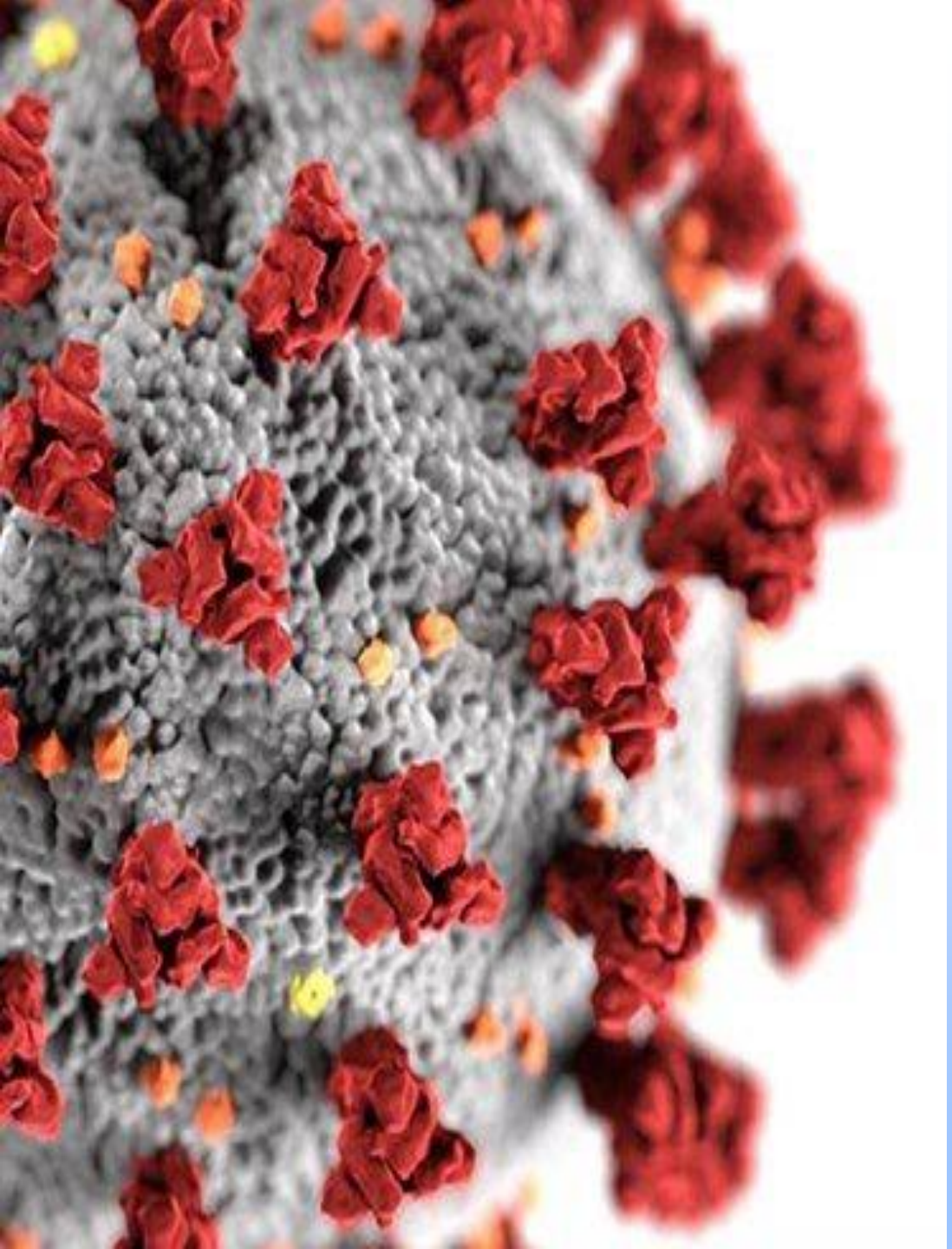

COVID-19 Pathogenesis

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Done by Raghad Salem

Objective

- Introduction
- Mode of transmission
- Clinical features
- Viral structure and cell entry
- Pathogenesis
- Gross change
- Microscopic change

Introduction

- At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, in China.
- It rapidly spread, resulting in an epidemic throughout China, with pandemic cases reported globally.

Mode of transmission

Mode of transmission

- SARS-CoV-2 is primarily spread from person to person through **respiratory droplets**, which are typically released when an infected person coughs or sneezes. Prolonged exposure to an infected person (being within 2 m for at least 15 minutes) and briefer exposures to individuals who are symptomatic (eg, coughing) are associated with higher risk for transmission.

- **Contact surface spread** (touching a surface with virus on it) is another possible mode of transmission. SARS-CoV-2 may persist on cardboard, plastic, and stainless steel for days.

Clinical features

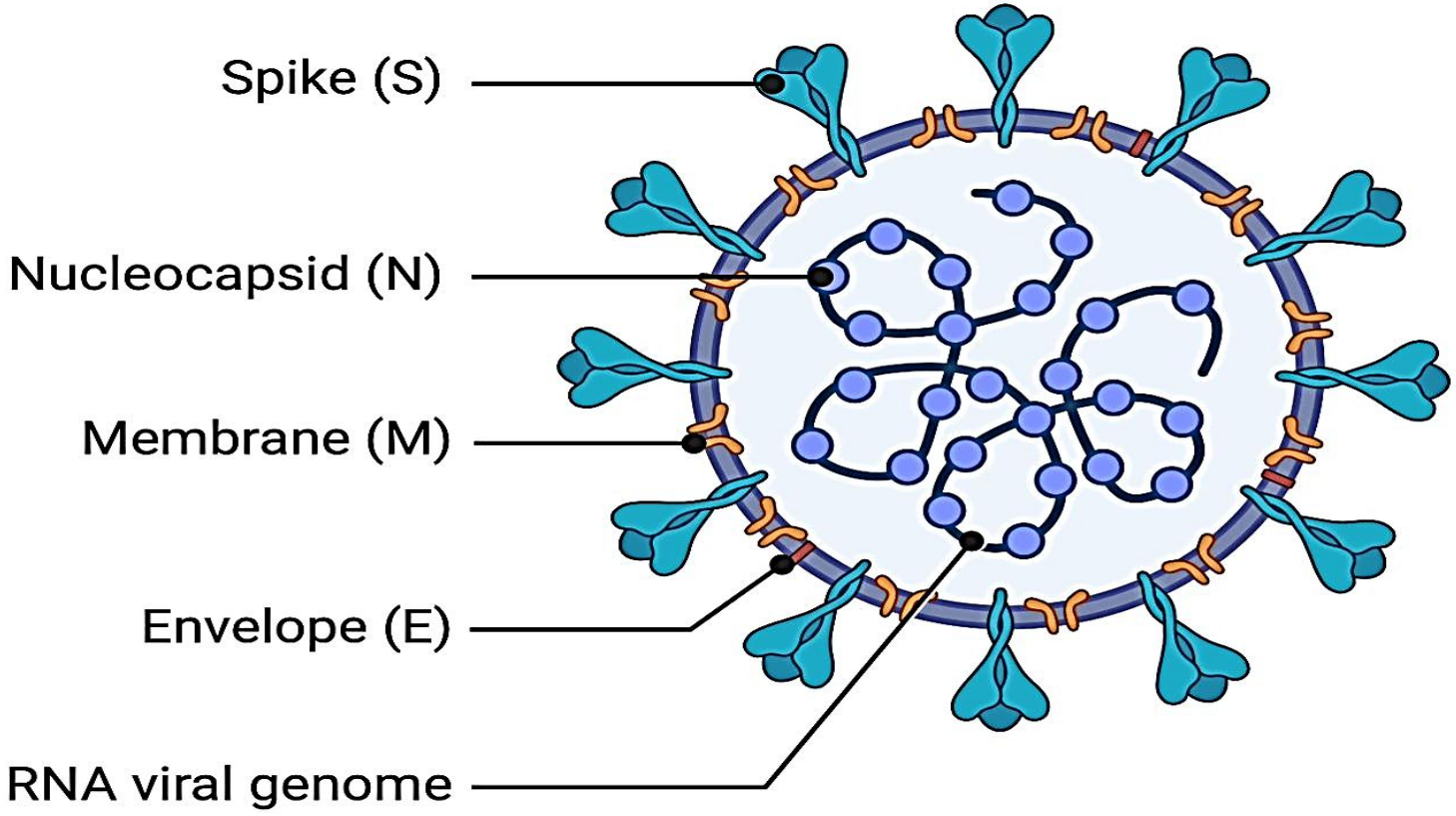
- The viral incubation period ranges from 4–14 days (median: 5).
- Many patients are asymptomatic carriers whereas others can become gravely ill.
- Symptomatic patients typically complain of cough, fever, myalgias, headache, and upper respiratory tract manifestations
- whereas approximately 10% have nausea, diarrhea, or a loss of sense of taste and/or smell.

Viral structure and cell entry

Viral structure and cell entry

- SARS-CoV-2 is a large , enveloped, single-stranded RNA virus that contains spike proteins.
- The spike protein is composed of two subunits, S1 and S2, that are required for viral entry into cells.
- **The S1** subunit binds the **angiotensin converting enzyme-2 (ACE2) receptor** (must abundant in type 2 alveolar pneumocyte)
- **Whereas S2** is cleaved by transmembrane serine protease-2 (TMPRSS2) (present in host cells), there by facilitating viral fusion with the cell membrane

Coronavirus Structure



Pathogenesis

Divided into three phases:

- Asymptomatic phase
- Invasion and infection of the upper respiratory tract
- Involvement of the lower respiratory tract and progression to acute respiratory distress syndrome (ARDS)

Asymptomatic phase

- The SARS-CoV-2 which is received via respiratory aerosols binds to the nasal epithelial cells in the upper respiratory tract.
- The main host receptor for viral entry into cells is the **ACE-2**, which is seen to be highly expressed in adult nasal epithelial cells.
- The virus undergoes local replication and propagation, along with the infection of ciliated cells in the conducting airways.

- This stage lasts a couple of days and the **immune response generated during this phase is a limited one**.
- In spite of having a low viral load at this time, the individuals are **highly infectious**, and the virus can be detected via nasal swab testing.

Invasion and infection of the upper respiratory tract

- In this stage, there is migration of the virus from the nasal epithelium to the upper respiratory tract via the conducting airways.
- Due to the involvement of the upper airways, the disease manifests with symptoms of fever, malaise and dry cough.

- There is a greater immune response during this phase involving the release of **CXCL-10** and interferons (IFN-β and IFN-λ) from the virus-infected cells.
- The majority of patients do not progress beyond this phase as the mounted immune response is sufficient to contain the spread of infection.

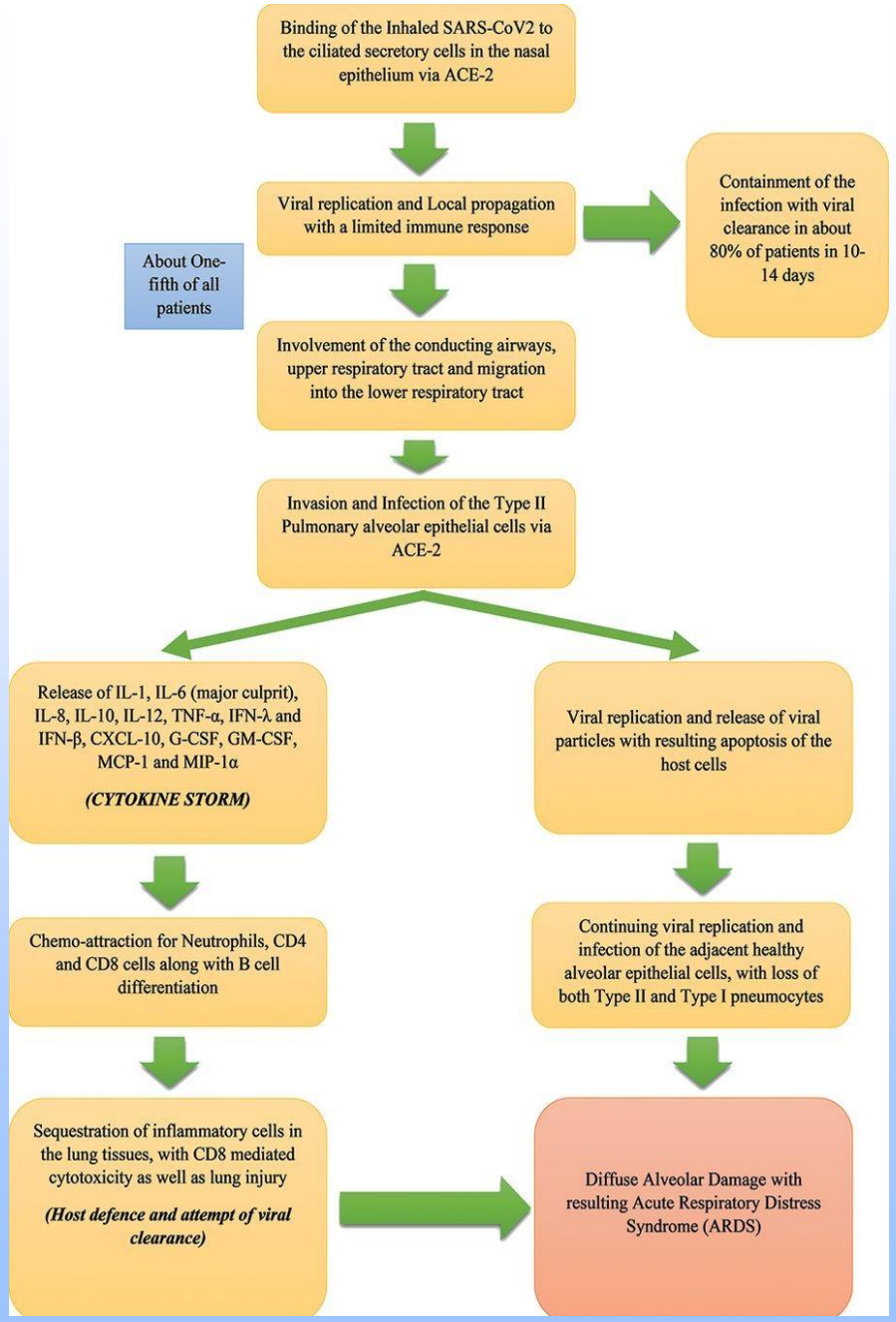
Involvement of the lower respiratory tract and progression to Acute RESPIRATORY DISTRESS SYNDROME (ARDS)

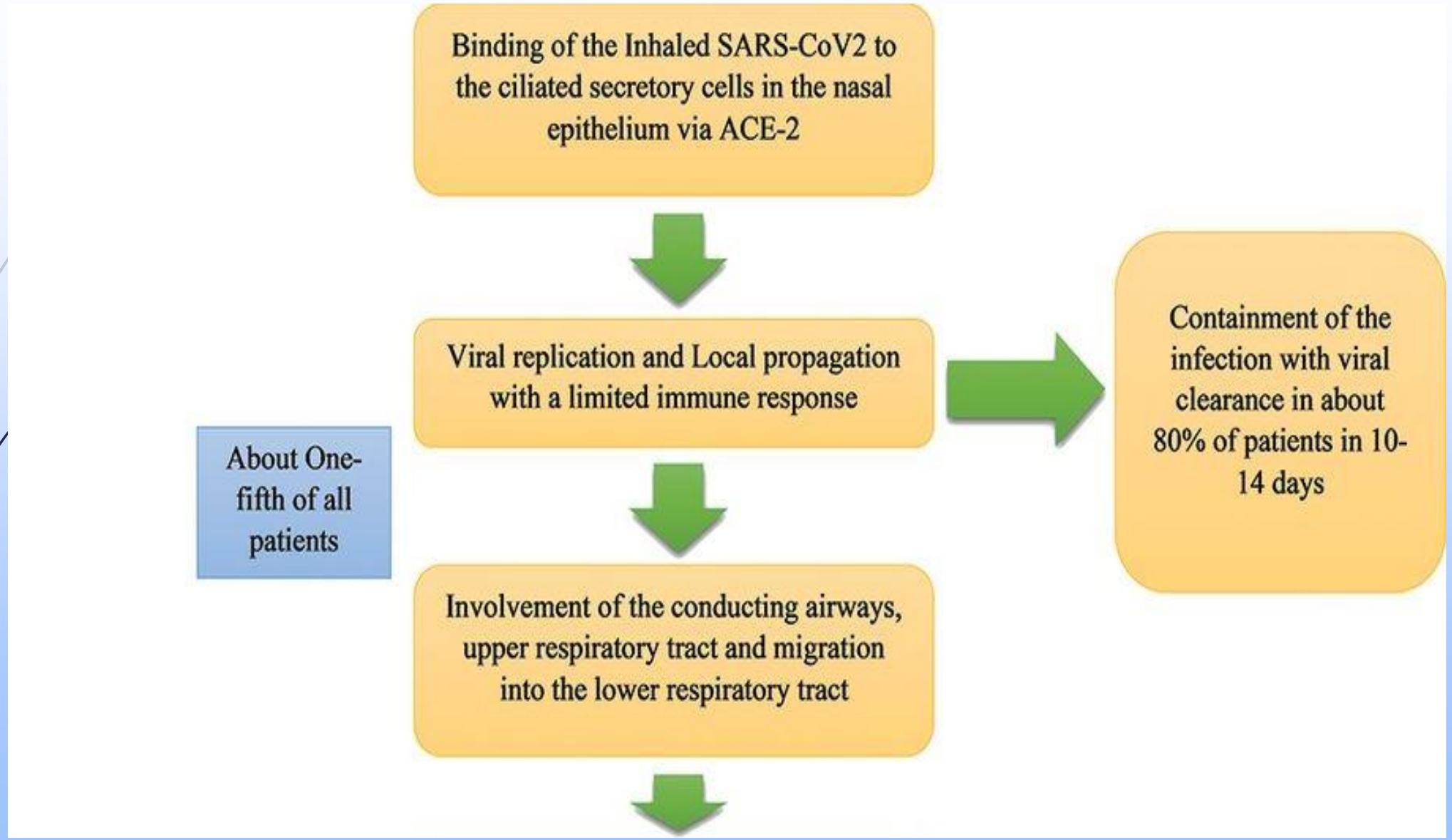
- About one-fifth of all infected patients progress to this stage of disease and develop severe symptoms.
- The virus invades and enters the type 2 alveolar epithelial cells via the host receptor ACE-2 and starts to undergo replication to produce more viral Nucleocapsids.

- The virus-laden pneumocytes now release many different cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumor necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α).

- This ‘cytokine storm’ acts as a chemoattractant for neutrophils, CD4 helper T cells and CD8 cytotoxic T cells, which then begin to get sequestered in the lung tissue.
- These cells are responsible for fighting off the virus, but in doing so are responsible for the subsequent inflammation and lung injury.

- The host cell undergoes apoptosis with the release of new viral particles, which then infect the adjacent type 2 alveolar epithelial cells in the same manner.
- Due to the persistent injury caused by the sequestered inflammatory cells and viral replication leading to loss of both type 1 and type 2 pneumocytes, there is diffuse alveolar damage eventually culminating in an acute respiratory distress syndrome.


Binding of the Inhaled SARS-CoV2 to the ciliated secretory cells in the nasal epithelium via ACE-2
Viral replication and Local propagation with a limited immune response
Containment of the infection with viral clearance in about 80% of patients in 10-14 days
About One-fifth of all patients
Involvement of the conducting airways, upper respiratory tract and migration into the lower respiratory tract
Invasion and Infection of the Type II Pulmonary alveolar epithelial cells via ACE-2
Release of IL-1, IL-6 (major culprit), IL-8, IL-10, IL-12, TNF-α, IFN-λ and IFN-β, CXCL-10, G-CSF, GM-CSF, MCP-1 and MIP-1α
(CYTOKINE STORM)
Viral replication and release of viral particles with resulting apoptosis of the host cells
Chemo-attraction for Neutrophils, CD4 and CD8 cells along with B cell differentiation
Continuing viral replication and infection of the adjacent healthy alveolar epithelial cells, with loss of both Type II and Type I pneumocytes
Sequestration of inflammatory cells in the lung tissues, with CD8 mediated cytotoxicity as well as lung injury
(Host defence and attempt of viral clearance)
Diffuse Alveolar Damage with resulting Acute Respiratory Distress Syndrome (ARDS)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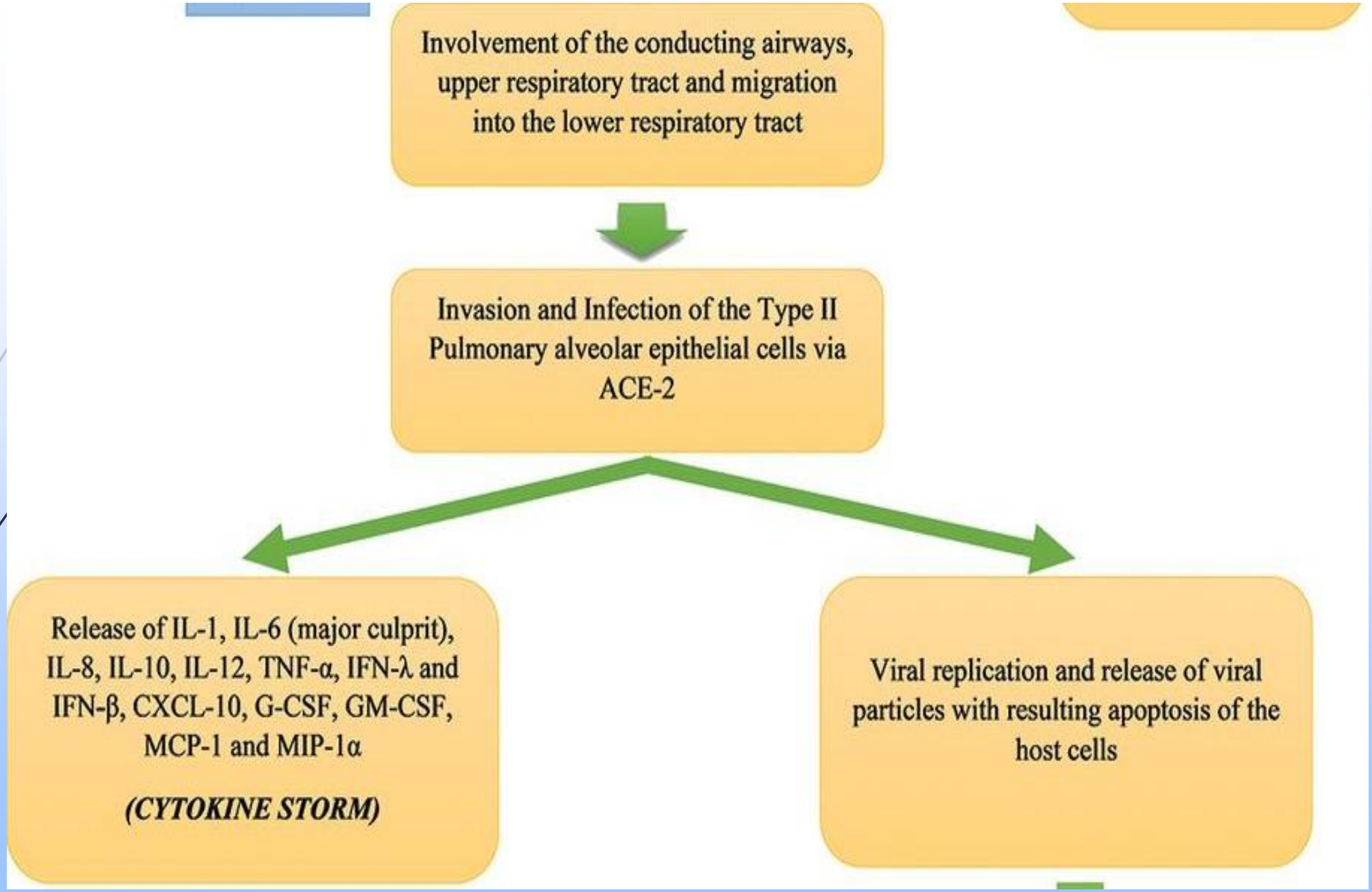
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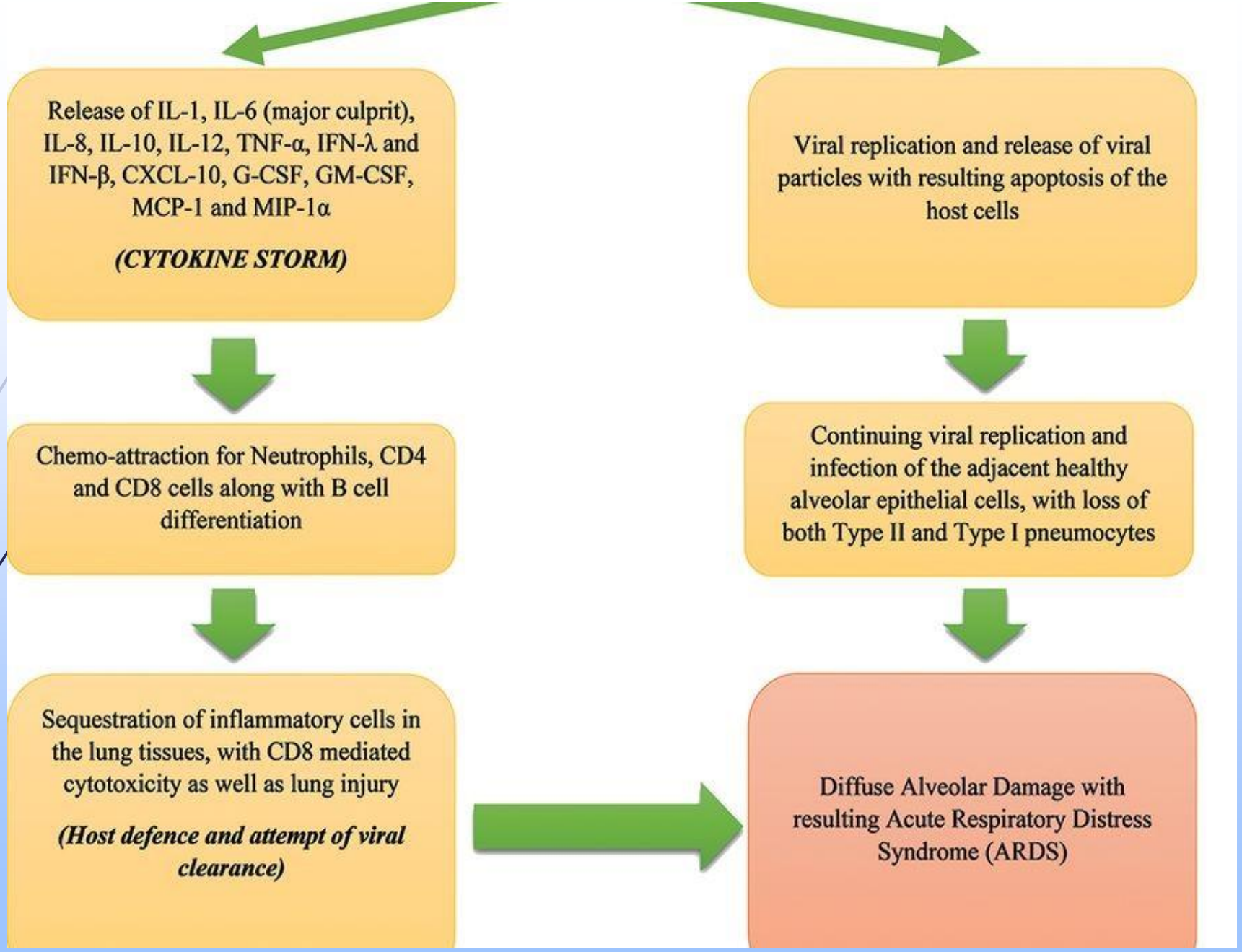
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Diffuse Alveolar Damage with resulting Acute Respiratory Distress Syndrome (ARDS)

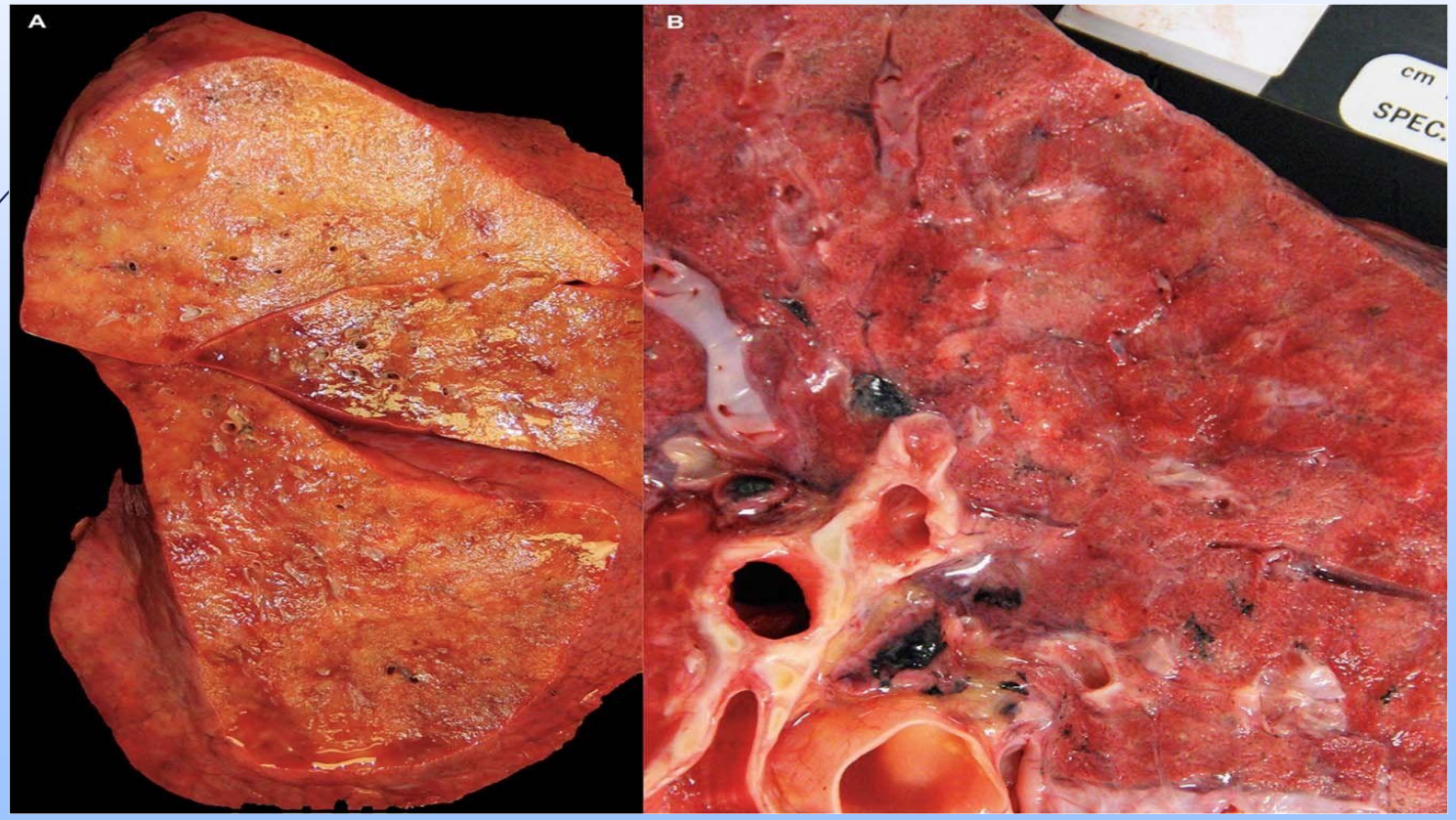
Pathological features

Diffuse alveolar damage include 3 phases:

- Exudative phase: hyaline membrane formation, desquamation of pneumocytes, proteineous exudate, alveolar hemorrhage, fibrinoid necrosis of small blood vessels.
- Organizing phase: interstitial & intra-alveolar proliferation of fibroblasts, lymphocytic infiltrate, pneumocyte II hyperplasia& fibrin deposition.
- Fibrotic phase: dense collagenous fibrosis & architectural remodeling.

Gross change

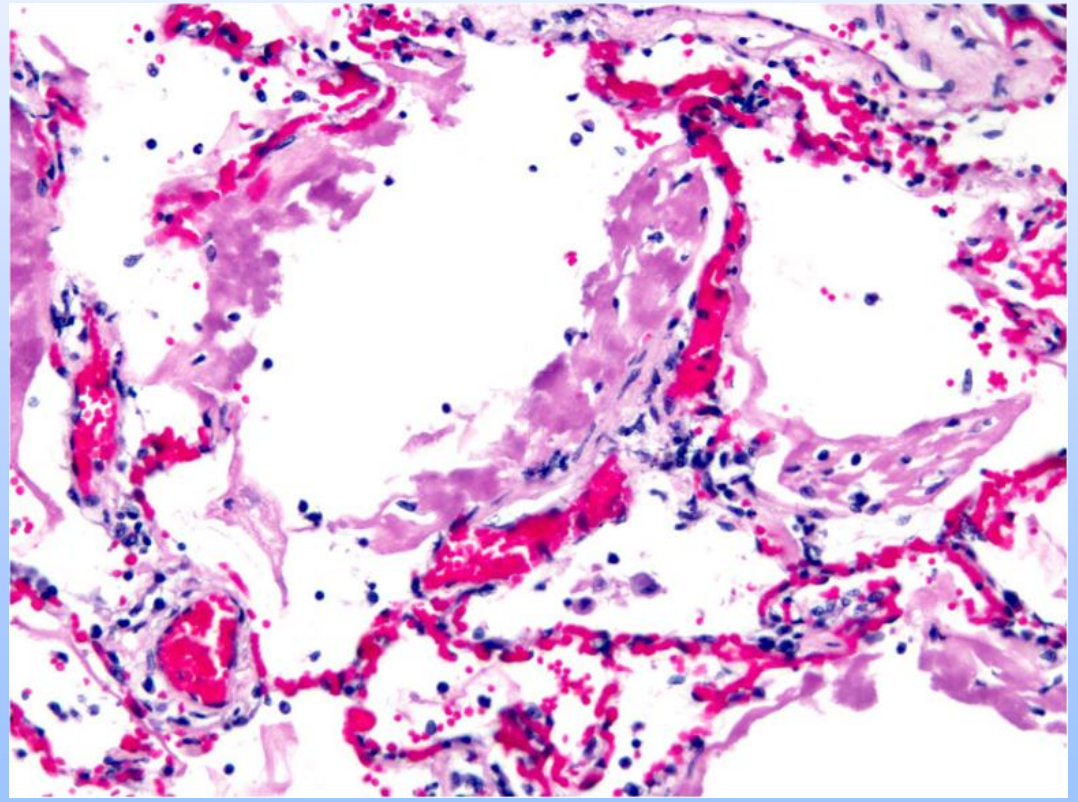
- In the acute phase of ARDS, the lungs are dark red, firm, airless, and heavy .



Microscopic change

- Microscopic examination reveals capillary congestion, necrotic alveolar epithelial cells, interstitial and interalveolar edema and hemorrhage, and collections of neutrophils in capillaries.
- The most characteristic finding is the presence of hyaline membranes, particularly lining the distended alveolar ducts.

Covid 19 patient
Hyaline membrane in alveoli



Systemic changes

Endothelial and cardiac injury

- endothelial cells express ACE2 and TMPRSS2 and, thus, are potentially infected by SARS-CoV-2, most data suggest that endothelial damage in the context of COVID-19 results from immune activation of endothelial cells by cytokines, IL-6 induction, and complement activation.
- Histopathology of cardiac injury is not frequently associated with inflammation or myocardial necrosis. Microvascular injury is central to the proposed mechanism of cardiac injury among patients with SARSCoV-2 infection.

COVID-19 and the brain

- any patients with COVID-19 develop neuropsychiatric symptoms, most of which reflect aberrant inflammatory responses, microvascular injury, and thrombosis in the brain. Single-nucleus transcriptome analyses have failed to detect viral transcripts in the brains of patients with COVID-19.

Gastrointestinal effects of SARS-CoV-2

- Both ACE2 and TMPRSS2 are highly expressed in the gastrointestinal tract and, thus, it is not surprising that gastrointestinal infection by SARS-CoV-2 is relatively common.
- Approximately 20% of infected patients develop gastrointestinal symptoms, particularly abdominal pain, bloody diarrhea, or non-bloody diarrhea.

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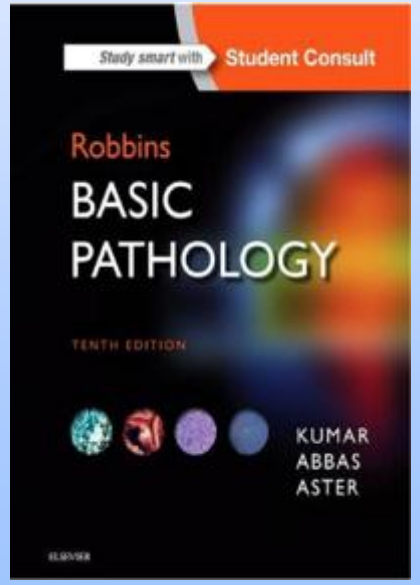


THANK YOU!