients with COVID-19–related pneumonia.

CAP = community-acquired pneumonia; COVID-19 = coronavirus disease 2019.

Metlay and Waterer, Ann Intern Med 2020; doi:10.7326/M20-2189

Can PCT Help Identify Secondary Bacterial Infection in COVID-19?



When to Give Antibiotics in COVID -19

- Antibiotic decisions in those with COVID-19, need to be made
  - For those with infiltrates at the time of admission
  - For those suspected of VAP
- Antibiotics are used for many without documented infection. Need strategies to reduce usage.
- BAL can help reduce the use of antibiotics
- PCT may also be able to guide antibiotic use
  - Withhold if low on admit
  - Serial measurement in ventilated patients may help diagnose VAP

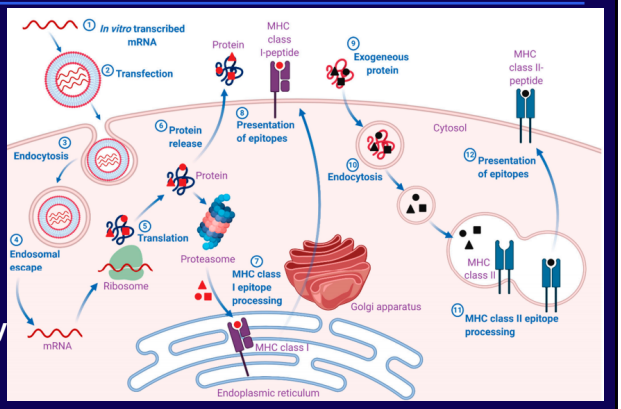
Vaccine Clinical Trials

Sponsor	Mechanism	Doses[d]	Results
Pfizer, BioNTech	mRNA-based vaccine	2	43,661 participants, 95% effective beginning 28 days after the 1st dose [a]
The University of Oxford; Astra Zeneca; IQVIA; Serum Institute of India	Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	2	23,000 participants 90% efficacy as half dose, followed by full dose 1 month later [b]
Moderna	mRNA-based vaccine	2	30,000 participants, 94.5% vaccine efficacy [c]
CanSino Biologics	Recombinant vaccine (adenovirus type 5 vector)	1	
Sinovac	Inactivated vaccine (formalin with alum adjuvant)	2	
Bharat Biotech; National Institute of Virology	Inactivated vaccine	2	
Johnson & Johnson	Non-replicating viral vector	1/2	
Wuhan Institue of Biological Products; Sinopharm	Inactivated vaccine	2	
Novavax	Nanoparticle vaccine	2	

RNA Based Vaccines

Advantages

- Highly adaptive
- Easier/faster to produce
- Less expensive to produce



Disadvantages

- Needed to prove ability to elicit immune response
- Less clinical safety data
- Needs to be stabilized prefusion

- Wadhwa A, et al. *Pharmaceutics*. 2020;12:102

Conclusions

- COVID-19 is still a disease of wide ranging severity, with mortality in those with the most severe illness.
- Interventions vary based on timing and severity of symptoms.
- Mortality may be dropping as we learn when and how to utilize mechanical ventilation
- For those on oxygen therapy, dexamethasone and remdesivir are now standard of care and dexamethasone may reduce mortality
  - Tocilizumab may also reduce mortality in this population
  - Other anti-cytokine therapy is still being evaluated. Timing and patient selection may be key.
- Repurposed medications (ivermectin, chlorquine, fluvoxamine) have limited value in hospitalized patients
- Convalescent antibody therapy may have limited value, and early monoclonal antibody therapy may be useful for those not in hospital
- Vaccination is promising , and boosters are coming for all vaccines