Current Understanding of the Pathophysiology of COVID-19 in the Lung

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No disclosures.

Objectives

- The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2)
- Viral Entry
- Host Defense
- Pathophysiology
- Clinical Correlates
- Autopsy Findings

REVIEW

PHYSIOLOGY 35: 288–301, 2020.

Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression

Mary Kathryn Bohn,[1,2] Alexandra Hall,[1] Lusia Sepiashvili,[1,2] Benjamin Jung,[1,2] Shannon Steele,[1] and Khosrow Adeli[1,2,3]

Published August 12, 2020

JAMA | Review

Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19)

A Review

W. Joost Wiersinga, MD, PhD; Andrew Rhodes, MD, PhD; Allen C. Cheng, MD, PhD; Sharon J. Peacock, PhD; Hallie C. Prescott, MD, MSc

Published July 10, 2020

Case

Mr. Z is a 62 year-old man who recently went to an indoor party to celebrate his grandson’s birthday. A total of 35 people attended.

Objectives

- **The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2)**
- Viral Entry
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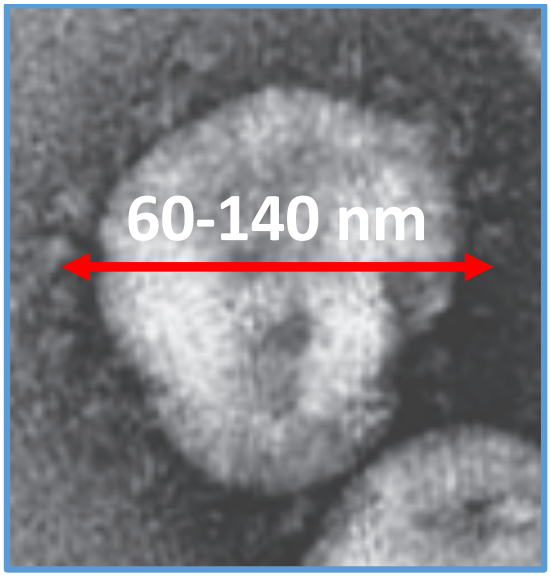
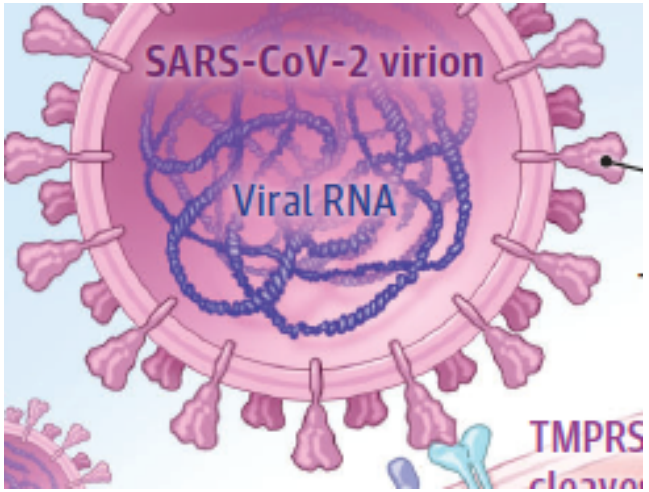
Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) **BASICS**

- Causative agent of coronavirus disease 2019 (COVID-19)
- Over 35 million confirmed cases worldwide
- Range of illness severity from asymptomatic to severe disease requiring hospitalization, ICU admission (~5% of cases)
- Mortality rates range <u>widely</u> – preliminary data from UCH, approximately 20% mortality for patients admitted to the ICU



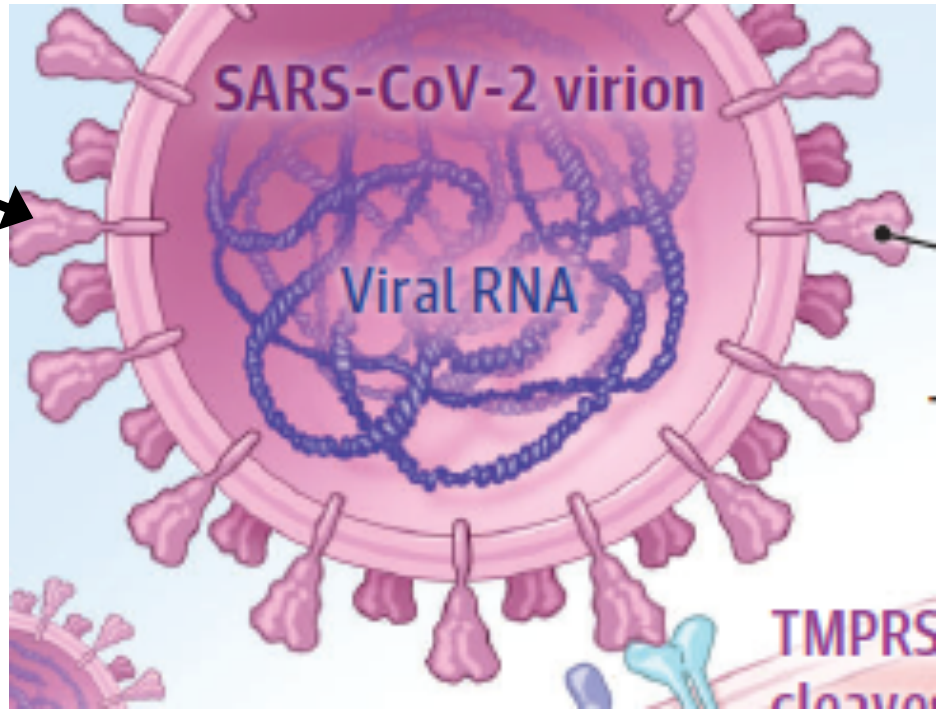
Adapted from Zhu, et al. NEJM. 2020.



Wiersinga, et al. JAMA 2020.

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) **STRUCTURE**

- **“S”**pike protein
- **Single-strand of RNA**
- **“M”**embrane protein
- **“E”**nvelop protein
- **“N”**ucleocapsis protein
- Lipid Membrane



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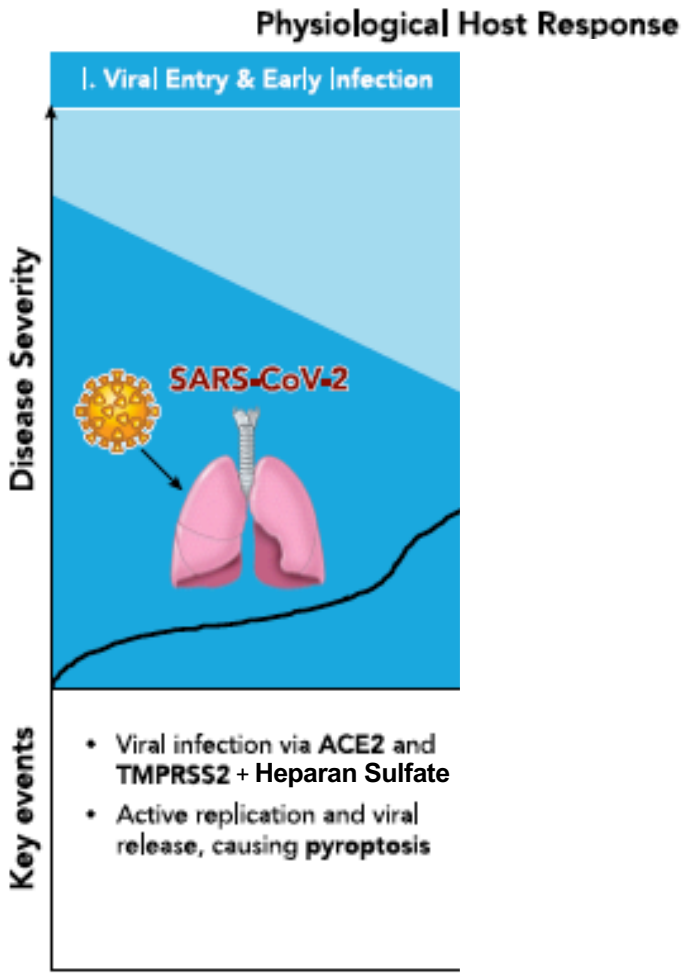
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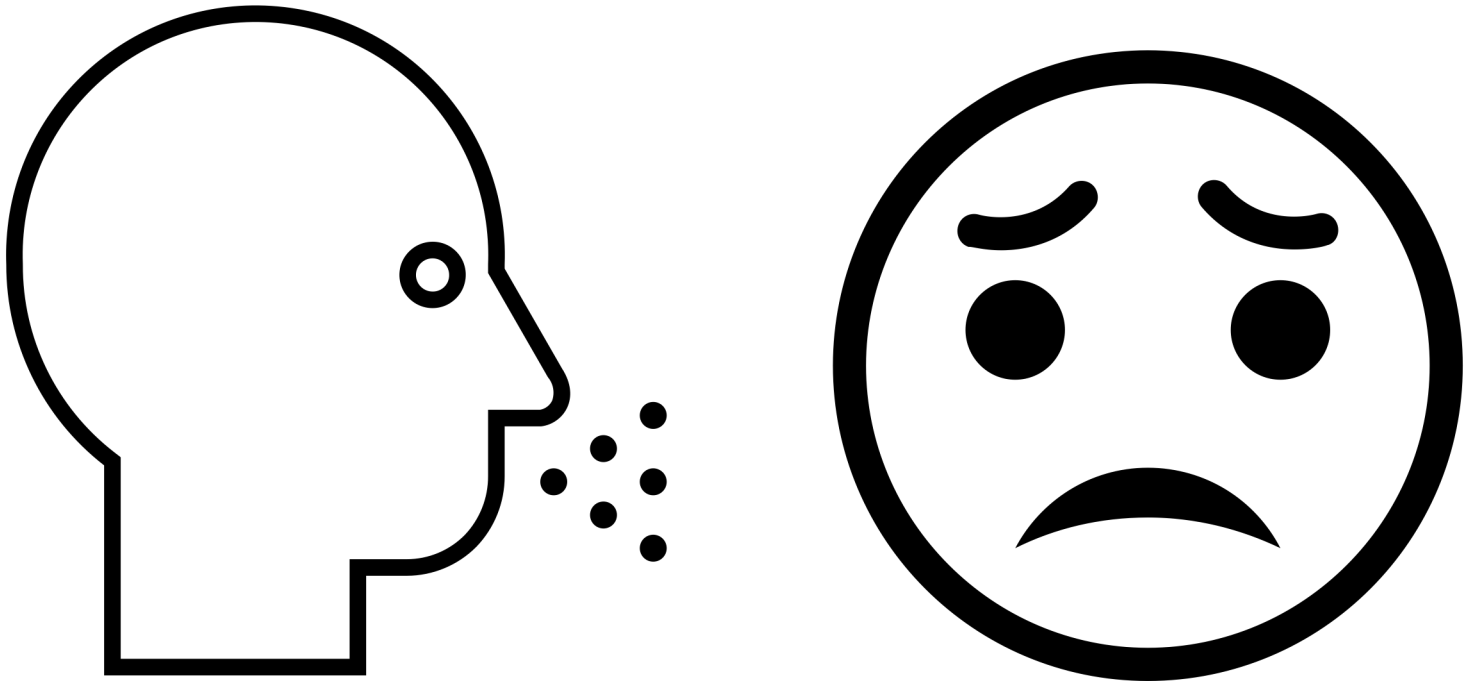
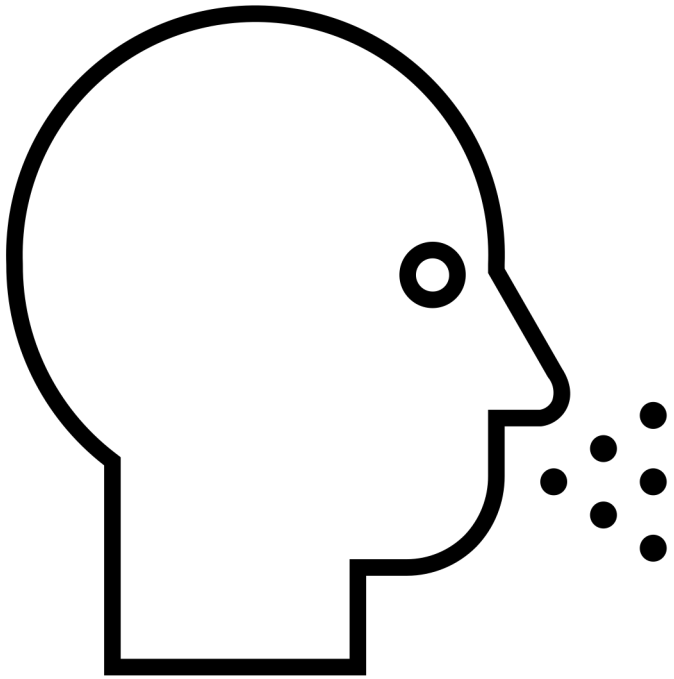
Viral Transmission

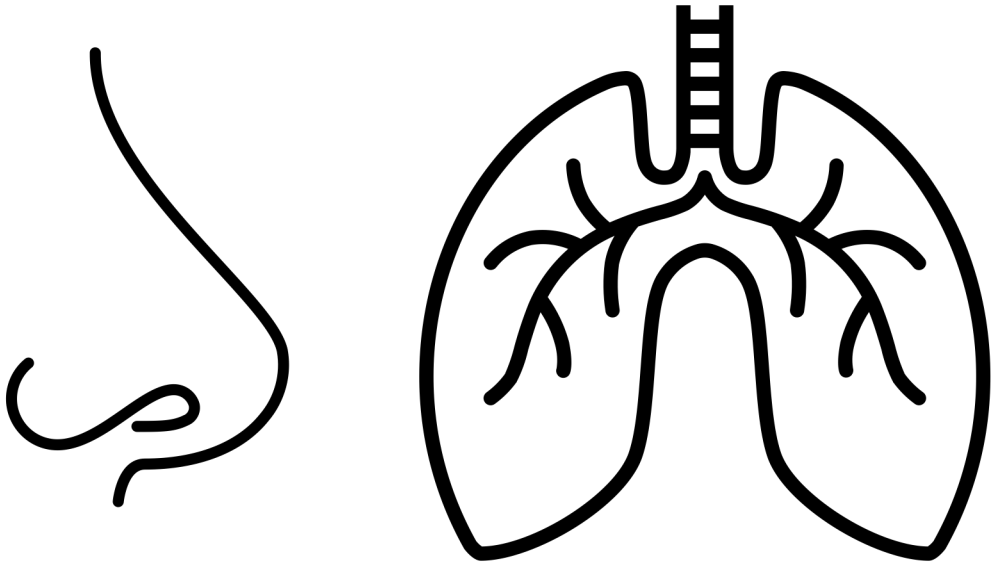


Viral Transmission



- <u>Droplets</u>
  - Talking, coughing, sneezing
  - Exposure > 15 mins within 6 feet
  - Riskiest if person is symptomatic
- *Other means:* Surfaces (48-72h?), aerosolization

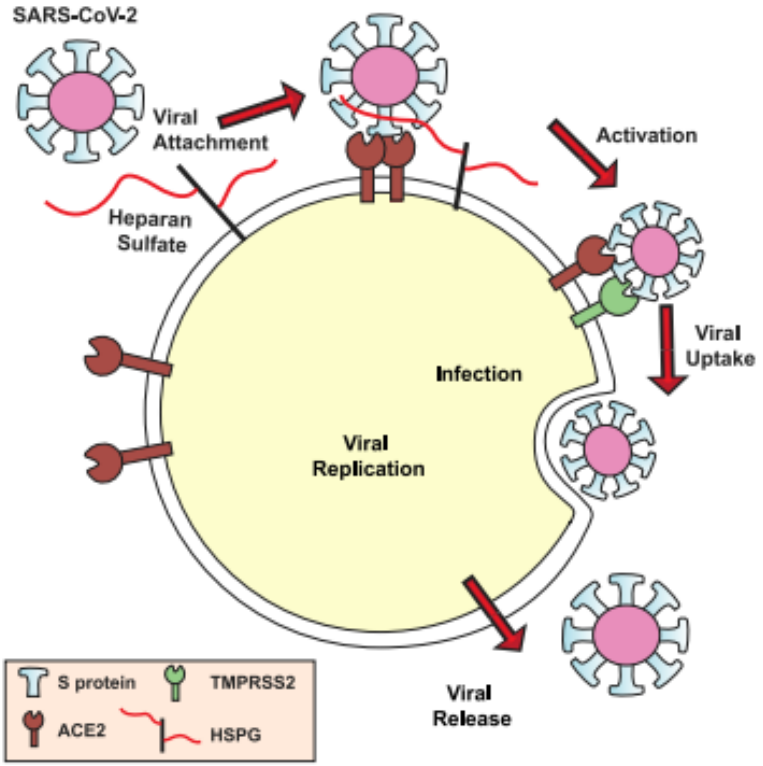
Viral Entry



- Nasal ciliated cells
- Bronchial epithelial cells
- Aleolar epithelial type II cells

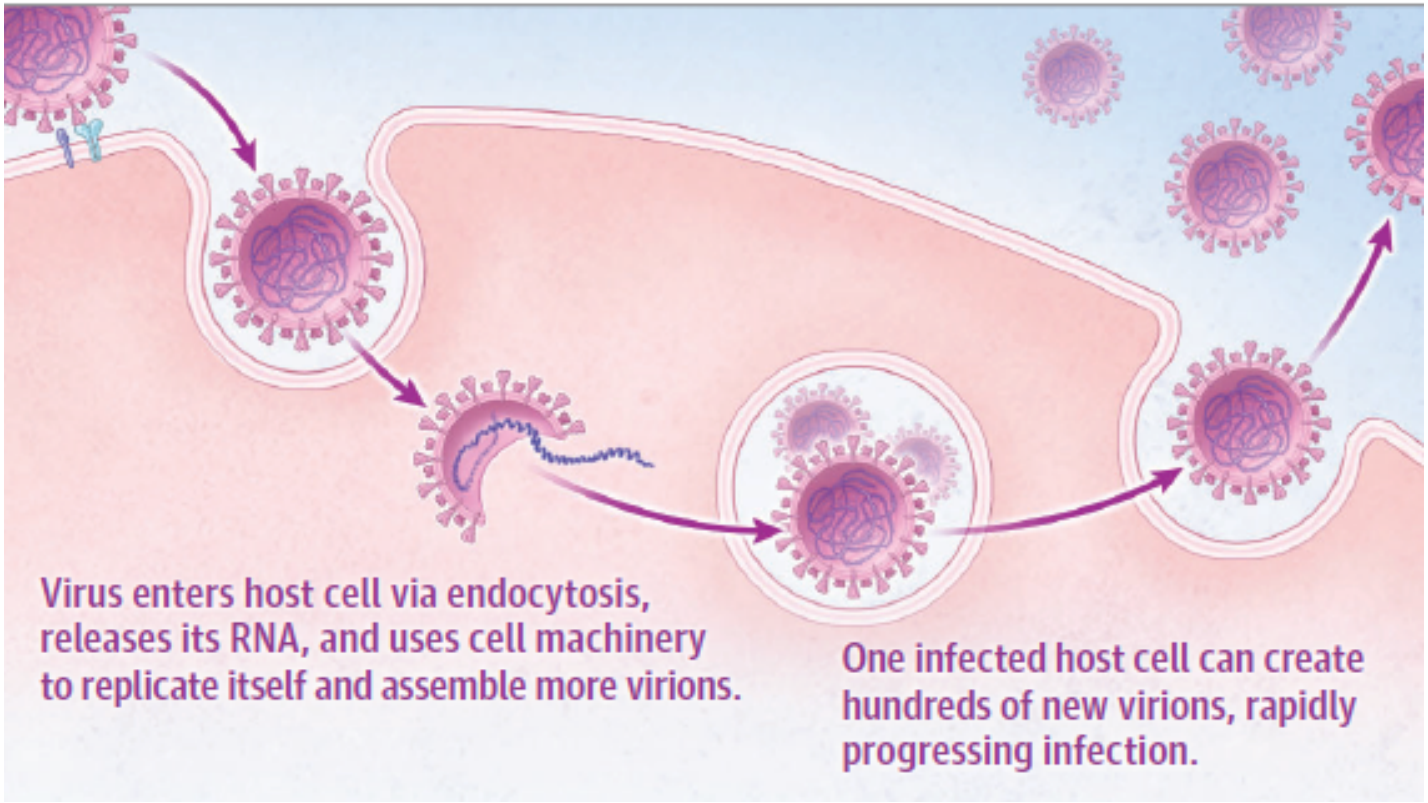
Viral Entry – *Zooming in*

- **S**pike-**protein** interacts with cell-surface heparan sulfate[1] and **ACE2**
- **TMPRSS2** (Serine-protease) cleaves/ activates S-protein
- **Virus Internalized**

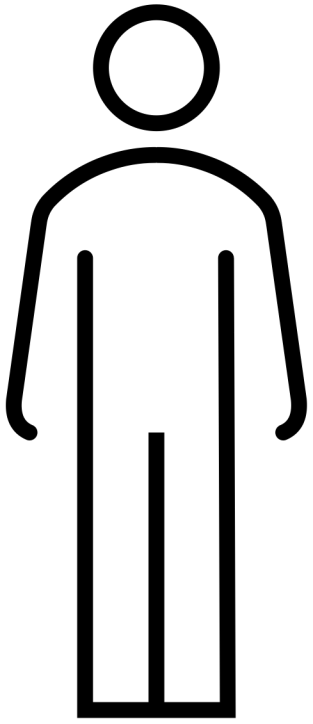


1. Clausen TM, et al. SARS-CoV-2 Infection depends on cellular Heparan Sulfate and ACE2. *Cell*. 2020.

RNA inside, virus replicates, cells die…



Viral Entry



ACE2-expressing organs

- Small Intestine
- Kidneys
- Heart
- Thyroid
- Testis
- Adipose tissue

Case

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T 38.4°C, P 82, SaO2 94%

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Objectives

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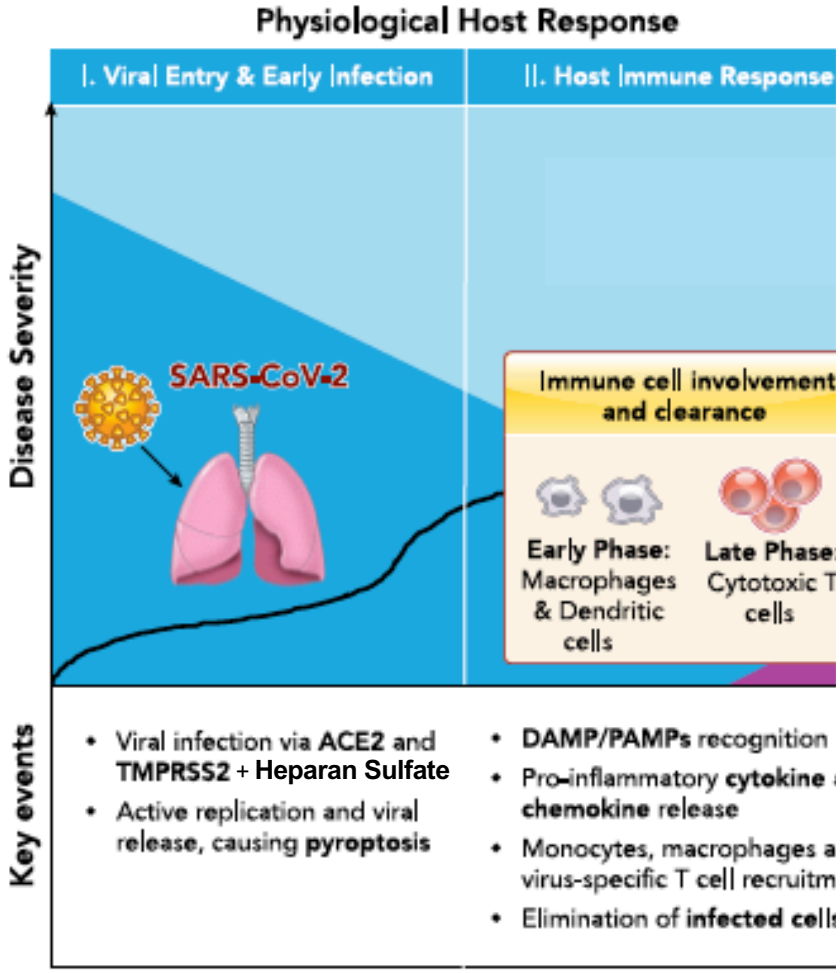
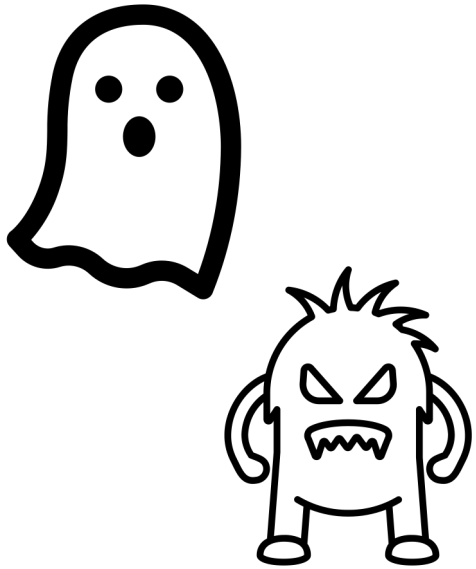
- Viral Entry
- **Host Defense**
- Pathophysiology
- Clinical Correlates
- Autopsy Findings


Physiological Host Response
I. Viral Entry & Early Infection
II. Host Immune Response
Disease Severity
SARS-CoV-2
Immune cell involvement and clearance
Early Phase: Macrophages & Dendritic cells
Late Phase: Cytotoxic T cells
Key events
• Viral infection via ACE2 and TMPRSS2 + Heparan Sulfate
• Active replication and viral release, causing pyroptosis
• DAMP/PAMPs recognition
• Pro-inflammatory cytokine
chemokine release
• Monocytes, macrophages a
virus-specific T cell recruitm
• Elimination of infected cell

Host Response: DAMPs/PAMPs

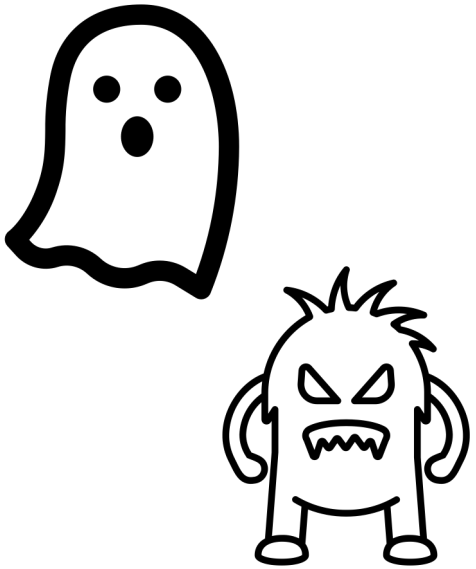
- Damage-associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs) **Released**



Host Response: Cytokines

- Damage-associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs) Released
- Inflammatory mediators released in defense
  - *Interferon*
  - *Interleukin-6*
  - *MCP-1*
  - *IP-10*
  - *Others*

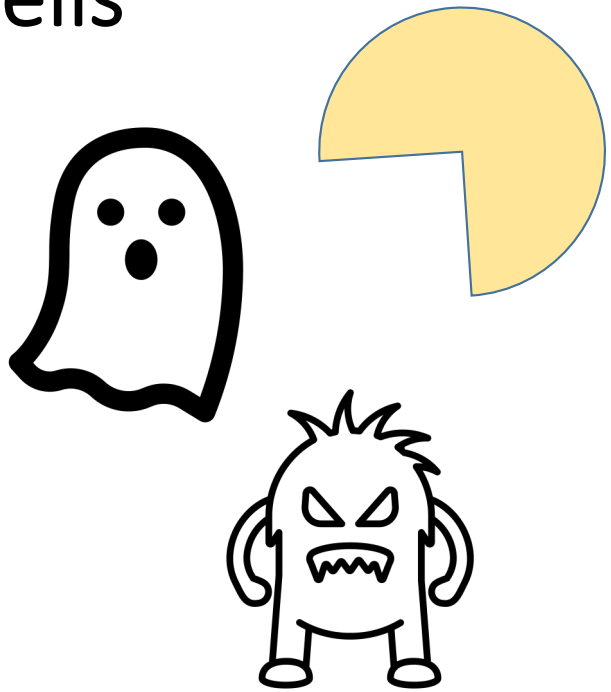
Tocilizumab



Host Response: Inflammatory Cells

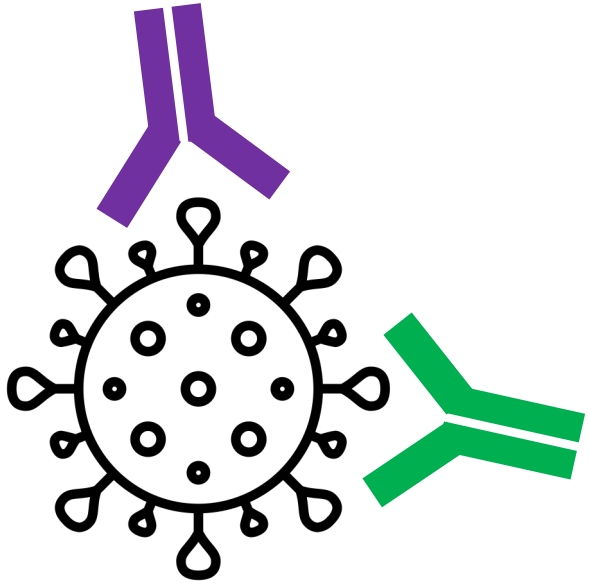
- Damage-associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs) Released
- Inflammatory mediators released in defense
- Inflammatory cells are recruited
  - T-cells
  - Macrophages
  - Dendritic Cells
  - Neutrophils

Steroids



Host Response: Antibodies

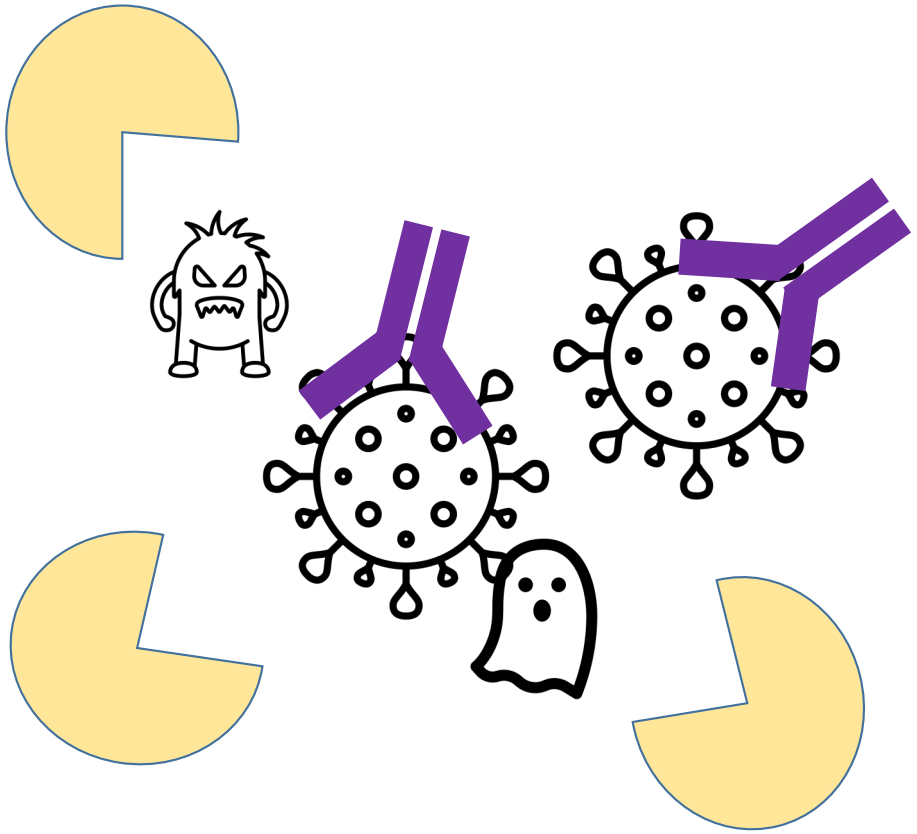
- Damage-associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs) Released
- Inflammatory mediators released in defense
- Inflammatory cells are recruited
- Antibody generation (7-14 d)



Convalescent Plasma

Other Antibody Products

Host Response: Clearance = **Recovery**



Case

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Vitals: T 38.7°C, P 104, SaO2 83%, RR 23

He is admitted to the hospital for further care and placed on 3LPM.

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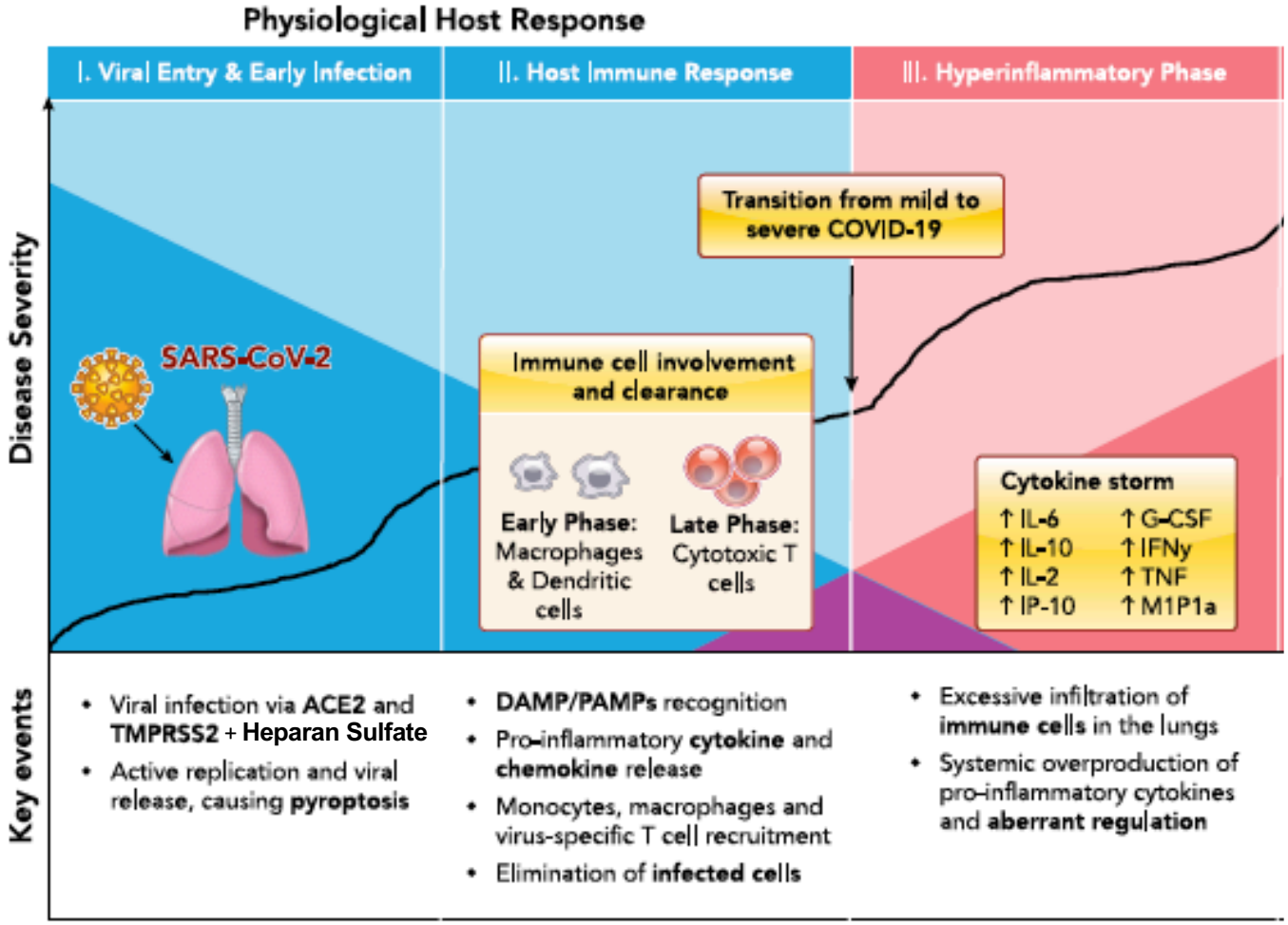
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III. Hyperinflammatory Phase
Disease Severity
SARS-CoV-2
Transition from mild to severe COVID-19
Immune cell involvement and clearance
Early Phase: Macrophages & Dendritic cells
Late Phase: Cytotoxic T cells
Cytokine storm
↑ IL-6
↑ IL-10
↑ IL-2
↑ IP-10
↑ G-CSF
↑ IFNγ
↑ TNF
↑ M1P1a
Key events
• Viral infection via ACE2 and TMPRSS2 + Heparan Sulfate
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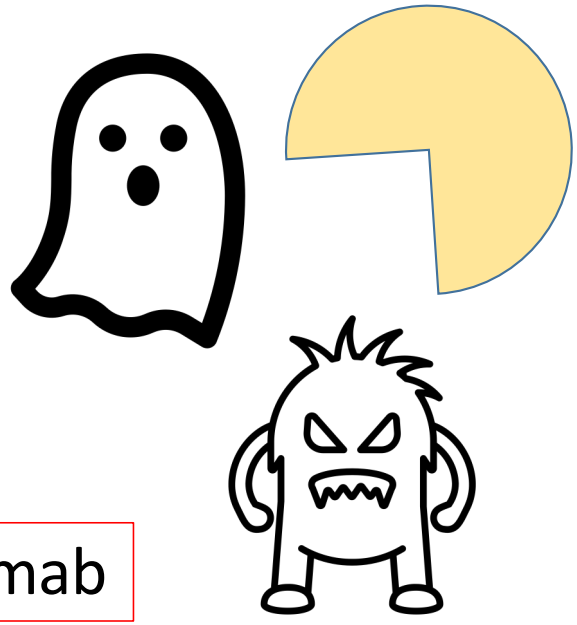
• DAMP/PAMPs recognition
• Pro-inflammatory cytokine and chemokine release
• Monocytes, macrophages and virus-specific T cell recruitment
• Elimination of infected cells
• Excessive infiltration of immune cells in the lungs
• Systemic overproduction of pro-inflammatory cytokines and aberrant regulation

1. Maladaptive Response: Cytokine Storm

- Inflammatory mediators released in defense
- Inflammatory cells recruited



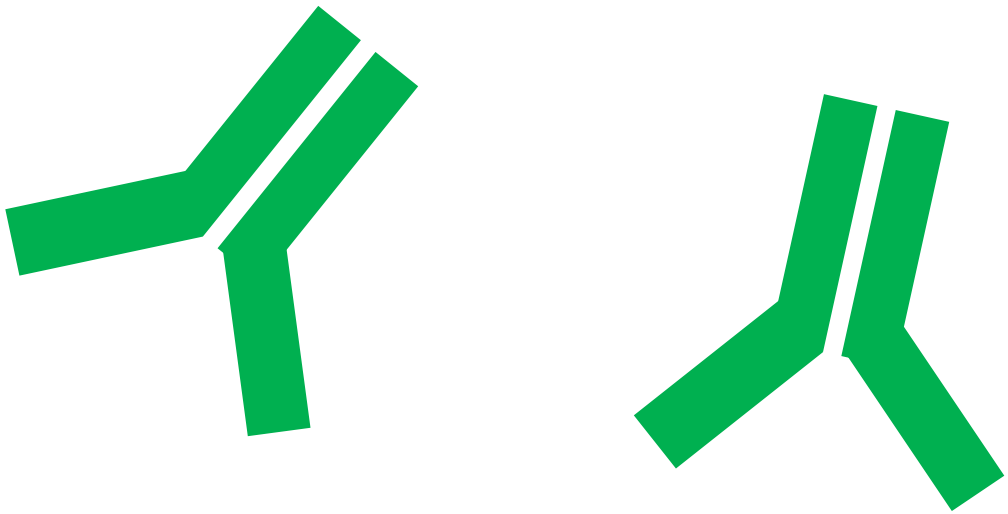
Tocilizumab

Steroids

2. Maladaptive Response: ROS + Protease Release

3. Maladaptive Response: Bad Antibodies?

- Antibody levels tend to be higher in very sick patients



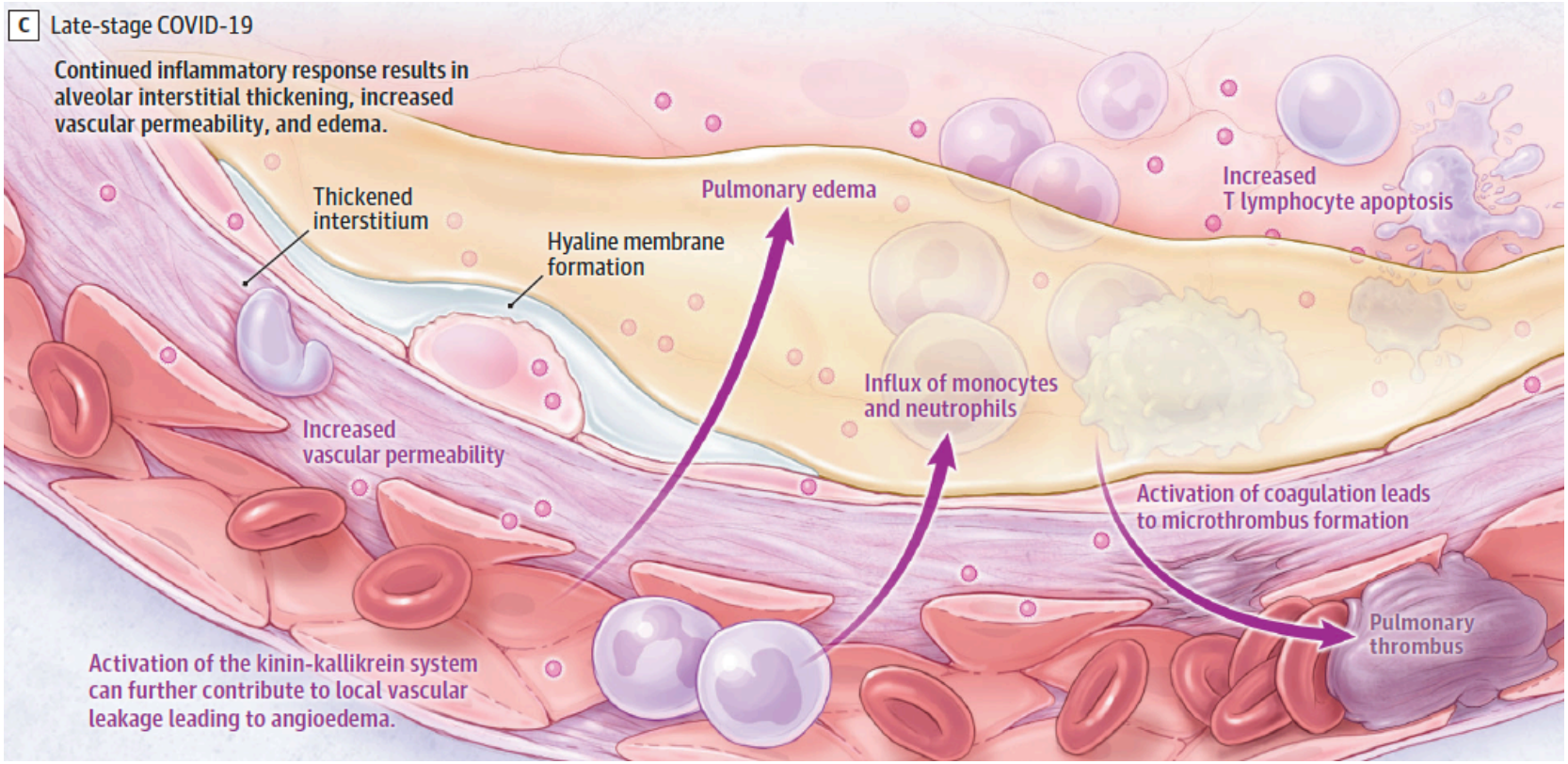
4. Coagulopathy?

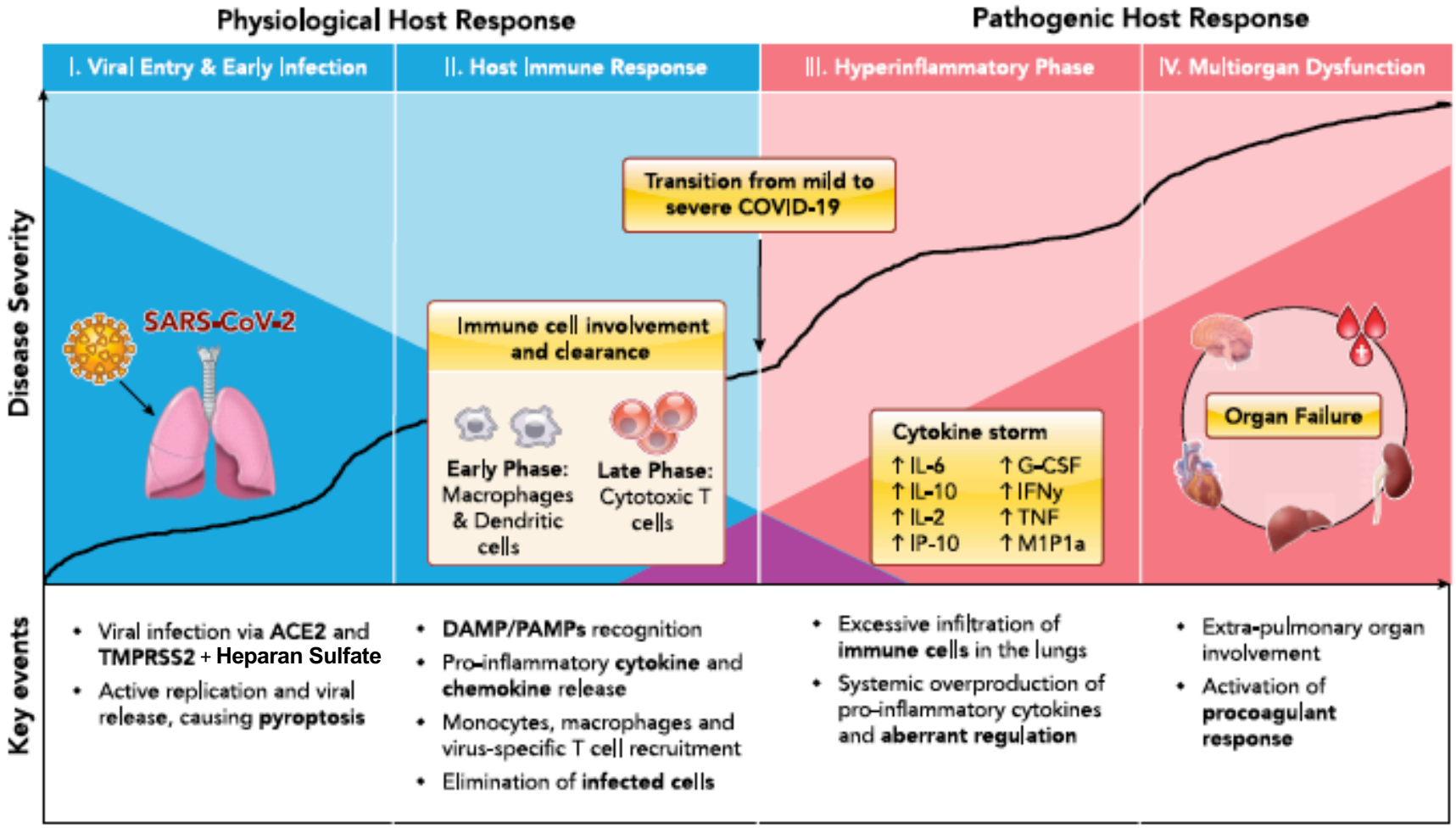
- DIC common in patients who die
- Fibrin-rich microthrombi at autopsy
- High prevalence of Venous Thromboembolism[1]
  - 8% in Non-ICU patients
  - 23% in ICU patients
- Bleeding also common

Anticoagulation

1. Nopp, et al. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. *Res Pract Thromb Haemost.* 2020.

5. ARDS


C Late-stage COVID-19
Continued inflammatory response results in alveolar interstitial thickening, increased vascular permeability, and edema.
Thickened interstitium
Hyaline membrane formation
Pulmonary edema
Increased T lymphocyte apoptosis
Influx of monocytes and neutrophils
Increased vascular permeability
Activation of coagulation leads to microthrombus formation
Pulmonary thrombus
Activation of the kinin-kallikrein system can further contribute to local vascular leakage leading to angioedema.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III. Hyperinflammatory Phase
IV. Multiorgan Dysfunction
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Cytokine storm
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Organ Failure
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• Pro-inflammatory cytokine and chemokine release
• Monocytes, macrophages and virus-specific T cell recruitment
• Elimination of infected cells
• Excessive infiltration of immune cells in the lungs
• Systemic overproduction of pro-inflammatory cytokines and aberrant regulation
• Extra-pulmonary organ involvement
• Activation of procoagulant response

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Pathologic and Clinical Correlates

- **Epithelial and endothelial damage** due to direct effects of viral replication, cell lysis and immune response
- Resultant **non-cardiogenic pulmonary edema**
  - Imaging: peripheral ground glass or alveolar filling process on CT and CXR
  - Clinical: progressive hypoxemia due to diffusion impairment, loss of alveolar-capillary membrane units
- Prolonged need for mechanical ventilation: **type II Pneumocyte predominantly affected** which is the repair cell of the lung

High Risk Groups

- **Older age, comorbidities, lower-income, minority,**

Speculation

- **Epithelial repair**: Reduced ability in elderly to repair alveolar epithelium
- **Pre-existing endothelial dysfunction**: Pre-existing in those with male sex, smoking, HTN, DM2, obesity, cardiovascular disease
- **Disparities** in housing (density?), transportation, employment, and health

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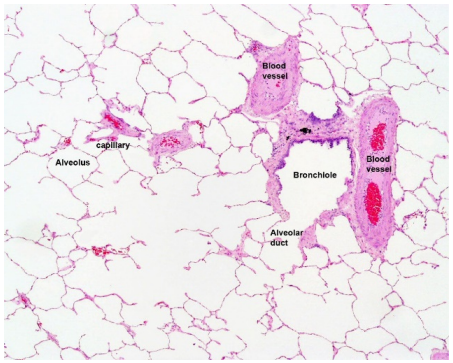
Autopsies in COVID-19

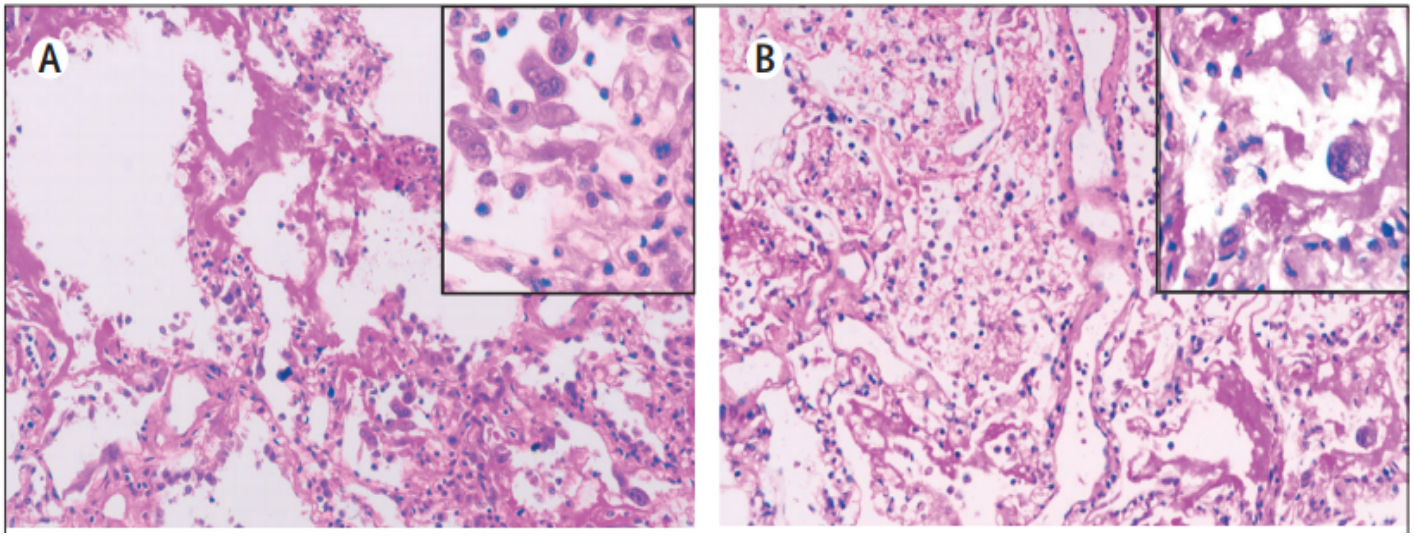
- Many with pulmonary thrombi
- **Diffuse alveolar damage** in most cases, organization found in those with a longer course
- CD8 T-cell depletion
- Acute Tubular Injury as a cause of kidney failure
- *Other odd findings*: lymphocytic myocarditis, pancreatitis, adrenal microinfarction, pericarditititis, disseminated mucormycosis, aortic dissection, marantic endocarditis.

Schaller T, et al. Postmortem examination of patients with COVID-19. *JAMA*. 2020.
Hanley B, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet.* 2020.

Pathology Specimens

- Bilateral, diffuse alveolar damage with cellular exudates
- Desquamation and hyaline membrane formation
- Interstitial inflammatory infiltrates in the alveolar septa





Lancet Resp Med 2020

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