COVID-19:
Pathophysiology of Symptoms

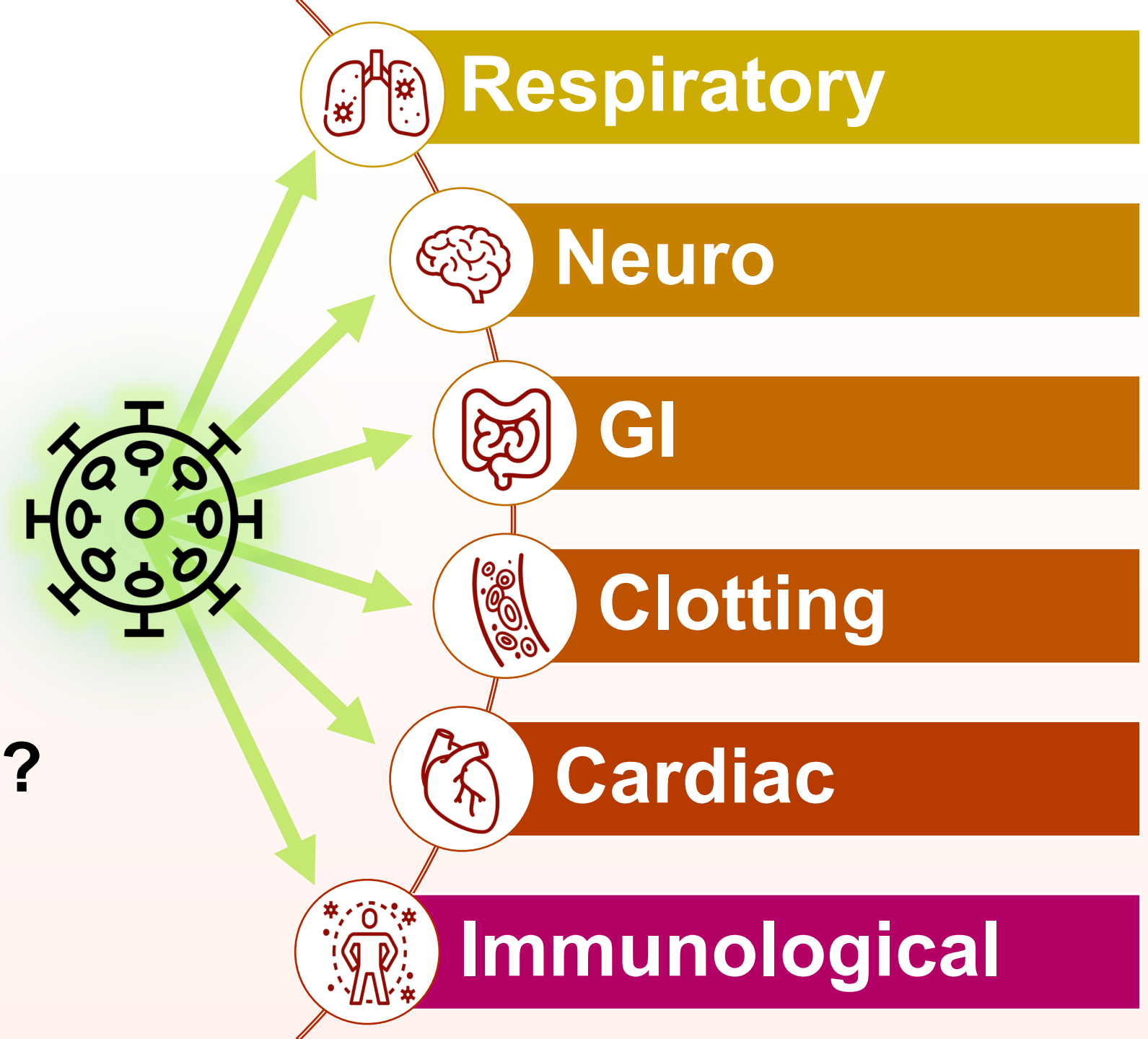
1 Feb 2021

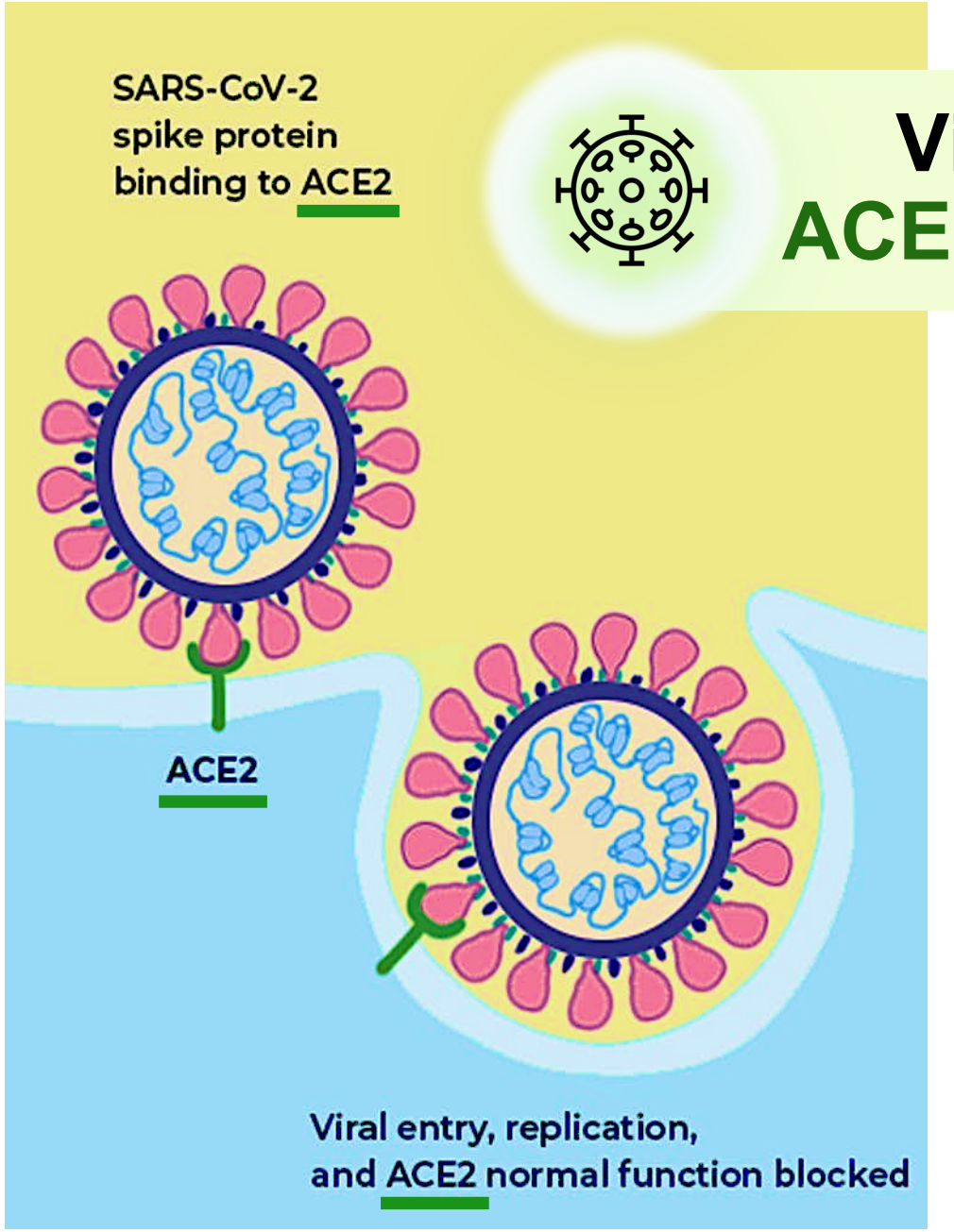
RNnext.com

Raney Linck
DNP, RN

A self-study guide: *All references are active hyperlinks.*

How does a **respiratory virus** affect so many other organs/systems?





Virus invades cell by attaching to ACE2 protein *("receptor")* on cell's surface

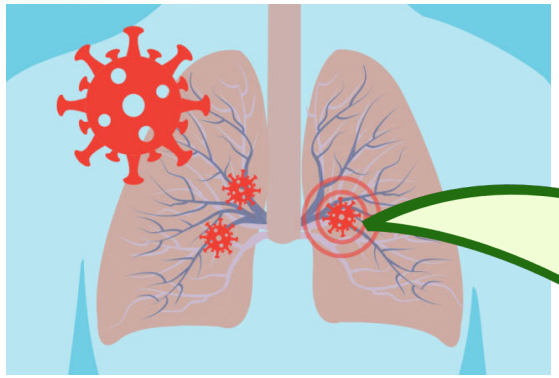
What is ACE2 protein?

- Normally breaks down ANGII in body.
- This function helps regulate body's RAAS–it's a healthy, protective "brake"
- If unchecked, ANGII will ↑ **inflammation** & cell death in **lungs** and **heart**

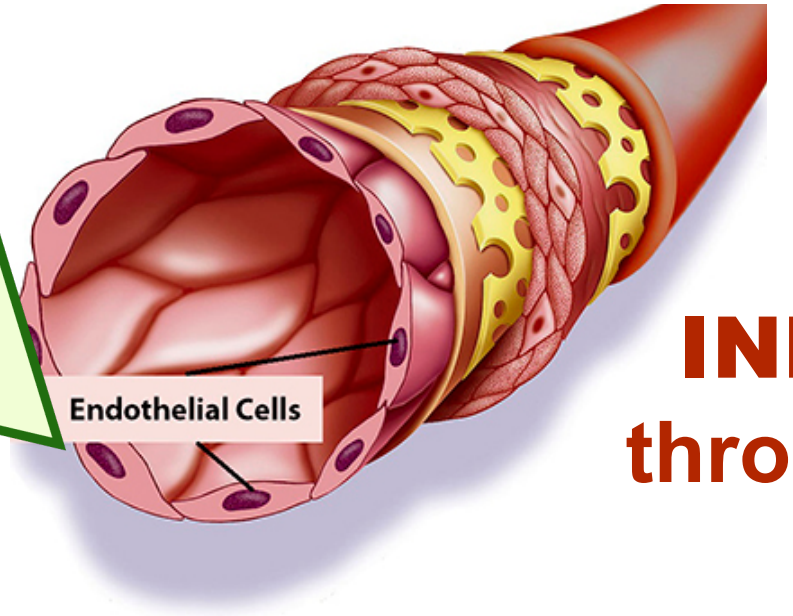
ACE2: *angiotensin converting enzyme 2*
ANGII: *angiotensin II*
RAAS: *renin-angiotensin-aldosterone system*

Siriam et al., 2020; Nishiga et al., 2020

SARS-CoV-2 infects inner lining *(endothelium)* of blood vessels



*Because all of these cells have **ACE2 proteins** too…*



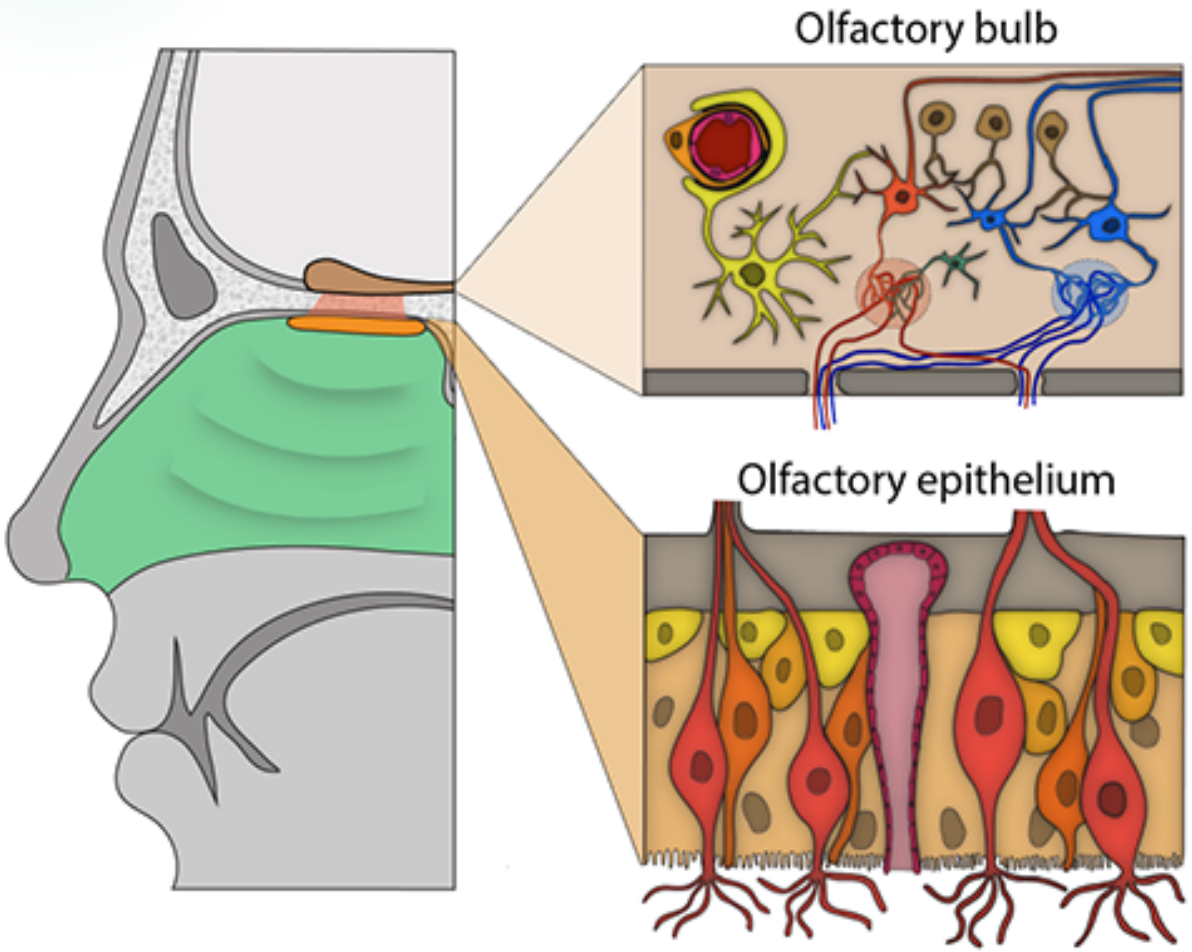
This causes CLOTS & INFLAMMATION throughout the body.

Also: infects endothelium of

- **GI tract**
- **heart**

Ackermann et al., 2020; Begley, 2020; Pons et al., 2020; Smith, 2020

Ansomia *(loss of smell)*



Current thinking:

- **SARS-CoV-2 does ***NOT*** infect *neurons* in brain's olfactory bulb** *(no ACE2 proteins)*.

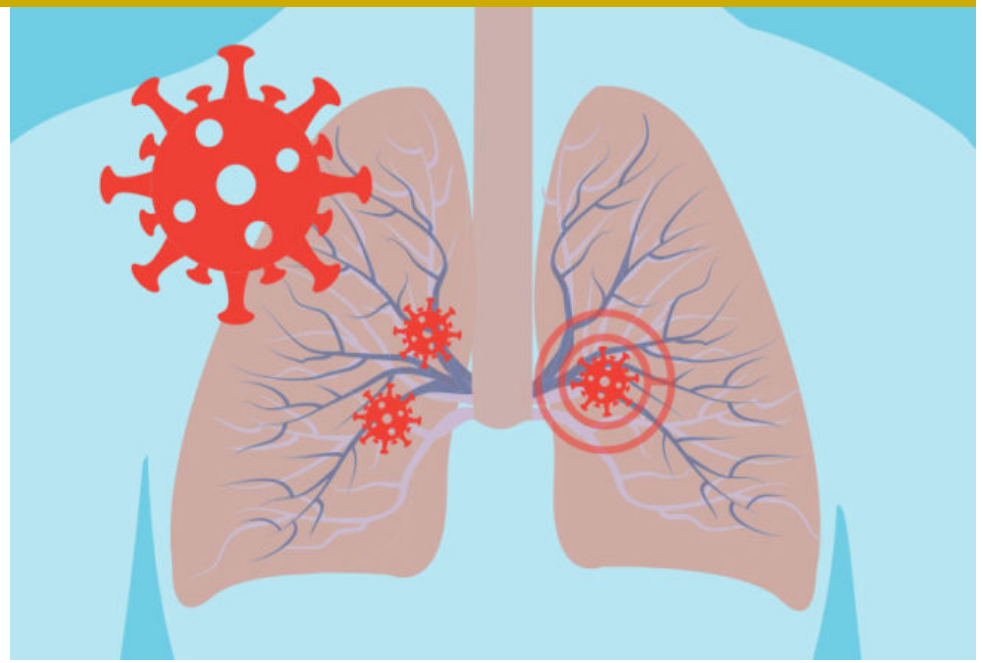
Virus infects ***olfactory epithelial cells***

in nasal cavity that provide support to neurons.

- *Return of smell in weeks not consistent with neuron damage.*

Brann et al., 2020; Jiang, 2020

Respiratory symptoms



- **Cough**
- **↑ mucus production**
- **Pneumonia** *(**mild** or **severe**)*

➢ **Ground Glass Opacities**

- ***GGO = abnormal chest imaging*** *(x-ray or CT scan: next slide)*

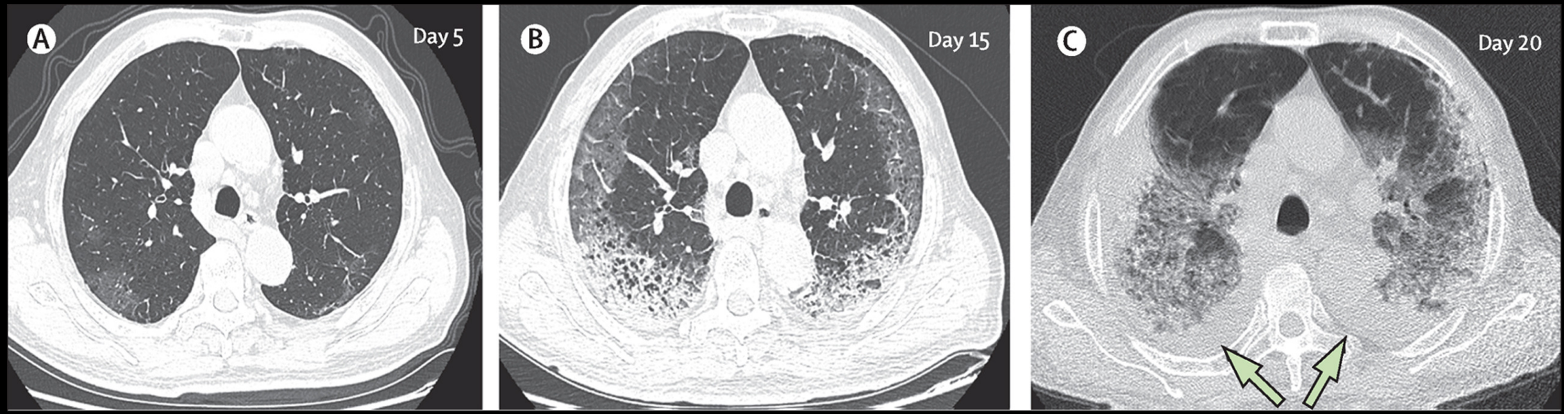
➢ **ARDS: Acute Respiratory Distress Syndrome**

Cleveland Clinic, 2020b; Harding et al., 2020

Ground Glass Opacities (GGO)

COVID-19 patient *(male, age 77, from Wuhan):*

“patchy” GGO noted on Day 5, then progressively worsened…



Day 5 **Day 15** **Day 20**

Shi et al., 2020

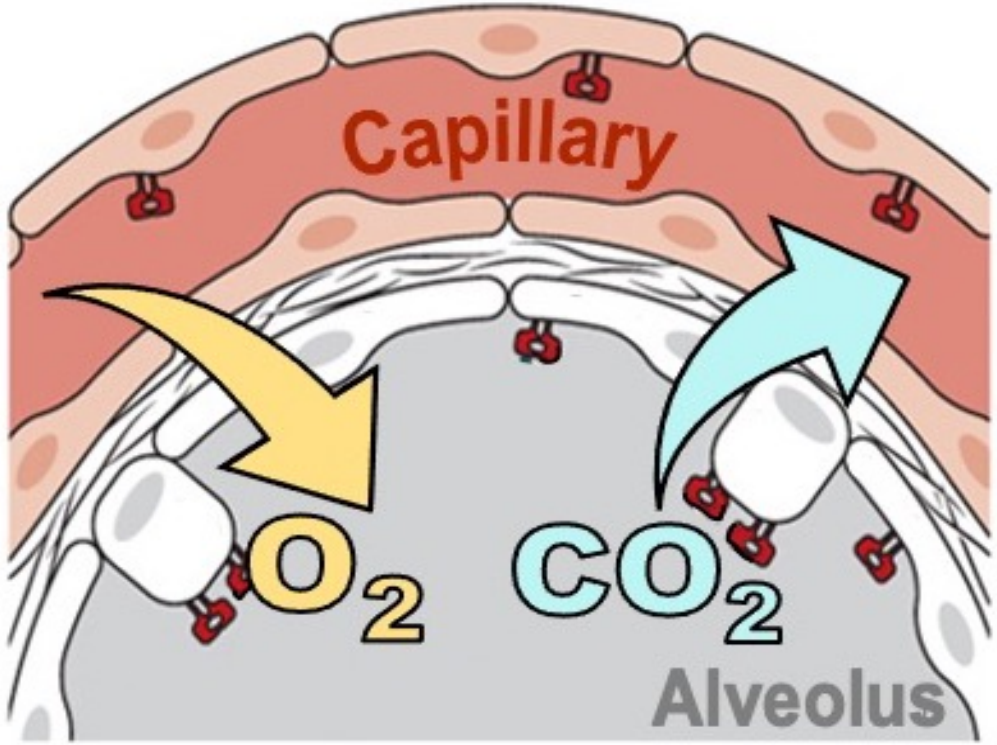
NORMAL: *gas exchange in lungs*

normal

alveolus *(plural: alveoli)*

microscopic air sacs in lungs where **oxygen** & **carbon dioxide** are exchanged

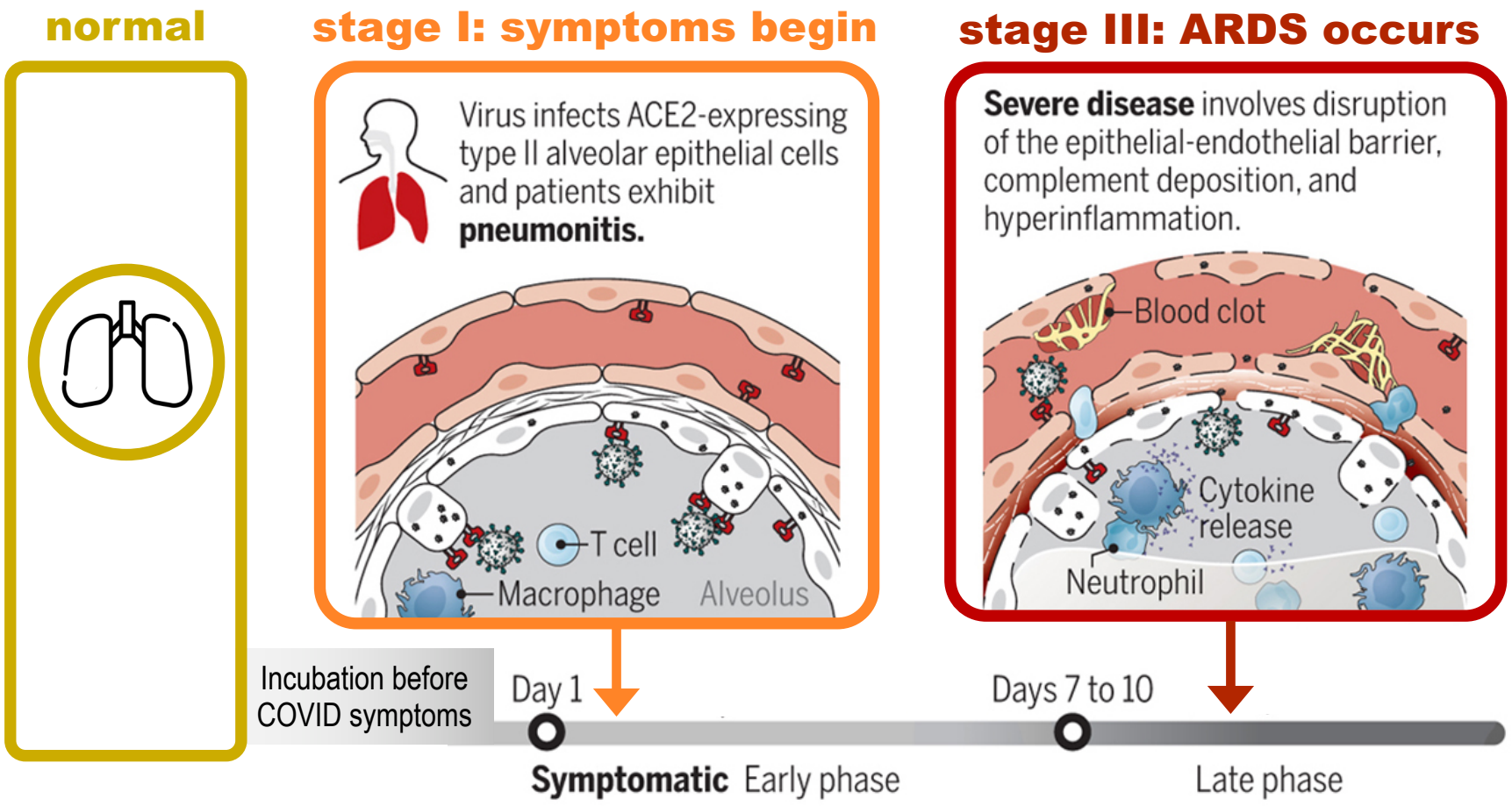
- membrane does *not* allow fluid to cross
- alveoli should be filled with air, *never* fluid



Matheson & Lehner, 2020; Harding et al., 2020

ARDS: *Acute Respiratory Distress Syndrome*

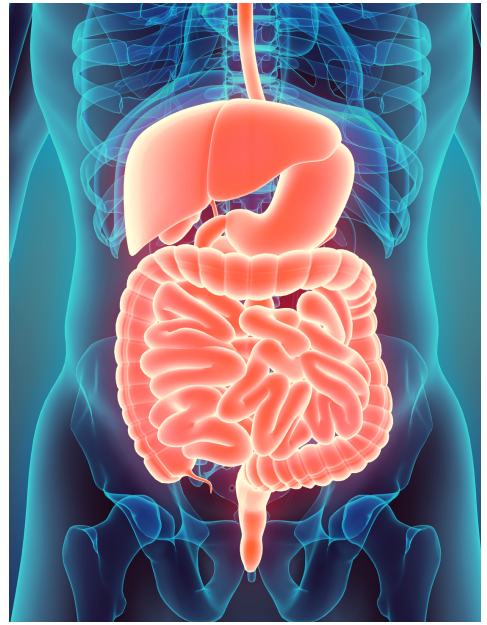
Hyperinflammatory reaction damages alveolar membranes making them "leaky" (permeable) – causes alveoli to be flooded with fluid



Matheson & Lehner, 2020; Harding et al., 2020

Gastrointestinal symptoms

- **50-60% cases report at least one GI symptom:**
  - **loss of appetite** *(anorexia)*
  - **nausea or vomiting**
  - **diarrhea**
  - **bloating, abdominal pain, etc.**

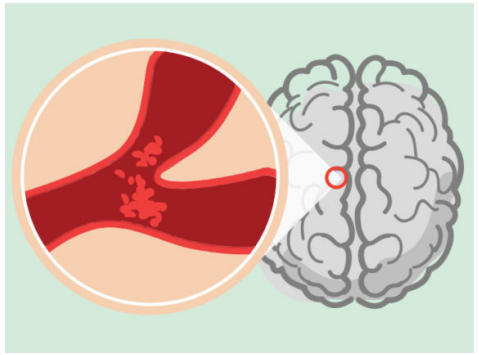


- **May begin with <u>only</u> GI symptoms**
  - *Wuhan study of 1141 cases:* ***16% presented with <u>only</u> GI symptoms***

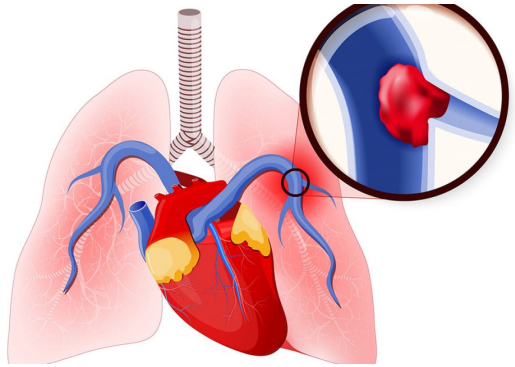
Vane, 2020; Luo et al., 2020; *image*

Clotting can occur…

in BRAIN:
ischemic stroke

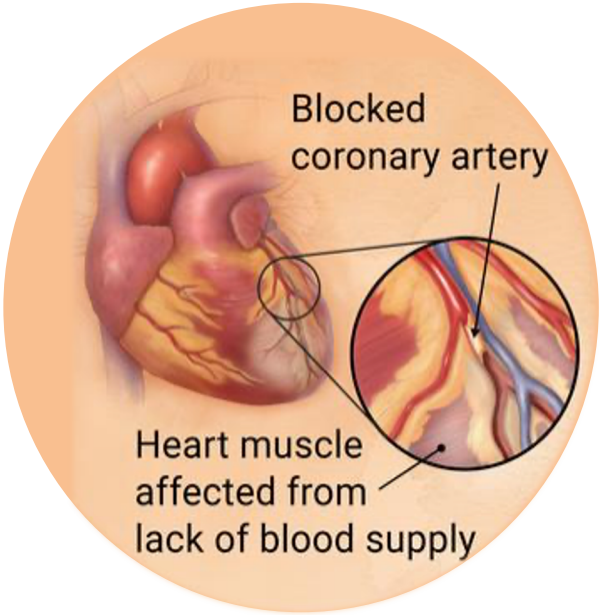


in LUNG:
PE (pulmonary embolism)



in LEG:
DVT (deep vein thrombosis)

in CORONARY ARTERIES:
MI (myocardial infarction)



Use anticoagulant as prophylaxis for *all* hospitalized patients

Low molecular weight *(LMW)* heparin preferred

Also: COVID-19 inflammation can cause existing ***atherosclerotic plaques in coronary arteries to rupture****, resulting in clots.*

Cuker & Peyvandi, 2020; Pinto, 2020; Weill Cornell Medicine, 2020; *Images: 1, 2, 3, 4*

"COVID Toe" *(chilblain-like acral lesions)*

Chilblain *(or pernio)* **lesions** are **painful red or purple lesions** that emerge on fingers or toes *(acral surfaces)* due to cold temps in winter.

Hypotheses:

- caused by ***microclots*** *and/or* ***inflammation*** *(?)*

- more common in **mild or asymptomatic** COVID-19 *(?)*

Feldman et al., 2020; Hernandez & Bruckner, 2020; Rabin, 2020

PRE-EXISTING Cardiovascular…

PRE-EXISTING

cardiovascular disease

↑ susceptibility & severity of COVID-19

Underlying comorbidities:

- Hypertension
- Coronary heart disease
- Diabetes

heart failure
can be pre-existing
or new complication

CV disorders = higher risk to get COVID...

[Nishiga et al., 2020]

NEW-ONSET Cardiovascular…

COVID can also cause new CV disorders…

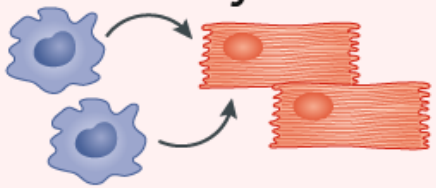
23% developed new-onset HF in Wuhan…

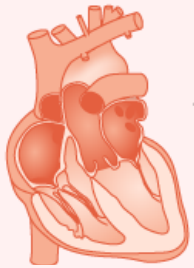
heart failure
can be pre-existing
or new complication

NEW-ONSET complications

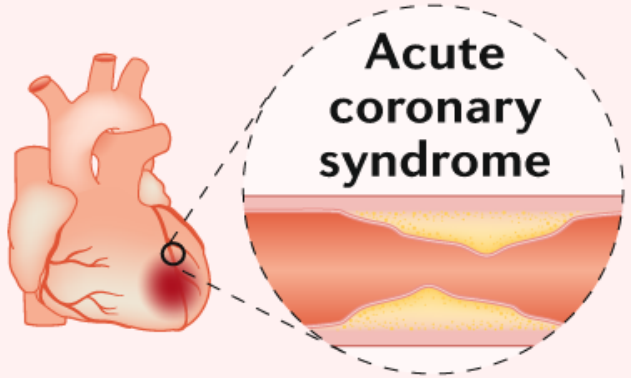
inflammation of heart muscle

Myocarditis

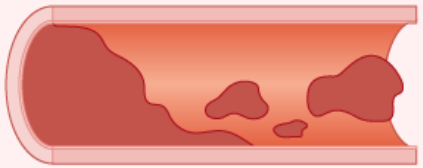




Acute cardiac injury
↑ Troponin level



Thromboembolism



clot breaks off & obstructs another blood vessel

Arrhythmia

- QT prolongation
- VF or VT
- AF

abnormal rhythm

Nishiga et al., 2020; Ranard et al., 2020

ALL Cardiovascular Issues

PRE-EXISTING

cardiovascular disease

↑ susceptibility & severity of COVID-19

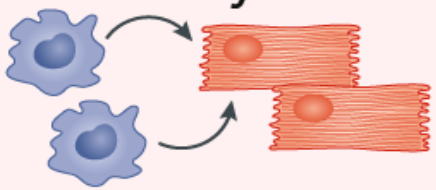
Underlying comorbidities:
- Hypertension
- Coronary heart disease
- Diabetes

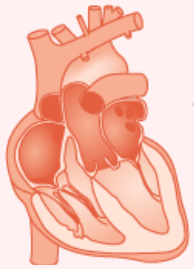
heart failure
can be pre-existing
or new complication

NEW-ONSET complications

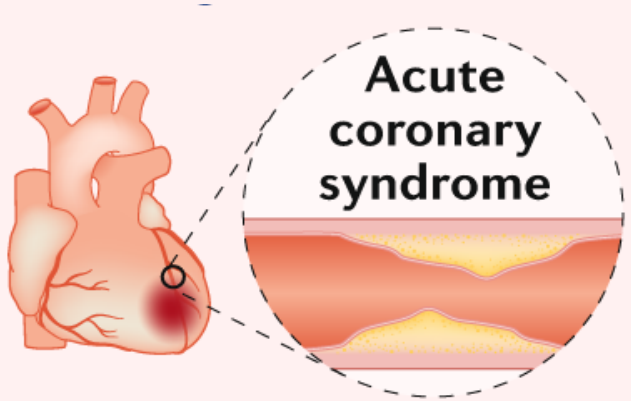
inflammation of heart muscle

Myocarditis

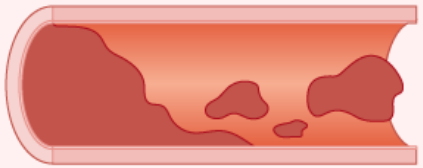




Acute cardiac injury
↑ Troponin level



Thromboembolism



clot breaks off & obstructs another blood vessel

Arrhythmia

- QT prolongation
- VF or VT
- AF

abnormal rhythm

Nishiga et al., 2020

Definitions:

HEART FAILURE: heart unable to pump sufficient blood to meet body's oxygen needs

- *23% w/COVID developed new-onset HF in Wuhan*

CARDIOMYOPATHY: abnormal remodeling of heart muscle to be enlarged, thicker, or more rigid

- *caused by conditions that overwork/stress heart*

ACUTE CORONARY SYNDROME *(angina or MI):* **cause sudden reduced flow blood flow to heart**

- *MI can cause acute cardiac injury*

How much damage…?

Small randomized study of 100 adults w/ COVID-19:

(2/3 were mild; 1/3 were severe)

- **78% had cardiac involvement**
  abnormal MRI *(remodeling heart muscle)*
- **60% had ongoing myocardial inflammation**
  troponin *(enzyme released by damaged cardiac cells)*

Puntmann et al., 2020; Ranard et al., 2020; Harding et al., 2020

Cardiovascular complications

primarily caused by

SYSTEMIC
(body-wide)
inflammation

Clarification: "systemic" is
not* LOCALIZED (one part of body)
such as broken ankle, infected wound, UTI

***new-onset* heart failure**

Acute cardiac injury
↑ Troponin level

Myocarditis

Acute coronary syndrome

Arrhythmia
- QT prolongation
- VF or VT
- AF

Thromboembolism

OTHER CAUSES may also include:

virus directly infecting cardiac cells *(?)*

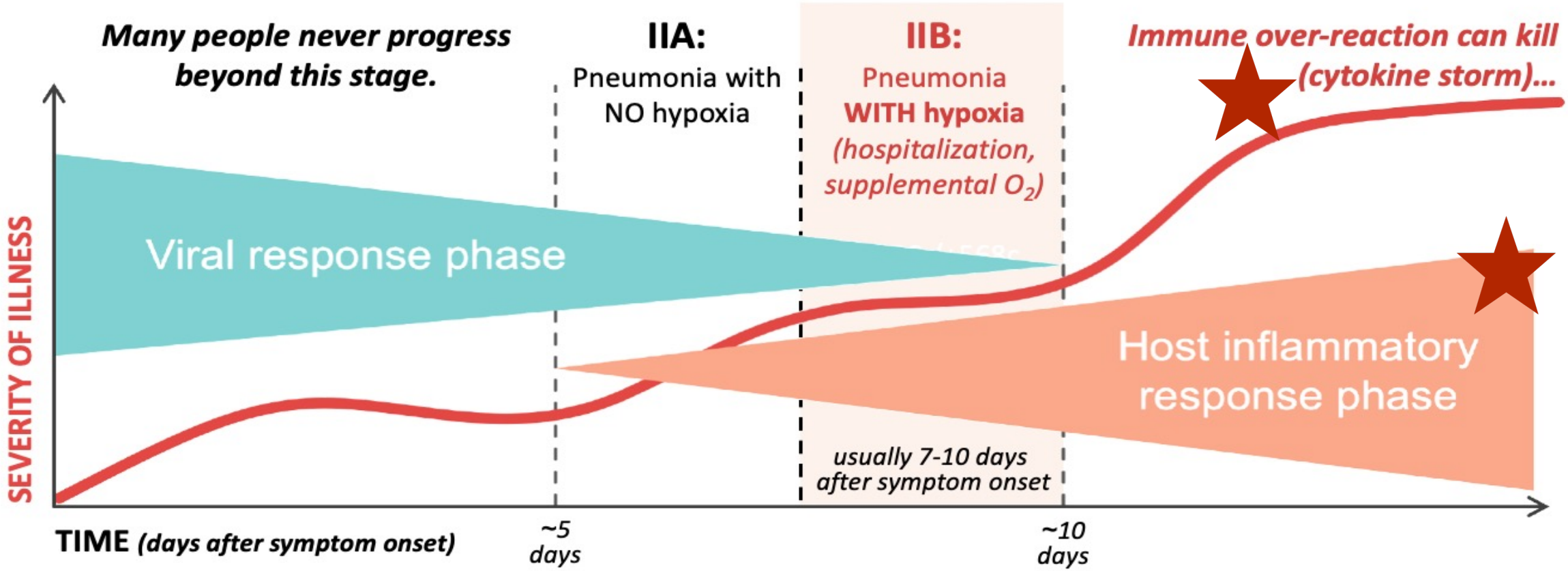
adverse side effects of some meds

Nishiga et al., 2020

STAGES OF COVID-19

REVIEW

	Stage I (Early infection)	Stage II (Pulmonary phase)	Stage III (Hyperinflammation)
symptoms:	*mild: fever, fatigue, cough*	*pneumonia*	*ARDS, shock, cardiac injury*
test results:	*low WBC in Stage I = poorer outcome*	*abnormal chest imaging*	*↑ inflam. & cardiac biomarkers*



RNnext

Siddiq & Mehra, 2020; Akhmerov & Marbán, 2020; Wiesbauer, 2020

Immunological Effects

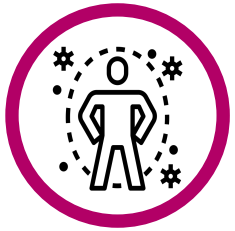
Exaggerated Immune Response: "Cytokine storm"

Stage III Hyperinflammation

- Massive release of inflammatory mediator proteins *(cytokines & chemokines)*
- **Immune system attacks own body cells, resulting in cell death**

In Stage III, **dexamethasone *(steroid)*** can suppress immune ***over-***response.
(Do not give in earlier stages or will suppress healthy immune response.)

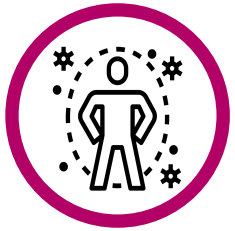
Anesi, 2020; Goodman, 2020; Sinha et al, 2020; Ye et al., 2020; *image*



Early Warning: Risk of ARDS & Mortality

Blood Test / Biomarker	*If abnormally high, this indicates:*	*FYI*
1. CRP (C-reactive protein)	↑ **acute or chronic inflammation**	**Direct measure of inflammation** *(does not reveal exact cause or location)*
2. Ferritin	↑ **severe inflammation, cytokine storm**	**Pro-inflammatory cytokines ↑ ferritin release into bloodstream** *(to keep iron from being used by pathogens)*
3. PCT (procalcitonin)	↑ **bacterial infection, sepsis**	**Rises in response to bacterial** *(rather than viral or non-infectious)* **inflammation.**
4. D-Dimer	↑ **MI, PE, DVT, or diffuse (body-wide) hypercoagulation**	**Indicates blood clots**

Huang et al., 2020; Gulhar et al., 2020; Cron & Behrens, 2019



FYI: More Details on Lab Tests

#1-3 are **Acute Phase Reactants** *(proteins that indicate acute inflammation)*

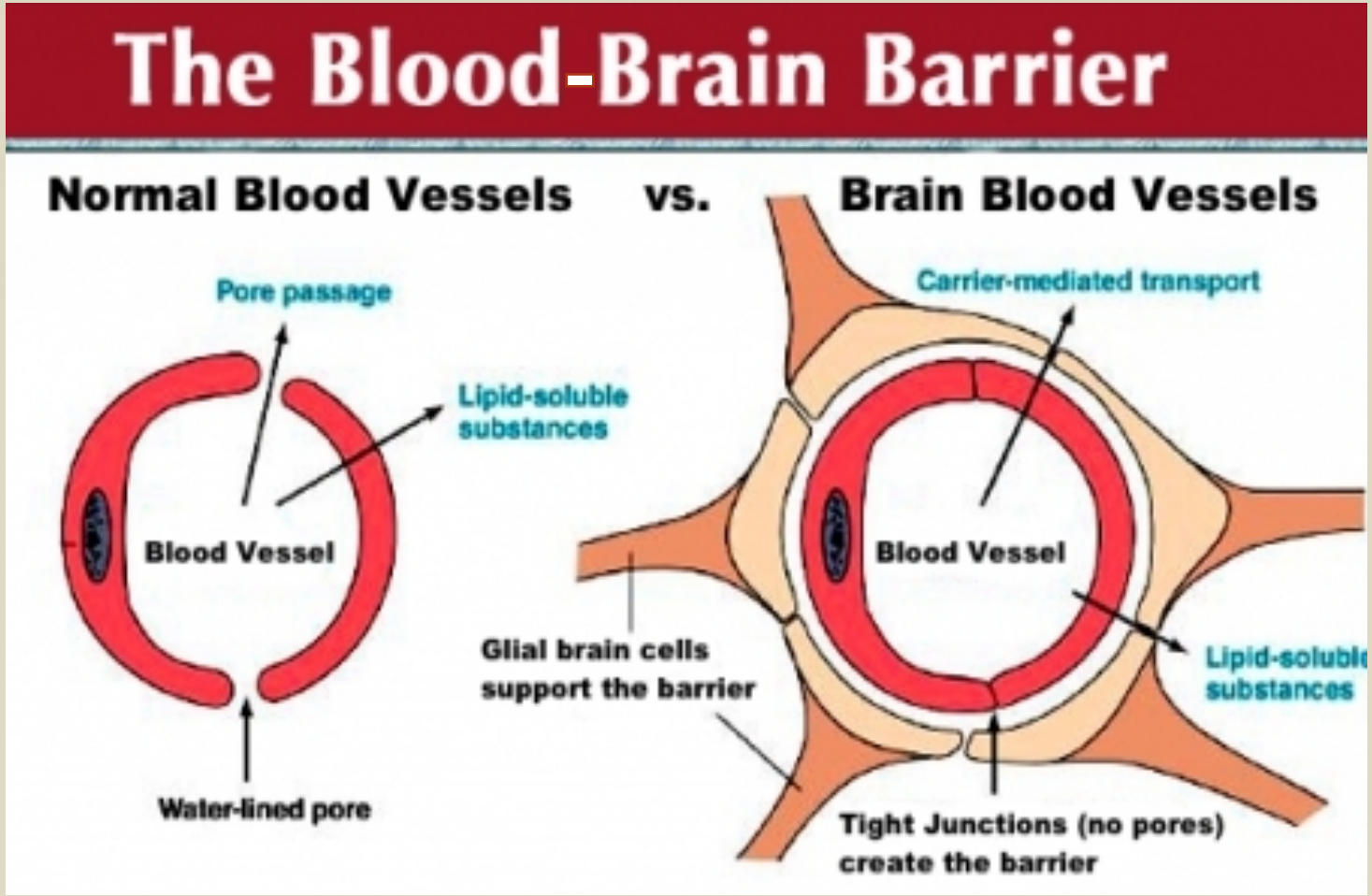
1. CRP (C-reactive protein)	Protein produced by liver in response to inflammation.
2. Ferritin	Protein that stores iron for future use. Also monitored in anemia (low). In inflammation: WBCs called macrophages cause its release, which keeps iron from being scavenged by pathogens.
3. PCT (procalcitonin)	Precursor (pro-protein) of calcitonin, hormone that balances body's calcium and phosphorus levels. Normally produced only by thyroid. Bacterial inflammation causes multiple organs to produce PCT and release directly into bloodstream.
4. D-Dimer	Protein fragment created when body dissolves a clot.

Huang et al., 2020; Gulhar et al., 2020; Cron & Behrens, 2019

Cytokine storm damages Blood-Brain Barrier *(BBB)* causing cerebral edema

Current thinking:

*<u>Severe</u> CNS symptoms are from **brain swelling** rather than virus directly acting on brain cells.*



Capillaries in cross-section

Fotuhi et al., 2020; *image: Maddox, 2016*

Neurologic symptoms *(severe)*

Central nervous system (CNS):

- **Encephalopathy** *(general term for brain dysfunction)*
  - *can manifest as* **confusion, delirium, seizures** *or* **coma**
- **Ischemic stroke**
- **Anoxic brain injury** *(lack of O_2 to brain)*

Peripheral nervous system (PNS):

- **Guillain-Barré syndrome** *(temporary paralysis)*

Elkind et al., 2020; Toscana et al., 2020; *image*

Pregnancy & Pediatrics

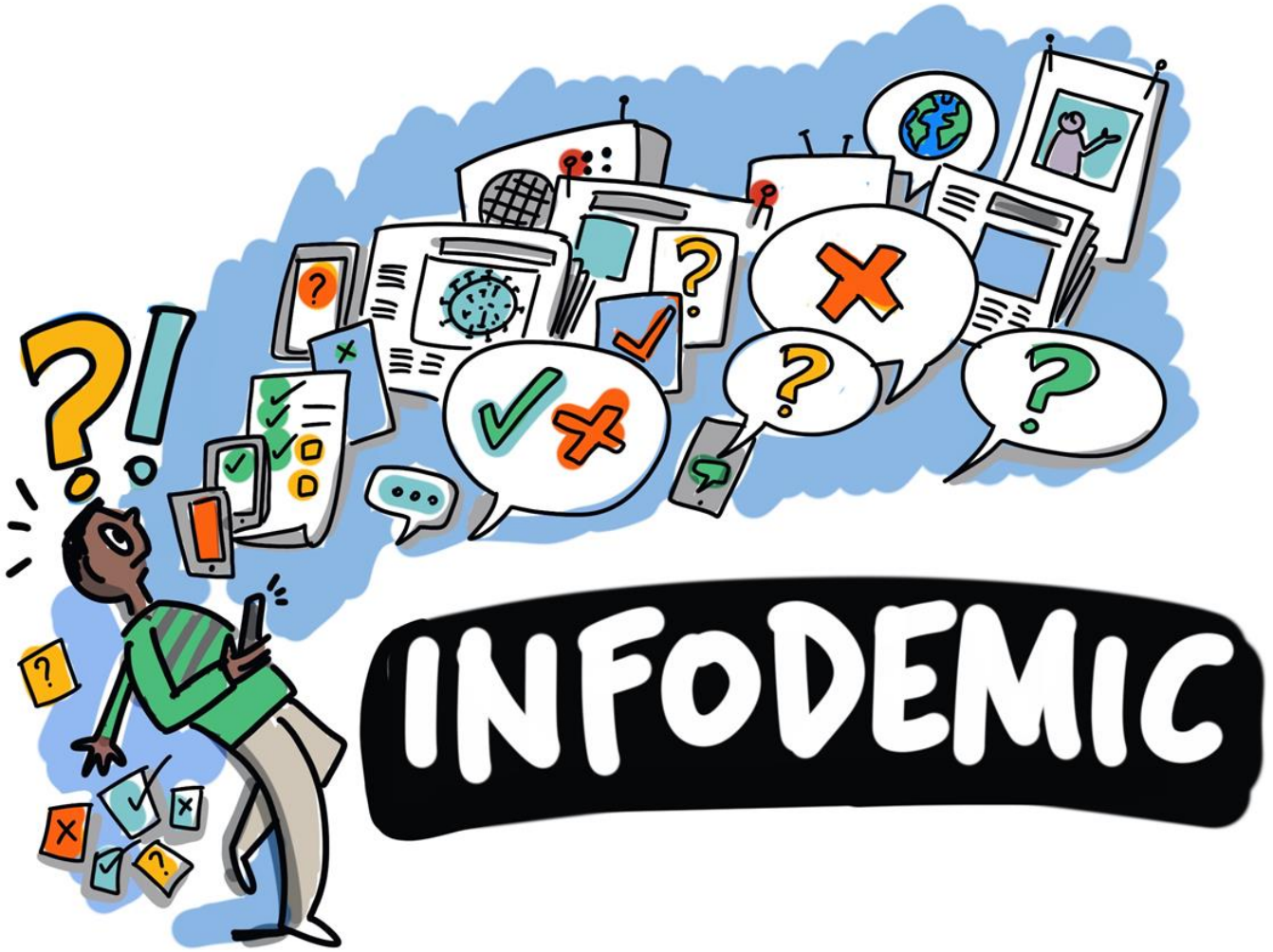
- **Risks for pregnant women and infants** *(JAMA Pediatrics):*
Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China

- **New complications in children** *(Minnesota Department of Health):*
Multisystem Inflammatory Syndrome In Children (MIS-C)

Please use your knowledge:

Help manage the "*infodemic*"

Overabundance of information – some accurate and some not – occurring during a pandemic, which can undermine public safety.

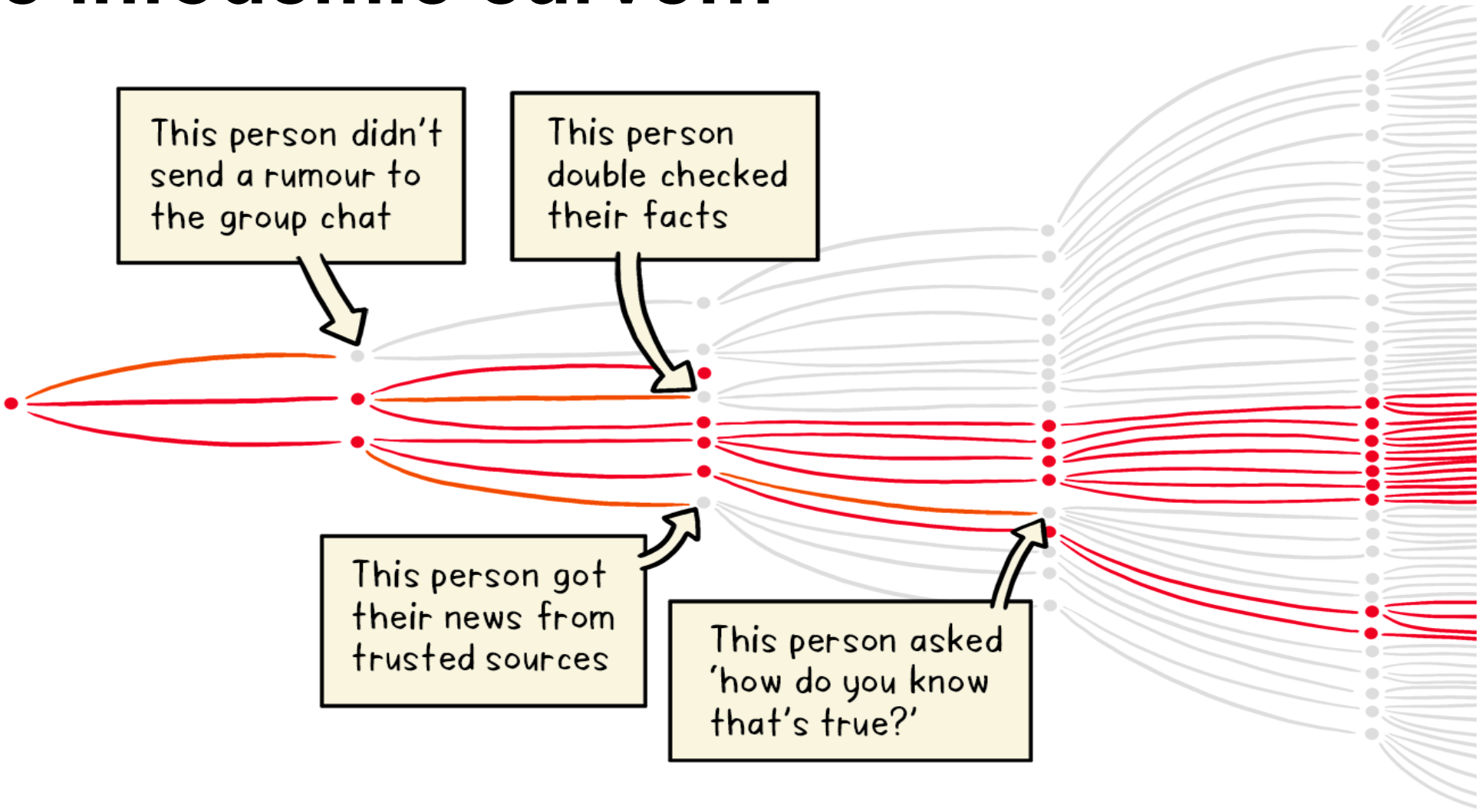


WHO's virtual global conference on Infodemic Management:
https://www.who.int/teams/risk-communication/infodemic-management/3rd-virtual-global-who-infodemic-management-conference

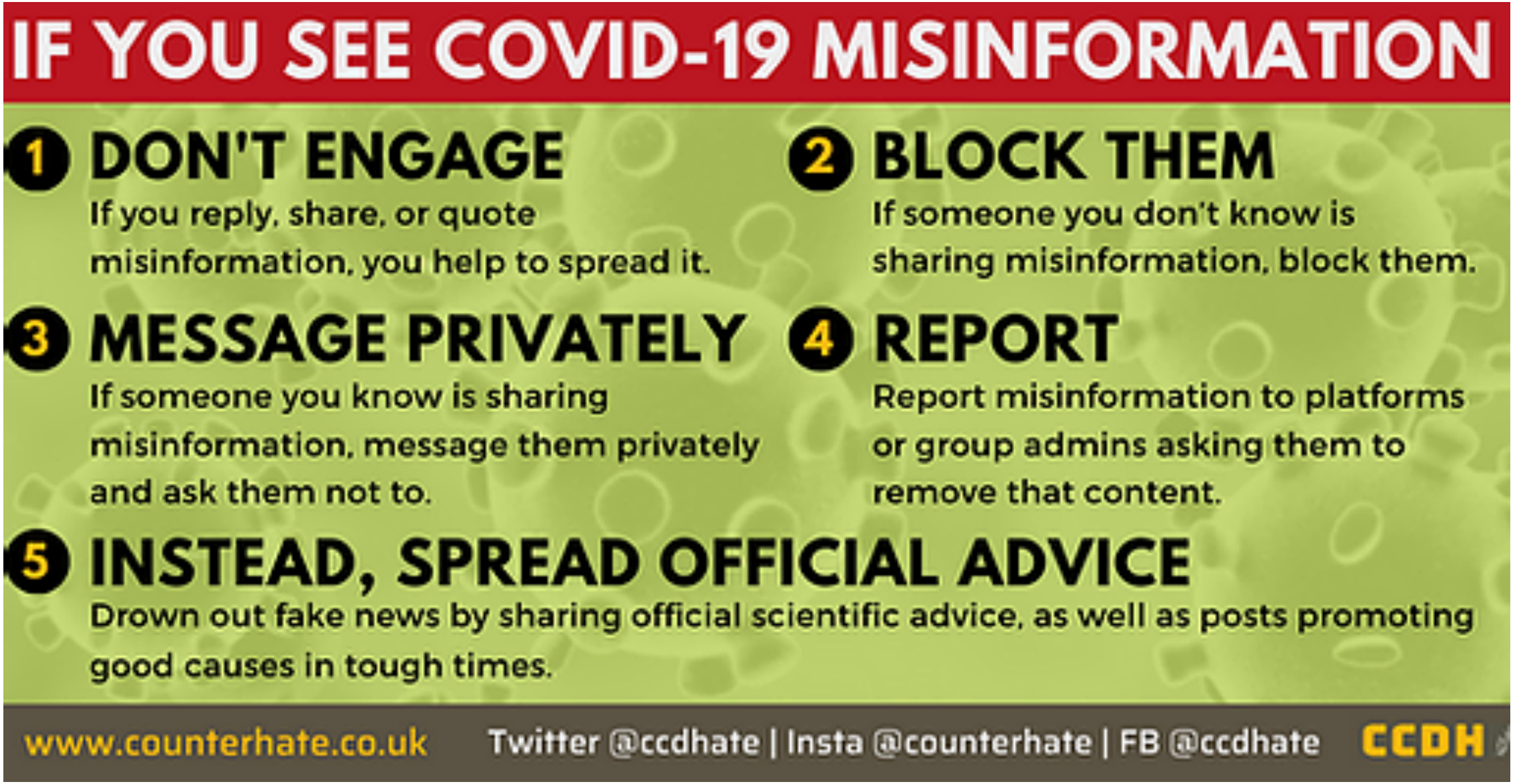
WHO, 2020a; *image*

Misinformation is like a virus: do your part to

Flatten the infodemic curve…

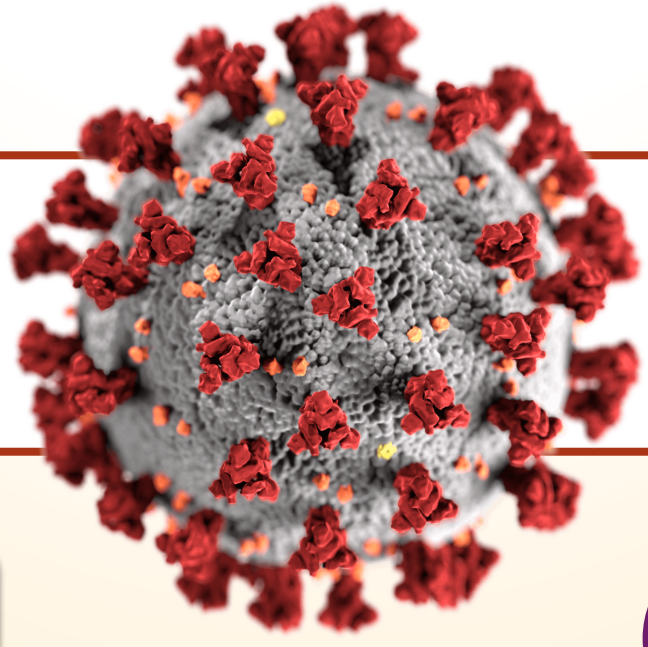


WHO, 2021


IF YOU SEE COVID-19 MISINFORMATION
1 DON'T ENGAGE
If you reply, share, or quote misinformation, you help to spread it.
2 BLOCK THEM
If someone you don't know is sharing misinformation, block them.
3 MESSAGE PRIVATELY
If someone you know is sharing misinformation, message them privately and ask them not to.
4 REPORT
Report misinformation to platforms or group admins asking them to remove that content.
5 INSTEAD, SPREAD OFFICIAL ADVICE
Drown out fake news by sharing official scientific advice, as well as posts promoting good causes in tough times.
www.counterhate.co.uk
Twitter @ccdhate | Insta @counterhate | FB @ccdhate
CCDH

CCDH, 2020

COVID-19



Raney Linck DNP, RN
RNnext

1. COVID-19 Overview
2. Patho-physiology
3. Transmission & Precautions
4. Virus Testing & Vaccines
5. Epidemiology & Tracing

+ Ethics, Peds/OB Mental Health

2. Pathophysiology of Symptoms: References

Ackermann et al. (2020, July 9). Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *New England Journal of Medicine, 383*(2), 120-128. https://doi.org/10.1056/NEJMoa2015432

Anesi, G. L. (2020, July 15). Coronavirus disease 2019 (covid-19): Critical care and airway management issues. *UpToDate.* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-critical-care-and-airway-management-issues

Begley, S. (2020, June 26). Watch: It's not just the lungs: The Covid-19 virus attacks like no other 'respiratory' infection. *STAT.* https://www.statnews.com/2020/06/26/from-nose-to-toe-covid19-virus-attacks-like-no-other-respiratory-infection/

Brann et al. (2020, July 28). Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Science Advances, eabc5801.* https://doi.org/10.1126/sciadv.abc5801

Cleveland Clinic. (2020b, March 20). Here's the damage coronavirus (COVID-19) can do to your lungs. https://health.clevelandclinic.org/heres-the-damage-coronavirus-covid-19-can-do-to-your-lungs/

Cron, R. Q., & Behrens, E. M. (Eds.). (2019). *Cytokine storm syndrome.* Springer. https://doi.org/10.1007/978-3-030-22094-5

Cuker, A., & Peyvandi, F. (2020, July 23). Coronavirus disease 2019 (COVID-19): Hypercoagulability. *UpToDate.* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-hypercoagulability

Elkind et al. (2020, July 21). Coronavirus disease 2019 (COVID-19): Neurologic complications and management of neurologic conditions. *UpToDate.* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-neurologic-complications-and-management-of-neurologic-conditions

Feldman et al. (2020, July 14). Coronavirus disease 2019: Cutaneous manifestations and issues related to dermatologic care. *UpToDate.* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-cutaneous-manifestations-and-issues-related-to-dermatologic-care

Fotuhi et al. (2020). Neurobiology of COVID-19. *Journal of Alzheimer's Disease, 76*(1), 3–19. https://doi.org/10.3233/jad-200581

Gulhar et al. (2020, May). Physiology, acute phase reactants. *StatPearls.* https://www.ncbi.nlm.nih.gov/books/NBK519570/

Harding et al. (2020). *Lewis's medical-surgical nursing (11th ed.).* Elsevier.

Huang et al. (2020). C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. *Therapeutic advances in respiratory disease*, *14*, 1753466620937175. https://doi.org/10.1177/1753466620937175

Jiang, K. (2020, July 24). How covid-19 causes loss of smell. *Harvard Medical School News and Research.* https://hms.harvard.edu/news/how-covid-19-causes-loss-smell

Luo et al. (2020). Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). *Clinical Gastroenterology and Hepatology*, *18*(7), 1636-1637. https://doi.org/10.1016/j.cgh.2020.03.043

Maddox, S. (2017, March 18). Blood-brain barrier and the spinal cord. *Christopher and Dana Reeve Foundation.* https://www.christopherreeve.org/blog/research-news/blood-brain-barrier-the-spinal-cord

Matheson, N. J., & Lehner, P. J. (2020). How does SARS-CoV-2 cause COVID-19? *Science, 369*(6503), 510–511. https://doi.org/10.1126/science.abc6156

McIntosh, K. (2020a, April 4). Coronavirus disease (COVID-19). *UpToDate.* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19

Nishiga et al. (2020). COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. *Nature Reviews Cardiology, 17*(9), 543–558. https://doi.org/10.1038/s41569-020-0413-9

Noun Project. (2020). *Icons for everything.* https://thenounproject.com

Pinto, D. S. (2020, June 5). Coronavirus disease 2019: Myocardial infarction and other coronary artery disease issues. *UpToDate.* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-myocardial-infarction-and-other-coronary-artery-disease-issues

Pons et al. (2020). The vascular endothelium: The cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Critical Care, 24*(1). https://doi.org/10.1186/s13054-020-03062-7

Rabin, R. C. (2020, May 5). What is 'covid toe'? Maybe a strange sign of coronavirus infection. *New York Times.* https://www.nytimes.com/2020/05/01/health/coronavirus-covid-toe.html

Ranard et al. (2020, June 5). Approach to acute cardiovascular complications in Covid-19 infection. *Circulation: Heart Failure, 13*(7). https://dx.doi.org/10.1161/circheartfailure.120.007220

Shi et al. (2020). Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: A descriptive study. *The Lancet Infectious Diseases, 20*(4), 425–434. https://doi.org/10.1016/s1473-3099(20)30086-4

Siriam et al. (2020, May 14). What is the ACE2 receptor, how is it connected to coronavirus and why might it be key to treating COVID-19? The experts explain. *The Conversation.* https://theconversation.com/what-is-the-ace2-receptor-how-is-it-connected-to-coronavirus-and-why-might-it-be-key-to-treating-covid-19-the-experts-explain-136928

Smith, D. G. (2020, May 29). Coronavirus may be a blood vessel disease, which explains everything. *Medium.* https://elemental.medium.com/coronavirus-may-be-a-blood-vessel-disease-which-explains-everything-2c4032481ab2

Toscano et al. (2020). Guillain–Barré Syndrome associated with SARS-CoV-2. *New England Journal of Medicine, 382*(26), 2574–2576. https://doi.org/10.1056/nejmc2009191

Tran, J. (2020, July 23). Can hydroxychloroquine and chloroquine be used to treat coronavirus (COVID-19)? *GoodRx.* https://www.goodrx.com/blog/coronavirus-medicine-chloroquine-hydroxychloroquine-as-covid19-treatment/

Vane, S. V. (2020, July 13). Coronavirus disease 2019: Issues related to gastrointestinal disease in adults. *UpToDate.* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-issues-related-to-gastrointestinal-disease-in-adults

Weill Cornell Medicine. (2020, July 2). *What is known about Covid-19 and abnormal blood clotting.* https://news.weill.cornell.edu/news/2020/07/what-is-known-about-covid-19-and-abnormal-blood-clotting

Ye et al. (2020). The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *The Journal of Infection*, *80*(6), 607–613. https://doi.org/10.1016/j.jinf.2020.03.037

Zimmer, K. (2020a, July 17). Could covid-19 trigger chronic disease in some people? *The Scientist.* https://www.the-scientist.com/news-opinion/could-covid-19-trigger-chronic-disease-in-some-people-67749