UNDERSTANDING THE IMMUNE RESPONSE AND COVID-19

November 19, 2020
UNDERSTANDING COVID-19

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SARS-CoV2 (COVID-19): BASIC FACTS

- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2 virus)
- Causes COVID-19 (Corona virus disease 2019 illness)
- Single Stranded RNA Virus
- Binds cells and enters through ACE2 receptor
- Closely related to SARS-CoV1 (2002 SARS outbreak)
- First identified in Wuhan, China in late 2019
COVID-19: PANDEMIC SPREAD

10.1 Million Cases
240,000 Deaths

US CDC | 11/11/20
COVID-19: TRANSMISSION + PREVENTION

Fundamentals to Prevent Acquisition/Transmission of SARS-CoV2:

- Universal wearing of masks/face coverings.
- Maintain physical distance—at least 6 feet.
- Avoid crowds and congregated settings.
- Frequent washing of hands.
- Outdoors are better than indoors.
SPECTRUM OF COVID-19 DISEASE

Mild/Mod: 81%
Severe: 14%
Critical: 5%

Case-fatality rate: 2.3%

Fever
Cough
Fatigue
Loss of Appetite
Shortness of Breath
Muscle pain
Sore Throat
Nasal congestion
Headache
Diarrhea
Nausea
Loss of Smell
SPECTRUM OF COVID-19 DISEASE

- Acute Respiratory Distress Syndrome (ARDS)
- Hyperinflammation
- Heart dysfunction
- Kidney injury
- Neurologic disease
- Hypercoagulability
PATHOGENESIS OF COVID-19 DISEASE

1. Direct cytotoxic effect
   - Spike protein of SARS-CoV-2 binds to ACE2
   - TMPRSS2 facilitates entry of SARS-CoV-2

2. Dysregulation of the RAAS
   - Angiotensin II↑
   - Angiotensin 1-9
   - Angiotensin 1-7
   - ACE2 downregulated
   - Endothelial cell damage and apoptosis

3. Endothelial cell damage and thromboinflammation
   - Endothelial inflammation
   - Fibrinolysis↓
   - Thrombin production↑
   - IL-6↑

4. Dysregulated immune response
   - T cell lymphopenia
   - Inhibition of interferon signaling by SARS-CoV-2
   - Hyperactive innate immunity
   - Cytokine-release syndrome

- Tissue injury/remodeling
- Inflammation
- Vasoconstriction
- Vascular permeability

Blood vessel

Inflammation
Thrombosis

↑ D-dimer

IL-6
TNFα
ALTERED IMMUNE RESPONSE IN COVID-19

Clinical implications of SARS-CoV-2-induced immunopathology

The effect of lymphopenia on microbiota infection

The effect of elevated cytokine production on severe syndromes

Nature Signal Transduction and Targeted Therapy
COVID-19 COURSE: RESOLUTION OR DETERIORATION

A

Exposure to SARS-CoV-2
- No infection
- Infection
- Symptomatic

Asymptomatic
Mild → Moderate
Severe

Recovery
Recovery
Recovery
Death

B

PROTECTIVE IMMUNITY
- Neutralizing anti-S antibodies
- Cytotoxic CD8 cells
- Th1 responses

IMMUNE DYSREGULATION
- Acute inflammation → cytokine storm
- Acute lung injury → ARDS → coagulopathy
- Multiorgan system dysfunction

Frontiers in Immunology
British Medical Journal
COVID-19 THERAPIES

Christopher Ritchlin ’76, ’08M (MPH)
Chair,
Department of Allergy, Immunology, and Rheumatology
DEXAMETHASONE

Recovery Collab Group, NEJM July 2020
ANTIVIRAL TREATMENTS
REMDESIVIR
Act-1 Trial

Biegel, JH NEJM | Oct 2020
ANTI-IMMUNE TREATMENTS
ANTIBODY COCKTAILS

- **Lilly** - Neutralizing antibodies in the COVID-19 outpatient setting—September 16, 2020

- **Regeneron** - Antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients—September 29, 2020
CONVALESCENT PLASMA

FDA issues emergency use authorization for convalescent plasma as potential promising COVID–19 treatment.

Impact of convalescent plasma therapy in COVID-19 management:

• Clinical improvement
• Decrease in mortality
• Increase in viral clearance

Sarkar S., Medical Virology August 2020
Vaccine Platform Refresher

DNA-based vaccines work by inserting synthetic DNA of viral gene(s) into small DNA molecules (called plasmids). Cells take in the DNA plasmids and follow their instructions to build viral proteins, which are recognized by the immune system, and prepare it to respond to disease exposure.

Viral vector vaccines insert a gene for a viral protein into another, harmless virus (replicating or non-replicating), which delivers the viral protein to the vaccine recipient, triggering an immune response.

RNA vaccines introduce an mRNA sequence coded for a disease-specific antigen. Once this antigen is reproduced within the body, it is recognized and triggers an immune response.

Subunit vaccines introduce a fragment of the virus into the body. This fragment is enough to be recognized by the immune response and stimulate immunity.

Inactivated vaccines consist of the whole virus, which has been killed with heat or chemicals so it can't cause illness.

Live attenuated vaccines are made up of whole viruses that have weakened in a lab. They tend to elicit a stronger immune response than inactivated vaccines.
MAJOR COVID-19 TREATMENT TRIALS AT URMC

Christopher Palma ’11M (MD)
Assistant Professor,
Department of Allergy, Immunology, and Rheumatology
COVID-19 Interventional Trials at URMC

Nov 12, 2020

<table>
<thead>
<tr>
<th>Completed</th>
<th>Active</th>
<th>Hospitalized</th>
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<tbody>
<tr>
<td>ACTT1: Remdesivir</td>
<td>Mod/Severe</td>
<td></td>
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<tr>
<td>ACTT2: Remdesivir/Baricitinib</td>
<td>Mod/Severe</td>
<td></td>
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<tr>
<td>ACTT3: Remdesivir/INF beta</td>
<td>Mod/Severe</td>
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<tr>
<td>REGN-CoV2 (anti-S mAb)</td>
<td>Mod/Severe</td>
<td></td>
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<tr>
<td>RUXCOVID-DEVENT (ruxolitinib)</td>
<td>Severe/ARDS</td>
<td></td>
</tr>
<tr>
<td>CoVPN 3502 (Anti-S mAbs)</td>
<td>Prevention household contacts</td>
<td></td>
</tr>
<tr>
<td>ACTIV1 (host immunomodulators)</td>
<td>Mod/Severe</td>
<td></td>
</tr>
<tr>
<td>ACTIV2 (anti-S mAb)</td>
<td>Mild</td>
<td></td>
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</tbody>
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Convalescent Plasma

Asymptomatic/Mild

Novartis HCQ & Azithro

Mild/moderate
PRELIMINARY DATA ON COVID-19 TREATMENTS

Antiviral Antibodies (Regeneron/Lilly):

- Few risks/side effects
- Reduces viral load – much more effective in patients who present with high viral load and no antibodies → 99% reduction
- Improves symptoms
- Reduces need for further medical visits/hospitalizations
- No clear benefit for patients hospitalized with severe disease – too late to be effective likely
COVID-19 Interventional Trials at URMC
Nov 12, 2020

Fix The Host

Remdesivir
Mod/Severe

Remdesivir/Baricitinib
Mod/Severe

Remdesivir/INF beta
Mod/Severe

HCQ & Azithro
Moderate

HCQ & Azithro
Mild/moderate

Ruxolitinib
Severe/ARDS

REGN-CoV2 (anti-S mAb)
Mod/Severe

CoVPN 3502 (Anti-S mAbs)
Prevention household contacts

ACTT1
Remdesivir
Mod/Severe

ACTT2
Remdesivir/Baricitinib
Mod/Severe

ACTT3
Remdesivir/INF beta
Mod/Severe

ACTG/DMID
HCQ & Azithro
Mild/moderate

Novartis
HCQ & Azithro
Moderate

Convalescent Plasma
Asymptomatic/Mild

Ambulatory

Active

Hospitalized

Completed
PRELIMINARY DATA ON COVID-19 TREATMENTS

Baricitinib (anti-inflammatory)

• Improved time to recovery by 1 day (7 days instead of 8)
• Less people died – 5.1% vs 7.8% - but not clearly statistically significant
• Larger studies still ongoing to refine extent of benefit