Understanding the COVID-19 Pandemic: Epidemiology, Basic Science/Biology, and Current Interventions in Clinical Trials

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The views expressed are those of the presenter and do not necessarily reflect the official policies of the Department of Health and Human Services (HHS), nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Conflicts of Interest

- None to report
Learning Objectives

As a result of this activity, participants will be able to:

- Describe the current epidemiology of COVID-19 disease
- Explain the basic science/biology of SARS-CoV-2 infection
- Report current interventions being investigated in COVID-19 clinical trials
In this presentation, the following investigational drugs will be described:

- None of these drugs are licensed for treating COVID-19
- All are currently being investigated in ongoing clinical trials

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Epidemiology of COVID-19

Basic Science of SARS-CoV-2

Current Interventions in Clinical Trials
Epidemiology of COVID-19

Basic Science of SARS-CoV-2

Current Interventions in Clinical Trials
What does the global COVID-19 pandemic look like?

Total Confirmed
9,150,391

Confirmed Cases by Country/Region/soverignty
USA
Brazil
Russia
India
United Kingdom
Peru
Chile
Spain
Italy
Iran
France
Germany
Turkey
Mexico
Pakistan
South Africa
Bangladesh
Canada
South Africa
Qatar
China

Global Deaths
473,493

US State Level
Deaths, Recovered
127,674
26,976
1,701

Critical Trends
Confirmed cases have spread well beyond the initial hot spots.

https://coronavirus.jhu.edu/us-map
Federal guidelines advise that states wait until they experience a downward trajectory of documented cases within a 14-day period before proceeding to a phased opening.

- Bars: new cases/day/100k
- Line: 3-day moving average of new cases/day/100k
- Two-week window trend:
  - Orange (up)
  - Green (down)

Daily confirmed new cases are trending down in Maryland.

https://coronavirus.jhu.edu/data/new-cases-50-states/maryland
Are we really “flattening the curve”?

LOWER AND DELAY THE EPIDEMIC PEAK

Proactive measures:
- Slow the spread of disease
- Reduce burden on hospitals

Uncontrolled transmission

With controls

Healthcare system capacity (ICU beds, ER visits, etc.)

*Social distancing such as teleworking, limiting large gatherings, reducing travel or more assertive approaches.
What is the current nationwide trend in ER visits?

NSSP: Percentage of Visits for Influenza-Like Illness (ILI) and COVID-19-Like Illness (CLI) to Emergency Departments, Weekly National Summary, September 29, 2019 - June 6, 2020

[Graph showing the trend of visits for ILI and CLI to EDs]

What is the current nationwide trend in hospitalizations?

Laboratory-Confirmed COVID-19-Associated Hospitalizations

Preliminary cumulative rates as of Jun 06, 2020

[Graph showing trends over time]

Minorities are at greatest risk of COVID-19 disease.

Age-adjusted COVID-19-associated hospitalization rates by race and ethnicity, COVID-NET, March – June 6, 2020

- Non-Hispanic American Indian or Alaska Native: 193.8
- Non-Hispanic Black: 171.8
- Hispanic / Latino: 150.3
- Non-Hispanic Asian or Pacific Islander: 44.9
- Non-Hispanic White: 37.8

Epidemiology of COVID-19

Basic Science of SARS-CoV-2

Current Interventions in Clinical Trials
What is SARS-CoV-2?

- **SARS-CoV-2**: severe acute respiratory syndrome coronavirus 2
- **Family**: *Coronaviridae*
- **(+)**RNA viruses, 50+ strains
- **Natural reservoir**: bats, ferrets, felines, some birds
- **7 strains infect humans**
  - “Seasonal” 229E, OC43, NL63, and HKU1
- **High RNA replication error rate and recombination during mixed infections**
- **S spike glycoprotein binds ACE2 receptor**
  - Lung alveolar epithelial cells
  - Small intestine enterocytes
- **Novel shape of the S spike protein**
  - Allows high affinity binding to human ACE2
  - No cross-immunity from seasonal coronaviruses

What does seasonal coronavirus look like?

2010-2018

What is the incidence rate for seasonal coronavirus?
How does SARS-CoV-2 replicate in a cell?

1. Binding to ACE2 receptor
2. Fusion/endocytosis
3. Viral RNA uncoating
4. Protein synthesis
5. RNA synthesis
6. Virus assembly
7. Budding at the cell membrane

Adapted from Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19). 2020. JAMA Vol. 323 No. 18
What is the role of ACE2 in the Renin-Angiotensin System (RAS)?

RAS is controlled by Angiotensin Peptides:

- Angiotensin (Ang) I is converted into Ang II by Angiotensin Converting Enzyme (ACE)
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- Inhibitors of ACE and antagonists of AT₁R reduce blood pressure
How could ACE2 contribute to the pathogenesis of COVID-19?

ACE2 Knockout Mouse Model of Lung Injury:

- Increased vascular permeability
- Lung edema
- Neutrophil influx
- Decreased lung function
- Phenotype was rescued with a pharmacological inhibitor of the angiotensin II type 1 receptor (AT$_1$R)

How does SARS-CoV-2 binding to ACE2 impact RAS?:

- Does the virus block ACE2 function?
- Does the virus decrease degradation of Angiotensin II?
- Are the angiotensin peptides present during infection?
- Would inhibitors (AT$_1$R or ACE) affect the inflammatory response?

Epidemiology of COVID-19

Basic Science of SARS-CoV-2

Current Interventions in Clinical Trials
What are therapeutic targets for SARS-CoV-2 infection?
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1. Binding to ACE2 receptor
What are therapeutic targets for SARS-CoV-2 infection?

2. Fusion/endocytosis
What are therapeutic targets for SARS-CoV-2 infection?

3 Protein processing
What are therapeutic targets for SARS-CoV-2 infection?

**RNA synthesis**

- **Membrane fusion and endocytosis**
- **Uncoating**
- **Translation**
- **Polypeptides**
- **Proteolysis**
- **Nonstructural proteins**
- **RNA-dependent RNA polymerase (RdRp)**
- **Assembly**
- **Structural proteins**
- **Translation**
- **RNA synthesis**

**Agents:**
- Ribavirin
- Remdesivir
- Favipiravir

**Inhibits viral RdRp**
What are therapeutic targets for SARS-CoV-2 infection?
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- **Arbidol**: Targets S protein/ACE2 interaction, inhibits membrane fusion of the viral envelope.
- **Camostat mesylate**: Inhibits TMPRSS2, prevents viral cell entry.
- **Chloroquine Hydroxychloroquine**: Inhibits viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects.
- **Tocilizumab Sarilumab**: Binds IL-6 receptor, prevents IL-6 receptor activation, inhibits IL-6 signaling.
- **Soluble IL-6 receptor**: Exocytosis.
- **Lopinavir Darunavir**: Inhibits 3-chymotrypsin-like protease.
- **Ribavirin Remdesivir Favipiravir**: Inhibits viral RdRp.
Hydroxychloroquine

- **Drug Class:** 4-aminoquinoline

- **Historical Use:**
  - Prevention and treatment of malaria
  - Treatment of chronic inflammatory diseases including systemic lupus erythematosus and rheumatoid arthritis

- **Mechanism of Action**
  - Unknown, but may suppress immune function by interfering with the processing and presentation of antigens and the production of cytokines

- **Proposed Therapeutic Target in SARS-CoV-2 Infection**
  - Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification

- **Evidence Supporting Use in COVID-19**
  - *In vitro* activity against SARS-CoV-2 in the low micromolar range
    - EC$_{50}$=6.14 µM

Molecular Weight: 335.9 g/mol

$C_{18}H_{26}ClN_{3}O$
Azithromycin

- **Drug Class**: azalide, derived from erythromycin, and a member of a subclass of macrolide antibiotics

- **Historical Use**:  
  - Used to treat many different types of infections including respiratory infections, skin infections, ear infections, eye infections, and sexually transmitted diseases

- **Mechanism of Action**:  
  - Reversibly binds to the 50S ribosomal subunit of the 70S ribosome of sensitive microorganisms, thereby inhibiting the translocation step of protein synthesis

- **Proposed Therapeutic Target in SARS-CoV-2 Infection**:  
  - Increase in the pH of the trans-Golgi network and recycling endosome  
  - May alter the packaging of proteins or alter glycosylation of the ACE2 receptor

- **Evidence Supporting Use in COVID-19**:  
  - Limited *in vitro* studies  
  - Conflicting results – with or without hydroxychloroquine

Molecular Weight: 749 g/mol

C\textsubscript{38}H\textsubscript{72}N\textsubscript{2}O\textsubscript{12}

https://www.cebm.net/covid-19/what-is-the-evidence-for-use-of-macrolide-antibiotics-for-treatment-of-covid-19/
Drug Class: antiretroviral protease inhibitors

Historical Use:
- Both drugs used in combination in the therapy of HIV infection

Mechanism of Action
- Inhibit the production of infectious virus by inhibiting the HIV-1 protease enzyme which is required to cleave the Gag polyprotein

Proposed Therapeutic Target in SARS-CoV-2 Infection
- Inhibits the activity of 3CL protease, an enzyme that has been shown to be essential for SARS-CoV replication

Evidence Supporting Use in COVID-19
- Limited in vitro data: 4 µg/mL Lopinavir inhibited cytopathic effect of SARS-CoV infection
- Improved clinical outcome was observed in SARS-CoV patients treated with Lopinavir (400 mg)/Ritonavir (100 mg) orally every 12 hr for 14 days
**Remdesivir**

- **Drug Class**: monophosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside triphosphate analogue

- **Historical Use**:  
  - Potential antiviral activity against a variety of RNA viruses, including Coronaviruses and Flaviviruses (Ebola)

- **Mechanism of Action**  
  - RNA polymerase inhibitor

- **Proposed Therapeutic Target in SARS-CoV-2 Infection**  
  - Inhibits replication of the virus by targeting RNA replication

- **Evidence Supporting Use in COVID-19**  
  - Potent *in vitro* activity against SARS-CoV-2  
    - EC$_{50}=0.77$ µM  
    - EC$_{90}=1.76$ µM  
  - Prevented lung hemorrhage and reduced viral lung titers in murine lung infection models with MERS-CoV

Molecular Weight: 602.6 g/mol  
$C_{27}H_{35}N_6O_{8p}$

Drug Class: humanized monoclonal antibodies against the IL-6 receptor

Historical Use:
- Used to treat moderate to severe rheumatoid arthritis in adults

Mechanism of Action
- Bind soluble as well as membrane bound IL-6 receptors, hindering IL-6 from exerting its pro-inflammatory effects

Proposed Therapeutic Target in SARS-CoV-2 Infection
- Diminishes the severity of COVID-19 by inhibiting IL-6 and reducing the “cytokine storm”

Evidence Supporting Use in COVID-19
- Underlying pathophysiology of significant organ damage in the lungs and other organs may be caused by an amplified immune response and cytokine release
- IL-6 appears to be a key driver of this dysregulated inflammation based on early case series from China

Tocilizumab
Protein Weight: 148000 Da
\[ \text{C}_{6428}\text{H}_{9976}\text{N}_{1720}\text{O}_{2018}\text{S}_{42} \]

Sarilumab
Protein Weight: 150000 Da
\[ \text{C}_{6388}\text{H}_{9918}\text{N}_{1718}\text{O}_{1998}\text{S}_{44} \]
How many COVID-19 clinical trials are ongoing?

Hydroxychloroquine 225 Studies
Azithromycin 94 Studies
Lopinavir/Ritonavir 48 Studies
Remdesivir 35 Studies
Tocilizumab & Sarilumab 7 Studies

www.clinicaltrials.gov (as of June 19, 2020)
Federal Agency Halts Studies of Hydroxychloroquine, Drug Trump Promoted

The National Institutes of Health decided to stop one trial because the drug was unlikely to benefit patients, and another because not enough people enrolled.

The National Institutes of Health said Saturday that it had stopped two clinical trials of hydroxychloroquine, the malaria drug that President Trump promoted to treat and prevent the coronavirus, one because the drug was unlikely to be effective and the other because not enough patients signed up to participate.

The agency halted a trial that had aimed to enroll more than 500 patients after an independent oversight board determined that the drug did not appear to benefit hospitalized patients. The same day, the N.I.H. said it had closed another trial — of hydroxychloroquine and the antibiotic azithromycin — because only about 20 patients had enrolled in the planned study of 2,000 people.

The two trials the N.I.H. shut down represent the latest evidence that hydroxychloroquine has not lived up to its early promise of fighting the coronavirus.

The N.I.H. said Saturday that an independent oversight board that monitors safety met late Friday to discuss the 500-patient trial and “determined that while there was no harm, the study drug was very unlikely to be beneficial to hospitalized patients with Covid-19,” the disease caused by the virus.
Remdesivir for the Treatment of Covid-19 — Preliminary Report


BACKGROUND
Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), none have yet been shown to be efficacious.

METHODS
We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

RESULTS
A total of 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

CONCLUSIONS
Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)
Potential new formulation of Remdesivir?

An Open Letter from Daniel O’Day, Chairman & CEO, Gilead Sciences

Daniel O’Day - June 22, 2020

After receiving the green light from the FDA to move forward, Gilead is about to start trials of an inhaled version of remdesivir. We will screen healthy volunteers for Phase 1 trials this week and hope to begin studies in patients with COVID-19 in August. If the trials are successful, this could represent important progress. Remdesivir, our investigational antiviral medicine, is currently given to patients intravenously through daily infusions in the hospital. An inhaled formulation would be given through a nebulizer, which could potentially allow for easier administration outside the hospital, at earlier stages of disease. That could have significant implications in helping to stem the tide of the pandemic.
There are still many unknowns.

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine

For Immediate Release: June 15, 2020

Today, the U.S. Food and Drug Administration (FDA) revoked the emergency use authorization (EUA) that allowed for chloroquine phosphate and hydroxychloroquine sulfate donated to the Strategic National Stockpile to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was unavailable, or participation in a clinical trial was not feasible. The agency determined that the legal criteria for issuing an EUA are no longer met. Based on its ongoing analysis of the EUA and emerging scientific data, the FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use. This is the statutory standard for issuance of an EUA. The Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services originally requested the EUA covering chloroquine and hydroxychloroquine, and the FDA granted the EUA on March 28, 2020 based on the science and data available at the time. Today, in consultation with the FDA, BARDA sent a letter to the FDA requesting revocation of the EUA based on up to date science and data.

Remdesivir by Gilead Sciences: FDA Warns of Newly Discovered Potential Drug Interaction That May Reduce Effectiveness of Treatment

[Posted 06/15/2020]

AUDIENCE: Health Professional, Pharmacy, Patient

ISSUE: FDA is warning health care providers that co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended as it may result in reduced antiviral activity of remdesivir.

The agency is not aware of instances of this reduced activity occurring in the clinical setting but, is continuing to evaluate all data related to remdesivir.

BACKGROUND: Following an evaluation of the emergency use authorization criteria and the scientific evidence available, the FDA issued an emergency use authorization (EUA) in May 2020 allowing for remdesivir to be distributed in the U.S. and to be administered intravenously by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in adults and pediatric patients hospitalized with severe disease. The safety and efficacy of remdesivir for the treatment of COVID-19 continue to be evaluated, and preliminary clinical trial results have shown that on average, patients treated with remdesivir had more rapid time to recovery.

RECOMMENDATION: It is recommended that health care providers read the most up-to-date fact sheet when prescribing remdesivir. These fact sheets include information on possible side effects such as: increased levels of liver enzymes, which may be a sign of inflammation or damage to cells in the liver; and allergic reactions, which may include low
What NIH treatment guidelines are available?

www.covid19treatmentguidelines.nih.gov/whats-new
The world is still in the grip of the COVID-19 pandemic.

Virus entry through the ACE2 receptor may be linked to the pathology and severity of disease.

Current interventions in clinical trials aim at disrupting the virus life cycle or reducing the inflammatory response to the virus.
Acknowledgments

Johns Hopkins University
https://coronavirus.jhu.edu/map.html

CDC

U.S. National Library of Medicine
www.clinicaltrials.gov

NIH
www.covid19treatmentguidelines.nih.gov/whats-new

NIH
National Institutes of Health
Turning Discovery Into Health