(baocantho.com, n.d.)

Management of COVID-19 in Pregnancy

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25 February 2021

Presenters

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Disclosure

Navy Lt. Cmdr. Michael Miller and Dr. Jason Vaught have no relevant financial or non-financial relationships to disclose relating to the content of this activity.

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Commercial support was not received for this activity.

This activity discusses off-labeled uses of remdesivir and dexamethasone for purposes other than that for which the product(s) use was approved by the FDA.

Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Describe the Centers for Disease Control and Prevention (CDC) recommendations for the use of remdesivir in treating COVID-19.
2. Explain the CDC recommendations for the use of dexamethasone in treating COVID-19.
3. Comprehend and apply the appropriate escalation of supplemental oxygen in patients with COVID-19.
4. Recognize indications for escalation of care to the Intensive Care Unit (ICU) for patients with COVID-19.

- Current Status
- Current Therapeutics
- Risks

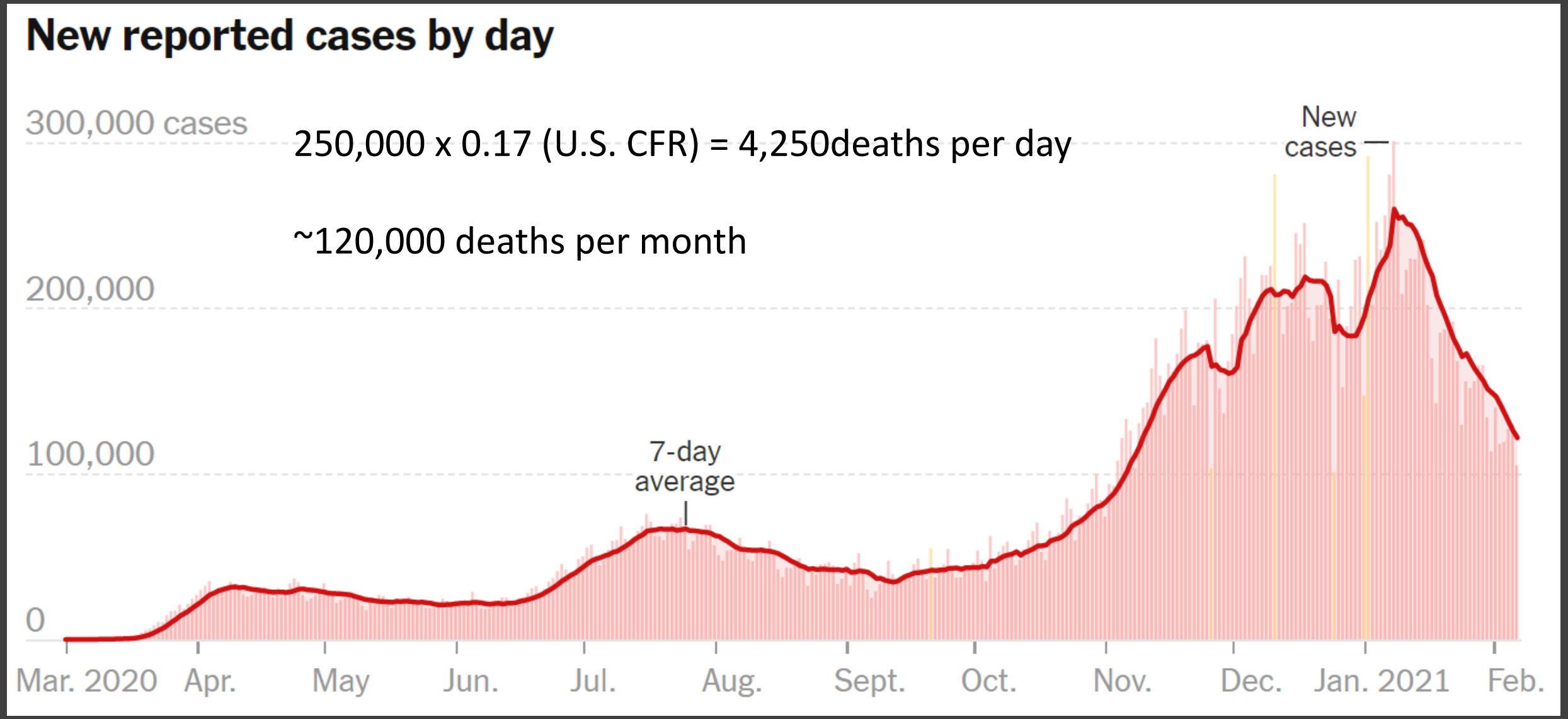
- Accumulated knowledge
- Past experiences
- Risk

Three Key Questions

- Future Therapeutics
- Vaccines

Main References

- National Institutes of Health (NIH) Coronavirus Treatment guidelines (NIH, 2021)
  - https://www.covid19treatmentguidelines.nih.gov/



250,000 x 0.17 (U.S. CFR) = 4,250deaths per day

~120,000 deaths per month

(nytimes.com, 2020)

U.S. deaths from wars and major pandemics

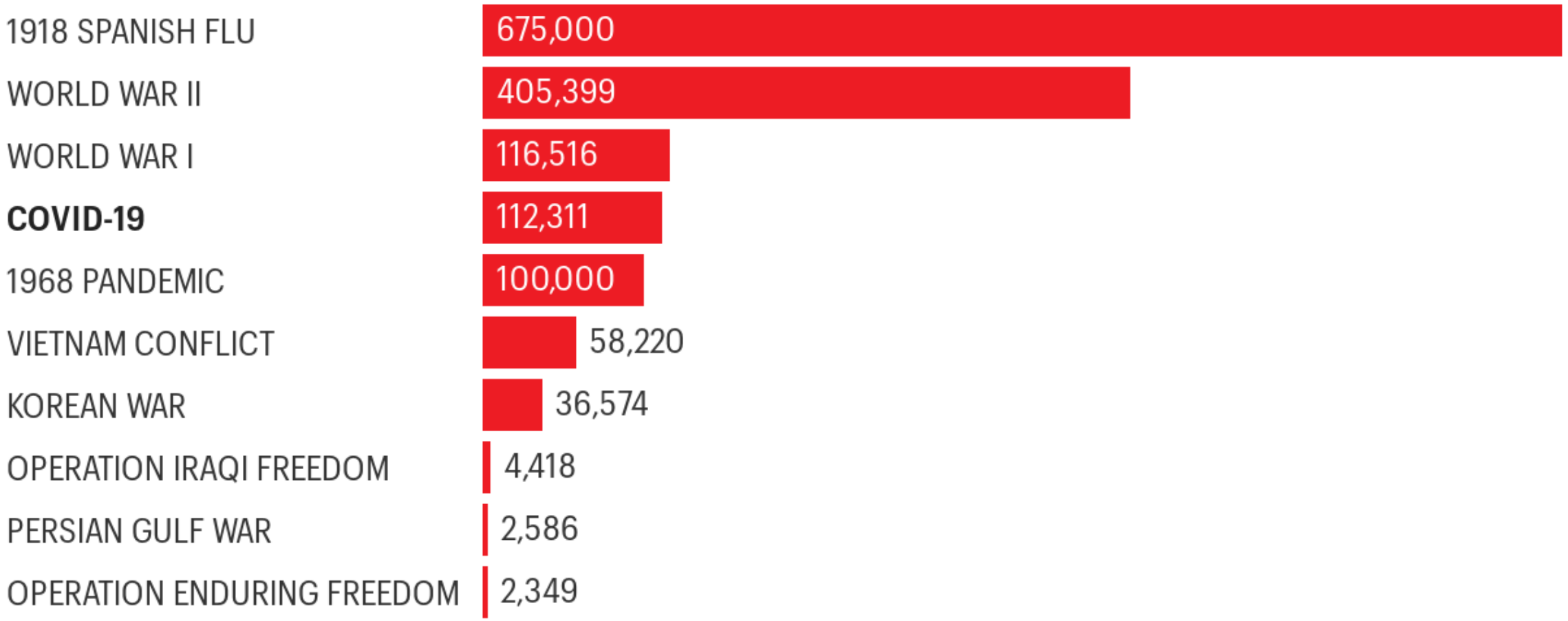


CHART: LANCE LAMBERT • SOURCE: JOHNS HOPKINS UNIVERSITY AND STATISTA

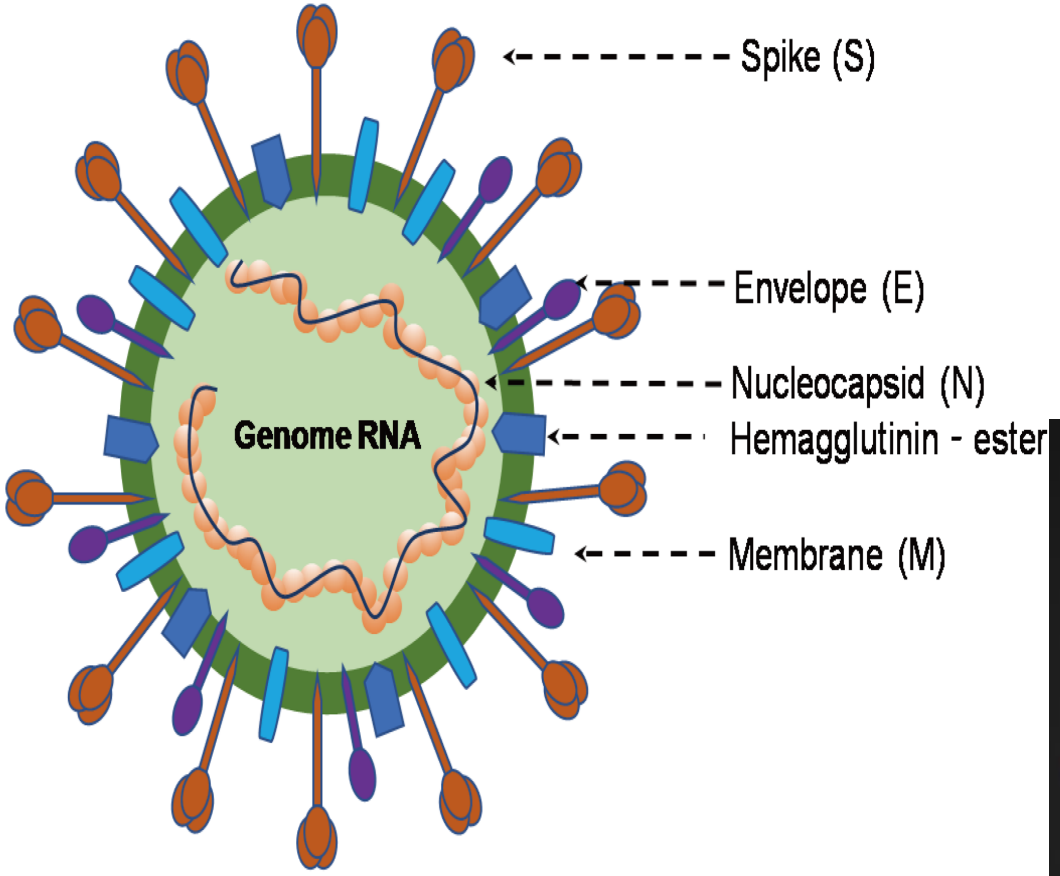
FORTUNE

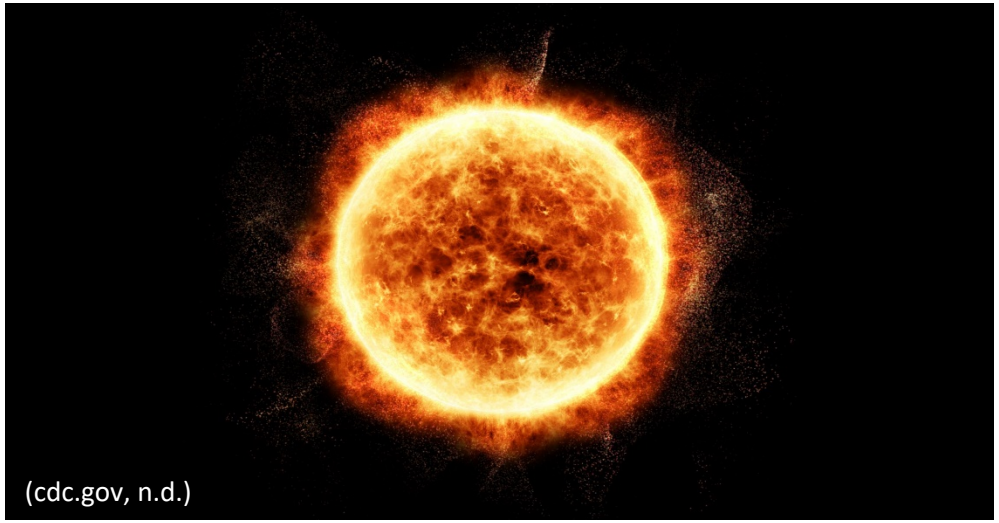
(fortune.com, 2020)

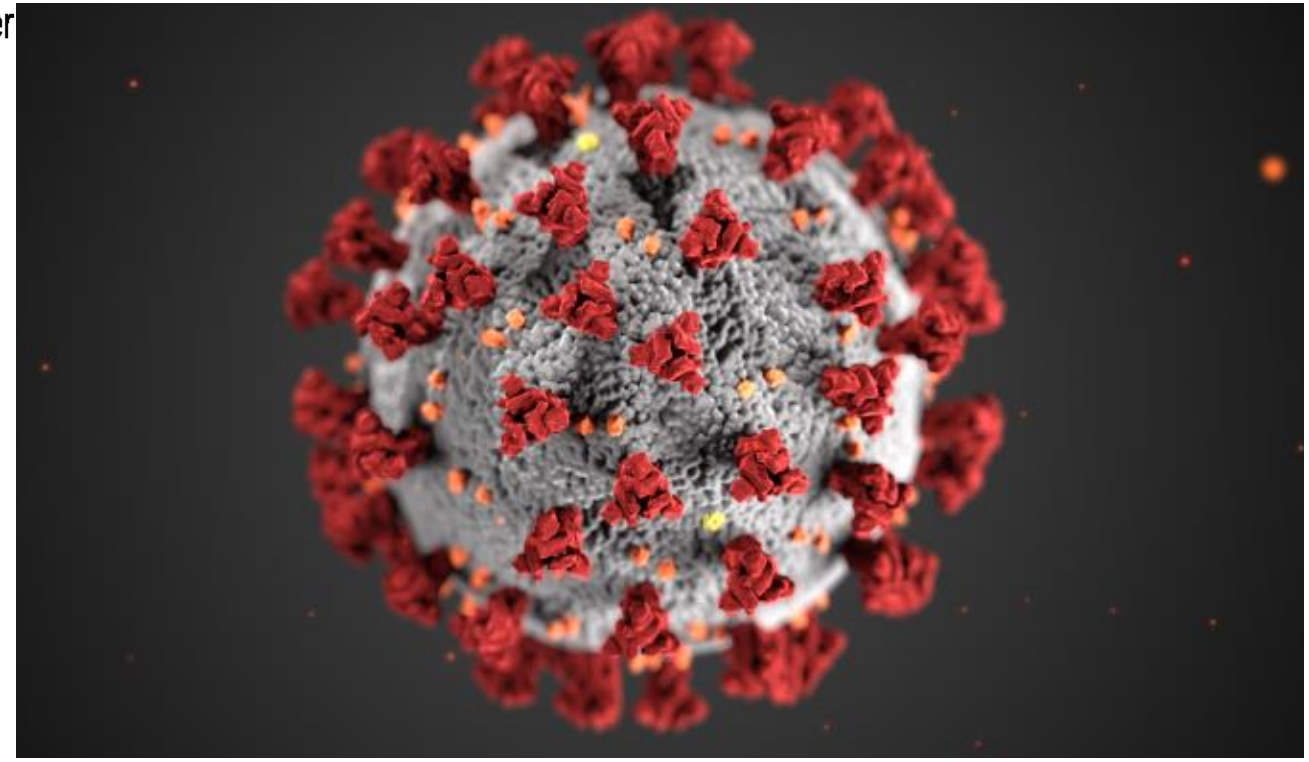
Pathophysiology

How does it function?

Pathophysiology

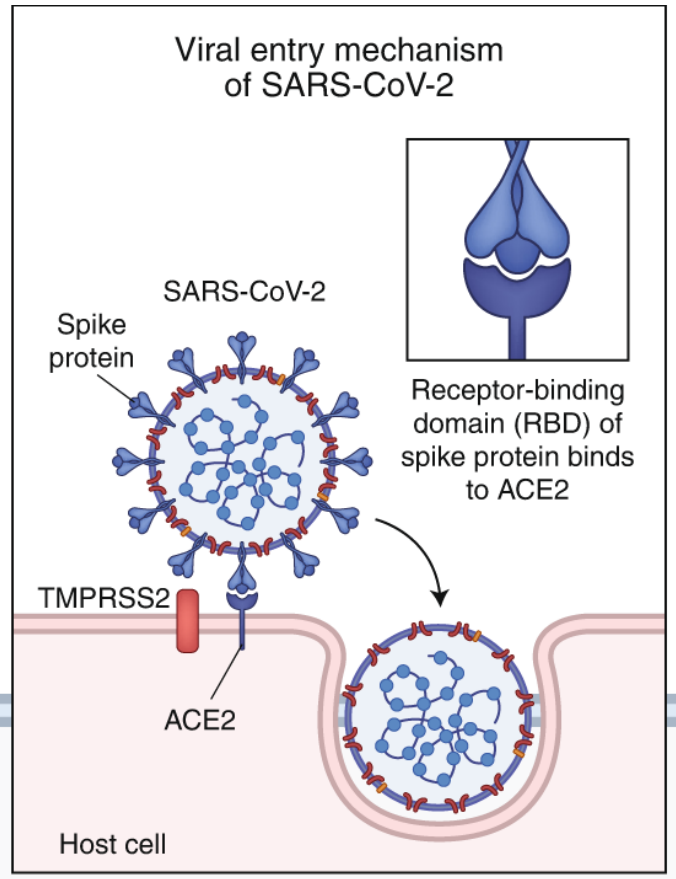


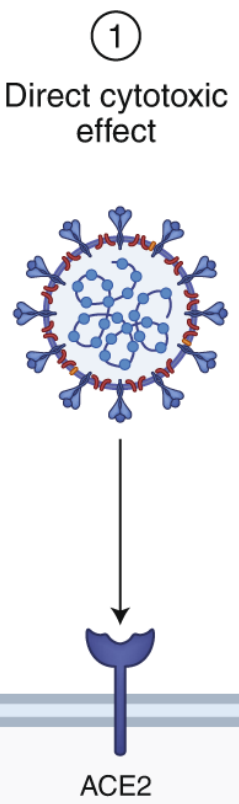


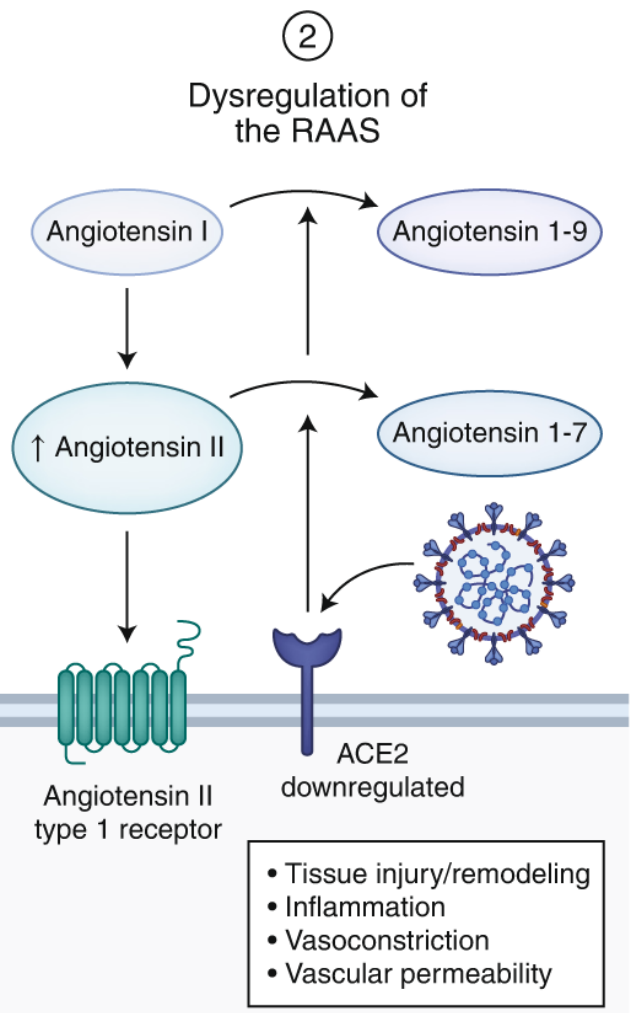


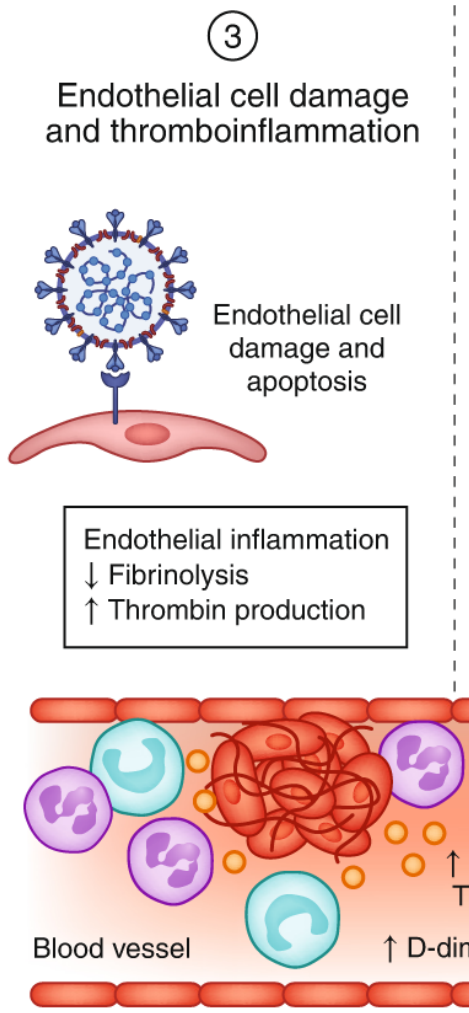
(Jin et al., 2021)

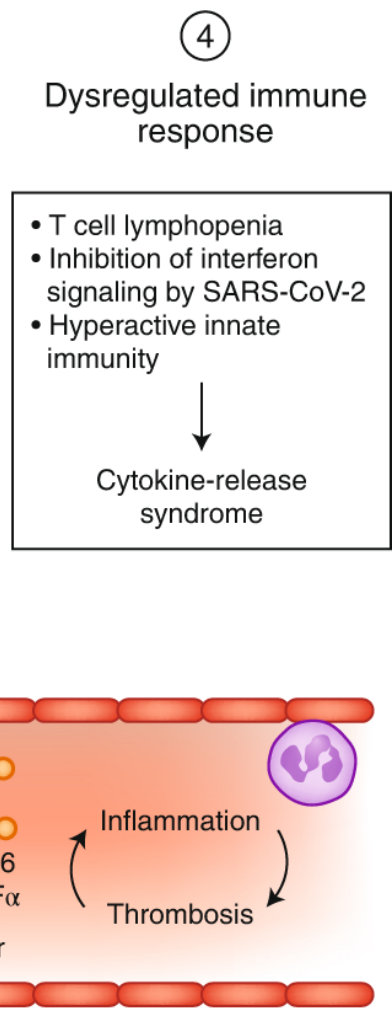
Pathophysiology







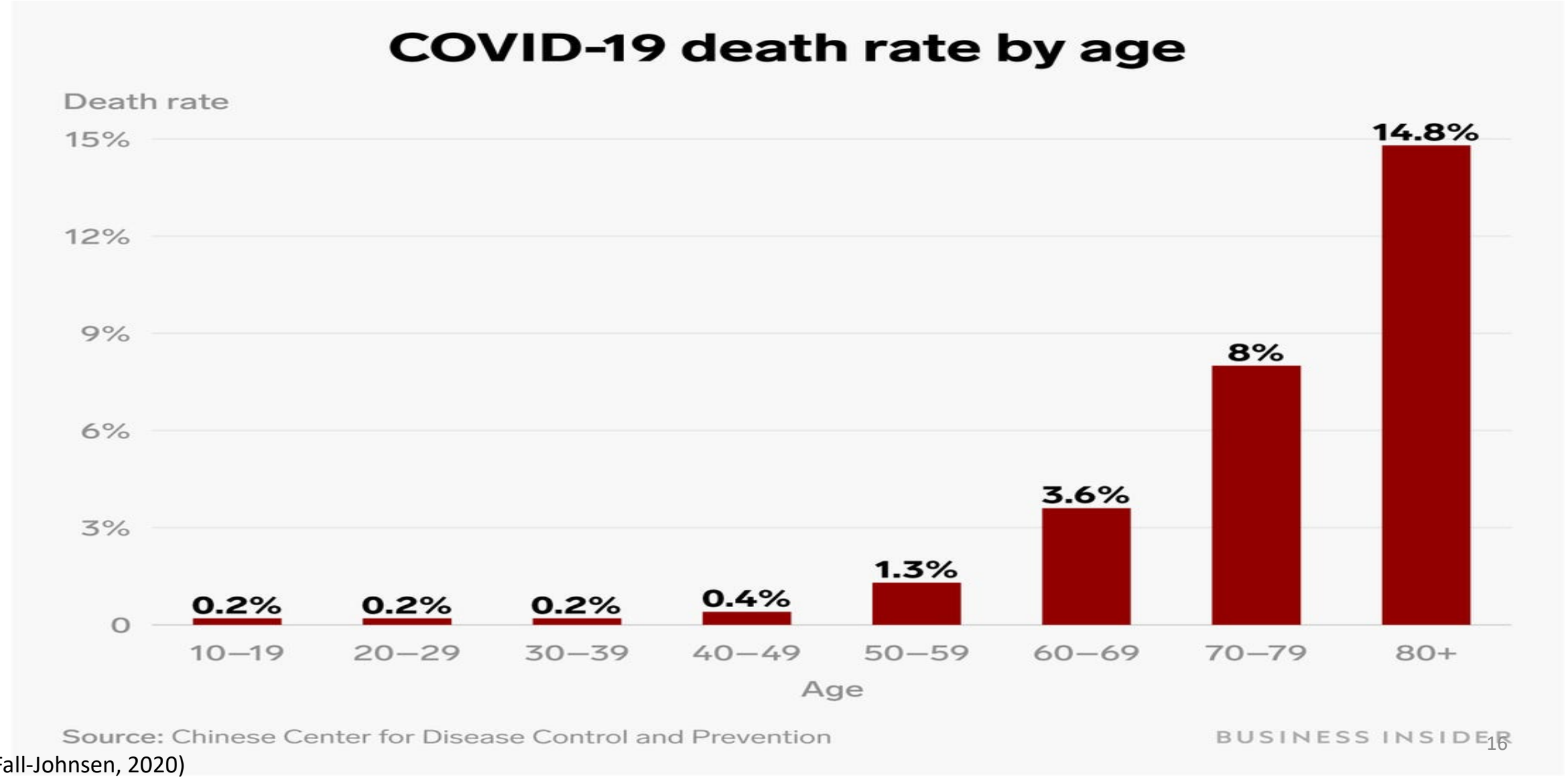




Host cell

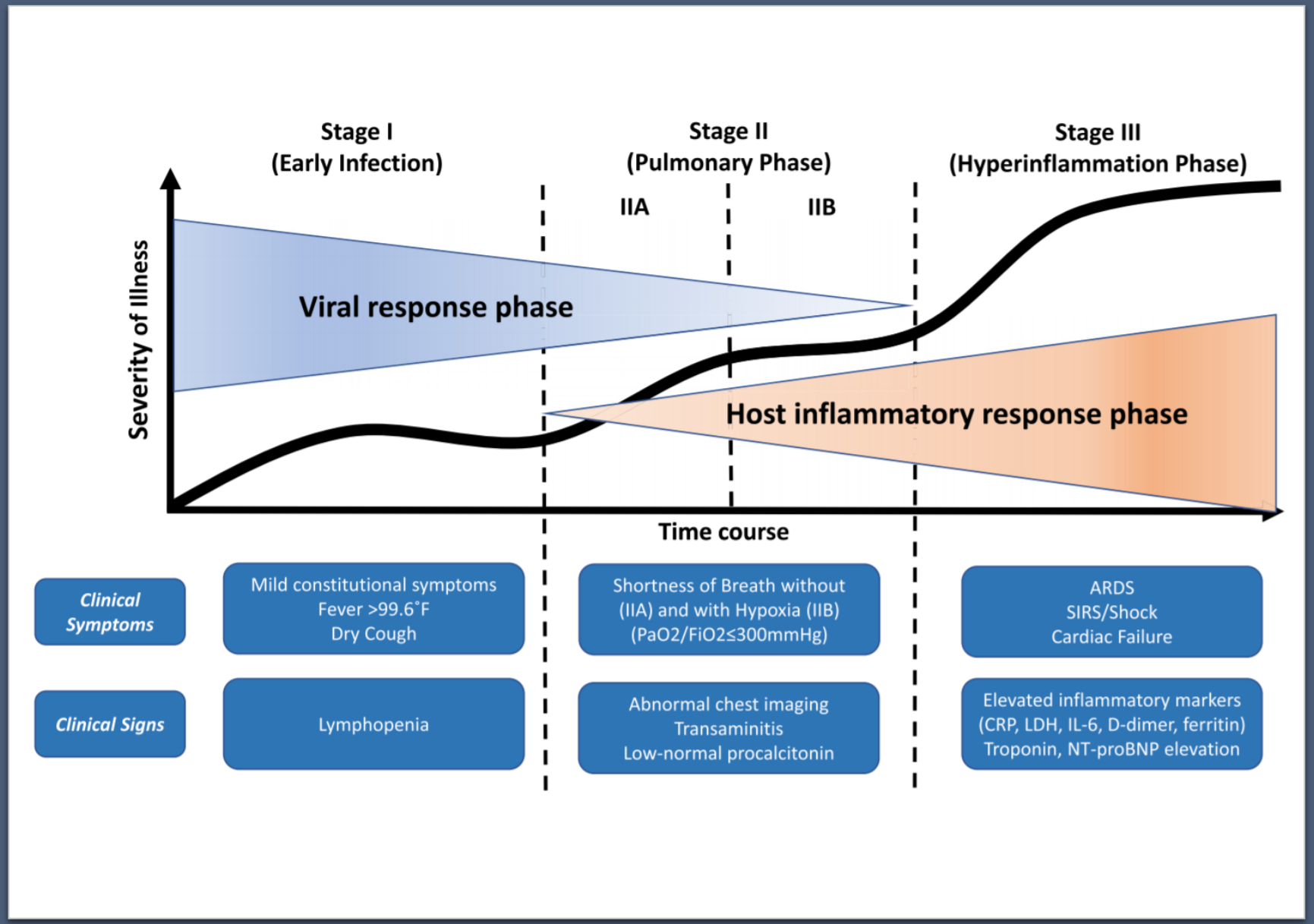
(Gupta et al., 2020)

80% of US coronavirus deaths have been among people 65 and older, a new CDC report says — here's what it reveals about the US cases



(McFall-Johnsen, 2020)

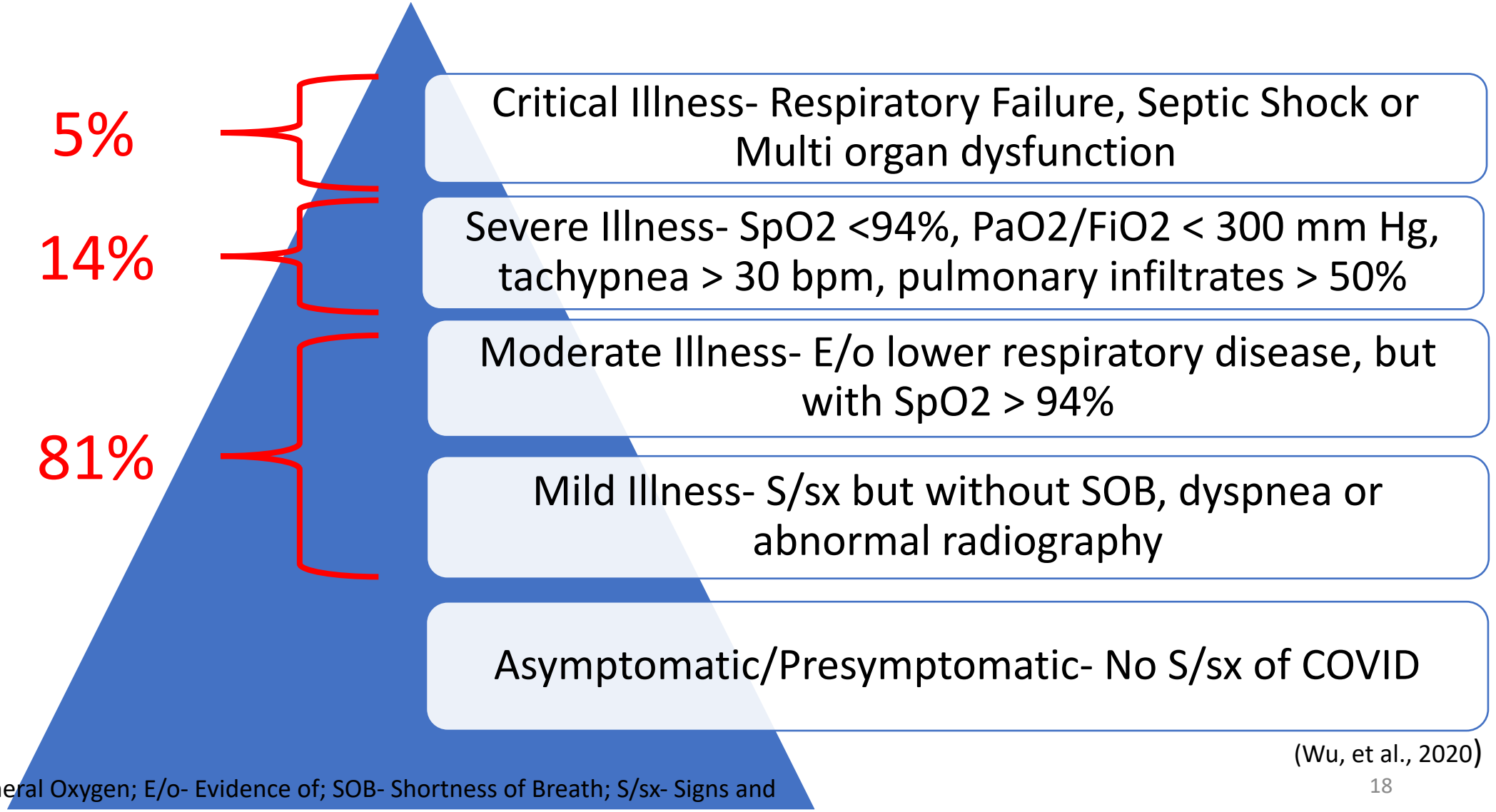
Stages of Disease



(Siddiqi et al., 2020)

ARDS- Acute Respiratory Distress Syndrome; Pa02- Partial Pressure of Oxygen; Fi02- Fraction of Inspired Oxygen; SIRS- Systemic Inflammatory Response Syndrome

COVID Severity of Illness



(Wu, et al., 2020)

Sp02- Saturation of Peripheral Oxygen; E/o- Evidence of; SOB- Shortness of Breath; S/sx- Signs and symptoms

Symptoms

What do we expect clinically?

...And have COVID-19

(Workman Publishing, 2016)

Morbidity and Mortality Weekly Report (*MMWR*)

- National Notifiable Diseases Surveillance System (NNDSS)

- 1.3 million women from Jan22-Oct3 2020 with laboratory + COVID
  - Pregnancy status available for 460k (35.5%)
  - 30k pregnant (6.6%)

- 89% of women were symptomatic

(Zambrano et al., 2020)

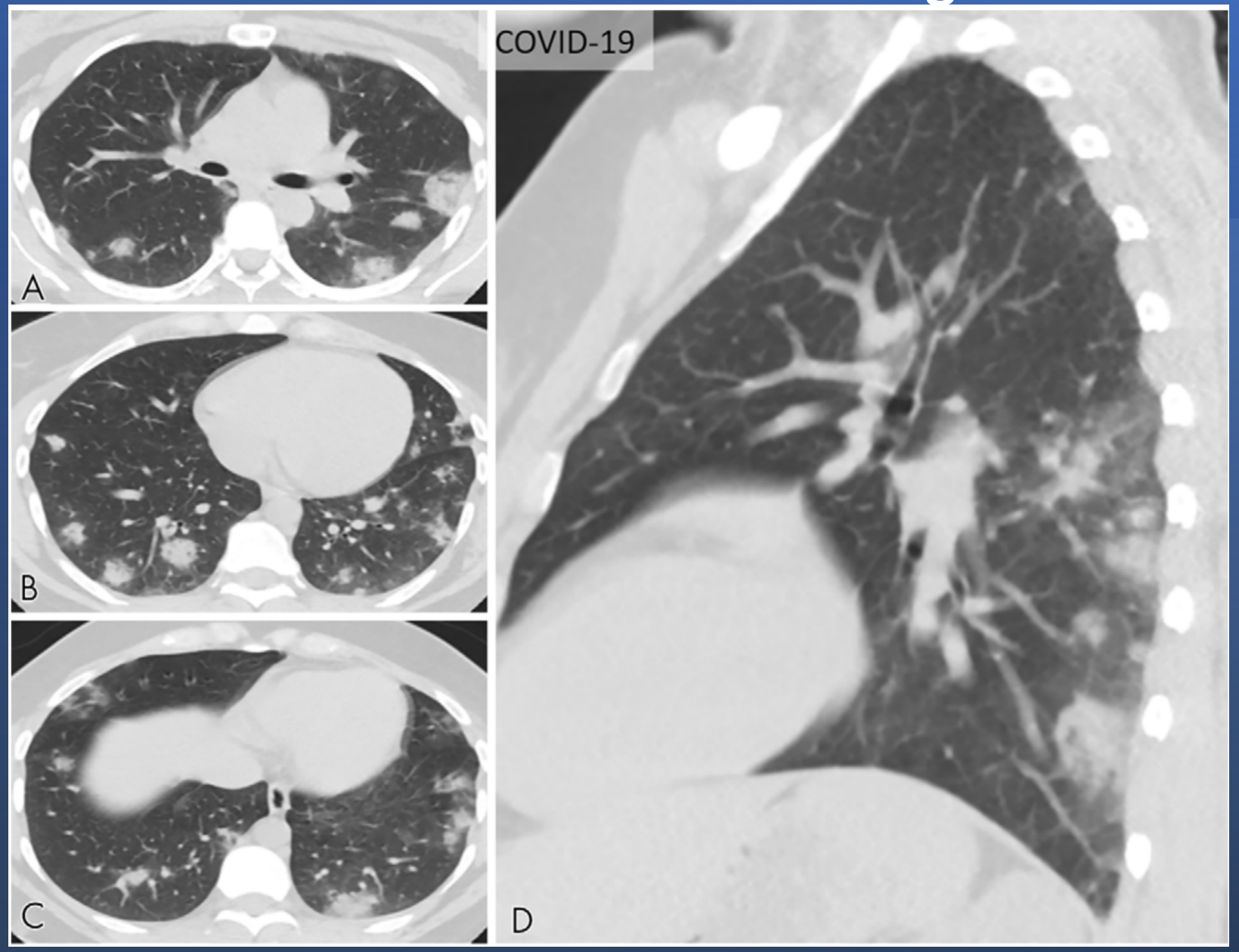
Most Common Symptoms

Characteristic	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Total (N = 409,462)
Signs and symptoms			
Known status of individual signs and symptoms[¶]	10,404	174,198	184,602
Cough	5,230 (50.3)	89,422 (51.3)	94,652 (51.3)
Fever**	3,328 (32.0)	68,536 (39.3)	71,864 (38.9)
Muscle aches	3,818 (36.7)	78,725 (45.2)	82,543 (44.7)
Chills	2,537 (24.4)	50,836 (29.2)	53,373 (28.9)
Headache	4,447 (42.7)	95,713 (54.9)	100,160 (54.3)
Shortness of breath	2,692 (25.9)	43,234 (24.8)	45,926 (24.9)
Sore throat	2,955 (28.4)	60,218 (34.6)	63,173 (34.2)
Diarrhea	1,479 (14.2)	38,165 (21.9)	39,644 (21.5)
Nausea or vomiting	2,052 (19.7)	28,999 (16.6)	31,051 (16.8)
Abdominal pain	870 (8.4)	16,123 (9.3)	16,993 (9.2)
Runny nose	1,328 (12.8)	22,750 (13.1)	24,078 (13.0)
New loss of taste or smell[††]	2,234 (21.5)	43,256 (24.8)	45,490 (24.6)
Fatigue	1,404 (13.5)	29,788 (17.1)	31,192 (16.9)
Wheezing	172 (1.7)	3,743 (2.1)	3,915 (2.1)
Chest pain	369 (3.5)	7,079 (4.1)	7,448 (4.0)

Most common symptoms were cough (50%), fever (32%), muscle aches (37%) and headache (43%).

(Zambrano et al., 2020)

Chest CT Findings



- Multi-focal
- Rounded
- Bilateral
- Ground glass opacities
- Peripheral

- Superimposed, intralobar septal thickening (i.e. “crazy paving”

(Simpson et al., 2020)

Recommended CT Reporting Language

COVID-19 pneumonia imaging classification	Rationale (6–11)	CT Findings*	Suggested Reporting Language
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia.	Peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy-paving") Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving") Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)	"Commonly reported imaging features of (COVID-19) pneumonia are present. Other processes such as influenza pneumonia and organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern." [Cov19Typ]†
Indeterminate appearance	Nonspecific imaging features of COVID-19 pneumonia.	**Absence of typical features AND** **Presence of:** Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are nonrounded or nonperipheral. Few very small GGO with a nonrounded and nonperipheral distribution	"Imaging features can be seen with (COVID-19) pneumonia, though are nonspecific and can occur with a variety of infectious and noninfectious processes." [Cov19Ind]†
Atypical appearance	Uncommonly *or* not reported features of COVID-19 pneumonia.	**Absence of typical or indeterminate features AND** **Presence of:** Isolated lobar or segmental consolidation without GGO Discrete small nodules (centrilobular, "tree-in-bud") Lung cavitation Smooth interlobular septal thickening with pleural effusion	"Imaging features are atypical or uncommonly reported for (COVID-19) pneumonia. Alternative diagnoses should be considered." [Cov19Aty]†
Negative for pneumonia	No features of pneumonia	No CT features to suggest pneumonia.	"No CT findings present to indicate pneumonia. (Note: CT may be negative in the early stages of COVID-19.) [Cov19Neg]†

GGO- Ground-glass Opacity

(Simpson et al., 2020)

Symptomatology

Characteristic	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Total (N = 409,462)
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Wheezing	172 (1.7)	3,743 (2.1)	3,915 (2.1)
Chest pain	369 (3.5)	7,079 (4.1)	7,448 (4.0)

Most symptoms are less prevalent in pregnant women than non-pregnant women

(Zambrano et al., 2020)

Risk of Adverse Outcomes

Outcome*/Characteristic	No. (per 1,000 cases) of symptomatic women		Risk ratio (95% CI)	
	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Crude†	Adjusted†,§
ICU admission¶				
All	**245 (10.5)**	**1,492 (3.9)**	**2.7 (2.4–3.1)**	**3.0 (2.6–3.4)**
Age group, yrs				
15–24	49 (7.6)	244 (1.8)	4.1 (3.0–5.6)	3.9 (2.8–5.3)
25–34	118 (9.1)	467 (3.5)	2.6 (2.1–3.1)	2.4 (2.0–3.0)
35–44	78 (19.4)	781 (6.4)	3.0 (2.4–3.8)	3.2 (2.5–4.0)
Race/Ethnicity				
Hispanic or Latina	89 (12.8)	429 (5.0)	2.6 (2.0–3.2)	2.8 (2.2–3.5)
AI/AN, non-Hispanic	0 (0)	13 (7.9)	NA	NA
Asian, non-Hispanic	20 (35.7)	52 (6.0)	5.9 (3.6–9.8)	6.6 (4.0–11.0)
Black, non-Hispanic	46 (13.6)	334 (6.2)	2.2 (1.6–3.0)	2.8 (2.0–3.8)
NHPI, non-Hispanic	5 (42.0)	22 (14.4)	2.9 (1.1–7.6)	3.7 (1.3–10.1)
White, non-Hispanic	31 (5.6)	348 (2.8)	2.0 (1.4–2.9)	2.3 (1.6–3.3)
Multiple or other race, non-Hispanic	8 (11.0)	37 (3.0)	3.7 (1.7–7.9)	4.1 (1.9–8.9)
Unknown/Not reported	46 (7.6)	257 (2.6)	2.9 (2.1–3.9)	3.4 (2.5–4.7)

Pregnant women had an absolute risk reduction (aRR) of 3.0 for admission to the Intensive Care Unit (ICU)

(Zambrano et al., 2020)

Risk of Adverse Outcomes

Outcome*/Characteristic	No. (per 1,000 cases) of symptomatic women		Risk ratio (95% CI)	
	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Crude†	Adjusted†,§
Invasive ventilation††				
All	**67 (2.9)**	**412 (1.1)**	**2.7 (2.1–3.5)**	**2.9 (2.2–3.8)**
Age group, yrs				
15–24	11 (1.7)	68 (0.5)	3.3 (1.8–6.3)	3.0 (1.6–5.7)§§
25–34	30 (2.3)	123 (0.9)	2.5 (1.7–3.7)	2.5 (1.6–3.7)§§
35–44	26 (6.5)	221 (1.8)	3.5 (2.4–5.3)	3.6 (2.4–5.4)
Race/Ethnicity				
Hispanic or Latina	33 (4.7)	143 (1.7)	2.8 (1.9–4.1)	3.0 (2.1–4.5)
AI/AN, non-Hispanic	0 (0)	5 (3.0)	NA	NA
Asian, non-Hispanic	4 (7.1)	19 (2.2)	NA	NA
Black, non-Hispanic	10 (3)	86 (1.6)	1.9 (1.0–3.6)	2.5 (1.3–4.9)
NHPI, non-Hispanic	4 (33.6)	10 (6.6)	NA	NA
White, non-Hispanic	12 (2.2)	102 (0.8)	2.7 (1.5–4.8)	3.0 (1.7–5.6)
Multiple or other race, non-Hispanic	0 (0)	8 (0.6)	NA	NA
Unknown/Not reported	4 (0.7)	39 (0.4)	NA	NA

Pregnant women had an aRR of 2.9 for invasive ventilation

Women aged 35-44 were at especially high risk

(Zambrano et al., 2020)

Risk of Adverse Outcomes

Outcome*/Characteristic	No. (per 1,000 cases) of symptomatic women		Risk ratio (95% CI)	
	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Crude†	Adjusted†,§
ECMO* **				
All	**17 (0.7)**	**120 (0.3)**	**2.3 (1.4–3.9)**	**2.4 (1.5–4.0)**
Age group,yrs				
15–24	6 (0.9)	31 (0.2)	4.0 (1.7–9.5)	NA†††
25–34	7 (0.5)	35 (0.3)	2.0 (0.9–4.6)	2.0 (0.9–4.4)§§
35–44	4 (1.0)	54 (0.4)	NA	NA
Race/Ethnicity				
Hispanic or Latina	6 (0.9)	35 (0.4)	2.1 (0.9–5.0)	2.4 (1.0–5.9)
AI/AN, non-Hispanic	0 (0)	1 (0.6)	NA	NA
Asian, non-Hispanic	0 (0)	1 (0.1)	NA	NA
Black, non-Hispanic	5 (1.5)	30 (0.6)	2.7 (1.0–6.9)	2.9 (1.1–7.3)
NHPI, non-Hispanic	0 (0)	2 (1.3)	NA	NA
White, non-Hispanic	4 (0.7)	29 (0.2)	NA	NA
Multiple or other race, non-Hispanic	0 (0)	3 (0.2)	NA	NA
Unknown/Not reported	2 (0.3)	19 (0.2)	NA	NA

Pregnant women had an aRR of 2.4 for Extracorporeal Membrane Oxygenation (ECMO)

(Zambrano et al., 2020)

Risk of Adverse Outcomes

Outcome*/Characteristic	No. (per 1,000 cases) of symptomatic women		Risk ratio (95% CI)	
	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Crude†	Adjusted†,§
Death§§§				
All	**34 (1.5)**	**447 (1.2)**	**1.3 (0.9–1.8)**	**1.7 (1.2–2.4)**
Age group, yrs				
15–24	2 (0.3)	40 (0.3)	NA	NA
25–34	15 (1.2)	125 (0.9)	1.2 (0.7–2.1)	1.2 (0.7–2.1)
35–44	17 (4.2)	282 (2.3)	1.8 (1.1–3.0)	2.0 (1.2–3.2)
Race/Ethnicity				
Hispanic or Latina	14 (2.0)	87 (1.0)	2.0 (1.1–3.5)	2.4 (1.3–4.3)
AI/AN, non-Hispanic	0 (0)	5 (3.0)	NA	NA
Asian, non-Hispanic	1 (1.8)	11 (1.3)	NA	NA
Black, non-Hispanic	9 (2.7)	167 (3.1)	0.9 (0.4–1.7)	1.4 (0.7–2.7)
NHPI, non-Hispanic	2 (16.8)	6 (3.9)	NA	NA
White, non-Hispanic	3 (0.5)	83 (0.7)	NA	NA
Multiple or other race, non-Hispanic	0 (0)	12 (1.0)	NA	NA
Unknown/Not reported	5 (0.8)	76 (0.8)	1.1 (0.4–2.6)	1.4 (0.6–3.6)

Pregnant women had an aRR of 1.7 for death

(Zambrano et al., 2020)

Racial Disparities with COVID-19

- Hispanic women are overrepresented in the COVID+/symptomatic population
  - COVID+ : 30% Hispanic/24% White
  - General pregnant population: 24% Hispanic/51% White

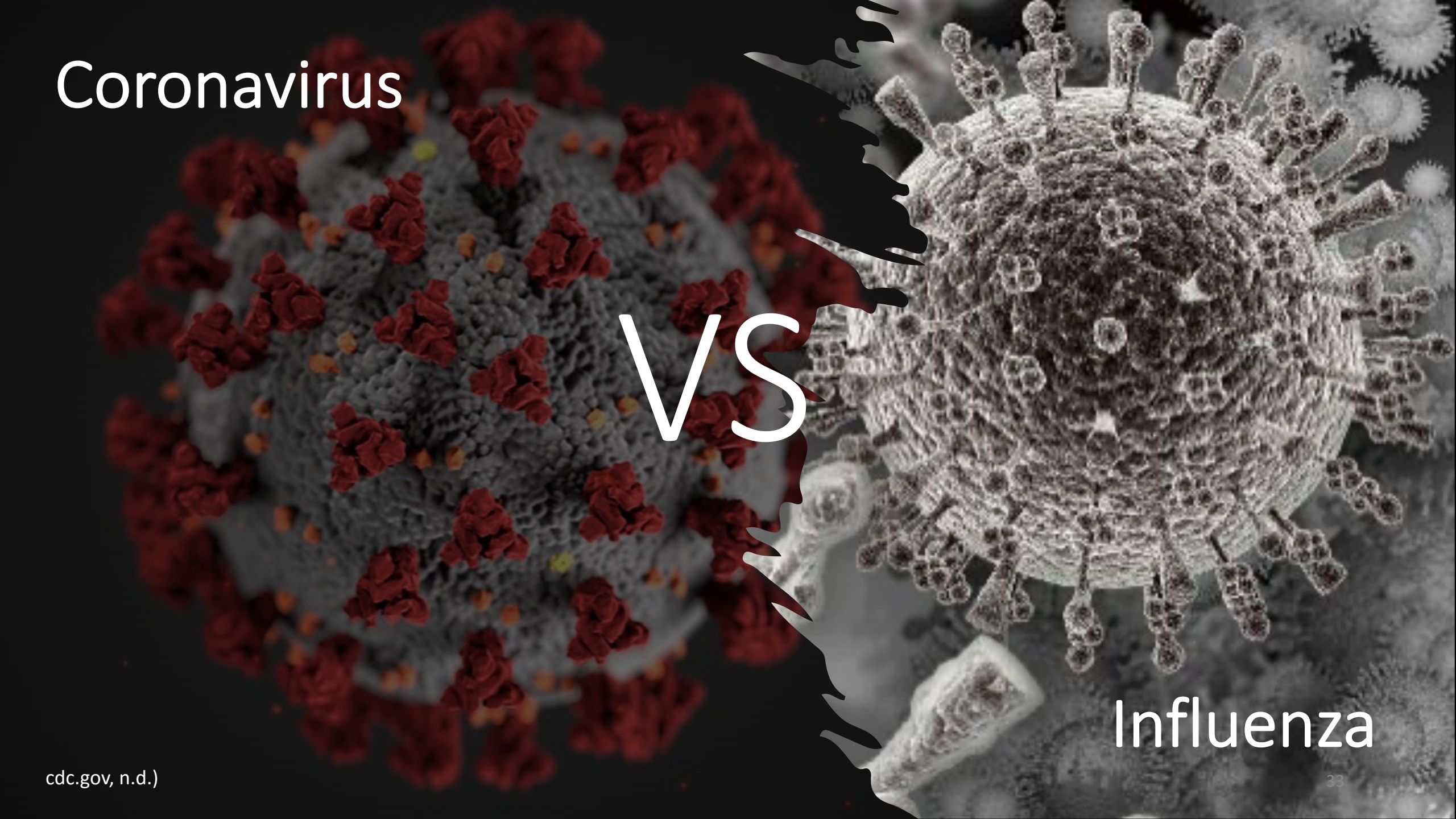
- Hispanic women were at increased for death (aRR = 2.4)

- Regardless of pregnancy status, non-Hispanic Black women were at increased risk for death (Odds Ratio (OR)= 3.1)

(Zambrano et al., 2020)

Coronavirus

VS



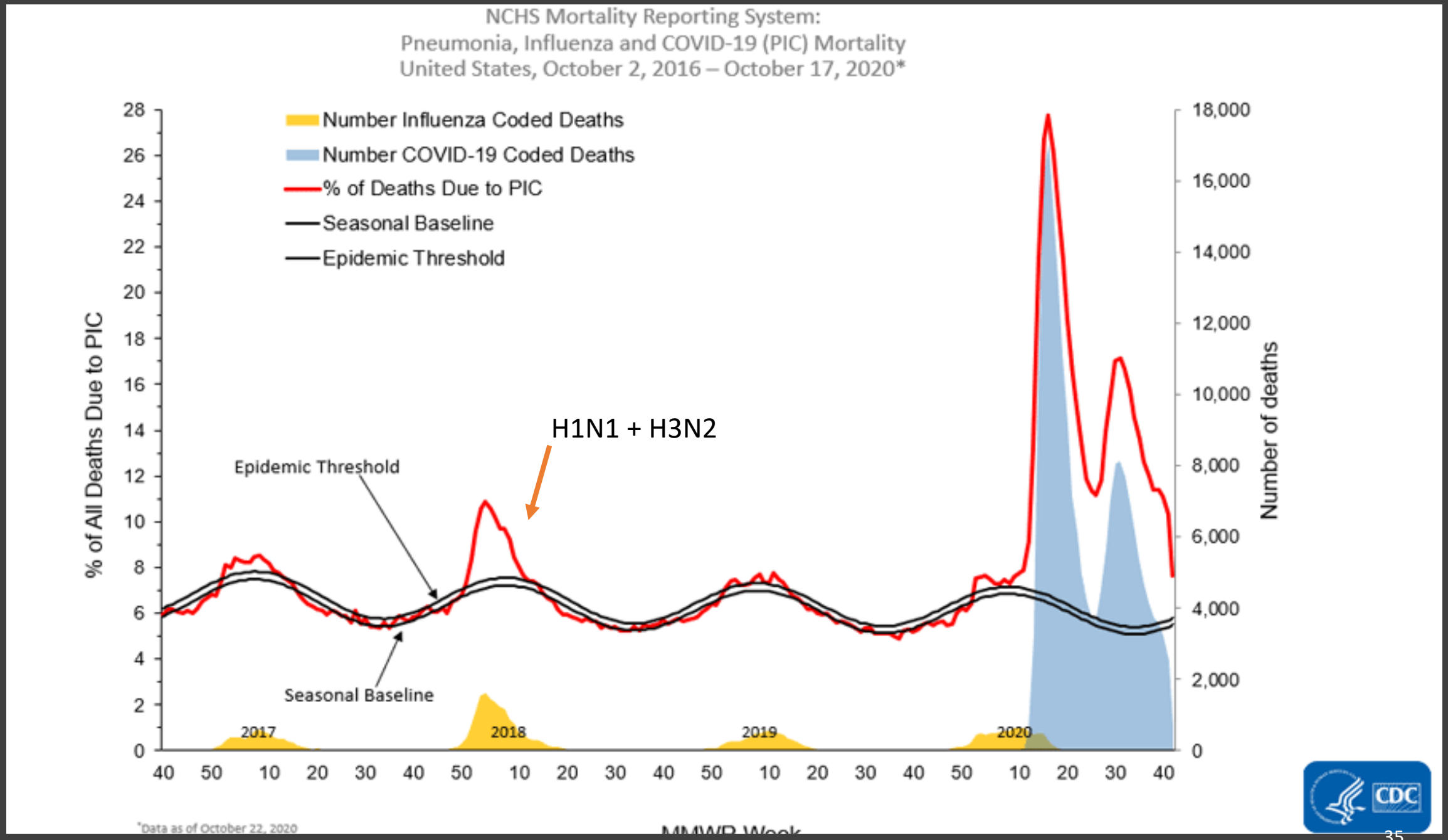
Influenza

cdc.gov, n.d.)

Comparison to Influenza

- Common knowledge says pregnancy= high risk from influenza
- Metaanalysis of 4k pregnant women has questioned this knowledge for SEASONAL influenza
  - Adjusted Odds Ratio (aOR)= 6.8 for hospitalization (95% Confidence Intervals (CI), 6.02-7.68)
  - aOR= 0.57 for ICU admission (95% CI, 0.48-0.69)
  - aOR= 1.0 for death (95% CI, 0.75-1.34)
- Prior studies have found increased risk with PANDEMIC influenza (H1N1 etc)

(Mertz et al., 2019)
(Creanga et al., 2011)


NCHS Mortality Reporting System:
Pneumonia, Influenza and COVID-19 (PIC) Mortality
United States, October 2, 2016 – October 17, 2020*
Number Influenza Coded Deaths
Number COVID-19 Coded Deaths
% of Deaths Due to PIC
Seasonal Baseline
Epidemic Threshold
H1N1 + H3N2
Epidemic Threshold
Seasonal Baseline
2017
2018
2019
2020
% of All Deaths Due to PIC
Number of deaths
MMWR Week
*Data as of October 22, 2020
CDC

(cdc.gov, 2020)

Recommendations

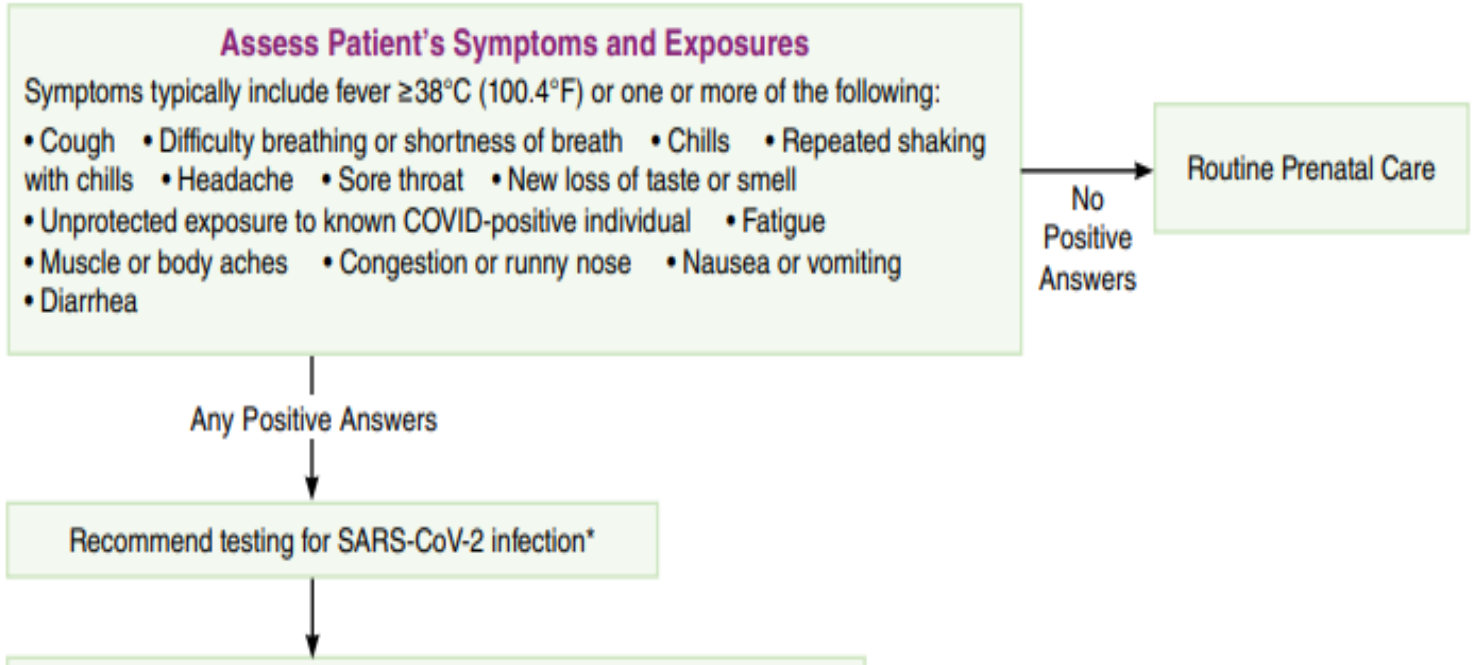
- Inform pregnant women of the risk of severe COVID associated illness
- Inform pregnant women of s/sx of COVID
- Limit unnecessary contact with people who may have been exposed
- When going out:
  - Wear a mask
  - Social distance
  - Avoid people not wearing masks
  - Wash hands frequently
- Keep up to date with general heath (seasonal flu vaccine, prenatal care)

(Zambrano et al., 2020)

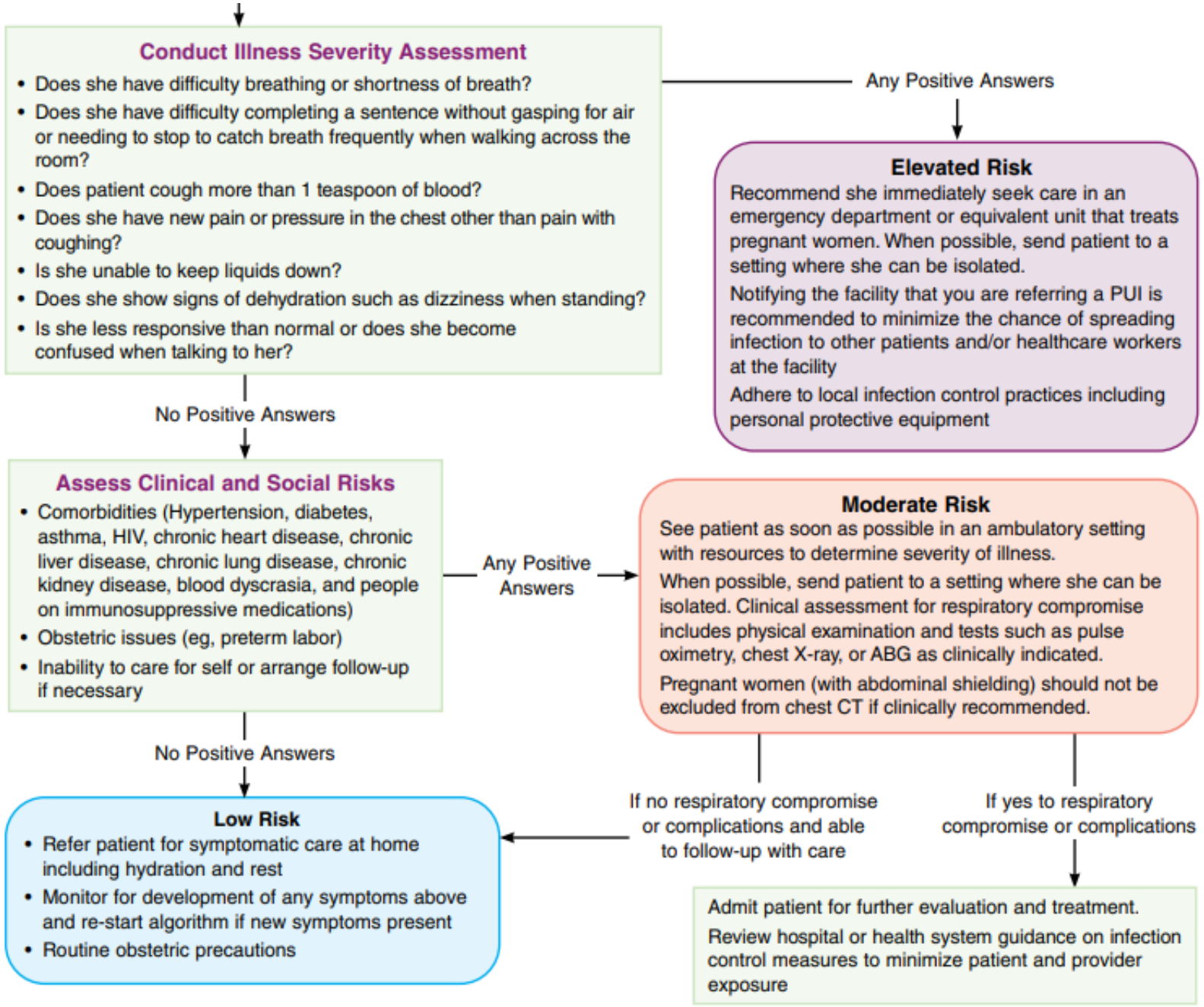
ACOG
The American College of Obstetricians and Gynecologists

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

Outpatient Assessment and Management for Pregnant Women With Suspected or Confirmed Novel Coronavirus (COVID-19)



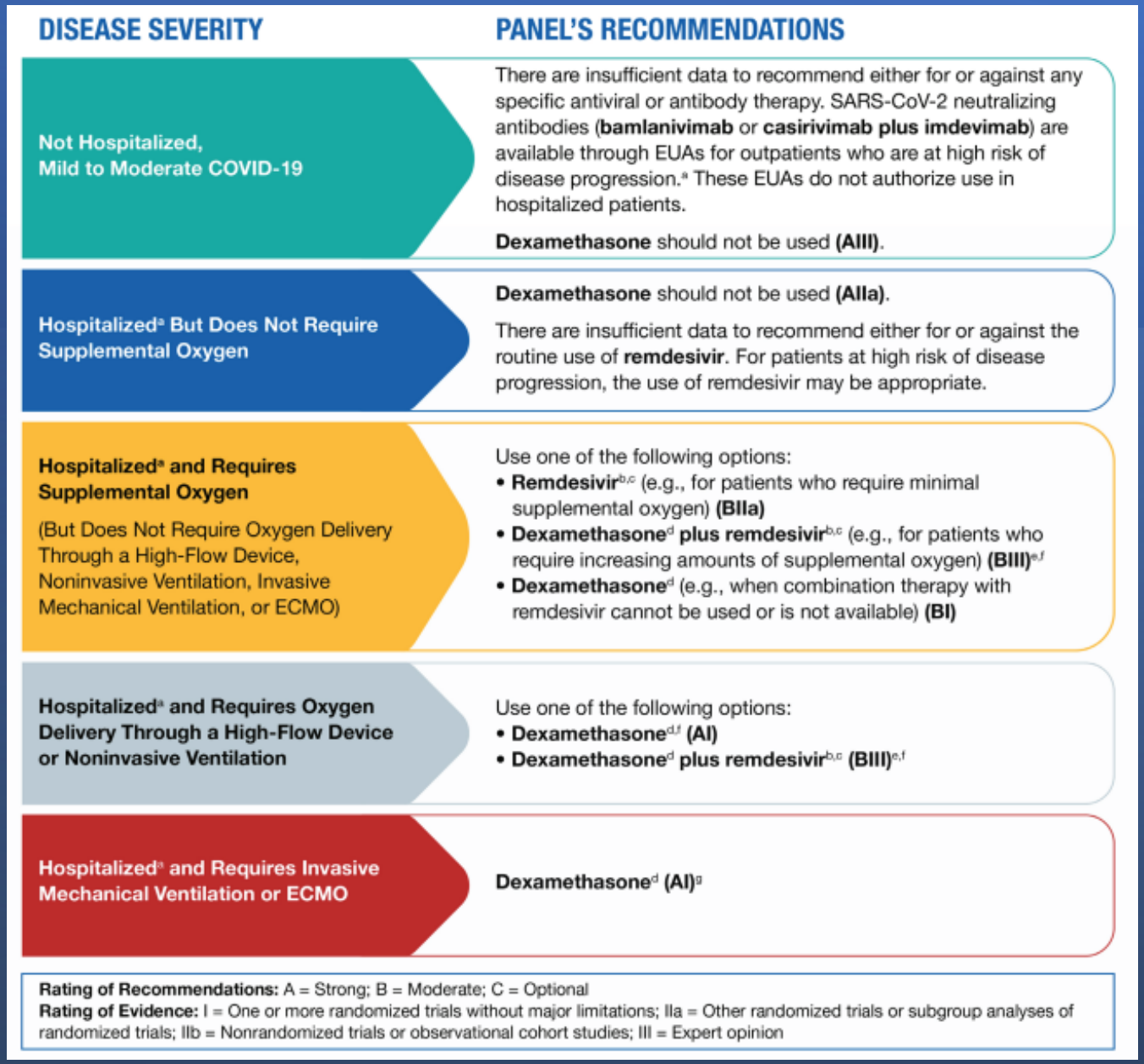
(acog.org, n.d.)


Conduct Illness Severity Assessment
• Does she have difficulty breathing or shortness of breath?
• Does she have difficulty completing a sentence without gasping for air or needing to stop to catch breath frequently when walking across the room?
• Does patient cough more than 1 teaspoon of blood?
• Does she have new pain or pressure in the chest other than pain with coughing?
• Is she unable to keep liquids down?
• Does she show signs of dehydration such as dizziness when standing?
• Is she less responsive than normal or does she become confused when talking to her?
Any Positive Answers
Elevated Risk
Recommend she immediately seek care in an emergency department or equivalent unit that treats pregnant women. When possible, send patient to a setting where she can be isolated.
Notifying the facility that you are referring a PUI is recommended to minimize the chance of spreading infection to other patients and/or healthcare workers at the facility
Adhere to local infection control practices including personal protective equipment
No Positive Answers
Assess Clinical and Social Risks
• Comorbidities (Hypertension, diabetes, asthma, HIV, chronic heart disease, chronic liver disease, chronic lung disease, chronic kidney disease, blood dyscrasia, and people on immunosuppressive medications)
• Obstetric issues (eg, preterm labor)
• Inability to care for self or arrange follow-up if necessary
Any Positive Answers
Moderate Risk
See patient as soon as possible in an ambulatory setting with resources to determine severity of illness.
When possible, send patient to a setting where she can be isolated. Clinical assessment for respiratory compromise includes physical examination and tests such as pulse oximetry, chest X-ray, or ABG as clinically indicated.
Pregnant women (with abdominal shielding) should not be excluded from chest CT if clinically recommended.
No Positive Answers
Low Risk
• Refer patient for symptomatic care at home including hydration and rest
• Monitor for development of any symptoms above and re-start algorithm if new symptoms present
• Routine obstetric precautions
If no respiratory compromise or complications and able to follow-up with care
If yes to respiratory compromise or complications
Admit patient for further evaluation and treatment.
Review hospital or health system guidance on infection control measures to minimize patient and provider exposure

(ACOG.org, n.d.)

Treatments

What can we do?



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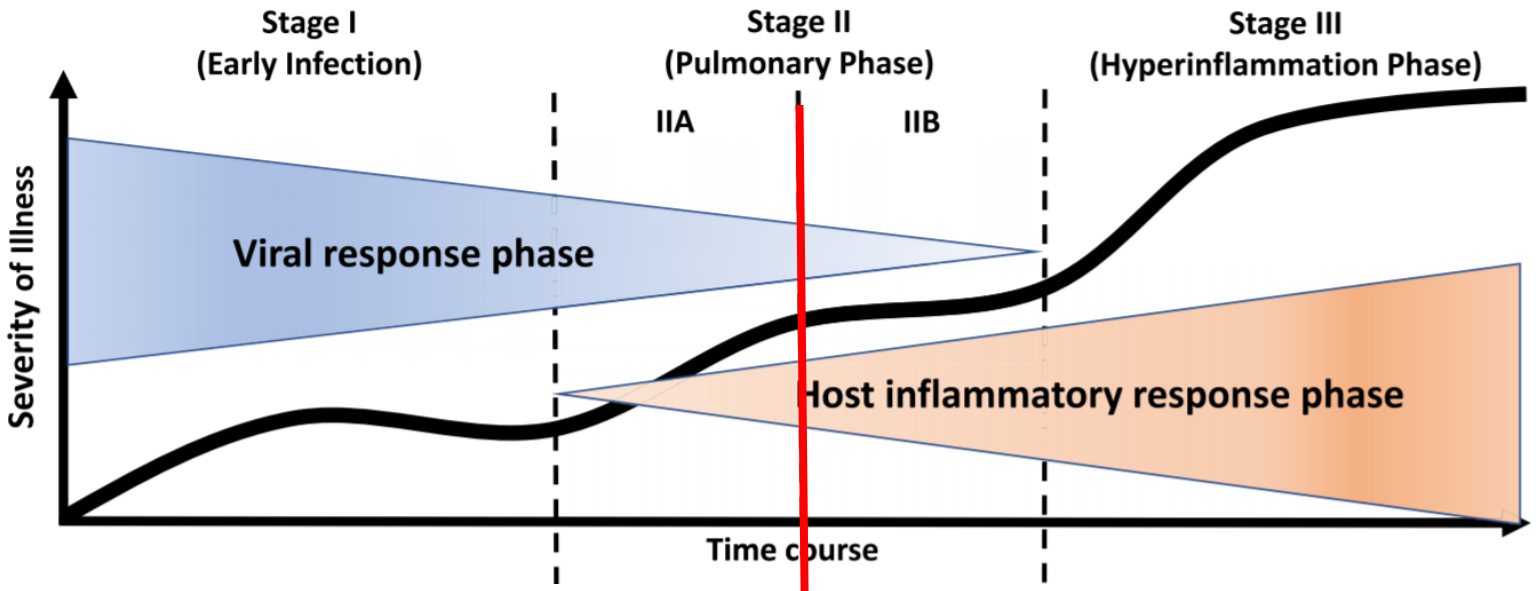
CDC COVID Treatment Guidelines

(NIH.gov, 2021)

Stages of Disease



Antivirals
- Remdesivir

Immune modulators
- Corticosteroids
- Interferons, Interleukin (IL) inhibitors, kinase inhibitors

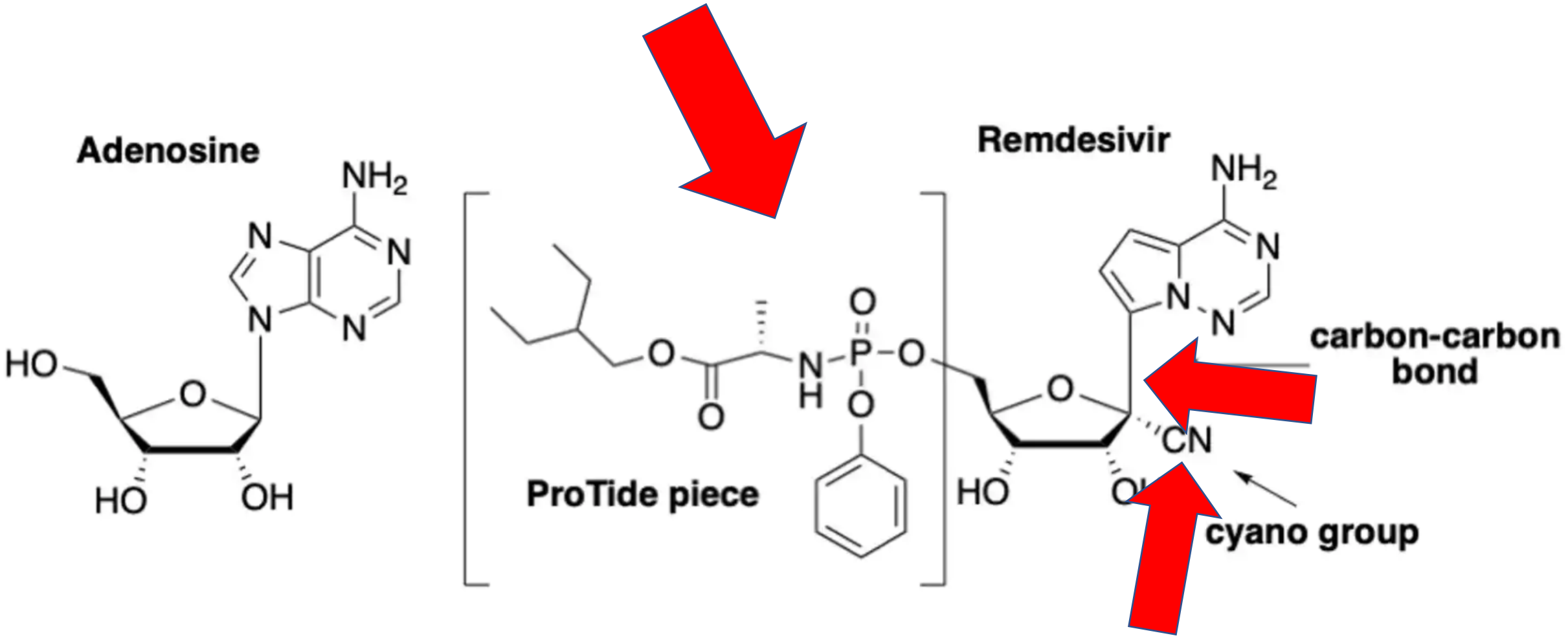
Blood derived products
- Convalescent Plasma
- Intravenous Immunoglobulin (IVIG)

(Siddiqi et al., 2020)

Remdesivir

- Nucleoside analogue of adenosine
- Prematurely terminates ribonucleic acid (RNA) replication
- Food and Drug Administration (FDA) approved for adults and peds (>age 12)
- FDA Emergency Use Authorization (EUA) peds < 12 years

(stock.adobe, n.d.)



Remdesivir

(Seley-Radtke, 2020)

Remdesivir Pregnancy

- Pregnant women were excluded from all of the remdesivir clinical trials
- Well tolerated with few serious adverse side effects during compassionate use
- Should not be withheld unless otherwise contraindicated

(Burwick et al., 2020)

Remdesivir Clinical Trials

- Adaptive COVID-19 Treatment Trial (ACCT-1)
  - Multinational, RCT
  - 1000 participants
  - Remdesivir (200 mg x 1d, 100 mg x 8d) vs Placebo

Primary Endpoint = Clinical Improvement

1. Not hospitalized, no limitations
2. Not hospitalized, with limitations
3. Hospitalized, no active medical problems
4. Hospitalized, not on oxygen
5. Hospitalized, on oxygen
6. Hospitalized, on high-flow oxygen or non-invasive mechanical ventilation
7. Hospitalized, on mechanical ventilation or ECMO
8. Death

(Beigel et al., 2020)

Remdesivir Clinical Trials

Positive

- Reduced the time to recovery
- Clinical improvement was higher on Day 15 (OR 1.5; 95% CI, 1.2-1.9)
- Hospitalized, on oxygen (group 5)
  - Recovery rate 1.45, 95% CI, 1.18-1.79
  - HR for death 0.28; 95% CI, 0.12-0.66

Negative

- Patients on high flow oxygen (group 6)
  - Recovery rate 1.09; 95% CI 0.76-1.57
  - HR for death 0.82; 95% CI, 0.40-1.69
- Patients on mechanical ventilation/ECMO
  - Recovery rate 0.98; CI

(Beigel et al., 2020)

Remdesivir Clinical Trials

- Randomized Controlled Trial (RCT) China
  - Single site study in China
  - Planned enrollment of 450, but stopped after 237
  - No improvement in time to clinical improvement -21d vs 23d
  - 28-day mortality was similar
  - Viral load (VL) at baseline and rate of decrease of VL were similar
  - Multiple possible confounders
    - 65% received steroids
    - 30% received lopinavir/ritonavir
    - 30% receive Interferon Alfa (IFA)

(Wang et al., 2020)

Remdesivir Clinical Trials

- Open label RCT
  - Single site
  - SARS-CoV-2 + “moderate” pneumonia (radiographic findings and SpO2>94%)
  - 600 patients (200 x 3 randomization groups
    - 10-days Remdesivir
    - 5-days Remdesivir
    - Standard treatment
  - Remdesivir [200 mg x 1 then 100 mg once a day (qday)]

(Spinner et al., 2020)

Remdesivir Clinical Trials

Positive

- 5-day remdesivir had better clinical status distribution on day 11 vs Standard care (OR 1.65; 95% CI 1.09-2.48)
- More hospital d/c by day 28 in remdesivir group (90% vs 83%)
- Low mortality in all groups (1-2%)

Negative

- Clinical status distribution for 10-day remdesivir was not different from standard care
- Higher proportion of patients in standard care received hydroxychloroquine (HCQ), lopinavir/ritonavir or azithromycin

(Spinner et al., 2020)

Remdesivir Clinical Trials

- Remdesivir Length of Treatment Trial
  - Manufacturer sponsored, multinational, randomized, open label trial
  - 400 patients (200 per group)
    - 10-day group had worse initial status compared to 5-day group
  - Age >12 with SARS-CoV-2 +radiographic pulmonary infiltrates
  - All had SpO2< 94% or were receiving supplemental O2, however, mechanical ventilation or ECMO were excluded
  - Remdesivir 10 days vs 5 days (200 mg x 1d, 100 mg qday)
  - Primary endpoint was time to clinical status on Day 14

(Goldman et al., 2020)

Remdesivir Clinical Trials

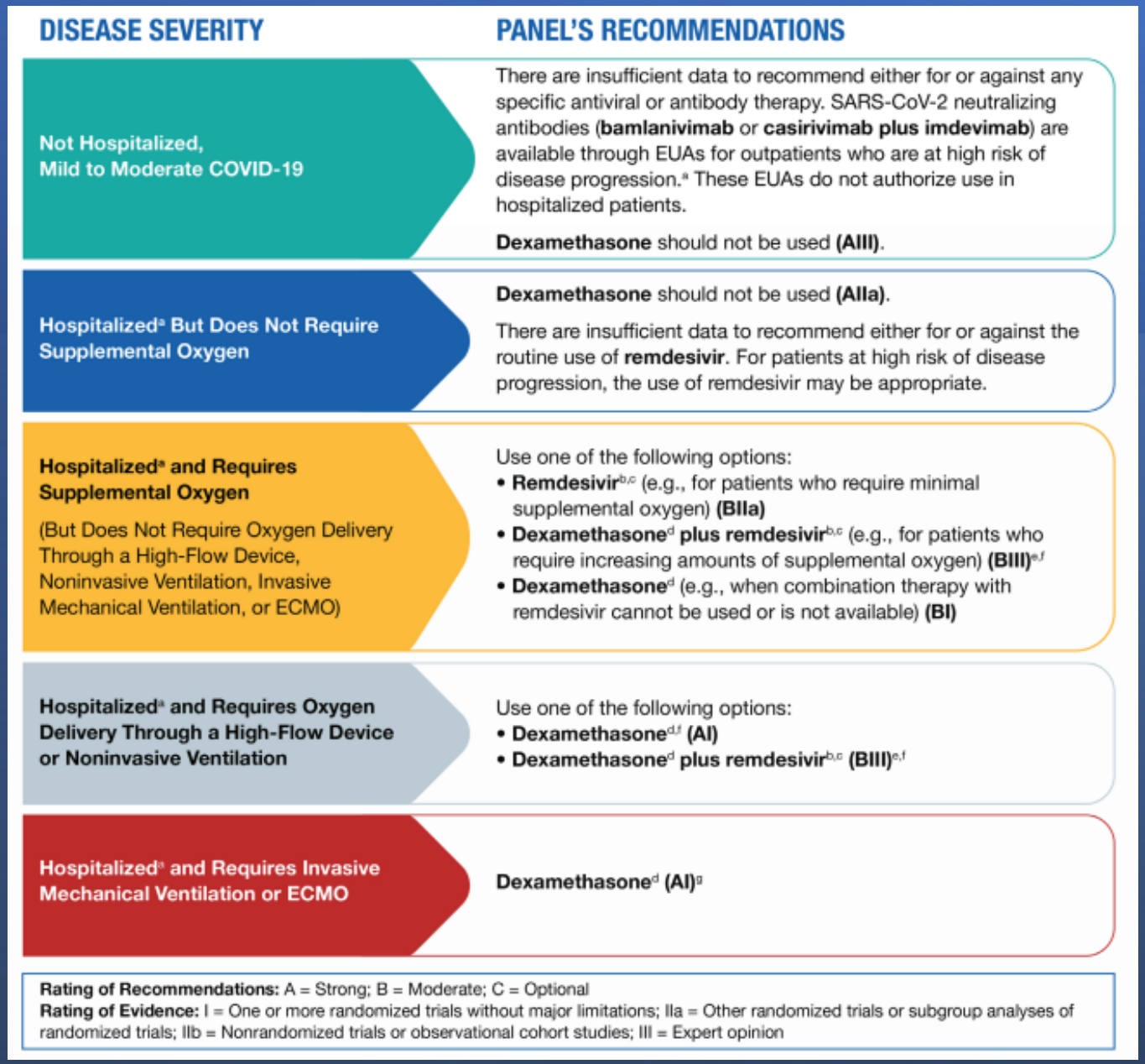
Positive

- None

Negative

- Day 14 distribution was similar between groups
- Time to achieve clinical improvement was similar
- Median duration of hospitalization was similar (7 days vs 8 days)
- Serious adverse events (AE) were more common in 10-day group 35% vs 21%

(Goldman et al., 2020)



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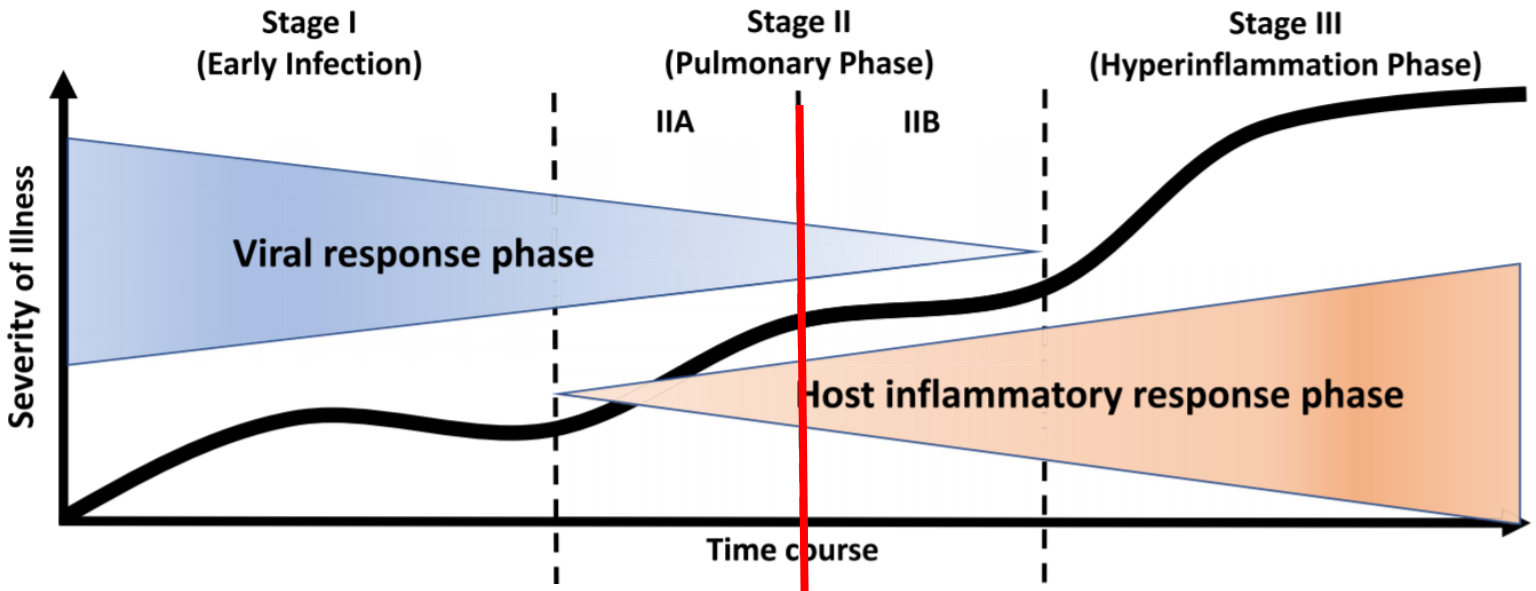
CDC COVID Treatment Guidelines

(NIH.gov, 2021)

Other Anti-virals

- Hydroxychloroquine/Chloroquine
  - EUA granted 28 Mar 2020
  - EUA rescinded 15 Jun 2020
- Ivermectin
- Lopinavir/Ritonovir

Stages of Disease



Antivirals
- Remdesiver

Immune modulators
- Corticosteroids
- Interferons, IL inhibitors, kinase inhibitors

Blood derived products
- Convalescent Plasma
- IVIG

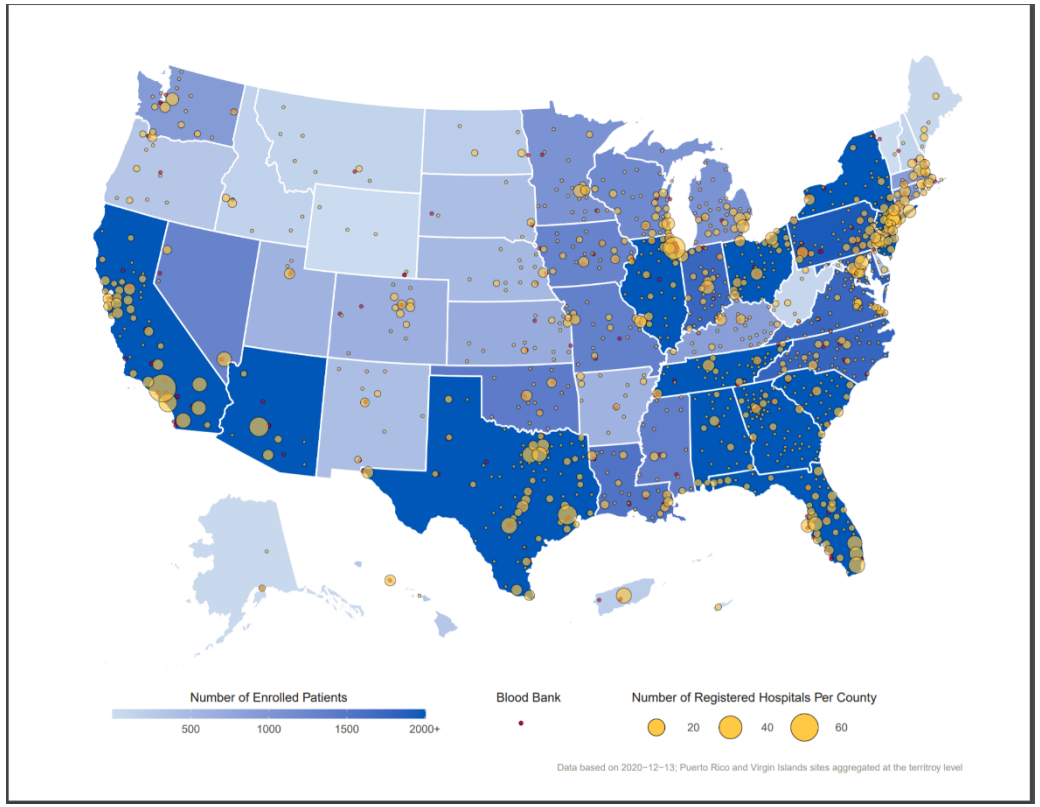
(Siddiqi et al., 2020)

Convalescent Plasma

- Used since 1800
- Initially used for diphtheria
- Only RCT showing efficacy was published in the 1970's
  - Argentine Hemorrhagic Fever
- Observational studies with severe acute respiratory syndrome (SARS) have suggested efficacy

Convalescent Plasma

- Mayo Clinic Expanded Access Program
- No difference in 7-day mortality between low and high titer
- In non-intubated patients
  - 7 day mortality was decreased from 14% to 11% for high vs low titers
- In patients < 80, treatment within 72 hrs of sx
  - 7-day mortality decreased from 11.3% to 6.3% for high vs low titer



(uscovidplasma.org, 2020)

Convalescent Plasma Safety

- Mayo Clinic Expanded Access Program
  - 20k patients
- 13 deaths (0.06%)
- 83 non-fatal serious adverse effects
  - 37 transfusion-associated circulatory overload (TACO) (0.18%)
  - 20 transfusion-related acute lung injury (TRALI) (0.10%)
  - 26 Allergic reactions (0.13%)
- Life threatening Adverse events
  - 87 venous thromboembolism (VTE) (0.16%)
  - 406 Hypotension (0.27%)
  - 643 Cardiac events (0.37%)
- Overall mortality 8.6%

(Joyner et al., 2020)

Immunoglobulins

- IVIG SARS-CoV-2
  - RCT are in development, but not yet enrolling
- IVIG non-SARS-CoV-2
  - Retrospective, non-randomized trial performed in China showed no benefit
  - Significant limitations
  - Commonly used in pregnancy (neonatal alloimmune thrombocytopenia (NAIT) etc) and has good safety profile

Monoclonal Antibodies

- FDA has issued EUA for two neutralizing monoclonal antibodies
  - Casirivimab/Imdevimab (Regeneron)
  - Bamlanivimab (Eli Lilly)
- For treatment of mild/moderate COVID
  - Not requiring hospitalization
  - At high risk for progression to severe COVID
- Should NOT be withheld from pregnant patients at high risk

REGENERON
SCIENCE TO MEDICINE®

(regeneron.com, n.d.)

Lilly

(lilly.com, n.d.)

(fda.gov, 2020)-Casirivimab/Imdevimab
(fda.gov, 2020)- Bamlanivimab

Monoclonal Antibodies

- High Risk Conditions:
  - Body Mass Index (BMI) ≥ 35
  - Chronic kidney disease (CKD)
  - Diabetes mellitus (DM)
  - Immunosuppressive disease
  - ≥ 65
  - ≥ 55 years and have cardiovascular disease (CVD) or hypertension (HTN) or chronic obstructive pulmonary disease (COPD)
- High Risk Pediatric conditions:
  - Age 12-17 with…
    - BMI > 85%
    - Hemoglobin sickle cell (Hgb SS) diagnosis
    - Congenital or acquired heart disease
    - Neurodevelopmental disorders
    - Medical-related technological dependence
    - Asthma requiring daily medication

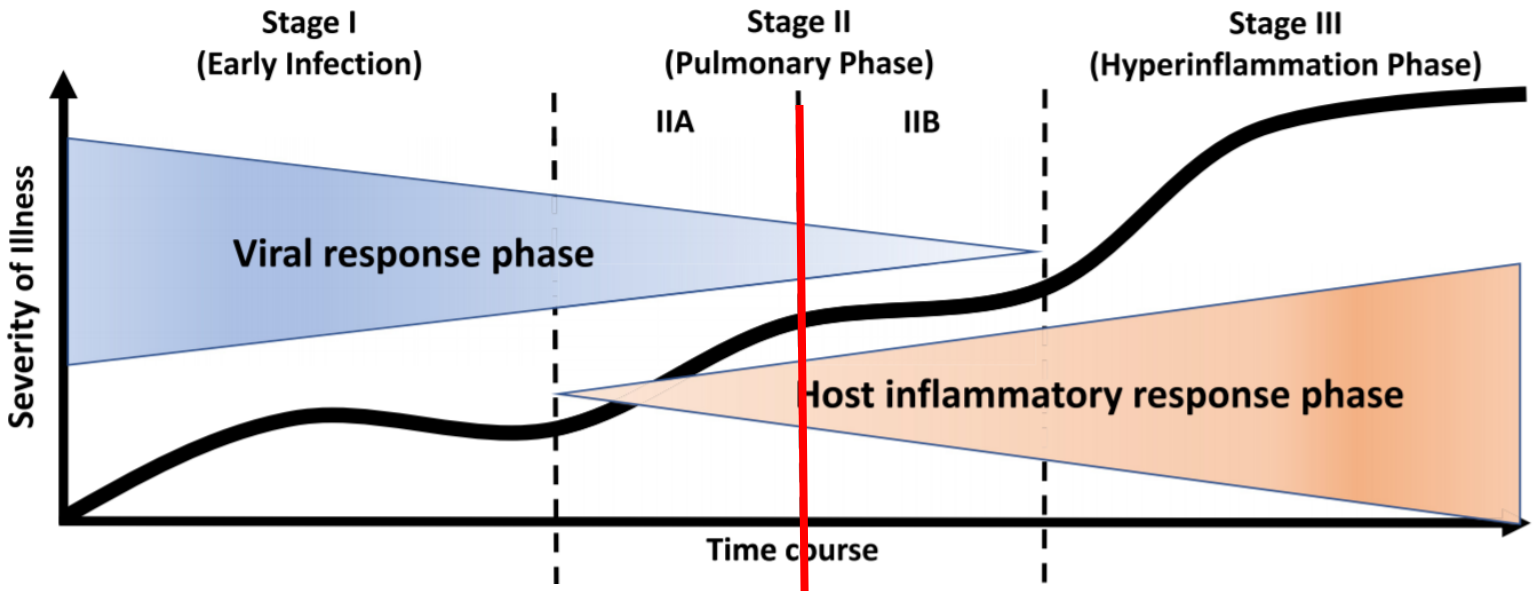
(fda.gov, 2020)- Casirivimab/Imdevimab
(fda.gov, 2020)- Bamlanivimab

Monoclonal Antibodies

- Benefit has not been observed in patients hospitalized
- May be associated with worse outcomes in hospitalized patients requiring high-flow nasal cannula (HFNC) or mechanical ventilation
- Not authorized for …
  - Hospitalized due to COVID-19
  - Require O2 due to COVID-19
  - Require an increased in baseline O2 for those on chronic supplemental O2

(fda.gov, 2020)- Casirivimab/Imdevimab
(fda.gov, 2020)- Bamlanivimab

Stages of Disease



Antivirals
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Blood derived products
- Convalescent Plasma
- IVIG

(Siddiqi et al., 2020)

Corticosteroids

- Corticosteroids have potent anti-inflammatory effects
- Steroids have decreased mortality in other respiratory diseases (PCP), however were associated with delayed viral clearance in Middle East respiratory syndrome (MERS) and SARS
- Corticosteroids have also been shown to decrease all cause mortality and length of mechanical ventilation in ARDS patients

RECOVERY Trial

- National Health Services (NHS) study
- Ongoing, multicentre, open label study
- 6400 patients (2100- dexamethasone; 4300- standard care)
- Primary endpoint
  - All cause mortality at 28 days after randomization
- Secondary endpoints- not yet reported
  - Time to hospital discharge
  - Cause specific mortality
  - Need for renal replacement
  - Major cardiac arrhythmia
  - Receipt and duration of mechanical ventilation

(Recovery Collaborative Group et al., 2020)

RECOVERY Trial Results

- Dexamethasone **decreased mortality at 28-days**
  - 22.9% vs 25.7%; RR 0.82; 95% CI, 0.75-0.94
- Benefit was **greatest in those who required mechanical ventilation**
  - 29.3% vs 41.3%; RR 0.82; 95% CI, 0.51-0.81
- Mortality was **decreased among those who required supplemental O2**
  - 23.3% vs 26.2%; RR 0.82; 95% CI, 0.72-0.94
- There was **no survival benefit in those who didn't require O2**
  - 17.8% vs 14.0%; RR 1.19; 95% CI, 0.91-1.55

(Recovery Collaborative Group et al., 2020)

World Health Organization (WHO) Meta-analysis

- 7 studies including 1700 critically ill patients
  - 678 received corticosteroids
  - 1000 received standard care

- Mortality was decreased with corticosteroids
  - 32.7% vs 41.5%; OR 0.66; 95% CI, 0.53-0.82
  - Dexamethasone: 1200 patients; OR 0.64; 95% CI, 0.50-0.82
  - Hydrocortisone: 374 patients; OR 0.69; 95% CI, 0.42-1.12
  - Methylprednisolone: 47 patients; OR 0.91; 95% CI, 0.29-2.87

(WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2020)

WHO Meta-analysis of Corticosteroids

- Limitations
  - Trials varied in many ways-
  - RECOVERY Trial accounted for 60% of patients
    - Several studies ended enrollment after RECOVERY preliminary report was released
  - Not all studies required confirmed SARS-CoV-2 infection
    - RECOVERY Trial had approximately 89% confirmed SARS-CoV-2

Results are likely driven primarily by the results of RECOVERY Trial

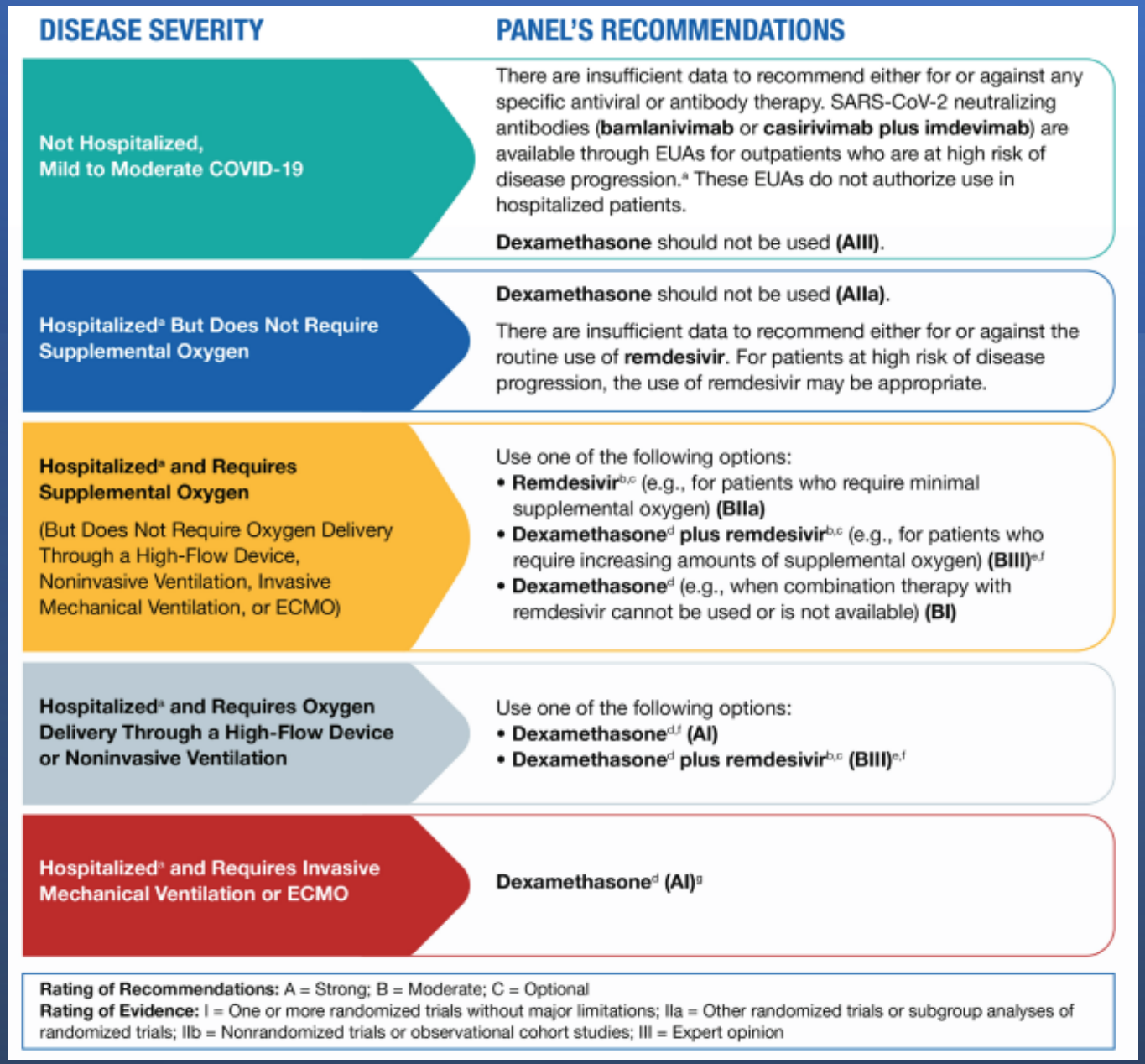
(WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2020)

Corticosteroids for Fetal Lung Maturity

- Corticosteroids for fetal lung maturity should be considered for all women admitted to the ICU and women deemed to be high risk for preterm delivery (PTD)

- In women receiving Dexamethasone for treatment of COVID-19
  - Give 6 mg twice a day (BID) x 4 doses (2 days)
  - …then, 6 mg qday x 8 doses to complete 10-day course

- Benefit from late preterm steroids (34w0d – 36w6d) may not outweigh potential risk of worsening pulmonary status or increased viral shedding in patient not otherwise on dexamethasone



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CDC COVID Treatment Guidelines

(NIH.gov, 2021)

Interferons (IFNs)/Interleukins

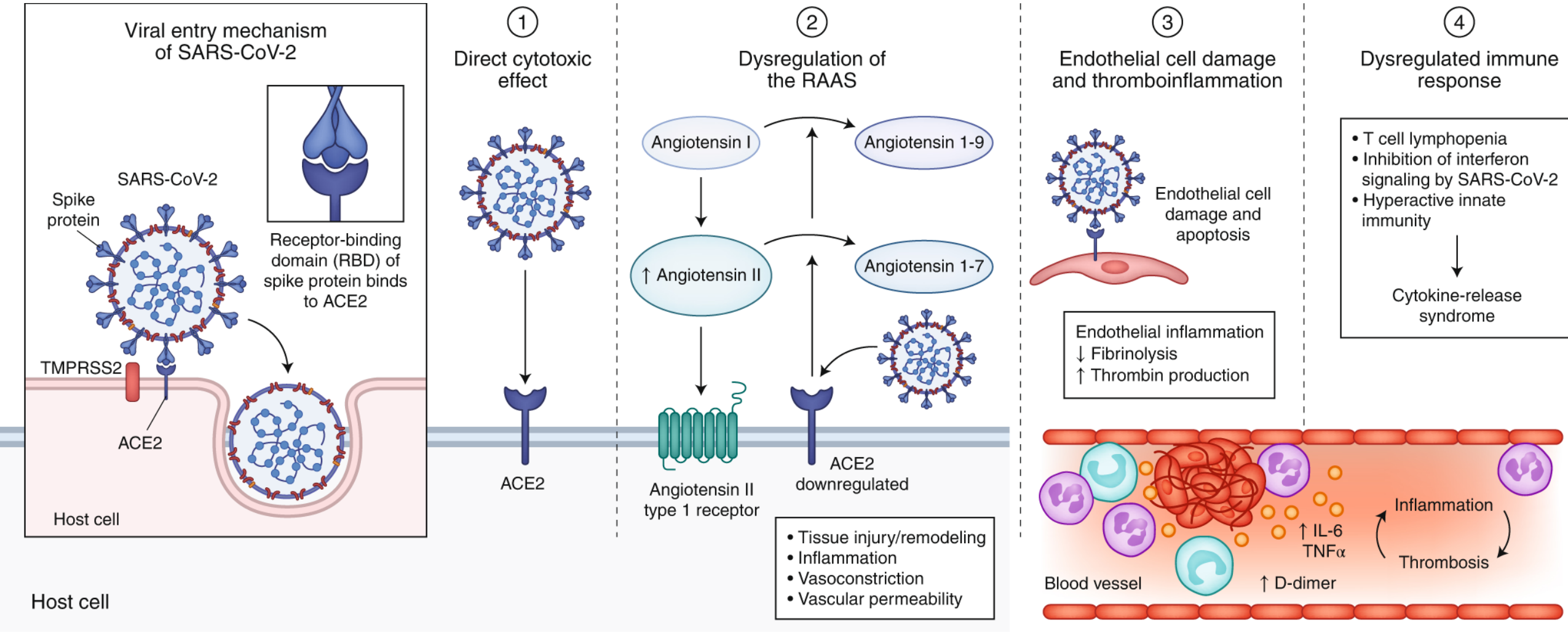
- IFNs are naturally occurring cytokines (proteins) with antiviral properties
  - Prior studies with SARS/MERS showed no effect
  - British biotech reported 79% decrease in development of severe COVID after treatment with inhaled IFN beta 1-a
- Interleukins are inflammatory cytokines elevated in COVID
  - IL-1 (Anakinra) and IL-6 (Tocilizumab et al) inhibitors have been studied, but have not shown efficacy.

COVID & Venous Thromboembolism (VTE)

What is the risk?

What is happening?

Pathophysiology

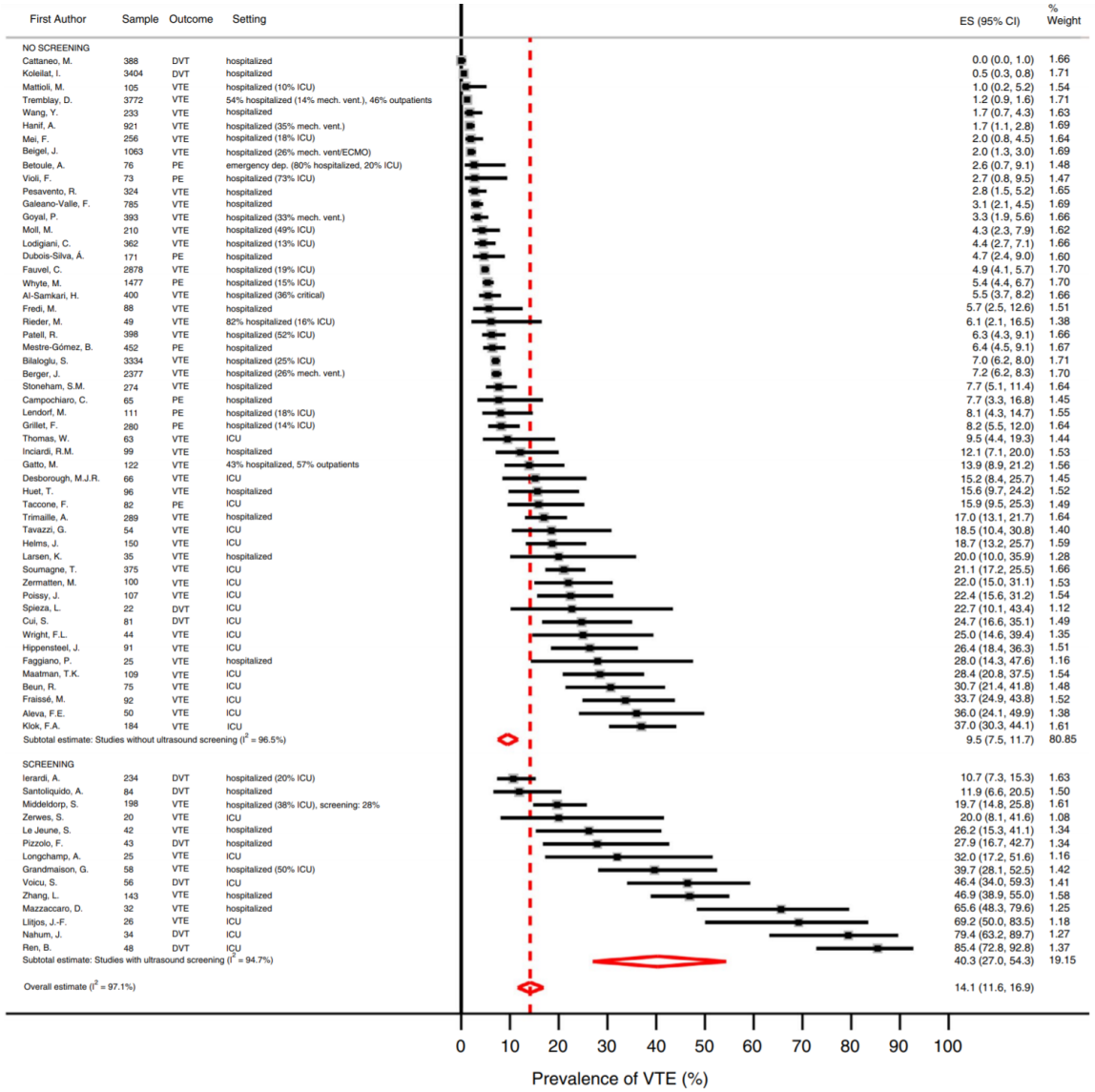


(Gupta et al., 2020)

COVID & VTE

- Leads to increased risk of VTE
  - Similar increased risk of VTE was seen in SARS, but not MERS
- Huge amount of current ongoing research
  - Meta-analysis included 66 studies
- Suggested pathomechanisms
- High prevalence of deep vein thrombosis (DVT) (up to 90%) leads to high prevalence of pulmonary embolism (PE)
  - Diffuse alveolar and vascular damage, microangiopathy and inflammation leads to in situ pulmonary thrombi

COVID & VTE



(Nopp et al., 2020)

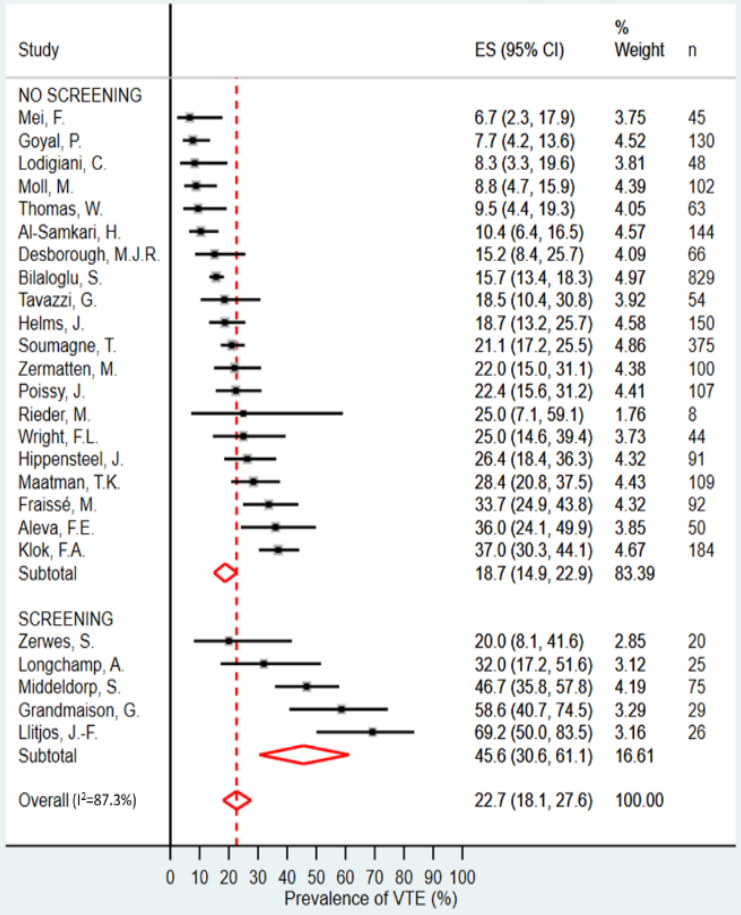
14% overall prevalence of VTE in hospitalized COVID-19 patients

9% prevalence of VTE in UNSCREENED populations

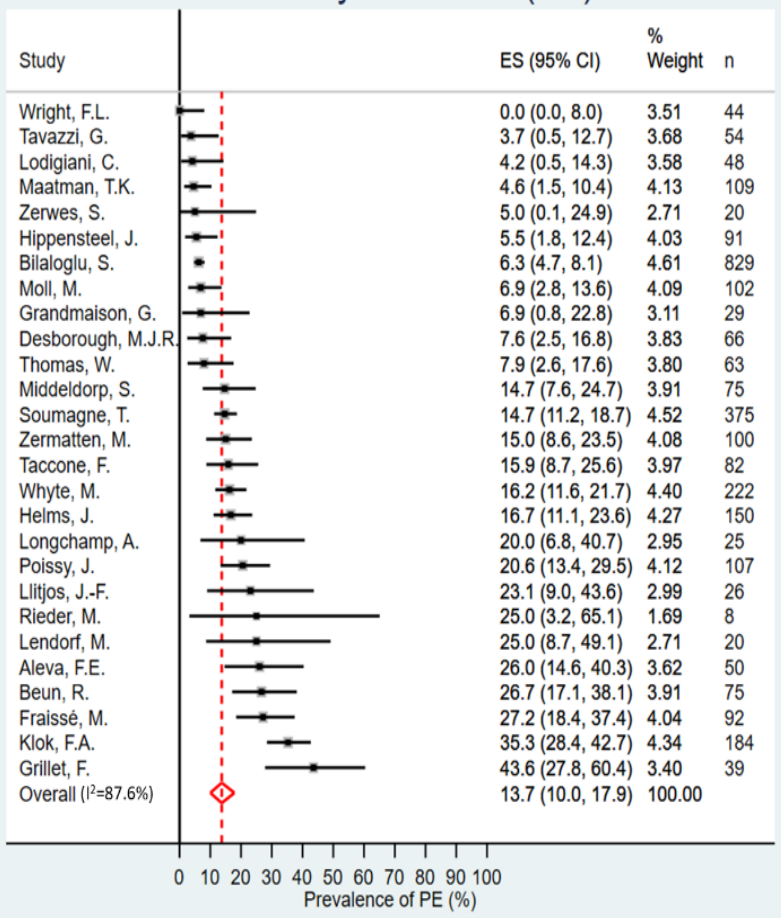
40% prevalence of VTE in SCREENED populations

ICU Patients

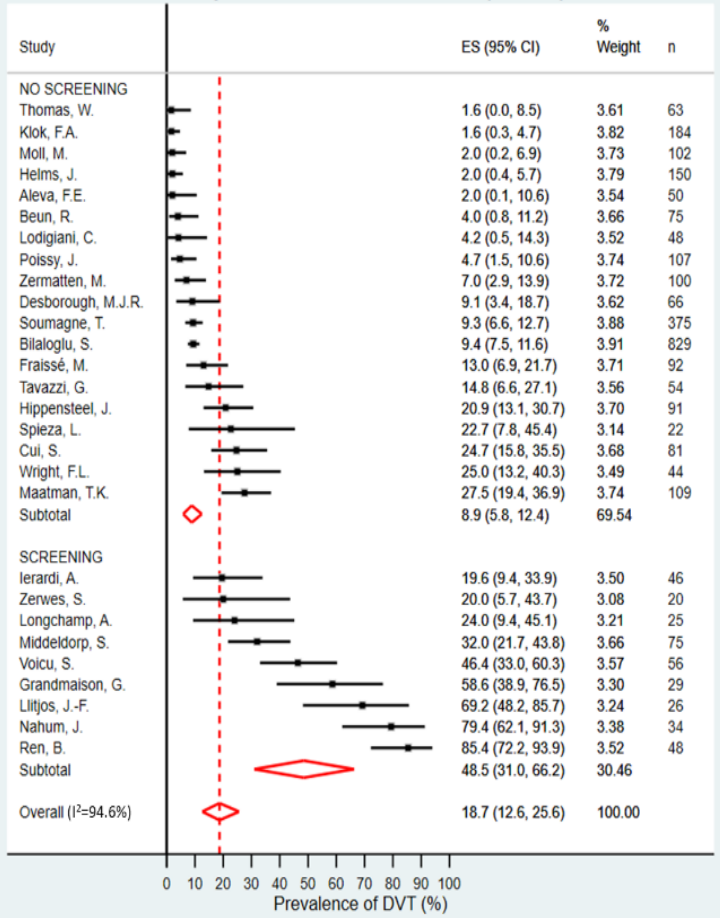
Venous thromboembolism (VTE)



Pulmonary embolism (PE)



Deep vein thrombosis (DVT)



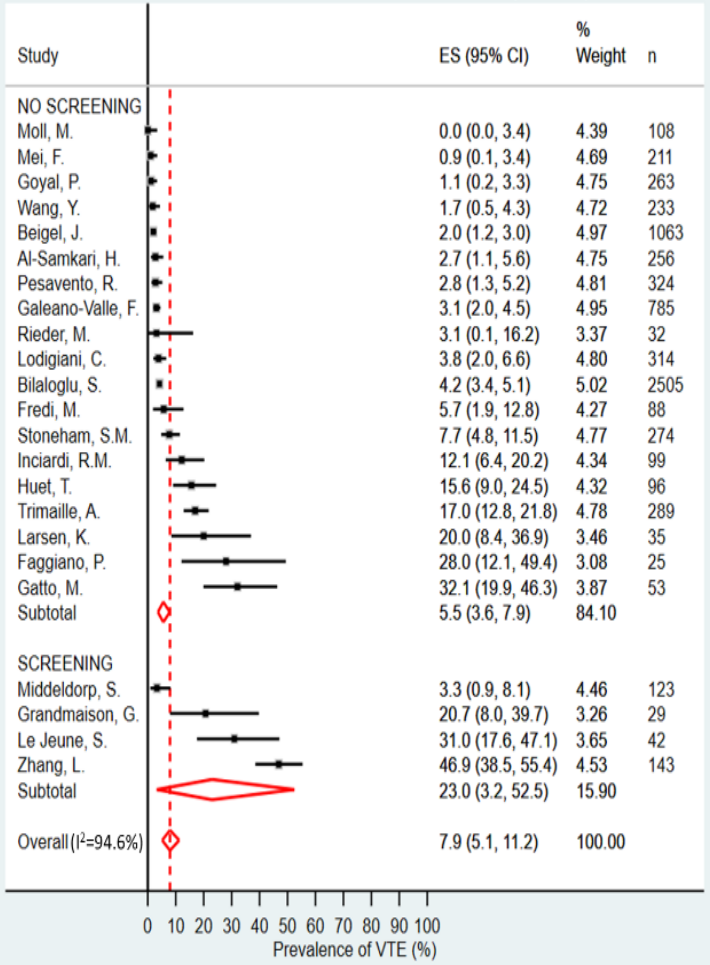
In ICU Patients, overall prevalence of VTE was 22%, PE was 14% and DVT was 19%

Using routine screening protocols, prevalence of VTE and DVT can be as high as 45-50%

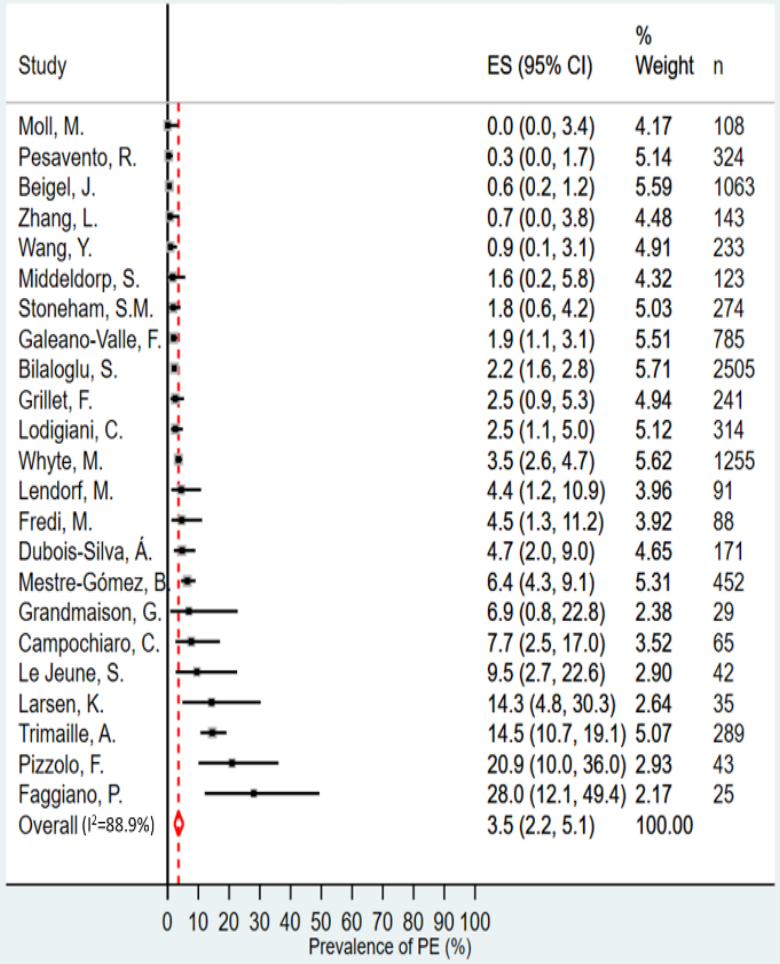
(Nopp et al., 2020)

Non-ICU Patients

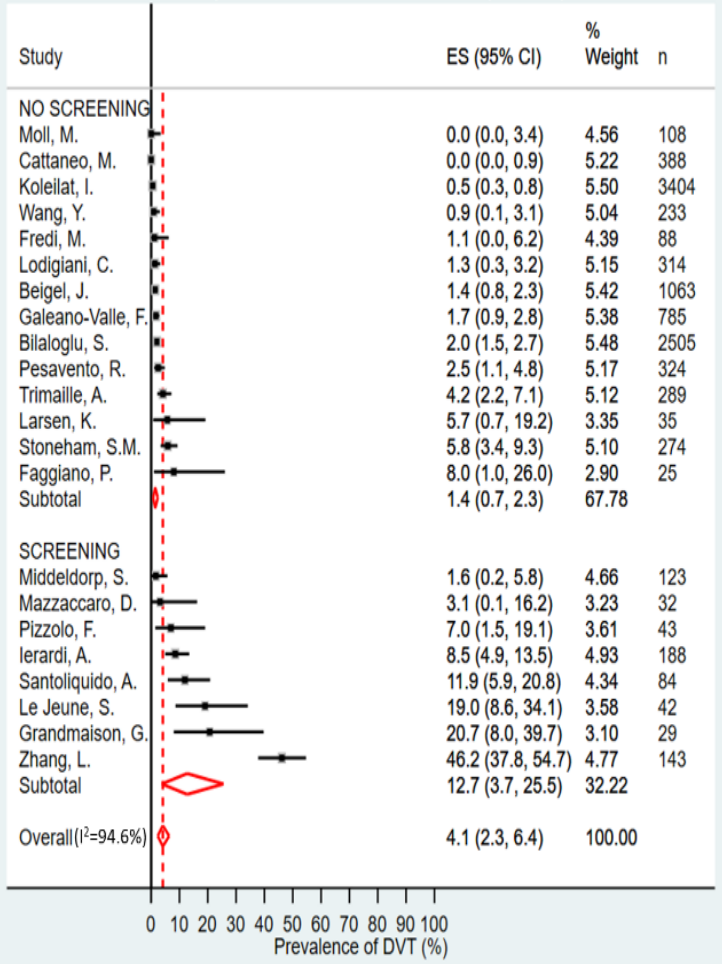
Venous thromboembolism (VTE)



Pulmonary embolism (PE)



Deep vein thrombosis (DVT)



In non-ICU Patients, overall prevalence of VTE was 8%, PE was 3.5% and DVT was 4%

(Nopp et al., 2020)

VTE Prophylaxis in COVID

- Mortality at 14-22 days was similar between VTE ppx and intermediate/therapeutic dosing
- PE was reduced from 98/1,000 → 10/1,000; OR 0.09
- Incidence of DVT or VTE were not significantly reduced
- Major bleeding increased from 84/1,000 → 260/1,000; OR 3.84

…suggests using **prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation** in patients with COVID-19 related critical illness who do not have suspected or confirmed VTE…

(American Society of Hematology, 2020)

VTE Prophylaxis in COVID

- Caveats:
  - An individualized assessment of the patients risk of thrombosis and bleeding is important
    - Unfractionated heparin (UFH) may be preferred over low-molecular-weight heparin (LMWH) due to ability to reverse if needed for delivery
    - LWMH may be preferred for patients receiving prophylaxis (ppx) anticoagulation due to decreased provider interaction
  - Higher intensity anti-coagulation may be preferred in patients at high thrombotic risk and low bleeding risk
  - There is no high-quality evidence comparing different types of anticoagulation

(American Society of Hematology, 2020)

ICU Considerations

Key Points

- Many Obstetric providers are uncomfortable in an ICU setting
- Many Intensivists have limited experience caring for pregnant/postpartum women….
- …and are therefore uncomfortable caring for a pregnant woman
- Both of you have knowledge that is needed to adequately care for a critically ill woman

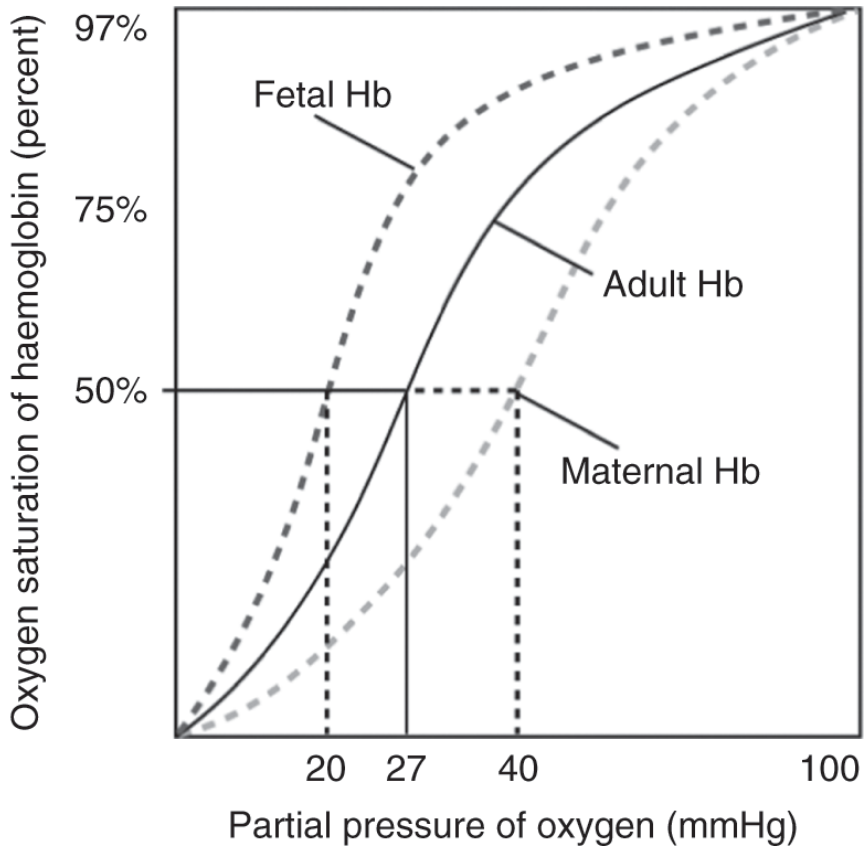
Maternal Adaptations to Pregnancy

- In pregnancy, nearly every system undergoes adaptation
- Clearly discuss normal and abnormal physiology
- Don’t assume anything is common knowledge

Increased	Plasma volume by 40 to 50 percent, but erythrocyte volume by only 20 percent	Dilutional anemia results in decreased oxygen carrying capacity
	Cardiac output by 40 percent	Increased CPR circulation demands
	Heart rate by 15 to 20 beats per minute	Increased CPR circulation demands
	Clotting factors susceptible to thromboembolism	
	Dextrorotation of the heart	Increased EKG left axis deviation
	Estrogen effect on myocardial receptors	Supraventricular arrhythmias
Decreased	Supine blood pressure and venous return with aortocaval compression	Decreases cardiac output by 30 percent
	Arterial blood pressure by 10 to 15 mm Hg	Susceptible to cardiovascular insult
	Systemic vascular resistance	Sequesters blood during CPR
	Colloid oncotic pressure (COP)	Susceptible to third spacing
	Pulmonary capillary wedge pressure (PCWP)	Susceptible to pulmonary edema
	Respiratory	**Effect**
Increased	Respiratory rate (progesterone-mediated)	Decreased buffering capacity
	Oxygen consumption by 20 percent	Rapid decrease of PaO_2 in hypoxia
	Tidal volume (progesterone-mediated)	Decreased buffering capacity
	Minute ventilation	Compensated respiratory alkalosis
	Laryngeal angle	Failed intubation
	Pharyngeal edema	Failed intubation
	Nasal edema	Difficult nasal intubation
Decreased	Functional residual capacity by 25 percent	Decreases ventilatory capacity
	Arterial PCO_2	Decreases buffering capacity
	Serum bicarbonate	Compensated respiratory alkalosis
	Gastrointestinal	**Effect**
Increased	Intestinal compartmentalization	Susceptible to penetrating injury
Decreased	Peristalsis, gastric motility	Aspiration of gastric contents
	Gastroesophageal sphincter tone	Aspiration of gastric contents
	Uteroplacental	**Effect**
Increased	Uteroplacental blood flow by 30 percent of cardiac output	Sequesters blood in CPR
	Aortocaval compression	Decreases cardiac output by 30 percent
	Elevation of diaphragm by 4 to 7 cm	Aspiration of gastric contents
Decreased	Autoregulation of blood pressure	Uterine perfusion decreases with drop in maternal blood pressure

(ACOG.org, 2019)

Maternal Acid Base Status



(Hegewald et al., 2011)

ABG Measurement	Nonpregnant State	Pregnancy State	
		First Trimester	Third Trimester
pH	7.40	7.42–7.46	7.43
Pa_{O_2} (mm Hg)	93	105–106	101–106
Pa_{CO_2} (mm Hg)	37	28–29	26–30
Serum HCO_3 (mEq/L)	23	18	17

Abbreviation: ABG, arterial blood gas

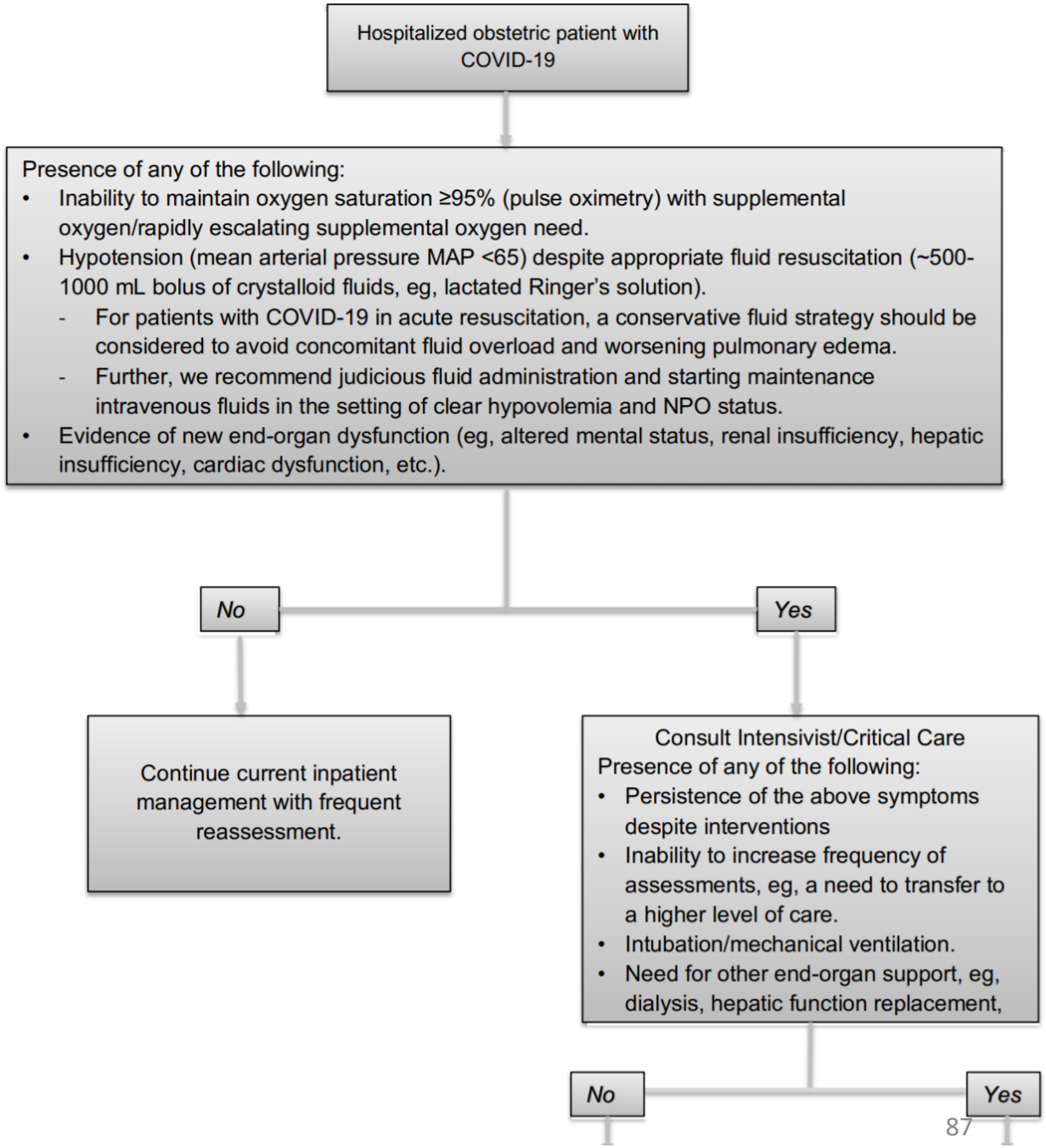
Reprinted from Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med 2011;32: 1–13.

"Normal" PaCO2 in pregnancy represents impending respiratory failure

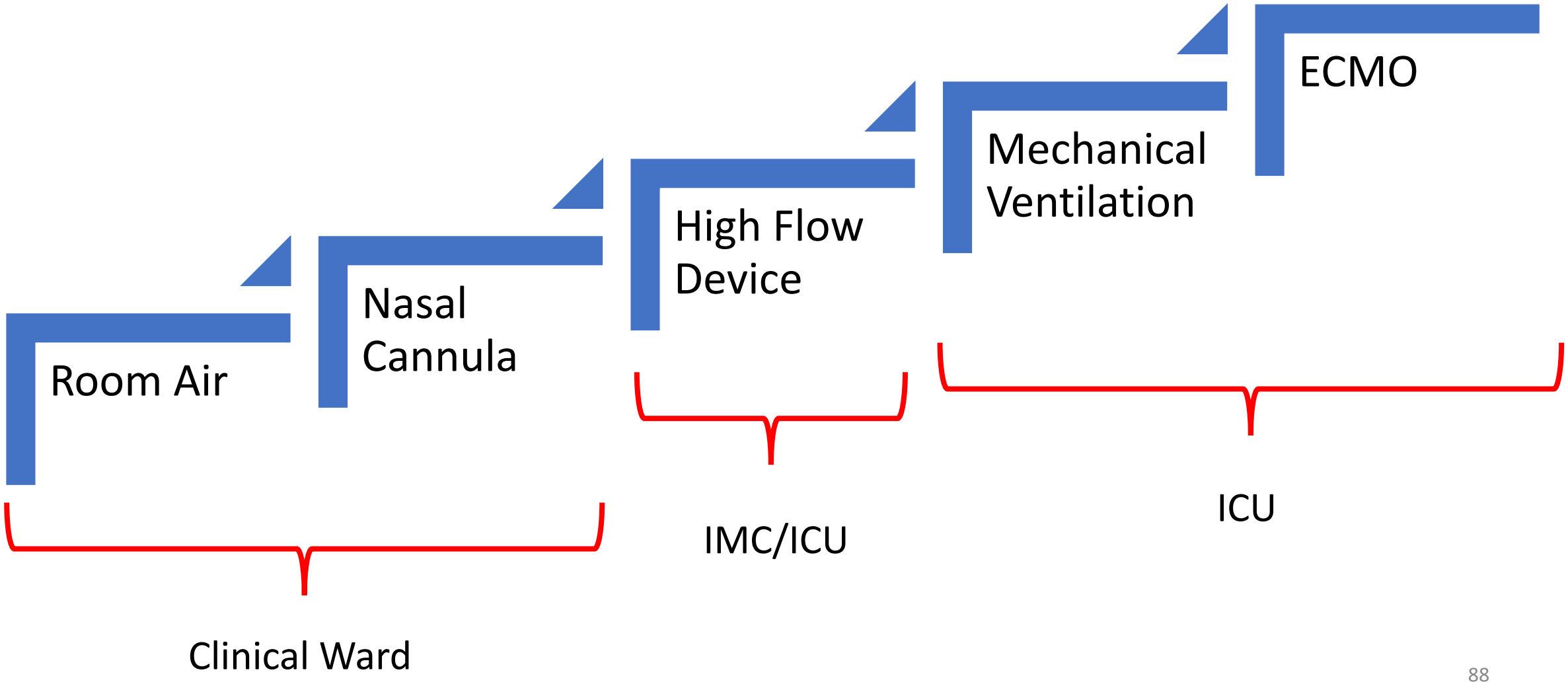
Indications for Intensive Care

- Inability to maintain Sp02 > 95%
- Hypotension despite resuscitation
- New onset end organ damage

(Society for Maternal Fetal Medicine, 2021)



Escalation of Supplemental Oxygen



Low Tidal Volume Ventilation

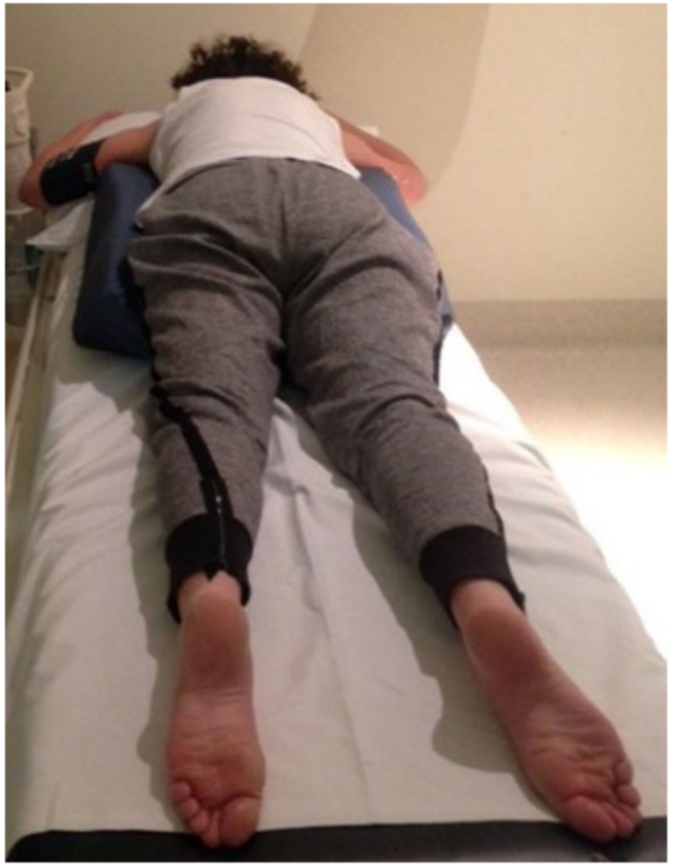
- Tidal volume (VT) 4-6 mL/kg of predicted BW
  - Plateau pressure (Pplat) < 30 cc H2O
  - Positive end-expiratory pressure (PEEP) adjusted as needed
- Standard of care for non-pregnant ARDS patients
  - ARDSNET study showed mortality benefit
  - Decreases barotrauma
  - Decreases inflammatory activation
- Permissive Hypercapnia
  - pH 7.35, PaCO2 > 45 mmHg well tolerated
  - Not studied in pregnancy
  - Sheep studies have shown decreased uteroplacental blood flow if PaCO2 > 60 mmHg

(stock.adobe, n.d.)

(Marik, 2015)

Low Tidal Volume Ventilation (LTVV)

- Options if LTVV fails…
  - Prone positioning
  - Neuromuscular blockade
  - Pulmonary vasodilators [i.e. inhaled Nitric Oxide (iNO)]
  - Alternative ventilatory modes
    - Airway pressure release ventilation (APRV) may be better option in pregnancy
  - ECMO
- Low VT strategies are reasonable
- If Low VT fails, APRV may be better option than high VT strategies



(Biomedcentral.com, n.d.)

Low Tidal Volume Ventilation is reasonable in pregnant women with ARDS

(Dennis et al., 2018)
(Marik, 2015)

Other Considerations

- Analgesia
  - All opioids are acceptable
- Sedation
  - Most benzodiazepines (BDZ) are appropriate
  - Propofol is acceptable, but…
  - Propofol infusion syndrome may occur faster than in non-pregnant women
  - Data is limited for dexmedetomidine, but likely ok
- Pulmonary vasodilators (iNO, inhaled prostacyclins)
  - Considered salvage therapy in refractory hypoxemia
  - Do not decease ventilator free days, ICU stay or mortality, but may improve oxygenation
  - Length of benefit may be temporary
  - Limited data in pregnancy, but can be trialed if needed
- Neuromuscular blockade
  - NMB has shown benefit in mod/severe ARDS
  - Limited data in pregnancy
  - Acceptable if needed
- Vasopressors-
  - Limited data, but essentially mirrors Surviving Sepsis guidelines
  - Norepinephrine generally considered 1st line
  - Phenylephrine 2nd line
  - All acceptable if needed

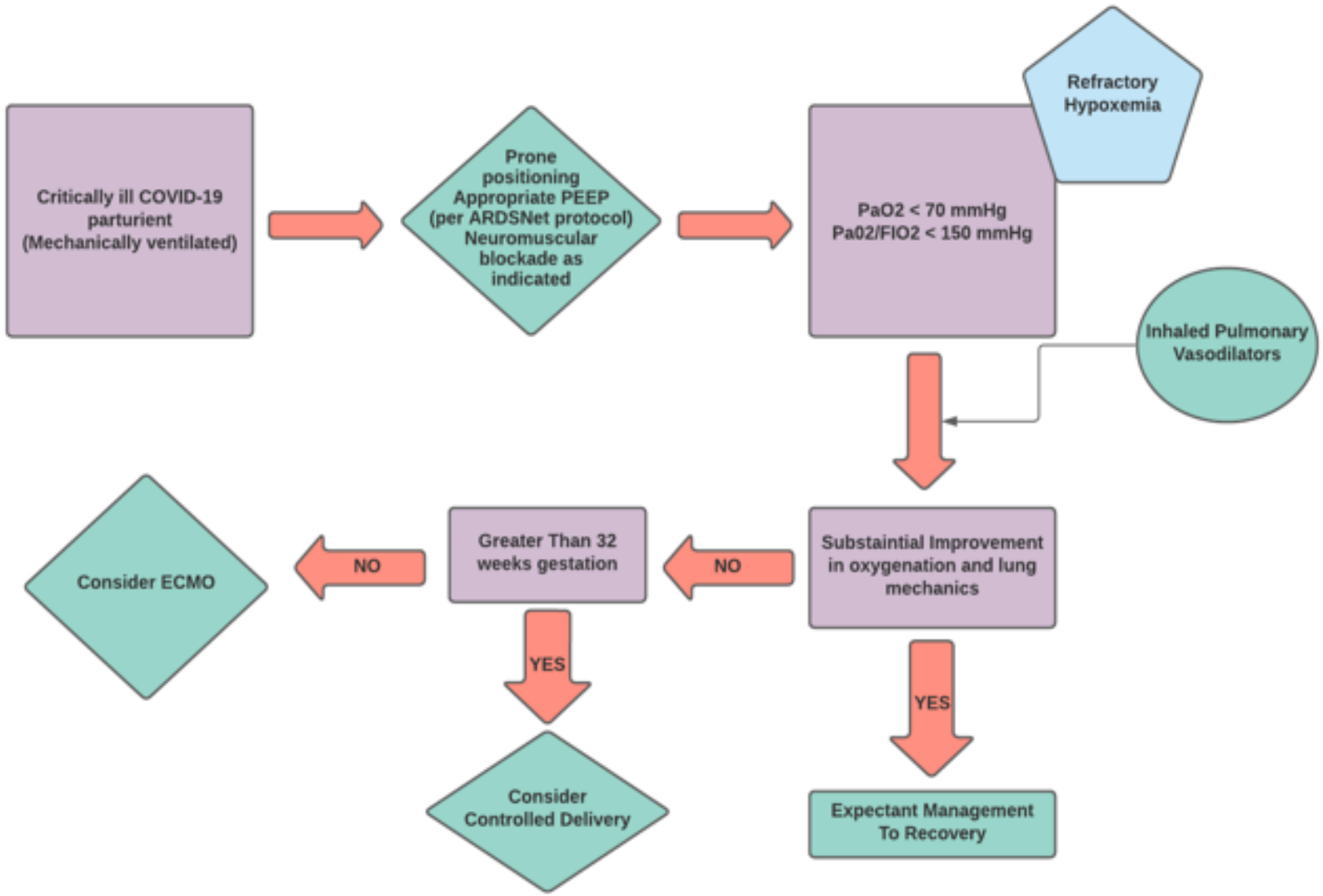
Learning Objectives

1. Describe the CDC recommendations for the use of remdesivir in treating COVID-19
2. Explain the CDC recommendations for the use of dexamethasone in treating COVID-19
3. Comprehend and apply the appropriate escalation of supplemental oxygen in patients with COVID-19
4. Recognize indications for escalation of care to the ICU for patients with COVID-19

Key Takeaways

- The CDC recommends giving remdesivir to hospitalized COVID-19 patients on supplemental O2, but not requiring high flow supplemental oxygen or mechanical ventilation
- The CDC recommends giving dexamethasone to hospitalized COVID-19 patients who require supplemental O2, high flow supplemental oxygen or mechanical ventilation
- The appropriate escalation of therapy for hypoxemia is room air → nasal cannula → high flow oxygen device → mechanical ventilation → ECMO. Therapy should be escalated until ventilation is sufficient to maintain a PaO2 of > 70 mmHg (~SpO2 95%) for pregnant patients.
- Indications for transfer to the ICU include an inability to maintain PaO2 > 70 mmHg, hypotension despite adequate ventilation or any sign of other end organ dysfunction

Figure 2: Algorithm for Refractory hypoxemia



(Society for Maternal Fetal Medicine, 2021)

Questions?

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