COVID 19 Virology and Pathophysiology

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No conflict of Interest
The only thing that is constant is change.

~ Heraclitus
Human Coronavirus (HCoV)

- **Common HCoVs (lower pathogenicity):**
  - HCoV-229E (alpha)
  - HCoV-NL63 (alpha)
  - HCoV-OC43 (beta)
  - HCoV-HKU1 (beta)

- **XXI Century HCoVs (higher pathogenicity):**
  - SARS-CoV (beta)
  - MERS-CoV (beta)


SARS-CoV & MERS-CoV Emergence in XXI Century

**China**

R⁰ ≈ 1.8-2.5

2002 SARS

8096 cases
774 deaths
32 countries

10%

**Middle East**

R⁰ ≈ 0.3-1.3

2012 MERS

2494 cases
858 deaths
27 countries

35%

ZOONOSIS

www.who.int access on 2020 Jan 21st
Coronavirus are found in Bats all over the world

Anthony et. al. A strategy to estimate unknown viral diversity in mammals. 2013 mBio. Photo: EcoHealth Alliance
Seven Human Coronaviruses (HCoVs)

- **Common HCoVs (lower pathogenicity):**
  - HCoV-229E (alpha)
  - HCoV-NL63 (alpha)
  - HCoV-OC43 (beta)
  - HCoV-HKU1 (beta)

- **XXI Century HCoVs (higher pathogenicity):**
  - SARS-CoV (beta)
  - MERS-CoV (beta)
  - SARS-CoV-2* (beta)

Drivers of Coronavirus (CoV) Evolution

- **CoV Genome Size:** 32Kb
- **CoV Mutation Rate:**
  - $10^{-6}$
  - Regulated Fidelity (nsp14: ExoN)
- **Environmental Change:**
  - Fidelity rates change
- **High Rates RNA Recombination:**
  - 25% during mixed infections
  - Modular evolution
- **Plastic Surface Glycoprotein:**
  - Tolerates high rates of mutation
  - Deletions and Insertions (tropism, antigenicity)
  - Recombination (modular evolution)
  - Host range, tissue tropism, transmissibility

![CoV Replicase Complex](image)

Nsp14 Removes 3' End mismatches
Phylogenetic Analysis of SARS-CoV-2 among Betacoronavirus


Lu R et al, Lancet 2020; 395: 565–74
SARS-CoV-2 (COVID19) Genome

Enveloped RNA virus with a genome size of 32 Kb

Interaction between SARS-CoV-2 and the Renin–Angiotensin–Aldosterone System.
SARS-CoV-2 (COVID19) Life Cycle

It uses **ACE2** for viral entry (angiotensin-converting enzyme 2)

Viral particles in the ultrathin sections were imaged using electron microscopy at 200 kV. The sample was from virus-infected Vero E6 cells. The inset shows the viral particles in an intra-cytosolic vacuole.

Schematic representation of SARS CoV infection mediating acute lung injury through angiotensin-converting enzyme (ACE) and ACE2 signaling pathways.

1) **SARS CoV binds to ACE2** causing downregulation of ACE2 through internalization of this membrane-bound protein and leading to viral replication in the cytoplasm.

2) **ACE2 inactivates AT II.** AT II binds the angiotensin II receptor 1a (AT1aR), leading to tissue damage and lung edema, or it binds the angiotensin II receptor 2 (AT2R) reducing tissue damage.

Consequences of Cytokine Storm and Immunopathology

Epithelial and endothelial cell apoptosis and vascular leakage.

Cytokine/Chemokines. IFNab, INFy, Fas-FasL or TRAIL-DR5 dependent mechanisms. TNF released by IMMS.

Apoptosis of epithelial and endothelial cells compromises lung microvascular and alveolar epithelial cell barrier resulting in endothelial damage and alveolar edema → HYPOXIA

Consequences of Cytokine Storm and immunopathology

**Suboptimal T cell response:**
CoV-specific T cells are crucial for virus clearance and limit further damage to host. Exuberant inflammatory responses caused by pathogenic hCoV diminish the T Cells response, in the case of SARS-CoV infection via TNF mediated T cell apoptosis, leading to Uncontrolled inflammatory response.

Consequences of Cytokine Storm and immunopathology

Accumulation of alternatively activated macrophages and altered tissue homeostasis:

In mice infected with SARS-CoV-Challenged STAT mice on B6 and B129 Background revealed an enhanced perivascular infiltration of alternatively activated macrophages, neutrophils and fibroblast and extensive fibrin deposition and alveolar collapse, features observed during ALI and ARDS in humans.

Consequences of Cytokine Storm and Immunopathology

ARDS

Inflammatory mediator plays an important role in the pathogenesis: Several pro-inflammatory cytokines, including IL-6, IL-8, IL-1B, and GM-CSF, reactive oxygen species and chemokines such as CCL2, CCL-5, IP-10, and CCL3. Uncontrolled epithelial cell proliferation and impaired tissue remodeling during later stages induce ARDS leading to pulmonary fibrosis and death.

SARS-CoV-2 (COVID19) Pathogenesis: ARDS

Acute Respiratory Distress Syndrome (ARDS) pathology

Acute diffuse alveolar damage, with pulmonary edema and formation of a hyaline membrane in a SARS-CoV patient

The airspaces are indicated by asterisks and some of the hyaline membranes lining the alveolar spaces are highlighted by arrows (hematoxylin and eosin stain; original magnification x100).

The Healthy Lung and the Exudative Phase of ARDS.
Endothelial Injury and loss of auto-regulation

Endothelial Injury and loss of Auto-regulation

Endothelial Injury and loss of auto-regulation

Endothelial Injury and loss of auto-regulation

Such mechanisms revolve around the loss of auto-regulation secondary to endothelial cell injury and altered retrograde endothelial cell-cell communication; impaired red blood cell deformability and increased blood viscosity

denudation of the glycocalyx (key biomechanical activities, including maintenance of blood flow and protection of the barrier function); platelet activation; leukocyte adhesion and rolling; and activation of the coagulation and complement systems.

Metabolic Reprograming as cell survival strategy
Regulation of the cell cycle

Mitophagy and Biogenesis

- Mitophagy
- Biogenesis

Dysfunctional mitochondria

Metabolic adaptation

- Glycolysis (Warburg)
- OXPHOS (FAO)

Cell cycle arrest

Adaptive metabolic re-programming

SARS-CoV-2

**ACE2 receptor**
**S protein**
**TMPRSS2**
**IL-6**
**Soluble IL-6 receptor**

**Arbidol**
**Chloroquine**
**Hydroxychloroquine**
**Camostat mesylate**

**Assembly**
**Structural proteins**
**Translation**

**Macrophage**

**Host Cell**

**Exocytosis**

**Host Cell**

**Uncoating**

**S**

**Lopinavir Darunavir**

**Ribavirin Remdesivir**

**Tocilizumab Sarilumab**

**Binds IL-6 receptor**
**Prevents IL-6 receptor activation**
**Inhibits IL-6 signaling**

**Inhibits TMMPRSS2**
**Prevents viral cell entry**

**Inhibits viral entry and endocytosis**
**by multiple mechanisms as well as host immunomodulatory effects**

**Targets S protein/ACE2 interaction**
**Inhibits membrane fusion of the viral envelope**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dosage/Use</th>
<th>Side Effects</th>
<th>Contraindications/Precautions</th>
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<tr>
<td>Hydroxychloroquine (Plaquenil/Generic)</td>
<td>400 mg by mouth every 12h x 1 d, then 200 mg by mouth every 12h x 4 d; alternative dosing: 400 mg by mouth daily x 5 d or 200 mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquine sulfate (salt) = 155 mg hydroxychloroquine base. Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution. Administration: Manufacturer does not recommend crushing tablets; however, some sources suggest that tablets can be crushed and dispersed with water or compounded into an oral solution.</td>
<td>Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative, or any component of the formulation</td>
<td>Adverse drug reactions similar to chloroquine but less common</td>
<td>May be used in pregnancy if benefit outweighs risks</td>
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<tr>
<td>Lopinavir/ritonavir (Kalera)</td>
<td>3CL protease 400 mg/100 mg by mouth every 12h for up to 14 d. Available as: lopinavir/ritonavir, 200-mg/50-mg tablets; lopinavir/ritonavir, 100-/50-mg tablets; lopinavir/ritonavir 400-/100-mg per 5-mL oral solution (can be given via feeding tubes compatible with ethanol and propylene glycol, contains 42% alcohol). Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution in hepatic impairment. Administration: Food restrictions: Tablets, take without regard to meals; oral solution: take with food. Do not crush tablets; oral solution not recommended with polyurethane feeding tubes.</td>
<td>Hypersensitivity to lopinavir/ritonavir or any of its ingredients, including ritonavir. Co-administration with drugs highly dependent on CYP450 3A. Co-administration with potent CYP450 3A inducers</td>
<td>Common: gastrointestinal intolerance, nausea, vomiting, diarrhea. Major: Pancreatitis, hepatotoxicity, cardiac conduction abnormalities</td>
<td>May be used in pregnancy; avoid oral solution if possible due to ethanol content</td>
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<td>Umifenovir (Arbidol)</td>
<td>S protein/ACE2, membrane fusion inhibitor 200 mg every 8h by mouth 7-14d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules. Dose adjustments: Kidney: no dose adjustment necessary. Hepatic: No specific recommendations available, caution in those with hepatic impairment. Administration: Bioavailability 40%</td>
<td>Known hypersensitivity to umifenovir</td>
<td>Allergic reaction, gastrointestinal upset, elevated transaminases</td>
<td>Contraindicated in children &lt;2 y of age (increased sensitivity)</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>RNA polymerase inhibitor 200 mg x 1, 100 mg every 24h IV infusion. Available as: 5-mg/mL vial (reconstituted). Dose adjustments: Kidney: Not recommended for GFR &lt; 30. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion</td>
<td>Exclusion criteria based on specific protocols</td>
<td>Elevated transaminases (reversible), kidney injury</td>
<td>Not a significant inducer/inhibitor of CYP enzymes, monitor with strong inducers/inhibitors</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>RNA polymerase inhibitor Doses vary based on indication, limited data available. Available as (not in the US): 200-mg tablet. Dose adjustments: Kidney: no dose adjustment recommended, limited data available. Hepatic: Dose adjustment considered in Child-Pugh class C, increased exposures observed in Child-Pugh class A to C. Administration: Tablet can be crushed or mixed with liquid, for oral solution</td>
<td>Exclusion criteria based on specific protocols</td>
<td>Hyperuricemia, diarrhea, elevated transaminases, reduction in neutrophil count</td>
<td>CYP2C8 and aldehyde oxidase inhibitor, metabolized by aldehyde oxidase and xanthine oxidase</td>
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