Pathogenesis of COVID-19

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Terminology

– Disease: Coronavirus Disease 2019 (COVID-19)
– Virus: Severe Acute respiratory syndrome Coronavirus 2 (SARS-CoV-2)/Novel Corona Virus
– SARS-COV-1- is the name of related virus responsible for SARS epidemic of 2003
Coronaviruses

- Large, enveloped, positive-strand RNA viruses
- 4 human (H)CoVs cause 10-30% of URTIs in adults
- Corona Virus which causes severe human infection;
  - SARS-COV-Epidemic in china 2003
  - MERS-COV, Epidemic in Middle east 2012
  - SARS-CoV-2-Pandemic 2019 Wuhan, China
The Origin of the SARS-CoV-2

- A previously unknown β-COV was discovered from Wuhun, China after
- Increased number of pneumonia after eating seafood
- RNA sequences resemble
  - SARS-CoV (79%) and
  - MERS-CoV (50%)

- SARS-CoV-2 bind to ACE-2 Receptors in LRT of human

- had a similar receptor-binding domain structure to that of SARS-CoV
Structure of the virus

Fig. 1. Structure of respiratory syndrome causing human coronavirus.
Transmission to Humans

**Graphical Abstract**

BatG13=96.2% genetic similarity with SARS-COV-2
Transmission to human

- Likely zoonotic infection: reservoir unclear
  - Bats?/ Pangolin? ——— ——— People
- Human to Human Transmission

Coronavirus
SARS-CoV-2

Though many think of them as reptiles, pangolins are actually mammals. They are the only mammals wholly-covered in scales and they use those scales to protect themselves from predators in the wild.
INFECTION CONTROL

The average number of people that one person with a virus infects, based on the R0 scale

**COVID-19:** 2–2.5*

- **Infected person** → **Average people infected**

**H1N1:** 1.2–1.6

- **Infected person** → **Average people infected**

**Ebola:** 1.6–2

- **Infected person** → **Average people infected**

**SARS:** 2–4

- **Infected person** → **Average people infected**

**MERS:** 2.5–7.2**

- **Infected person** → **Average people infected**

*As of February 28, 2020  **R0 calculated solely during the 2015 outbreak in South Korea

Sources: ScienceMag; WHO; Journal of the ISIRV
Pathogenesis

- Modes of transmission of the COVID-19 virus

- Respiratory infections can be transmitted through droplets of different sizes:
  - Particle size of >5-10 μm in Ø, they are referred to as *respiratory droplets*, (like case of COVID-19) → Not air born
  - Particles size of <5μm in Ø, they are referred to as *droplet nuclei* (air born)

- How Is Virus Spread?
  
  • Respiratory Droplets
    - Coughing
    - Sneezing
    - Contact with droplets
    - Viable on surfaces
    - Aerosolizing Procedures

- NOT Airborne
  
  • According to WHO and CDC

- In an analysis of 75,465 COVID-19 cases in China, airborne transmission was not reported
Pathogenesis

- SARS-COV-2 bind to ACE-2 receptor in the lung (Pneumocyte II)
- ACE-2 receptor is expressed in the following organ
  - Lung
  - Heart
  - Intestine
  - Kidney
  - Blood Vessel
  - Brain

↓↓ Decrease expression of ACE-2 receptor
Pathogenesis

Corona virus with spike protein

Lung, Alveoli Type two Pneumocyte
Pathogenesis

Severe COVID-19: Pathogenesis

The hypothetical link/binding site should NOT be construed as a reason to stop treatment with ACE-inhibitors.

Found on the surface of epithelial cells in:
- Lung
- Intestine
- Kidney
- Blood vessels

ACE2 expression increased by:
- ACE inhibitors
- Angiotensin II type 1 receptor blockers

Target cell binding: ACE-2

More binding sites for SARS-CoV-2
Pathogenesis

- The Virus get in to the body though
  - Mouth
  - Conjunctiva
  - Nose
- Results in the following clinical Condition

- 80% Mild
- 15% Severe
- Requires medical attention
- 5% Critical
  - Transfer to ICU
Pathogenesis of COVID-19

– Similar mechanisms may underlie the pathogenesis of both MERS and SARS

– Spike Protein binds to ACE-2, causing down regulation
  ▪ Lung injury occurs because of ACE2 naturally protects against acute lung injury
  ▪ Excessive Ang-II production by the related enzyme ACE1
  ▪ Excess Ang-II Causes excessive stimulation of type 1a angiotensin-II receptor (AGTR1A), which increases pulmonary vascular permeability, HTN and increased inflammation
  ▪ This explains the increased lung pathology when expression of ACE2 is decreased
Pathogenesis

SARS-CoV-2 spike protein binding to ACE2

Angiotensin-(1–9)

Angiotensin I

Angiotensin-(1–7)

Angiotensin II

Local or systemic infection or sepsis

ACE inhibitors

ARBs

ACE

Angiotensin II type 1 receptor

Viral entry, replication, and ACE2 down-regulation

Acute lung injury
Adverse myocardial remodeling
Vasoconstriction
Vascular permeability
Pathophysiologic Approach to the Management of Severe COVID-19 Cases!
Pathophysiology

Figure. Diagram representing the main metabolic pathways driven by angiotensin converting enzyme (ACE) and angiotensin-convertase enzyme-2 (ACE2) in the renin angiotensin system. The pharmacological targets for ACE inhibitors (ACEI) and angiotensin AT1 receptors blockers (ARB) are also shown. Ang, angiotensin.
Pathogenesis of COVID-19

Pathogenesis of COVID-19

Immunopathology

- Progression to acute respiratory distress syndrome (ARDS) is associated with the upregulation of pro-inflammatory cytokines and chemokines.
  - Interleukin-1β (IL-1β), IL-8, IL-6, CXC-chemokine ligand 10 (CXCL10) and CC-chemokine ligand 2 (CCL2).
- Patients who recovered from SARS (versus those who succumbed to the disease) have shown an early expression of interferon-α (IFNα), IFNγ, CXCL10, CCL2 and proteins that are encoded by IFN-stimulated genes.
- Adaptive immune response is vital to survival.
  - Severe disease pathology is related to the lack of a switch from an innate immune response to an adaptive immune response.

Diagram:

- Virus infects cell, stimulates production of interferon.
- New viruses produced.
- Antiviral proteins block viral reproduction.
- Interferon stimulates production of antiviral proteins.
- Host cell contains DNA.

List:

- [1] Interferon-α (IFNα) = anti-viral
  - Released by infected cell
- [2] Interferon-γ (IFNγ) = anti-viral
  - Released by immune cells
- [3] CXCL10 = chemoattractant
- [4] CCL2 = chemoattractant
Pathophysiology

- Infected Pneumocytes II produce and release;
  - Interferon gama, which Stimulate Pneumocyte I&II—→
    \[ \uparrow \text{antiviral peptide} \]
  - DAMP (Damage associated Molecular patterns)
  - Cytokines
    - Stimulate Alveolar macrophage
    - Macrophages Produce a number of cytokines and chemokines
      - IL1,
      - IL6,
      - IL8,
      - IL12
      - TNF-\(\alpha\),
      - IF gama
Pathophysiology

- Cytokines stimulate vascular endothelia cells resulting in:
  - Increase vascular permeability
  - Increase adhesive molecules
  - Accumulation of fluid in the interstitial space & alveoli
    - Interstitial edema
    - Alveolar edema
- Pulmonary edema → Dyspnea & Hypoxemia (↓Pao2) and Impaired CO2 diffusion (↑CO2)
- Respiratory acidosis
Pathophysiology

- IL1 & IL6 & other cytokines stimulate in the vascular endothelium & increased expression of special protein called VCAM (Vascular cell adhesive molecules)
- Increase VCAM pull Neutrophils to inflamed area

- Neutrophils migrate in to alveoli inflamed area and
  - Engulf virus and viral particles
  - Release toxic by product like (Oxygen specious, proteases)
  - Cause more tissue destruction (Type I & II)
  - Consolidation (accumulation of inflammatory cells)
  - Decrease gas exchange $\rightarrow$ Hypoxemia ($\downarrow$ PAO2)
  - Decrease Pneumocyte II $\rightarrow$ $\downarrow$ Surfactant $\rightarrow$ $\uparrow$ Surface tension $\rightarrow$ Alveolar Collapse $\rightarrow$ Hypoxemia
Pathophysiology

– Alveolar cell damage lead to other cytokines released
  • Leukotriene, Prostaglandin and bradikinin
  • stimulate the Vegas nerve ending which stimulate central respiratory center lead to stimulation of cough reflex
  • bronchial smooth muscle and \rightarrow bronchoconstriction \rightarrow Hypoxemia

– Excessive cytokine release lead to cytokine strom
  • Decreased level of anticoagulant
  • Increase Procoagulant
  • Hypercoagulable state, thrombosis and PTE

– **Systemic Inflammatory response syndrome (SIRS)**

– If the inflammatory cytokines reach systemic circulation induces systemic inflammatory response syndrome
  – Increase procoagulant activity
  – Decrease in anticoagulant
  – Increase in formation of thrombosis
  – DIC like picture
# Serotype of SARS-COV2

There are two types of serotypes:

<table>
<thead>
<tr>
<th>S-type</th>
<th>L-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td>Less severe &amp; Less aggressive</td>
<td>More severe &amp; More Aggressive</td>
</tr>
<tr>
<td>Zoonotic connection</td>
<td>Evolve from S-type</td>
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COVID-19 Related Hypoxia

Hypoxemia

Dysregulation of pulmonary perfusion

Phenotype L
- Low elastance
- Low V/Q
- Low lung weight
- Low recruitability
- Low PEEP

Phenotype H
- High elastance
- High R→L shunt
- High lung weigh
- Higher recruitability
- High PEEP

Pulmonary Micro-Thrombosis

Pulmonary edema-collapse-ARDS-like

Severity of disease
- Depth of the intrathoracic pressure
- Increased Tidal volume
- Leading to increased interstitial lung edema and P-SSLLI

20-30% of cases

Gattinoni L. et al. (2020) Intensive Care Medicine
Disease severity

- People get varying degree of severity with COVID-19
  - Mild Diseases (80%)
  - Severe Diseases (15%)
  - Life treating Diseases (5%)
    - Respiratory failure
    - Shock
    - Multiorgan Dysfunction

Patterns & Course of the Disease

- Hyperacute: Severe hypoxemia and respiratory distress leading to immediate intubation and MV
- Indolent (improving): Moderate hypoxemia and moderate WOB
- Biphasic: Initial Indolent course followed (5-7 days) by acute deterioration and hyperinflammation
Summary

- Loss of hypoxic vasoconstriction in pulmonary vasculature
- Dysregulation of Pulmonary Perfusion: V/Q
- Micro-thrombosis: Dead space increase
- Alveolar collapse and ARDS-like: Shunt
- Neurotropism
  - Mid brain & Cognitive dysfunction
  - Dissociation between WOB and perception of SOB
  - Cardiopulmonary Arrest
Thank you!