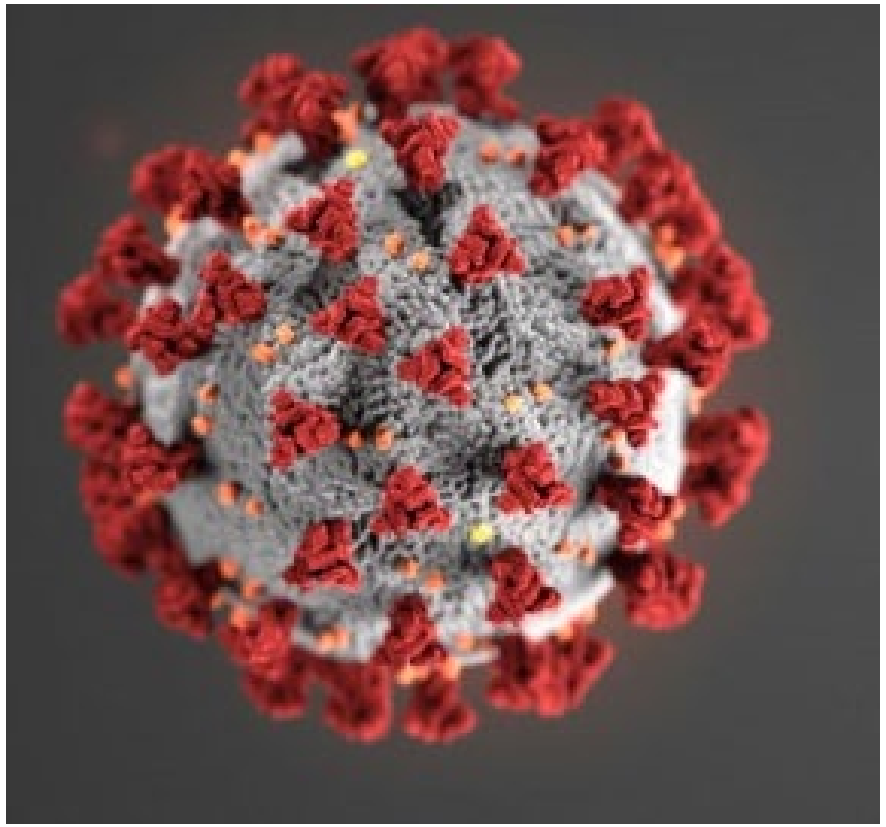
COVID and management for Non-critical patients



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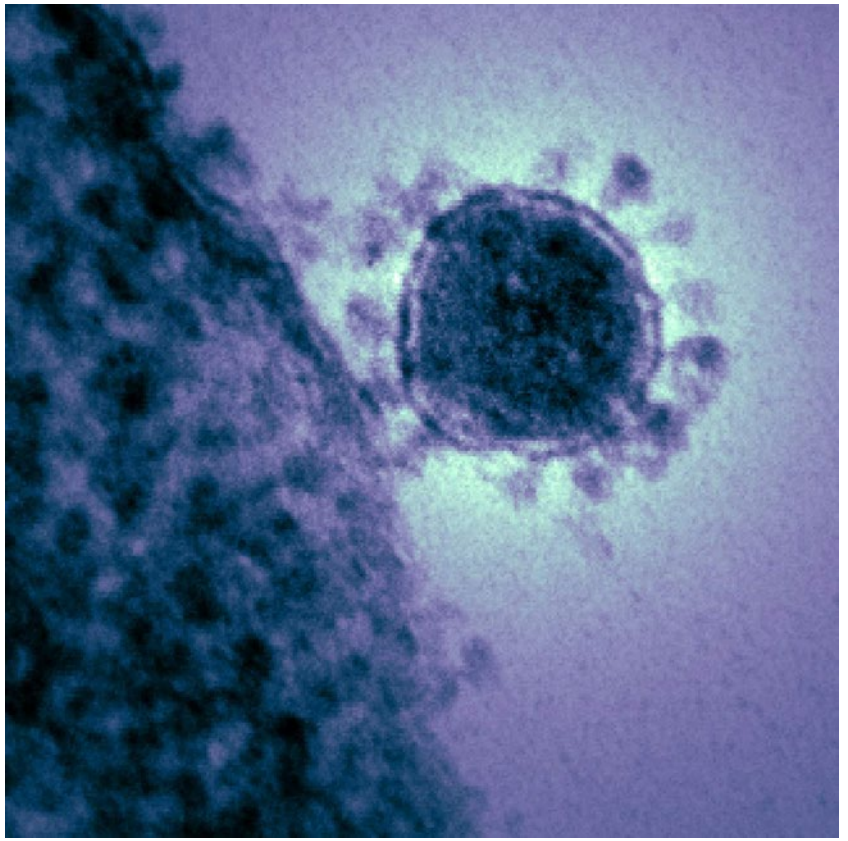
12th Annual Medical Connections Primary Care Conference

January 23, 2021 from 8:00 to 8:30 AM

No Financial disclosures

COVID-19 coronavirus
Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2)



- COVID-19 = disease
- novel coronavirus “Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) = pathogen

- Coronaviruses
  - enveloped, single-stranded RNA
  - Needs to invade a host cell to become pathological
  - infect humans and animals (camels, cats, and bats)

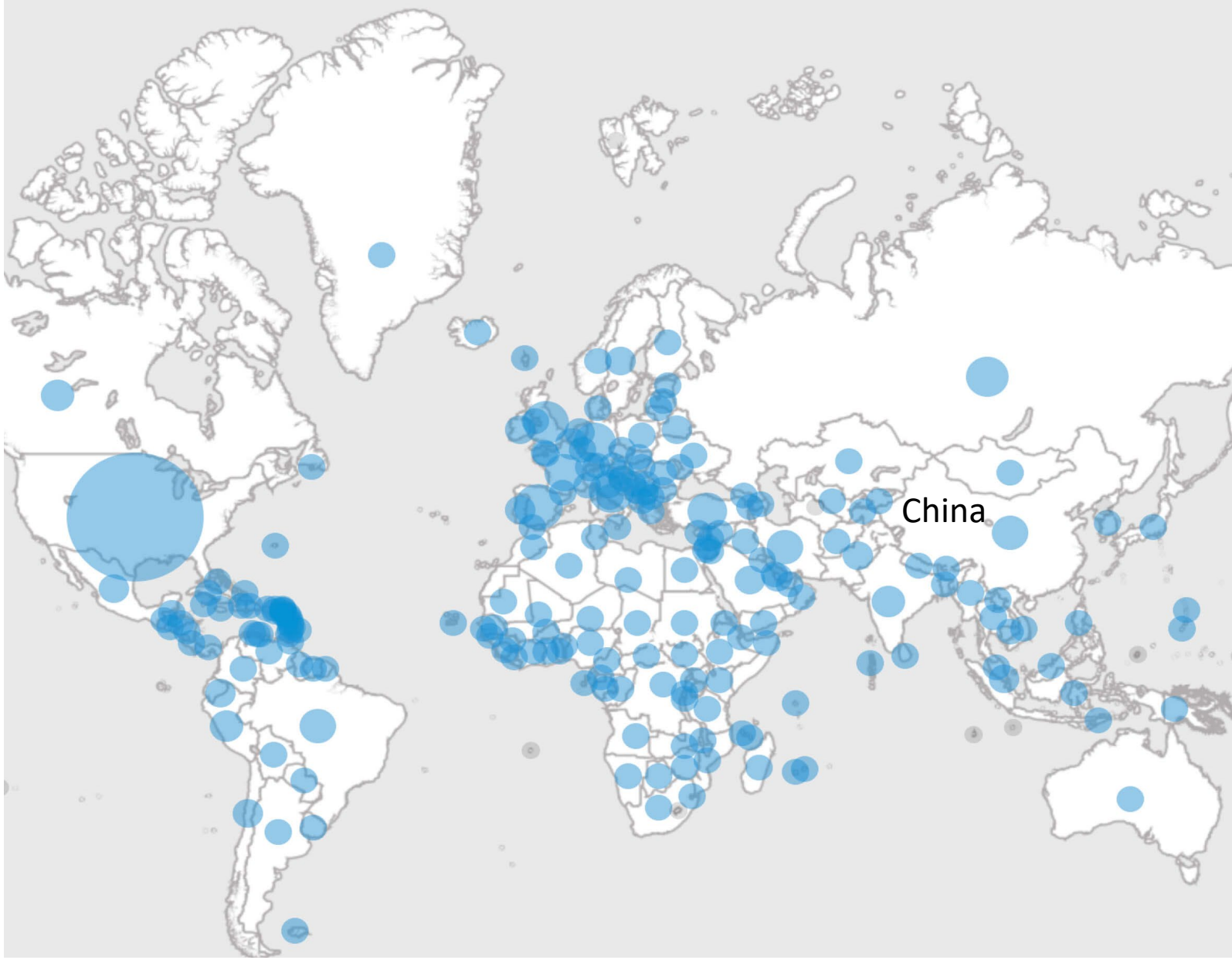
- Clinical span: asymptomatic → mild → severe → life threatening
  - 80% mild illness
  - 14% have serious
  - 5% have critical illness

- Incubation = 2 and 14 days after exposure, median incubation period of about 4-5 days.

www.who.int/emergencies/diseases/novel-coronavirus-2019

SARS-CoV-2 Pandemic

- December 2019, outbreak of pneumonia in Wuhan City, China
- December 2020
  - 75 million cases
  - 1.6 million deaths
- January 2021
  - 89 million cases
  - 1.9 million deaths



SARS-CoV-2: life cycle

- ***viruses must enter host cell to cause disease***

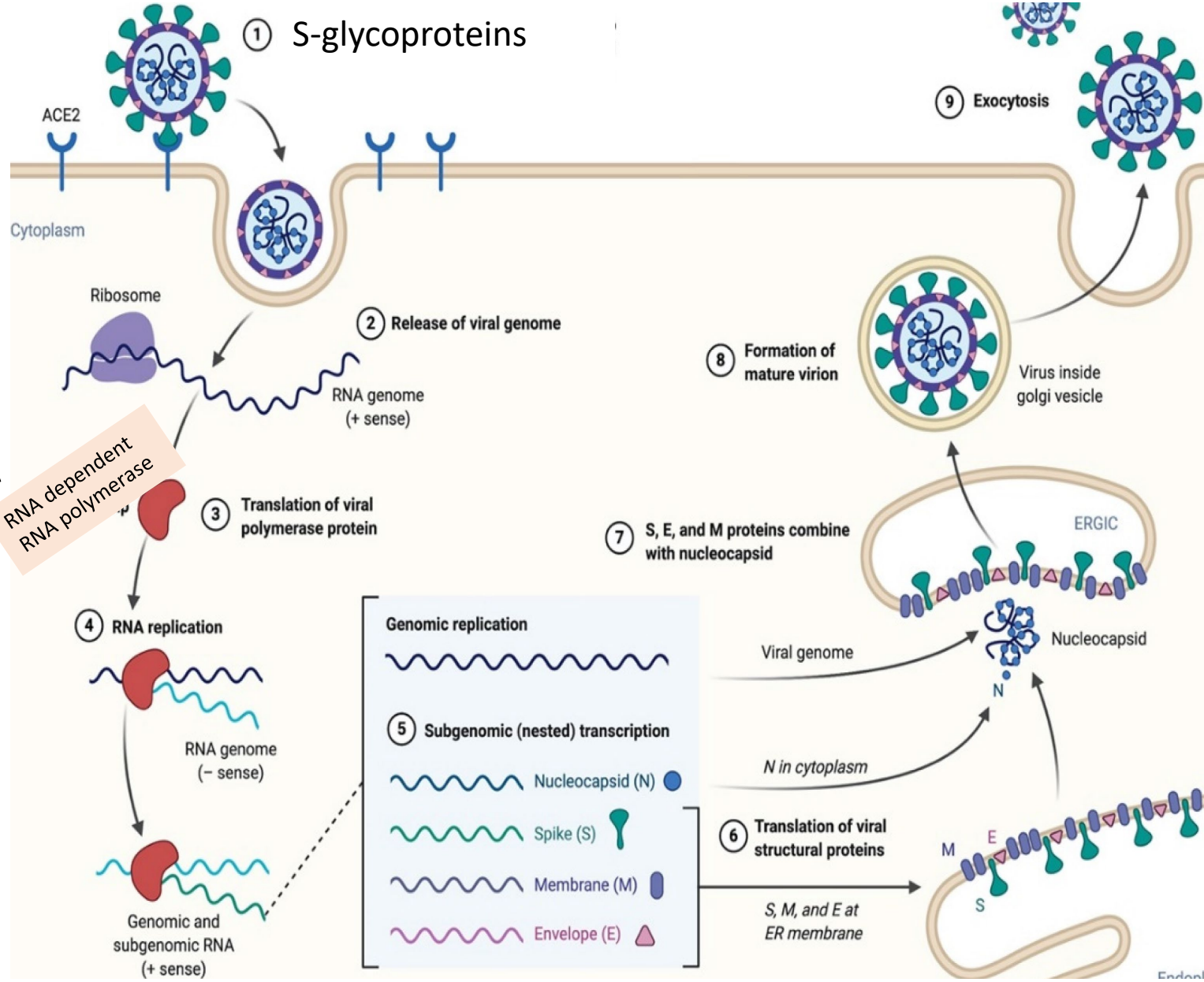
- Cell entry: spike-like protein (S proteins) binds to angiotensin converting enzyme-2 (ACE-2) receptor
  - *Found in lung, liver, GI tract, and kidney*

- Viral RNA translated to RNA dependent RNA polymerase by host cell machinery

- RNA copied by RNA dependent RNA polymerase → uses (−) RNA templates for new (+) RNA genomes

- (+) genomic RNA is translated into viral structure proteins

- Cellular machinery is used to make mature virions released from the infected cell

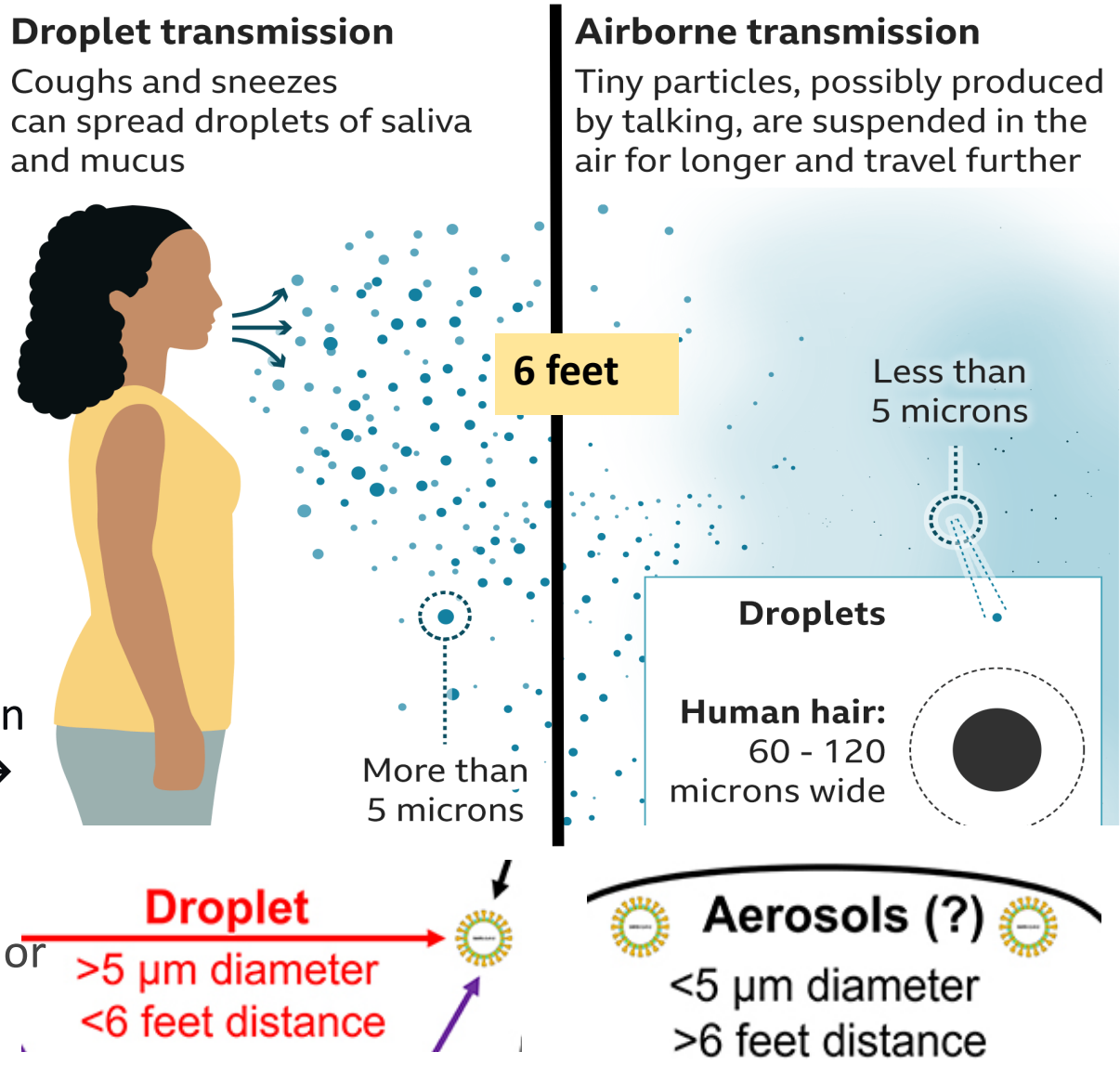


COVID-19: Transmission

- Droplet are **larger**, fall to ground quickly
  - Close contact (<6 ft)
  - Shorter exposure time
  - Masks = surgical or cloth

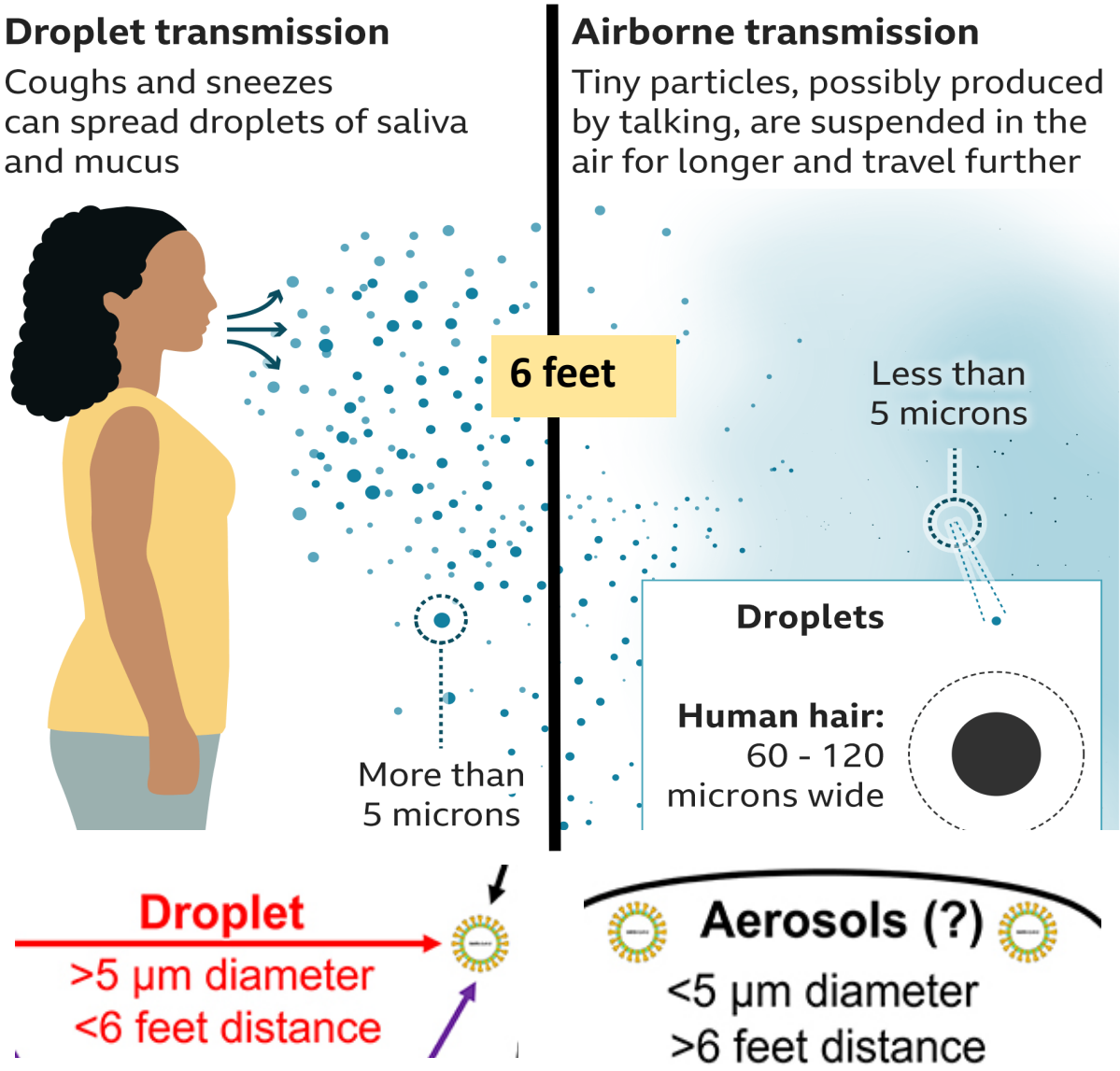
- Airborne are **smaller**, suspended, travel further
  - Distant contact (> 6ft)
  - Longer exposure times
  - Masks = N95 with air filters

- **Primary transmission = *droplets within 6 ft***
  - airborne is possible in enclosed spaces, poor ventilation or where infectious individuals are breathing heavily → exercising or singing
- Spread by contact with objects (Fomites)
  - Touch contaminated surface then touch mouth, nose, or eyes → likely important
- Saliva and feces→ likely not important
- Animals → likely not important
- Vertical → likely not important



COVID-19: Transmission

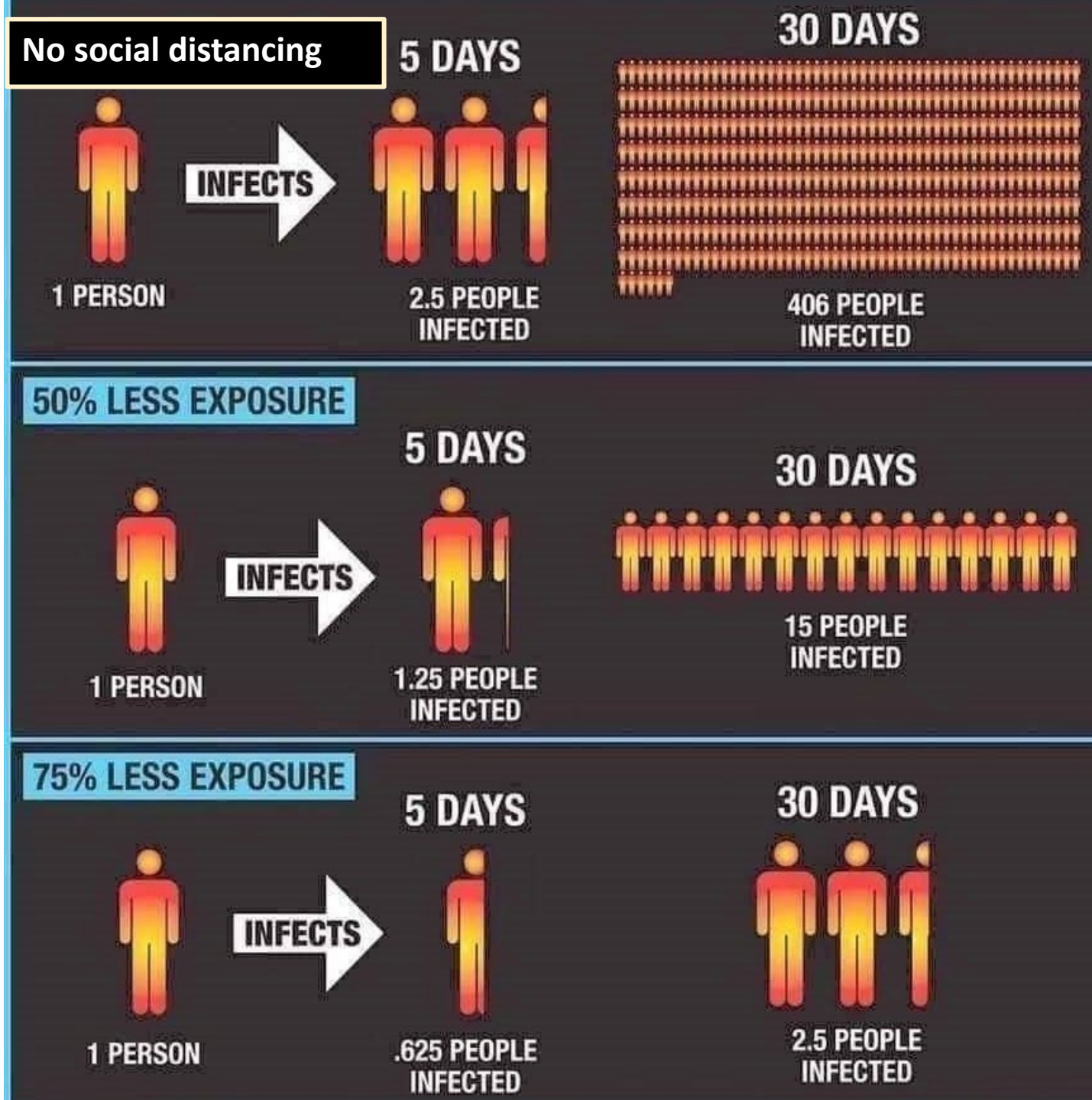
- **Asymptomatic spread happens**
  - Infectious period
    - starts = ~2.3 days prior to symptoms
    - peak = ~ 1 day prior to symptoms
- Requires viable virus
  - PCR alone cannot distinguish → may stay positive after infectious period
  - Viability
    - aerosols for hours
    - surfaces for days (depends on inoculum)
- **Risk varies by duration and viral load**
  - Close contacts for prolonged times
  - Immunocompromised shed higher loads for longer times
- **Prevent**
  - Masks
  - Avoid crowds (Outdoors is better)
  - Hand washing → especially before touching face



Physical Distancing Reduces Transmission

- Closure of public places (school, workplace),
- Restrictions on mass gatherings
- Early lockdowns
- Mandatory masking
- Quarantine new cases and their close contacts

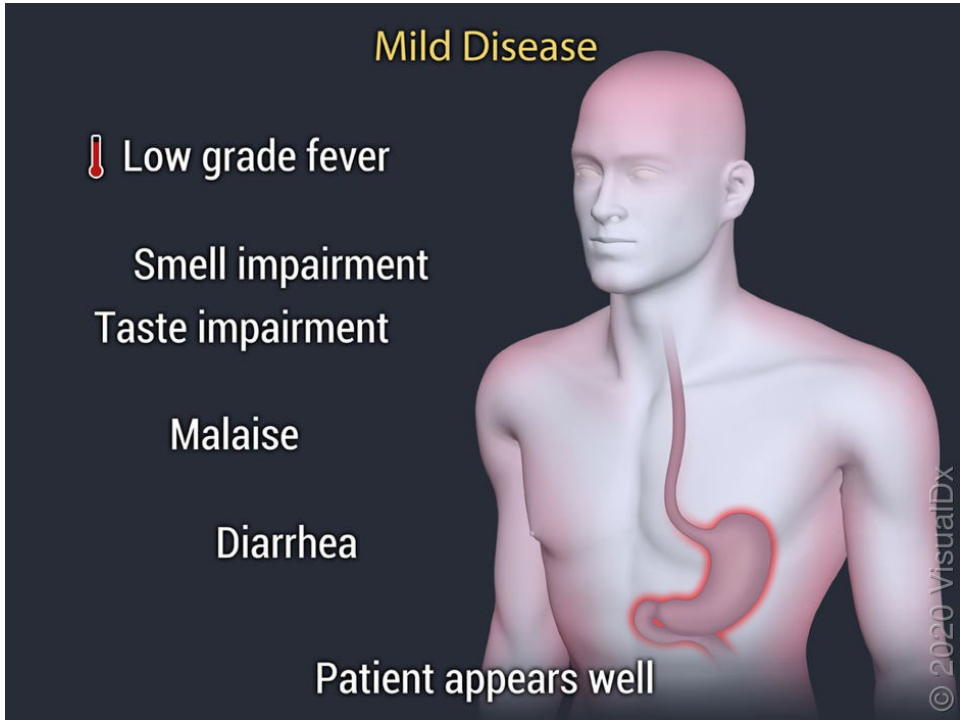
- Relaxing these = directly correlated with increased case numbers

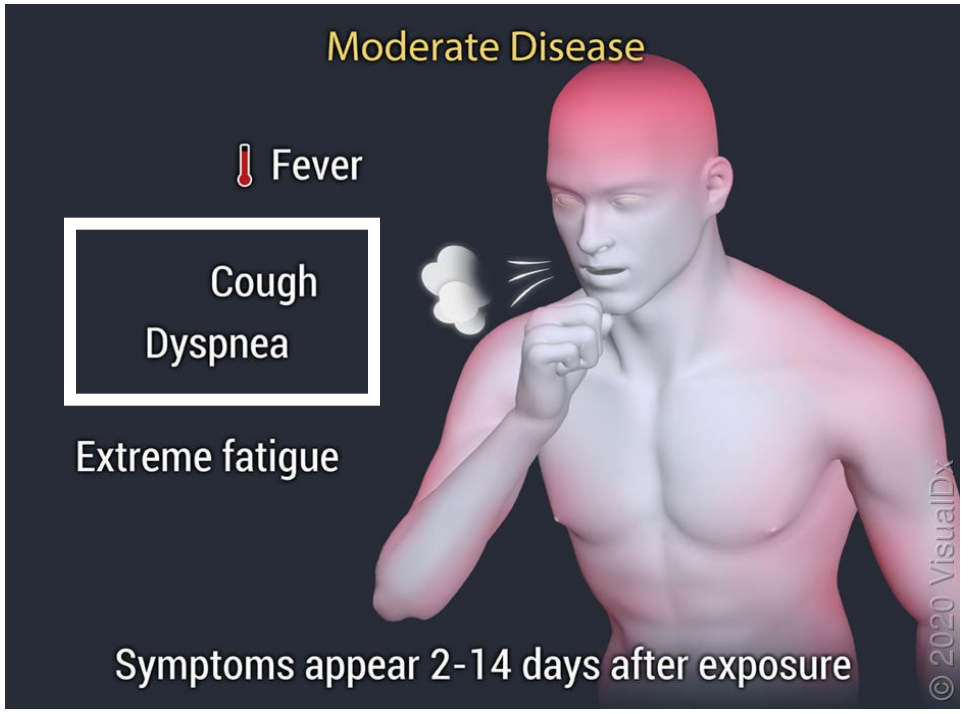


COVID-19 coronavirus: Illness severity

- *Mild Illness:* fever, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell
  - **do not have dyspnea, hypoxia or abnormal chest imaging.**

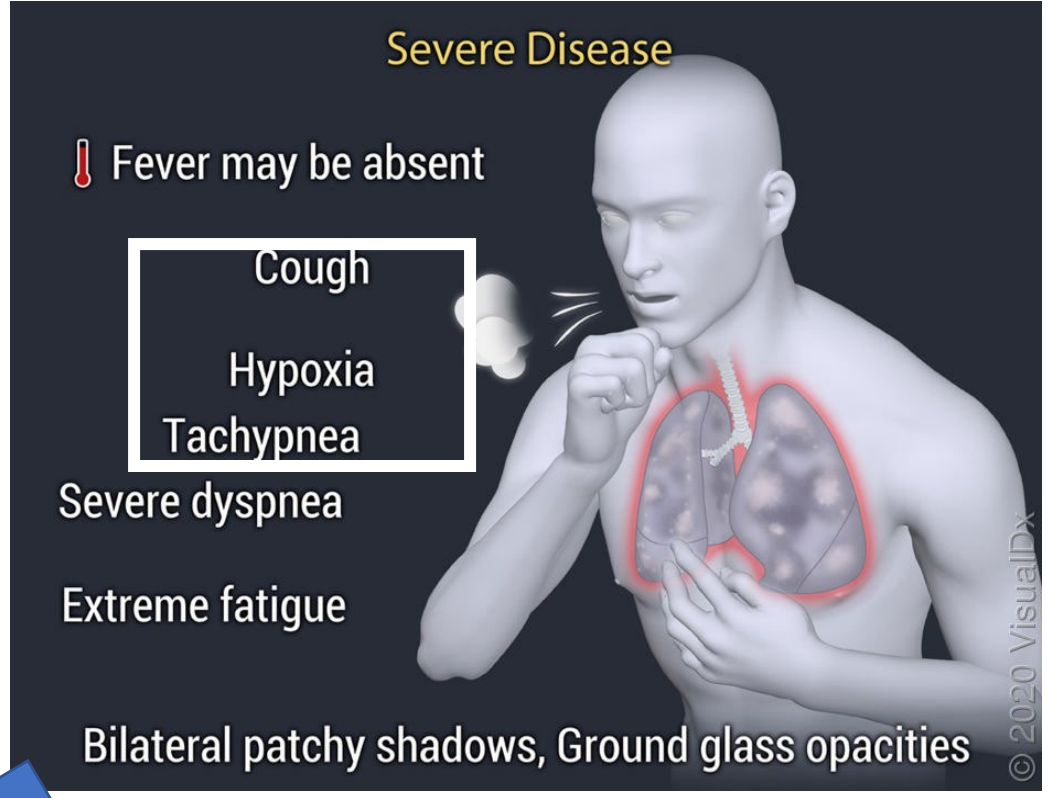
- *Moderate Illness:* evidence of lower respiratory disease during clinical assessment or imaging
  - **Dyspnea without Hypoxia**: saturation of oxygen (SpO_2) ≥94% on room air

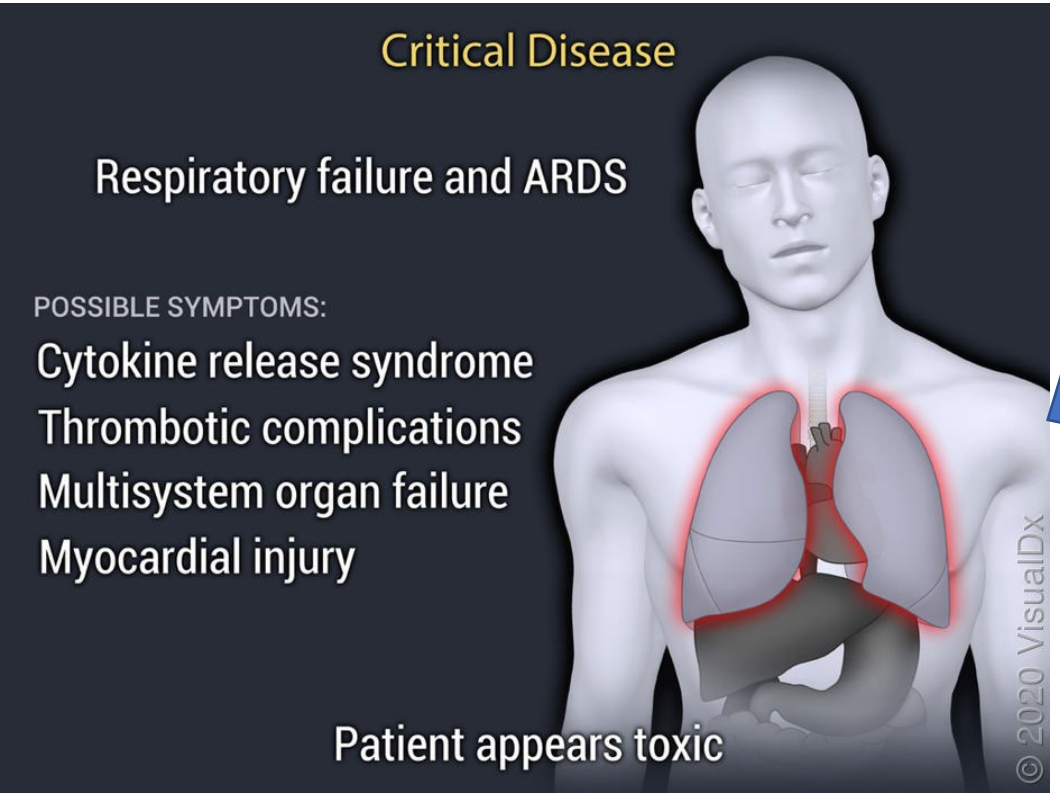




COVID-19 coronavirus: Illness severity

- *Severe Illness*: Hypoxia, SpO2 <94% on room air OR ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg
  - Tachypnea, respiratory frequency >30 breaths/min
  - Abnormal imaging: lung infiltrates >50%.





8-12 days

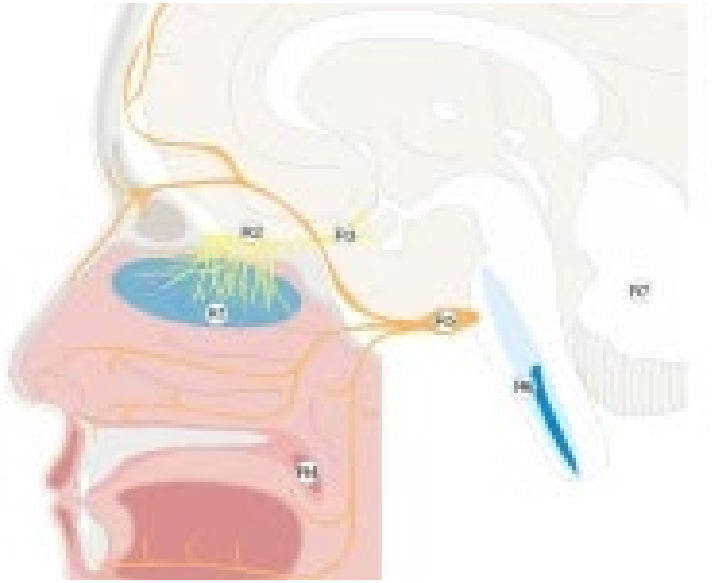
- median time to ARDS with severe illness is 8-12 days
- driven by an exaggerated immune/inflammatory response that leads to tissue damage

COVID-19: Risk for severity & poorer clinical outcome

Risks for poor outcome	
Strongest evidence	Cancer Age > 65 Chronic kidney disease COPD Cardiovascular disease (includes hypertension) Obesity Pregnancy Sickle cell disease Smoking Type 2 diabetes mellitus
Limited evidence	Asthma Cerebrovascular disease Use of corticosteroids Bone marrow transplantation HIV Liver disease Thalassemia Type 1 diabetes mellitus

COVID-19 coronavirus: Frequency of symptoms

- Signs and symptoms are variable and can mimic other illnesses
  - fever (90%)
  - cough (70%)
  - fatigue (70%)
  - **Loss of taste or smell (70%)**
    - **ACE-2 receptors in olfactory epithelium**
  - Dyspnea (35%),
  - Myalgias (30%),



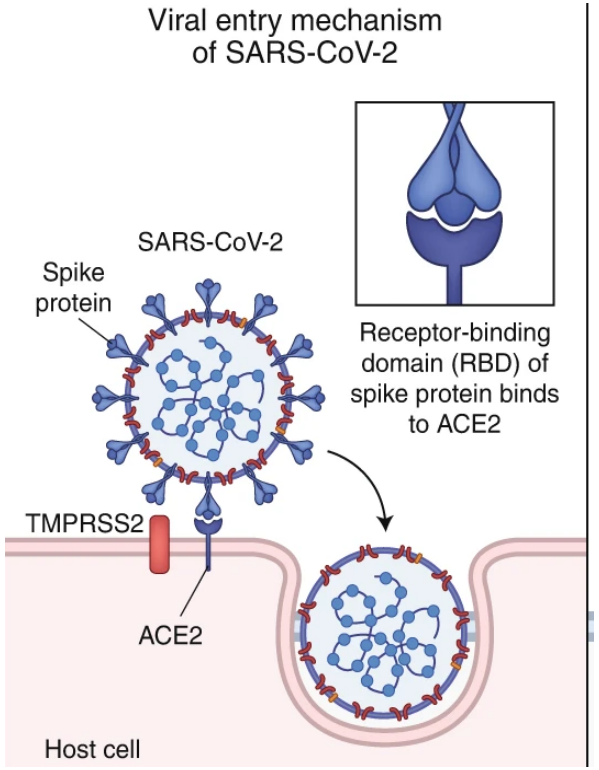
- URI symptoms: sore throat, headache, nasal congestion or rhinorrhea
- GI symptoms: nausea, vomiting and diarrhea

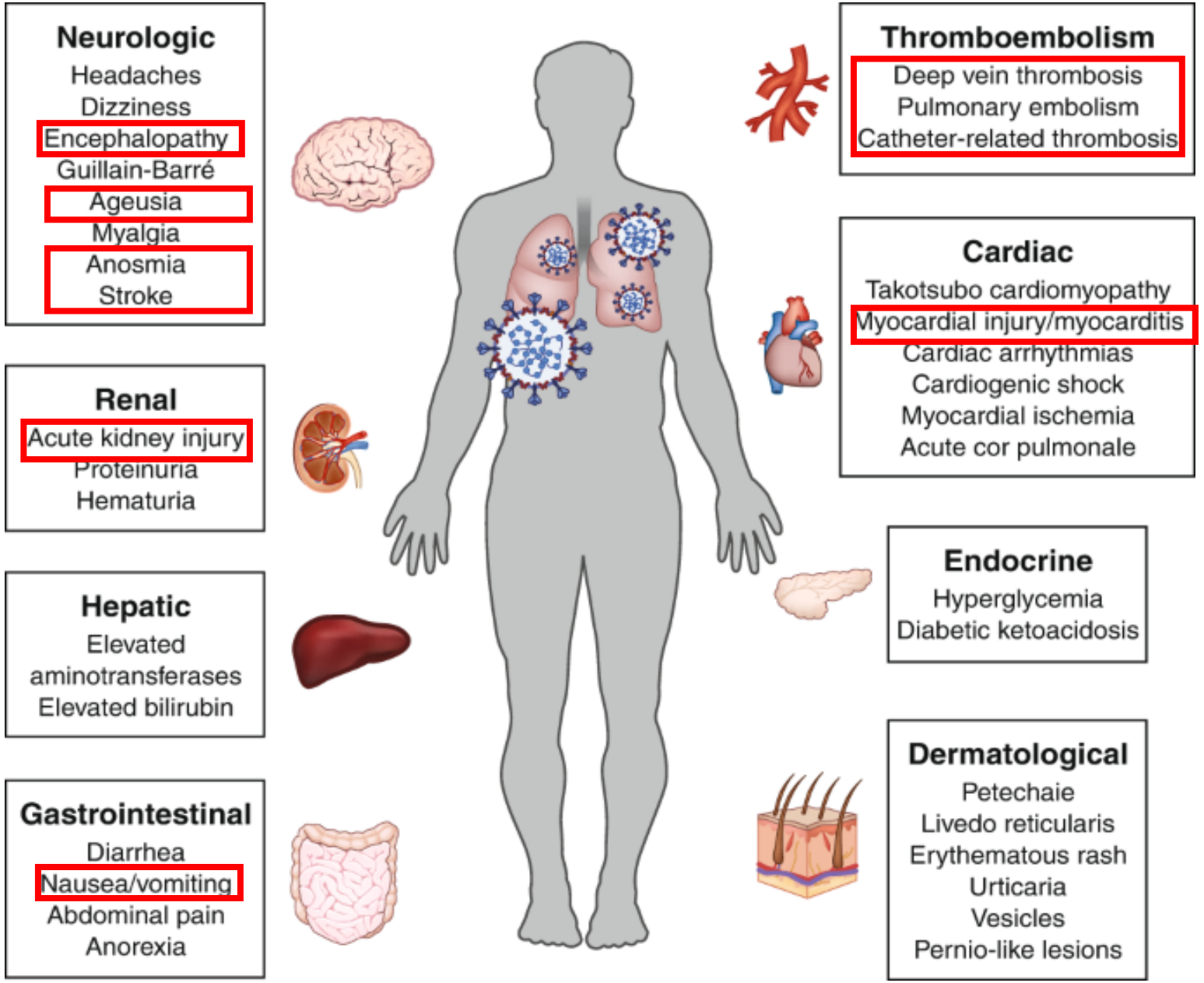
- **Respiratory distress can be delayed 7-10 days after symptom onset**

- **Unexplained loss of taste/smell may warrant self-isolation and testing**

COVID-19 coronavirus: Not just Respiratory

- Can attack any cell with ACE-2 receptors
  - Cardiac
  - Hematological (hypercoagulable state)
    - More common in critical care
  - Hepatic
  - Neurological
  - Renal (many need dialysis)
  - GI
  - Olfactory mucosa





Nat Med 26, 1017–1032 (2020)

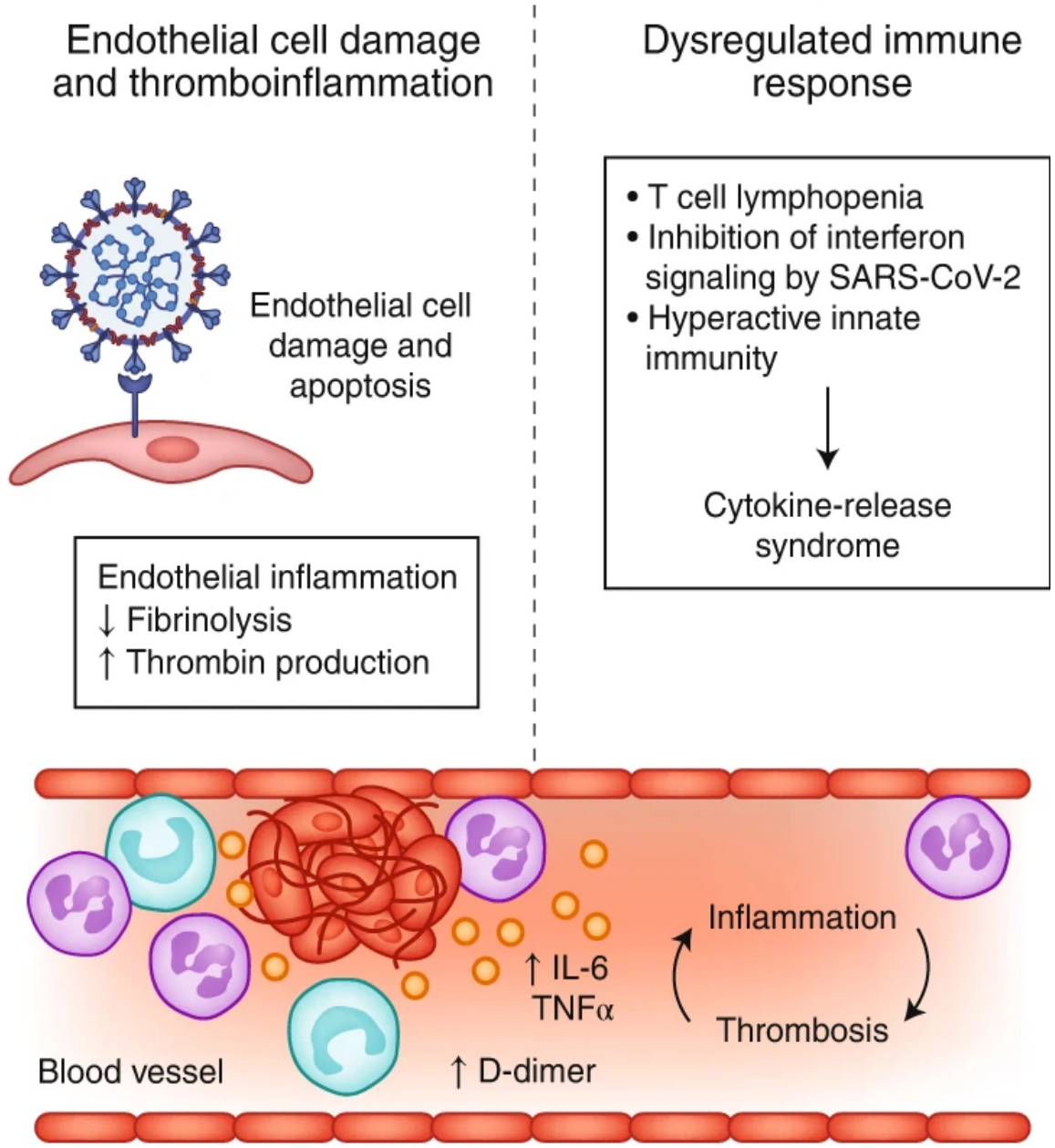
COVID-19 coronavirus: Hematologic

- Hyper-coagulopathy → ↑ D-dimers
  - Unlike DIC, PT and PTT generally remain normal
  - Thrombocytopenia may be mild
  - Upward trend has poor prognosis → associated w/ mortality

- ↓ Lymphopenia → marks impairment of cellular immunity → marker of more severe disease
- Inflammatory state: ↑ ferritin, ↑ ESR, ↑ CRP
- ↑ lactate dehydrogenase

- Clinical: venous and arterial thrombosis
  - MI, stroke, limb ischemia
  - DVT, PE, catheter associated
- All hospitalized should be on prophylaxis for venous thromboembolism → prefer heparin

- Role for post-hospitalization extended thromboprophylaxis ??



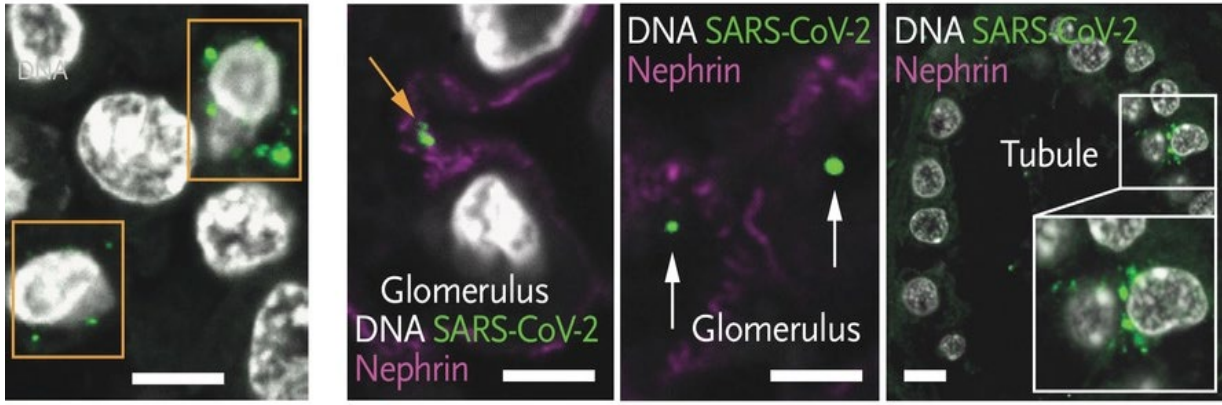
COVID-19 coronavirus: Renal

- Electrolyte abnormalities
- Proteinuria
- Hematuria
- Metabolic acidosis

- Unclear if this is direct effect on kidney cells or consequence of cytokine storm

- Viral inclusion seen in tubular epithelium, podocytes, and endothelium of glomerular capillaries

- Recommend
  - UA and protein-to-creatinine ratio at admission, given the association of proteinuria and hematuria with outcomes



- Both glomerular and tubular effects

Puelles, V.G. et al. Multiorgan and renal tropism of SARS-CoV-2. N. Engl. J. Med.

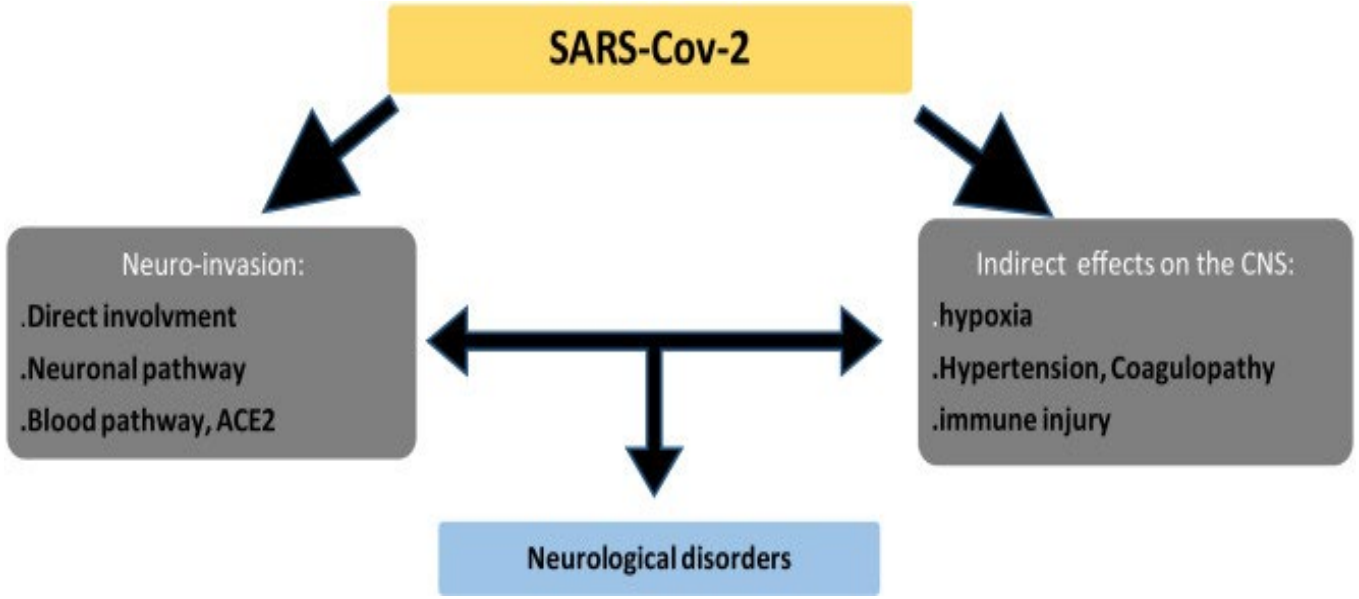
COVID-19: Neurologic

- Direct = virus gets access to brain → neuroinflammation
- Indirect = from systemic disease

- **In elderly may have only neurological sign → predates respiratory**
  - Depressed level of consciousness
  - Combative Delirium
  - Sleepiness
  - Weakness/dizziness → fall

- Encephalopathy = poor prognostic factor associated with longer hospitalization

- Post-infectious
  - Autoimmune
    - Guillain-Barré
    - Acute disseminated encephalomyelitis
  - Hypercoagulable
    - Stroke



Stroke
Hypoxic injury
Encephalopathy
Encephalitis
Guillain-Barré
Headache
Sleepiness
Dysgeusia/anosmia
Fatigue
Neuropathy

COVID-19 coronavirus: Biomarkers

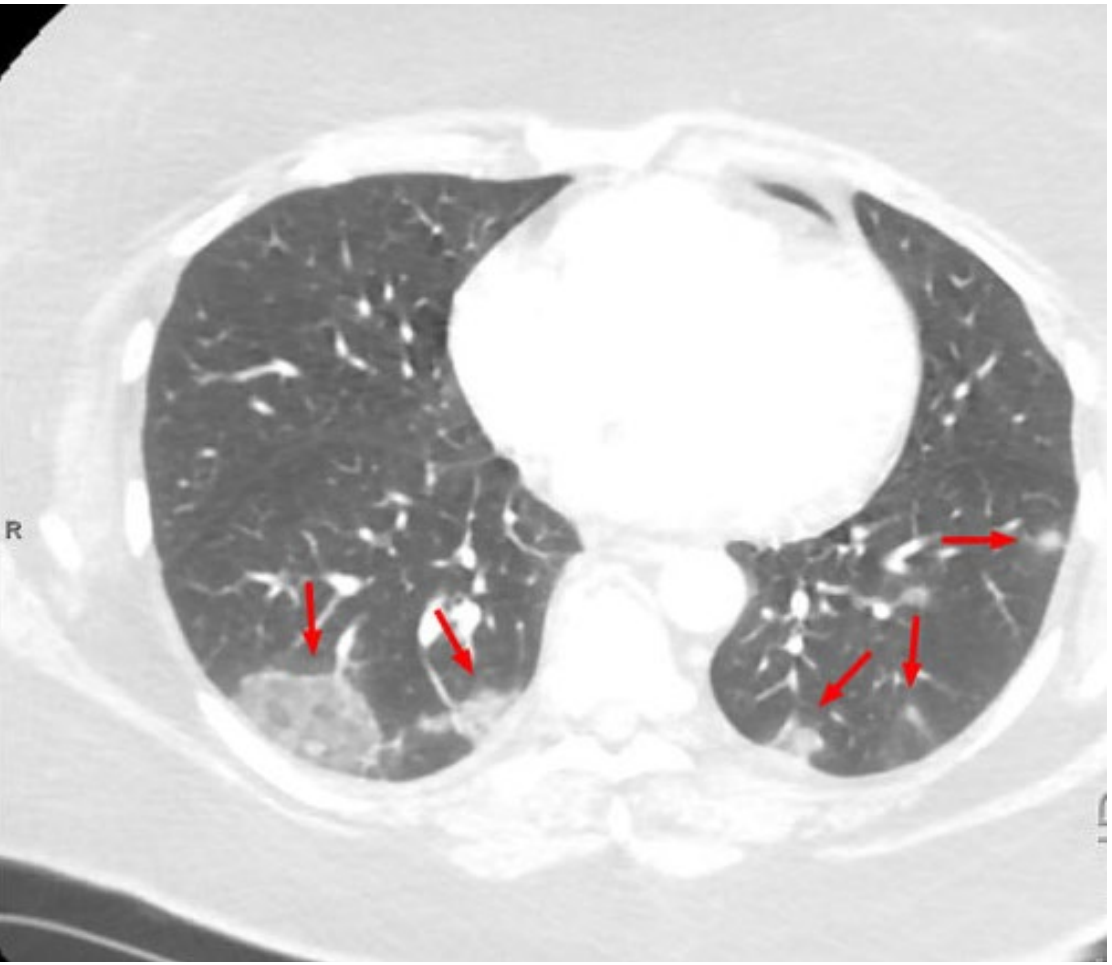
- Monitor markers for progression to critical illness.
  - WBC**, lymphocytes**, platelets (thrombocytopenia)
  - ↑ **Ferritin and CRP** (acute phase proteins)
    - Synthesized by liver in response to inflammation
    - Directly correlated with amount of inflammation
  - **D-dimers** (hypercoagulability) → mortality risk
  - Transaminitis
  - Low albumin
  - Troponin
  - BNP

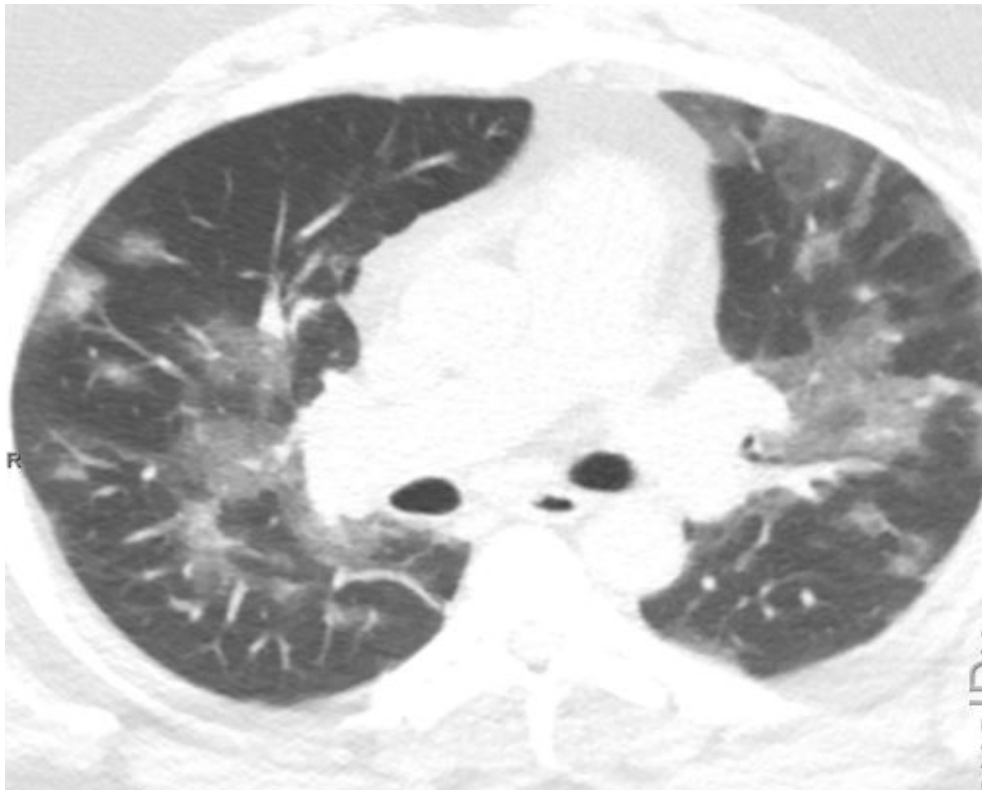
- Progressive **lymphopenia** → a hallmark sign of pending severity

- Procalcitonin may be used for bacterial pneumonia superinfection

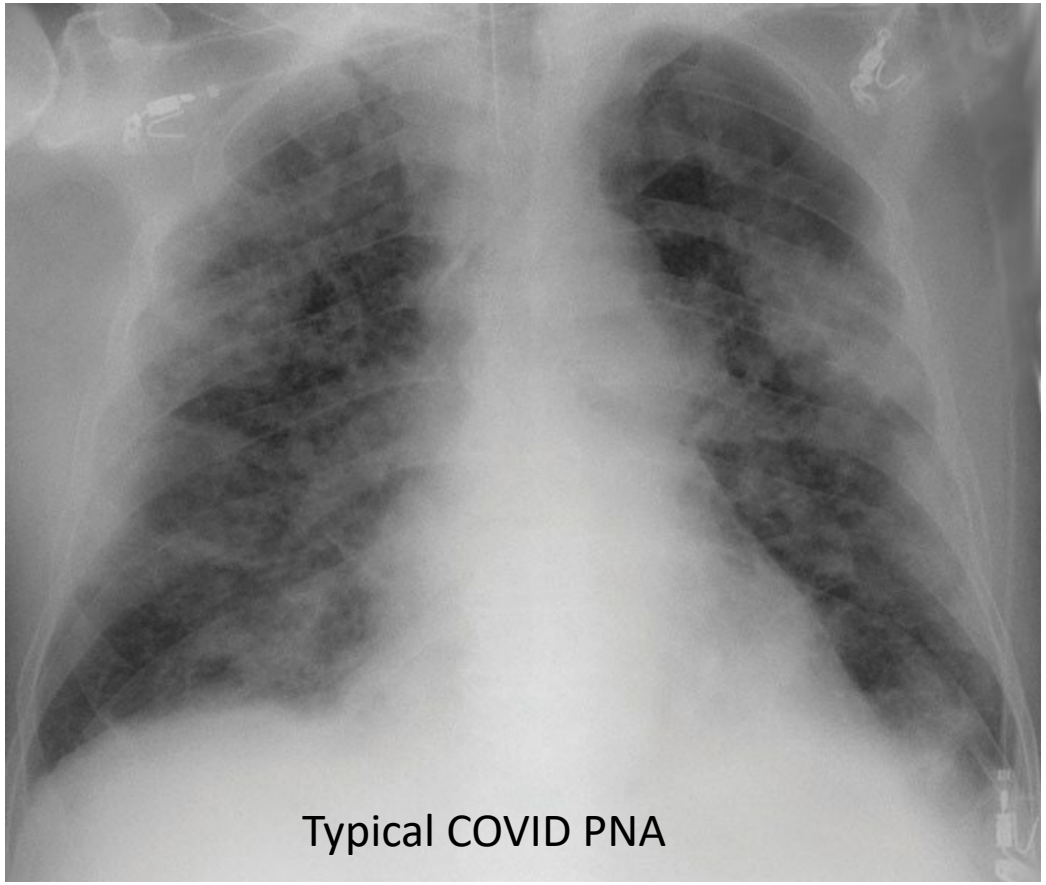
COVID-19 coronavirus: CT findings

Progressive Bilateral ground glass opacities
Later = areas of consolidation



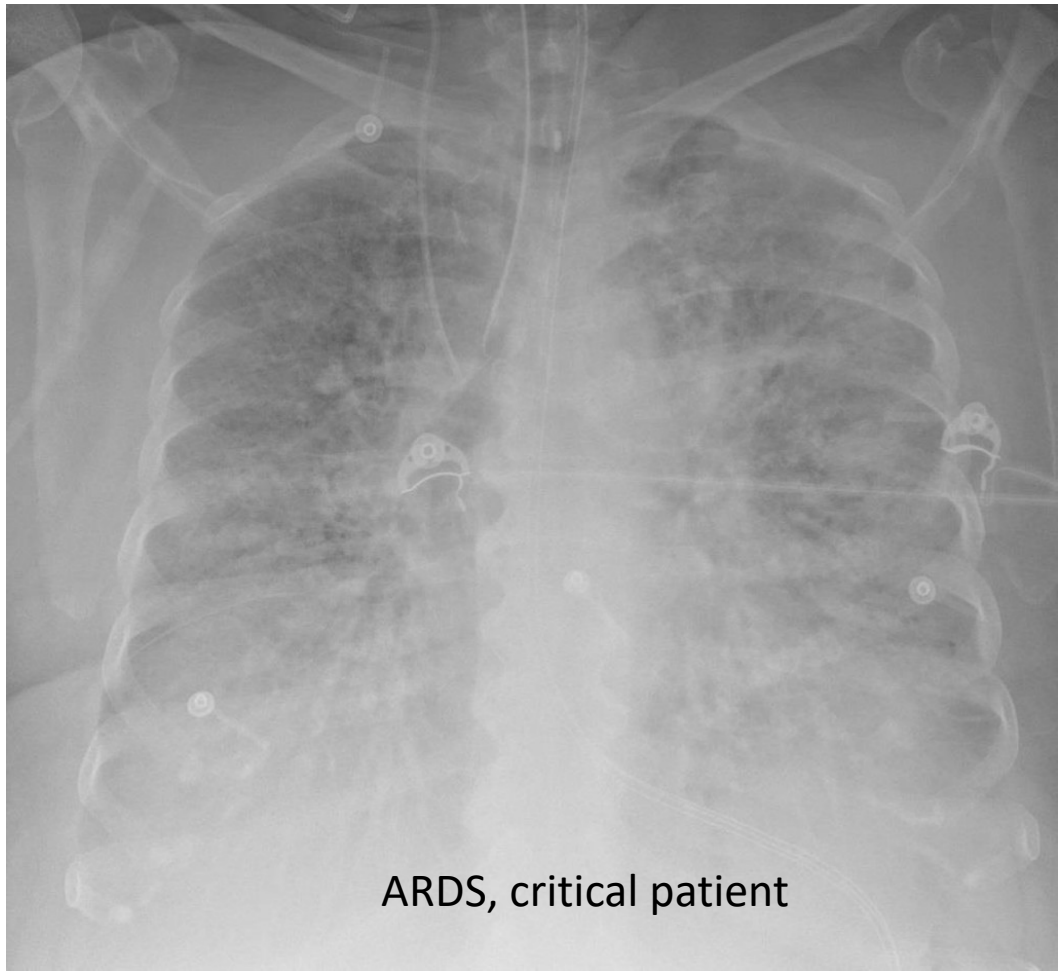


A negative chest CT does not rule out Covid-19, and an abnormal CT is not specific



Typical COVID PNA

Chest X-ray may be normal in early disease



ARDS, critical patient

COVID-19 coronavirus: Therapy
THIS IS AN EMERGING TOPIC

**Severe = SpO_2 ≤94% on room air
***Non-severe = SpO_2 > 94% on room air

- **Antiviral Medications**
  - Put up roadblocks in lifecycle to stop replication → slows viral spread ***after infection***
  - Work best if given EARLY in proliferation period

- **Immunomodulators**
  - Dampens intrinsic immune response
  - Prevents damage by tapering the response of body against its own tissues/organs
  - Works best if given LATER in disease process → may be harmful if given early

- **Neutralizing antibody therapies (passive immunity)**
  - Directly administer antiviral antibodies to help combat SARS-CoV-2
  - A more focused and robust immune response
  - Prevents patient from making their own immune response → no memory cells

- **Steroids**
  - Anti-inflammatory
  - reduces mortality in **severe cases characterized by high CRP and ***need for supplemental oxygen***
  - Potentially worsens outcomes in milder cases, likely due to immunosuppression

COVID-19 coronavirus: Therapy timing

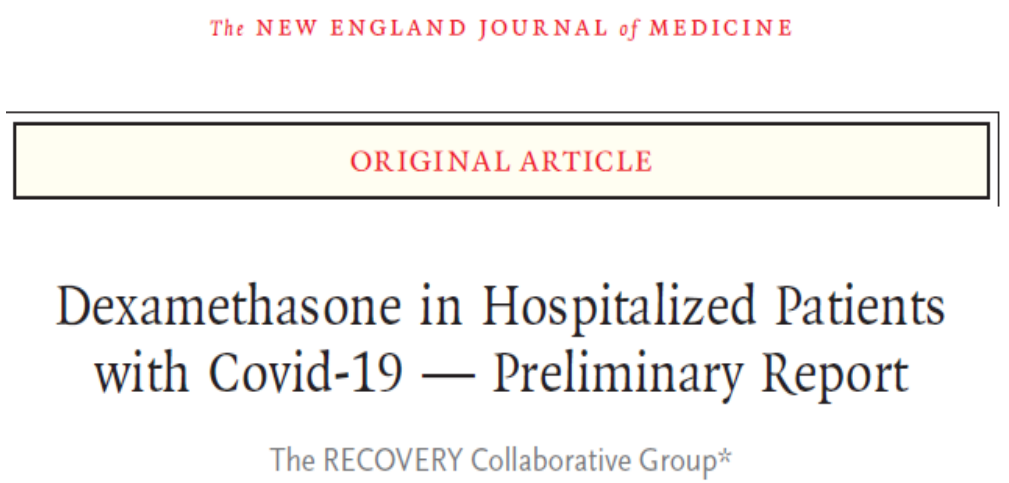
Syndrome	Early viral driven	Late hyperinflammatory
Mechanism	Active viral replication	Dysregulated host response
Symptoms	Flu-like illness Fever, cough, dyspnea, myalgia, headache, sore throat, fatigue	Organ damage Gastrointestinal, cardiovascular, Dermatologic, neurological, renal, hematologic
Rx	Antivirals monoclonal antibodies	Immunomodulators Steroids

Dexamethasone

- Decrease inflammatory response associated with ARDS
- Reduce risk for respiratory failure and death

- Reduced 28-day mortality by 36% in those receiving oxygen (not mechanically ventilated)
- greatest effect in those requiring mechanical ventilation
- **No benefit for those who did not require oxygen**

- **Adverse effect = immunosuppression = increase risk of secondary infection**



COVID-19 coronavirus: Therapy

- FDA sponsored Coronavirus Treatment Acceleration Program (CTAP) helps make available new treatments as quickly as possible while minimizing harm
- FDA has approved one drug, remdesivir (Veklury), for the treatment of COVID-19

590+

Drug development programs in planning stages[1]

390+

Trials reviewed by FDA[2]

8

COVID-19 treatments currently authorized for Emergency Use[3]

1

Treatments currently approved by FDA for use in COVID-19

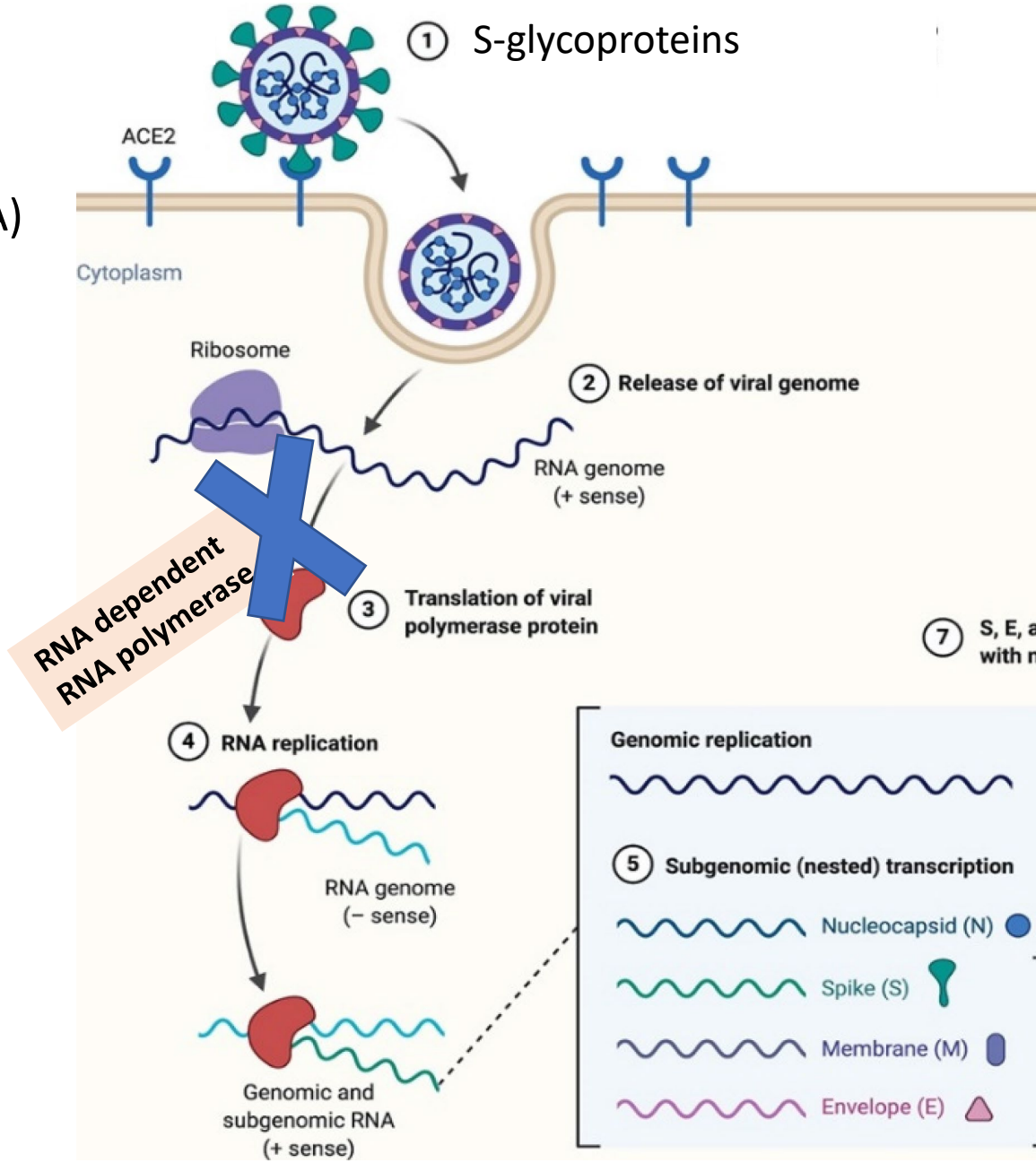
https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap

Remdesivir: Overview

- Adenosine nucleotide analogue (mimics building block of RNA)
  - Binds RNA-dependent RNA polymerase, stops replication
  - Causes premature termination of viral RNA transcription
  - Stops new viral particles from forming

- Broad-spectrum against several RNA viruses
- FDA approved for COVID-19 on October 22, 2020

- **Minimal Adverse Events**:
  - Elevated LFTs (typically 2-3x normal)
    - Monitor LFTs and INR, stop if > 10x normal
  - GI symptoms (nausea, vomiting, gastroparesis, bleeding)



Remdesivir: Overview

- Remdesivir trials have mixed results
- Evidence for use is generally weak
  - Some studies show marginal benefit while others show no benefit
- No evidence of a mortality benefit

- No strong evidence to suggest prevention of mechanical ventilation

- WHO currently recommend *against* use of remdesivir for any severity

- NIH suggests treatment with remdesivir, dexamethasone, or combination in hospitalized patients requiring supplemental oxygen

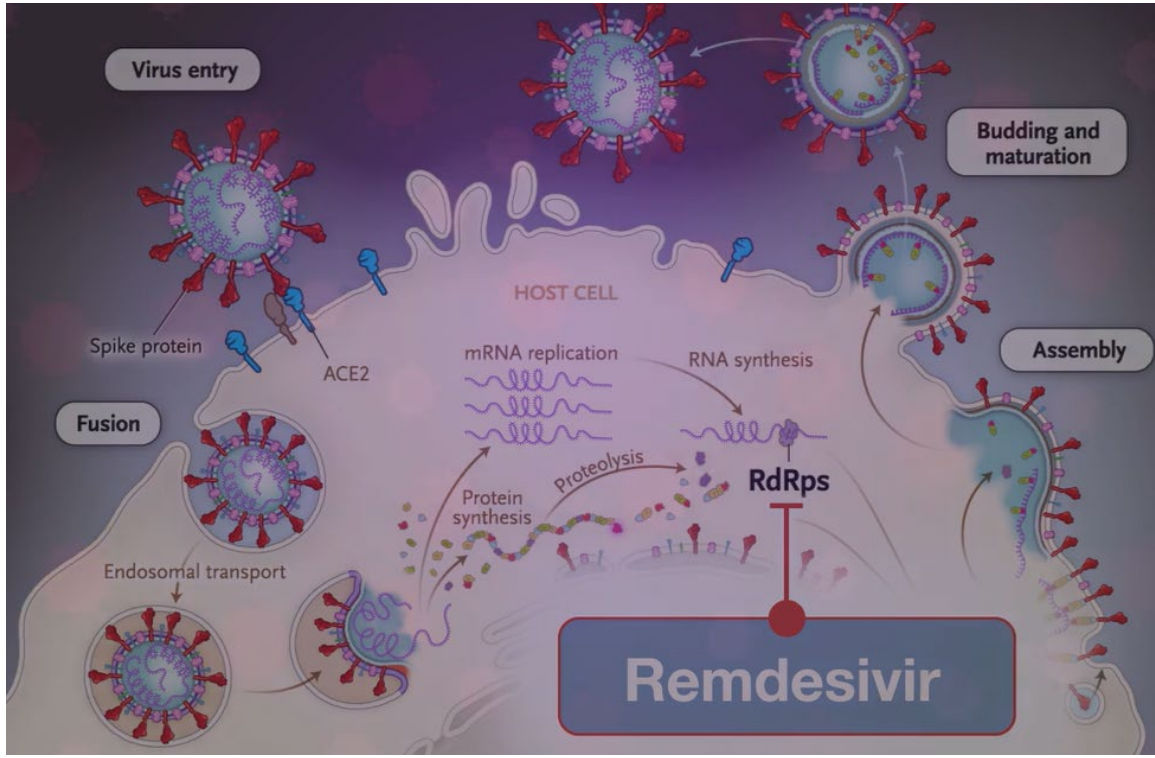
- IDSA recommends use of remdesivir over no antiviral treatment in hospitalized patients with severe COVID-19

Remdesivir: Evidence

**Severe = SpO_2 ≤94% on room air
***Non-severe = SpO_2 > 94% on room air

- A multicenter, double-blind, randomized, placebo-controlled trial of remdesivir in adults hospitalized with **evidence of lower respiratory tract involvement**

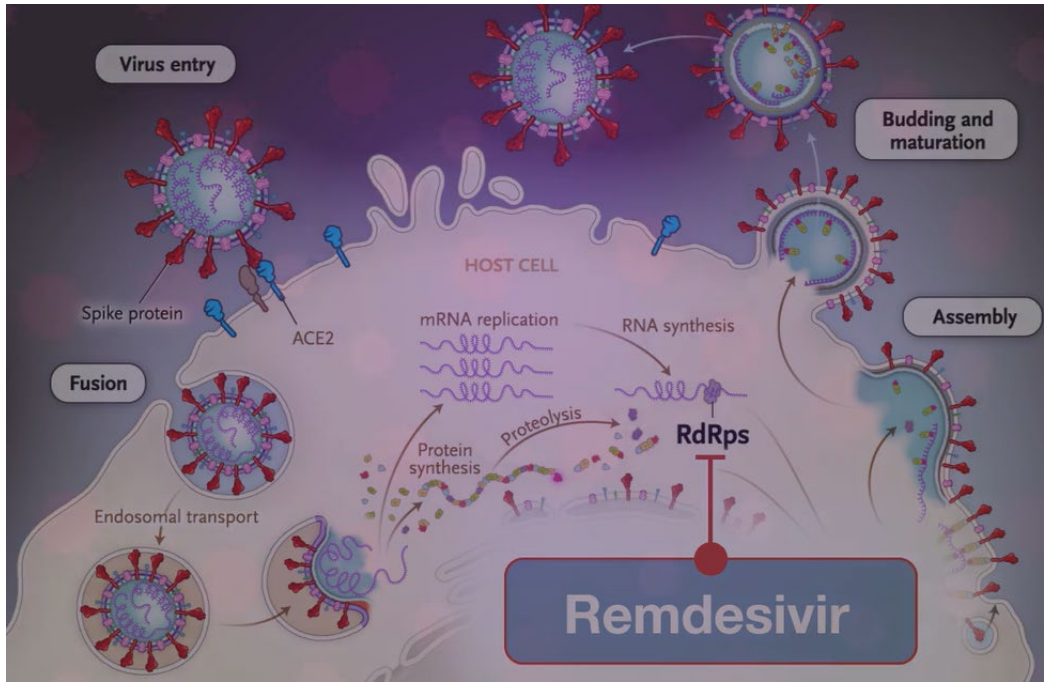
- **Inclusion Criteria (n = 1062)**
  - Age ≥18
  - One or more of the following:
    - Pulmonary infiltrates on chest imaging
    - Rales or crackles AND SpO2 ≤94% on room air
    - Requiring mechanical ventilation or supplementary oxygen



Remdesivir: Evidence

- A multicenter, double-blind, randomized, placebo-controlled trial of remdesivir in adults hospitalized with **evidence of lower respiratory tract involvement**

- **Primary Outcome**: Time to recovery (discharge or no longer requiring supplemental O2)
  - first day on which a patient met criteria for category 1, 2, or 3 on 8-category ordinal scale
  - 1, not hospitalized and no limitations of activities
  - 2, not hospitalized, with limitation of activities or home oxygen
  - 3, hospitalized, not requiring supplemental oxygen
  - 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions)
  - 5, hospitalized, requiring supplemental oxygen
  - 6, hospitalized, requiring noninvasive ventilation
  - 7, hospitalized, on mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
  - 8, death



Remdesivir: Evidence

**Severe = SpO_2 ≤94% on room air
***Non-severe = SpO_2 > 94% on room air

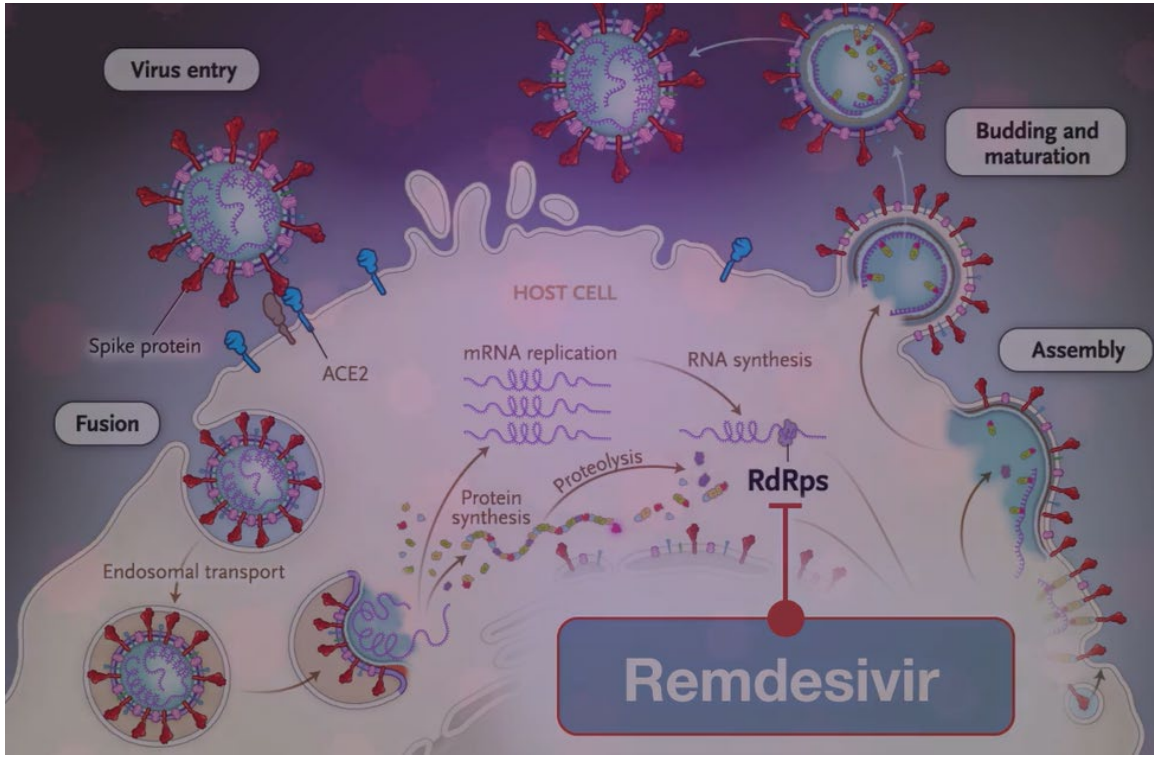
- Those who received remdesivir
  - median time to recovery reduced by 5 days (from 15 to 10) compared to placebo (rate ratio, 1.29 [95% CI, 1.12 to 1.49])
  - More likely to improve in the ordinal scale score at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9).

- Conclusion = Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized and had evidence of lower respiratory tract infection.

- **No significant effect on mortality**
- Benefit = fewer days on oxygen for those who need it

- **Only indicated for hospitalized patients who require oxygen above their baseline**

- Given high mortality despite remdesivir, this antiviral drug alone is not likely to be sufficient for all patients.



Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19
A Randomized Clinical Trial

- Objective = To determine the efficacy of 5 or 10 days of remdesivir compared with standard care on clinical status on day 11 after treatment

- Inclusion crietria
  - SpO2 >94% on room air at screening and radiographic pulmonary infiltrates

- Randomized in a 1:1:1 ratio
  - 10-day course of remdesivir (n = 197)
  - 5-day course of remdesivir (n = 199)
  - standard care (n = 200).

- Measured = day 11 clinical status by 7-point scale → ranging from death to discharged

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19
A Randomized Clinical Trial

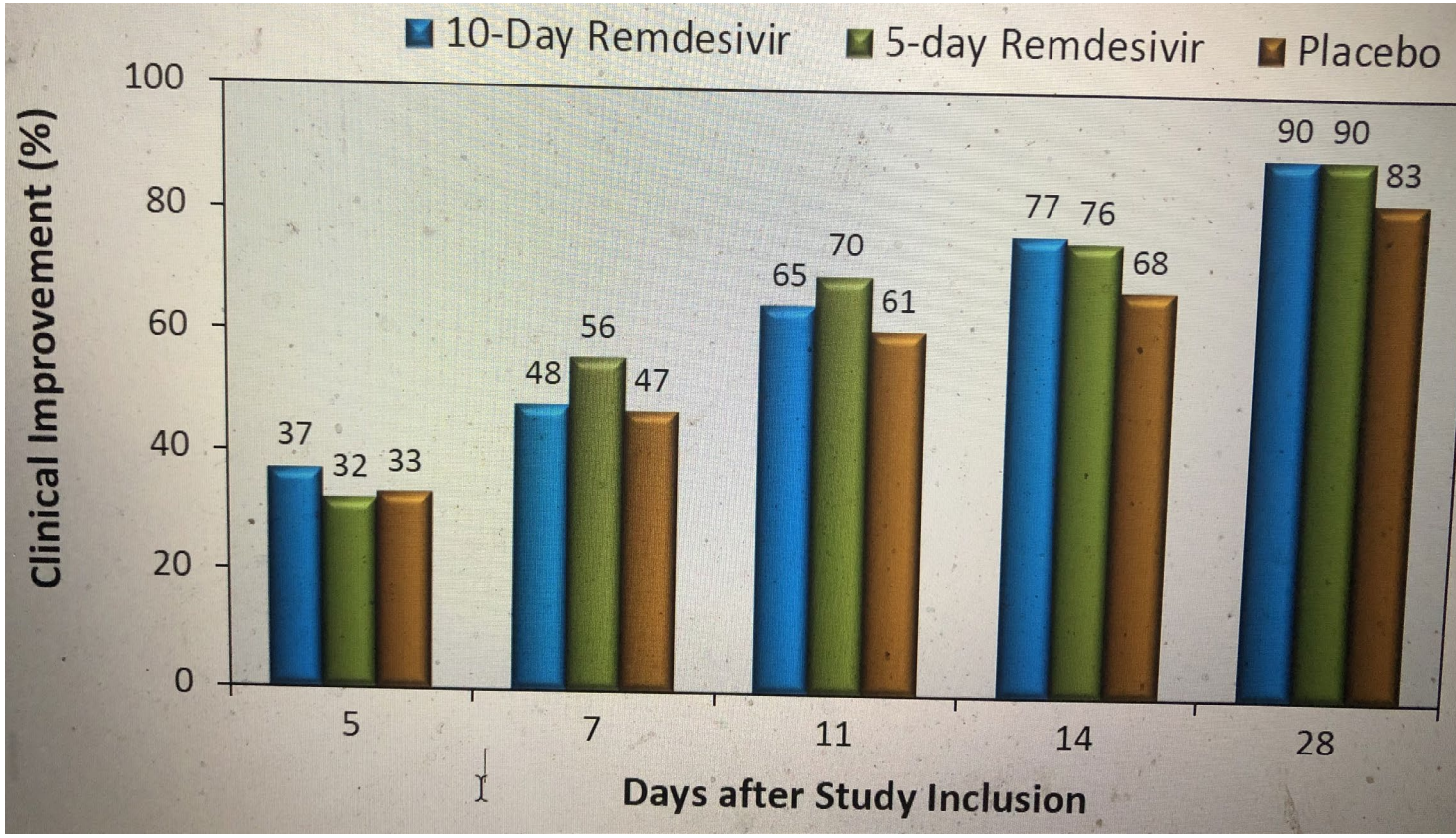
1: Death

2: Hospitalized, invasive mechanical ventilation
3: Hospitalized, noninvasive ventilation

4: Hospitalized, low-flow oxygen
5: Hospitalized, no supplemental oxygen
6: Hospitalized, no supplemental oxygen or ongoing medical care

7: Discharged

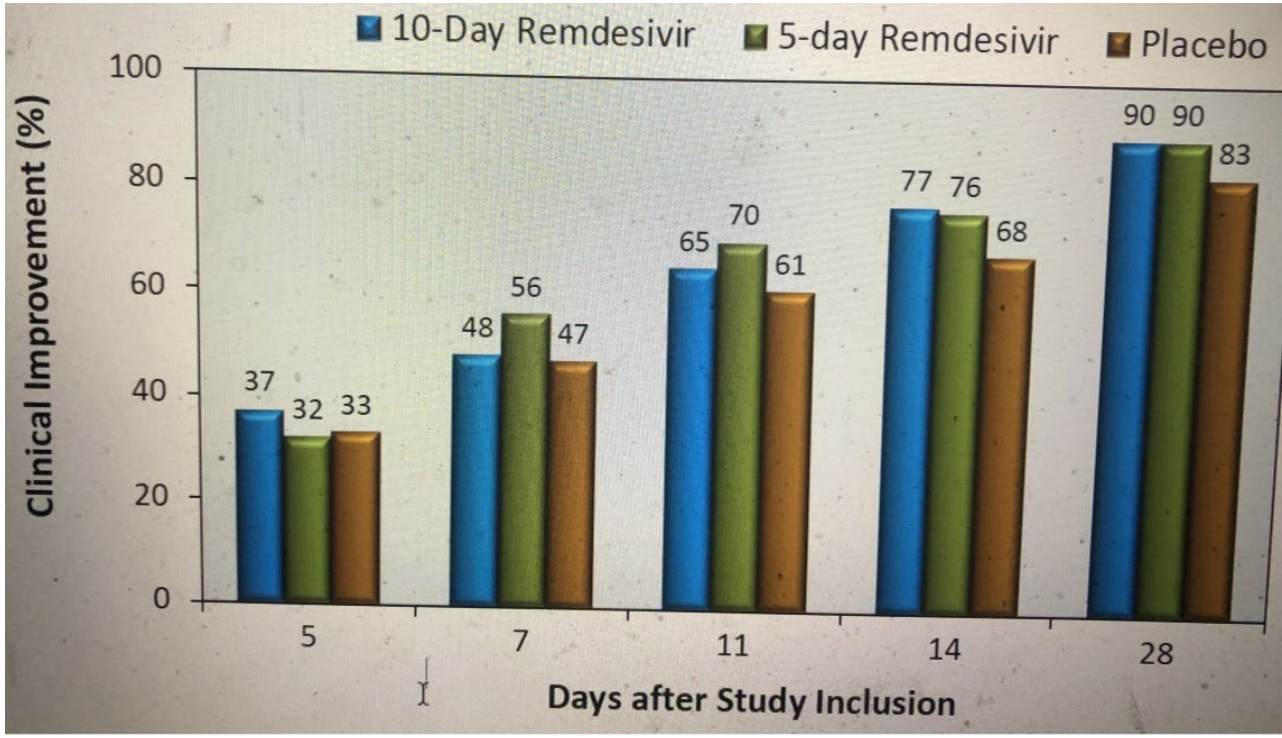
- 5-day course was significantly better than standard of care
  - Scored better on 7-point scale on day 11
- 10 days not significantly different than 5 days



An improvement of at least 2 points from baseline on 7-point ordinal scale

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19
A Randomized Clinical Trial: Conclusions

- Hospitalized patients with moderate COVID-19 randomized to a 5-day course of remdesivir had a statistically significantly better clinical status compared with those randomized to standard care at 11 days after initiation of treatment, **but the difference was of uncertain clinical importance**



Remdesivir: Recommendation

**Severe = SpO_2 ≤94% on room air
***Non-severe = SpO_2 > 94% on room air

- Has benefit in **severe disease (on supplemental oxygen)

- Hospitalized patients with **severe disease, not on mechanical ventilation, IDSA suggests treatment with 5 days of remdesivir
  - 200 mg on Day 1, followed by 100 mg on Day 2-5
  - **Not recommended with an estimated GFR < 30 mL/min**

- Hospitalized patients with severe**, non-critical

IDSA suggests dexamethasone
  - Dexamethasone 6 mg IV or PO for 10 days (or until discharge)

No Oxygen = No Remdesivir

- Hospitalized patients with non-severe*** COVID-19 without hypoxemia, IDSA is against the use of glucocorticoids or remdesivir

- **Despite the benefits of remdesivir, substantial morbidity and mortality due to Covid-19 remain**

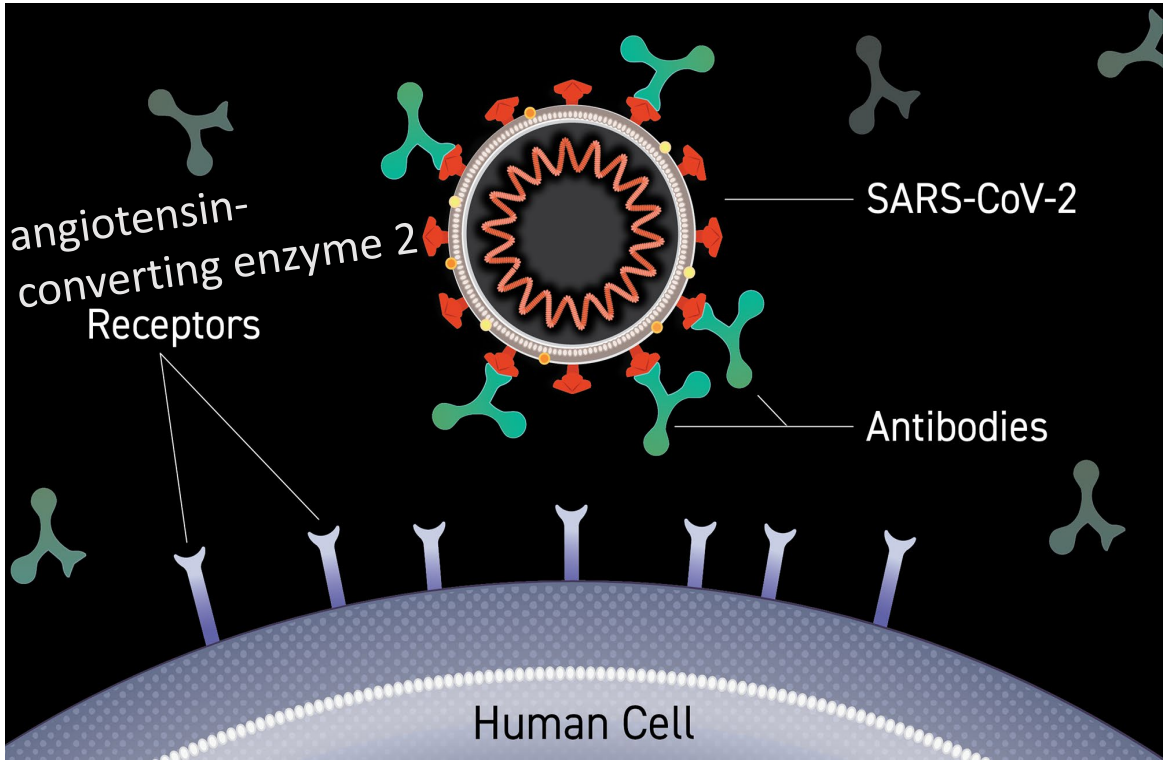
DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab** or **casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk of disease progression.[a] These EUAs do not authorize use in hospitalized patients. **Dexamethasone** should not be used **(AIII)**.
Hospitalized[a] But Does Not Require Supplemental Oxygen	**Dexamethasone** should not be used **(AIIa)**. There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized[a] and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[e,f] • **Dexamethasone**[d] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized[a] and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d,f] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)**[e,f]

Monoclonal antibodies: Not recommended

- Synthetic antibodies against key viral proteins
- Two regimens have been given EUA for non-hospitalized mild to moderate Covid-19 and high risk for progression to severe disease
  - Casirivimab and imdevimab (anti-spike protein)
  - Bamlanivimab (blocks receptor-viral binding)

- Neither has strong clinical evidence for benefit

- Hypothesized Benefits
  - Accelerate natural decline in viral load
  - Decrease need for further medical attention



Convalescent plasma

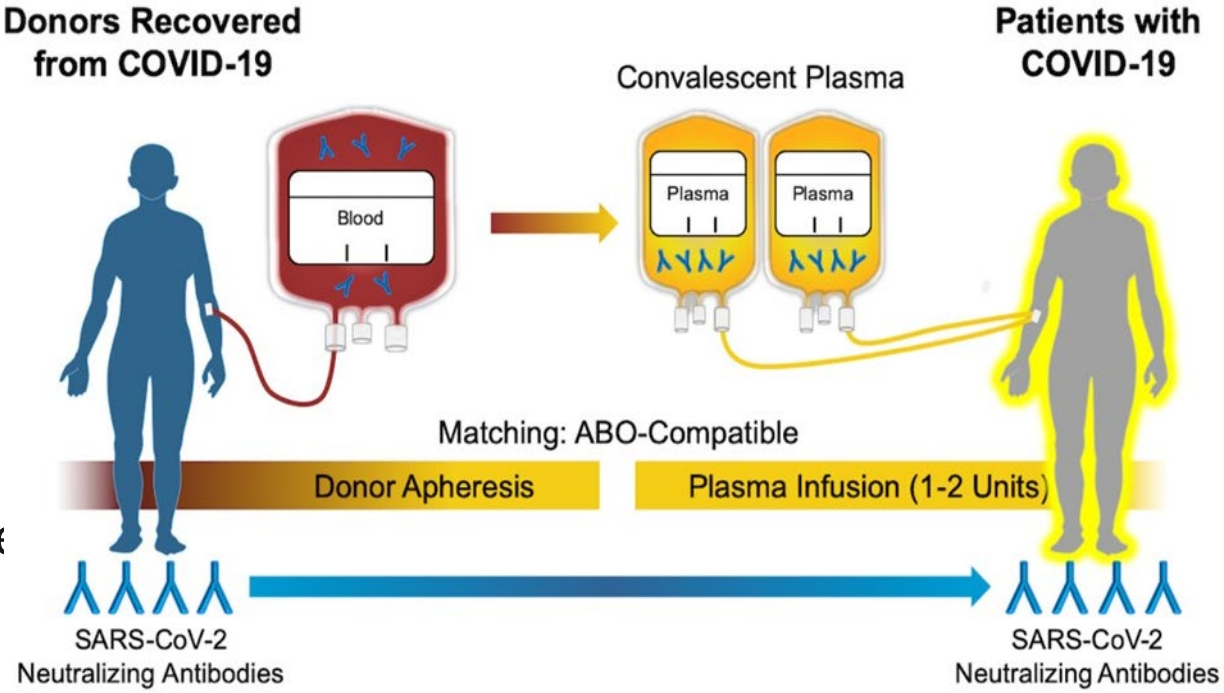
- Plasma from recovered person transfused to patient

- Neutralizing antibodies provide passive immunity

- May attenuate patients innate immune response
  - Patient can still get infected in future (no memory, no post infection immunity)
  - Less likely to get exaggerated immune response that can lead to cytokine storm and tissue damage

- Considered investigational and has EUA
- Insufficient data from well-controlled trials to evaluate true efficacy and safety

- Available data indicates no harm other than from standard plasma infusions (transfusion reactions)



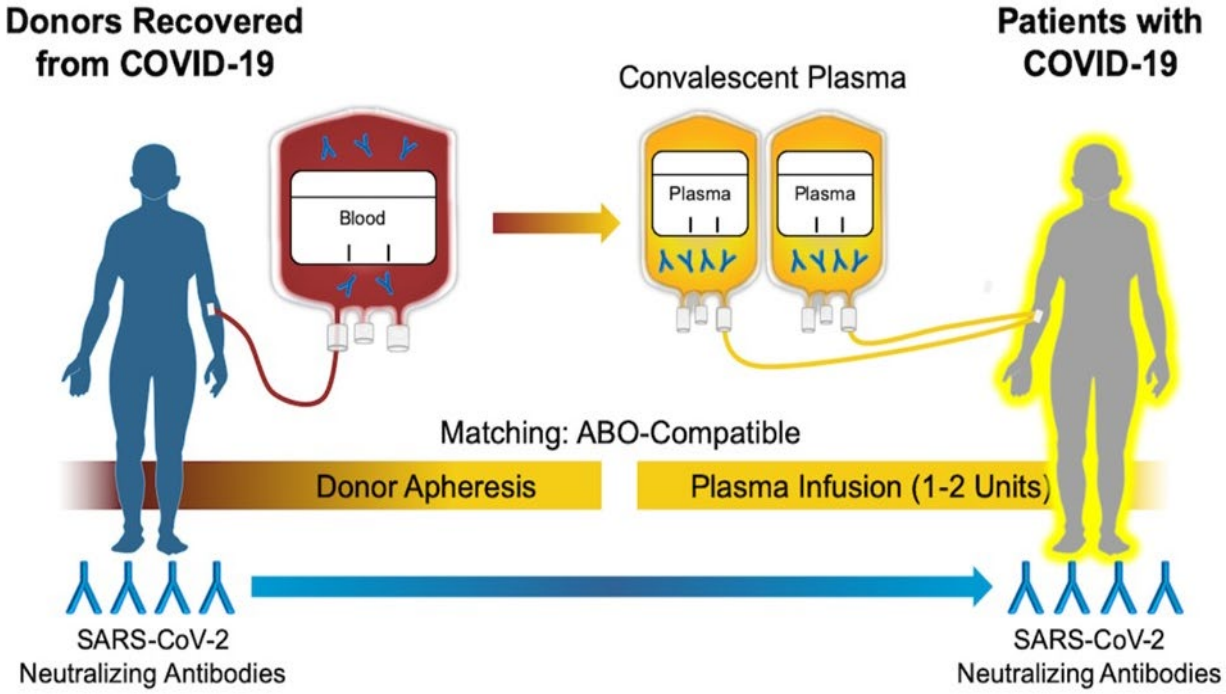
Dampens patients innate immune response by lowering viral load → decrease associated tissue damage

Convalescent plasma

- Best given
  - Early: 7-10 days post-infection → high viremia → largest effect
  - Mild disease may benefit
  - **No proof of benefit in moderate-severe**

- Unclear efficacy and levels in different donors
  - dose-response relationships
  - Transfusions with high antibody titers was associated with a lower risk of death than lower titers
- IDSA guideline: use for hospitalized patients only in the context of a clinical trial

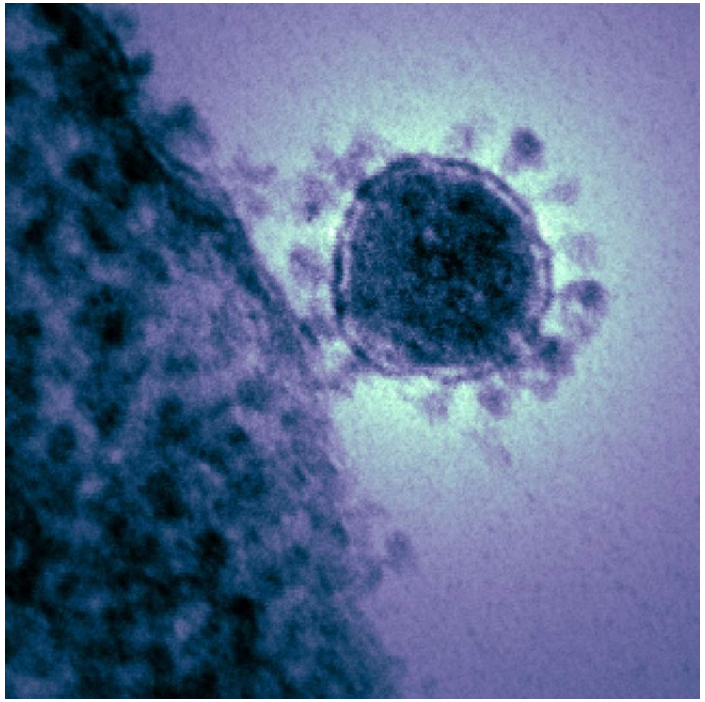
- FDA issued EUA: "Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials."



Dampens patients innate immune response by lowering viral load → decrease associated tissue damage

Summary and Pearls

- SARS-CoV-2 RNA virus that binds angiotensin converting enzyme-2 (ACE-2) receptor → found in many tissues
  - Neurologic symptoms may be the present BEFORE respiratory



- Clinical Severity is based on dyspnea, hypoxia and chest imaging
  - Most common symptoms: Fever, cough, fatigue and loss taste/smell

- D-dimers, lymphopenia, ferritin and CRP are biomarkers of severity and have prognostic value

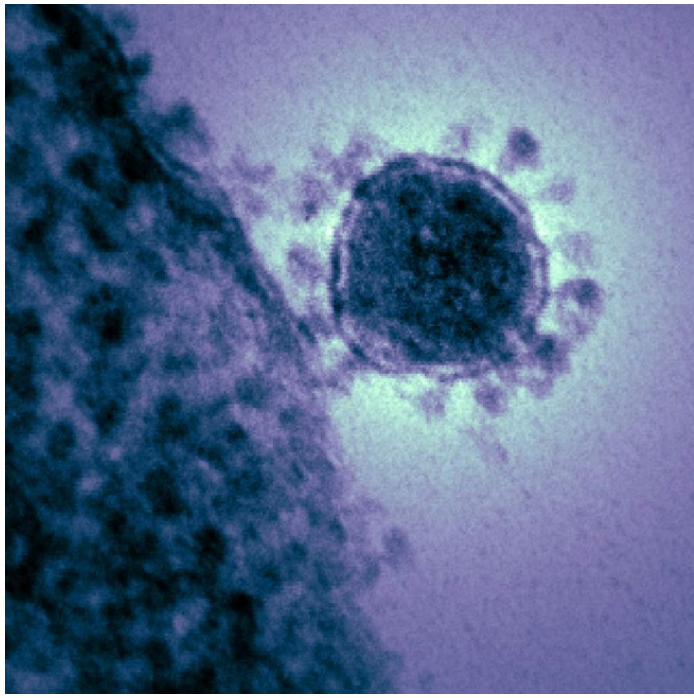
- Severity of illness does not appear to correlate with contagiousness

- Duration of viral shedding is uncertain
  - May begin before symptomatic stage
  - May outlast symptomatic stage
  - Immunocompromised and elderly may shed longer irrelevant of symptoms

Summary and Pearls

- Steroids have a mortality benefit only in those who require oxygen

- <u>Remdesivir is the only FDA-approved drug</u>
  - Used for hospitalized patients who require oxygen because it shortened length of stay and time to subjective improvement
  - **Does NOT have a mortality benefit or reduce the risk of progression to mechanical ventilation**
- Evidence is weak for all other treatment modalities



- Exposure to SARS-CoV-2 does not guarantee immunity
  - Multiple reports of re-infection have been described.

- Positive nasopharyngeal swab does not necessarily indicate presence of replication-competent virus
  - Swab PCR can remain positive in a non-infectious person
  - Negligible risk of recovering replication-competent virus 10 days after symptoms → irrelevant of test result

References and Resources

- www.who.int/emergencies/diseases/novel-coronavirus-2019
- COVID-19: An ACP Physician's Guide + Resources (Last Updated January 15, 2021) - Overview (acponline.org)
- www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms
- www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
- www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management

- *JAMA*. 2020;323(18):1824-1836
- The New England Journal of Medicine 383;19, November 5, 2020
- Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *medRxiv*. 2020
- *PLoS One*. 2020;15(11):e0240784