COVID-19 Treatments: Panacea for the Pandemic?

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Disclosure

The authors report no conflicts of interest.

There will be discussion of off-label uses of drugs during this presentation.
Learning Objectives

At the conclusion of this activity, *pharmacists* should be able to successfully:

1. Distinguish which agents are most likely efficacious based on clinical trial data
2. Select which patient populations are most appropriate for each therapeutic option
3. Recognize potential adverse events for each of the agents described
4. Examine the strengths and limitations of convalescent plasma and the rationale behind the pursuit of COVID-19 monoclonal antibodies
5. Assess our current knowledge of potential risks and benefits of the different COVID-19 vaccines in development, including novel mRNA vaccines
Learning Objectives

At the conclusion of this activity, pharmacy technicians should be able to successfully:

1. Illustrate the rationale for both antiviral and immunomodulatory therapy in COVID-19
2. Appraise the landscape of antiviral and immunomodulatory agents for COVID-19
3. Define passive immunity and describe the potential mechanism of action of convalescent plasma for COVID-19
4. Identify what makes the United States’ approach to vaccine development for COVID-19 unique, including the role of Operation Warp Speed
Coronavirus Life Cycle

Coronavirus Pathophysiology

• Viral RNA shedding can be prolonged
  • Has been detected for up to 83 days in the upper respiratory tract
  • Not likely to be important for illness or infectiousness

• Peak viral RNA levels most frequently occur between day 0 and day 5 of symptoms

• Live virus has not been cultured past 9 days of symptoms
Coronavirus Pathophysiology

Stage I (Early Infection)
- Mild constitutional symptoms
  - Fever >99.6°F
  - Dry Cough

Stage II (Pulmonary Phase)
- IIA: Shortness of Breath without Hypoxia (PaO2/FiO2 ≥ 300mmHg)
- IIB: Shortness of Breath with Hypoxia (PaO2/FiO2 < 300mmHg)

Stage III (Hyperinflammation Phase)
- ARDS
- SIRS/Septic Shock
- Cardiac Failure
- Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
- Troponin, NT-proBNP elevation

Potential Therapies
- Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
- Reduce immunosuppression (avoid excess steroids)
- Careful use of Corticosteroids; statins; human immunoglobulin, IL-1/IL-2/IL-6/αK inhibitors/GM-CSF inhibitors

Severity of Illness

Time course

Clinical Symptoms
- Lymphopenia

Clinical Signs
- Transaminitis
- Low-normal procalcitonin
Medications to Treat COVID-19

ANTIVIRALS AND IMMUNE-TARGETING THERAPIES
Agents

- Baricitinib
- Chloroquine/Hydroxychloroquine (HCQ)
- Colchicine
- Dexamethasone
- Famotidine
- Favipiravir
- Interleukin-6 (IL-6) inhibitors
  - Tocilizumab
  - Sarilumab
- Ivermectin
- Losartan
- Lopinavir
- Merimepodib
- Nitazoxanide
- Remdesivir
- Ruxolitinib
Hydroxychloroquine (HCQ) - *In Vitro*

- Has shown *in vitro* activity against SARS-CoV-2 in cell culture

- **Mechanism**
  - Alkalization of lysosome
  - Inactivating pH-dependent caspases
  - Preventing spike protein priming and viral entry

- **Caveat**
  - *In vitro* activity may be an artifact of cell lines used
  - Lacks activity in relevant human cell lines

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Putative COVID-19 Therapy Mechanisms

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

Arbidol
Targets S protein/ACE2 interaction
Inhibits membrane fusion of the viral envelope

Camostat mesylate
Inhibits TMPRSS2
Prevents viral cell entry

Tocilizumab
Sarilumab
Binds IL-6 receptor
Prevents IL-6 receptor activation
Inhibits IL-6 signaling

SARS-CoV-2

Membrane fusion and endocytosis

Exocytosis

Assembly

Structural proteins

Translation

RNA synthesis

RNA-dependent RNA polymerase (RdRp)

Nonstructural proteins

Proteolysis

Polypeptides

Translation

Ribavirin
Remdesivir
Favipiravir
Inhibits viral RdRp

Lopinavir
Darunavir
Inhibits 3-chymotrypsin-like protease

USHP

# HCQ - Clinical Data (RCTs)

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Setting</th>
<th>Outcome</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skipper et al. (n=423)</td>
<td>Outpatient within four days of symptom onset</td>
<td>Change in self-reported symptom severity (1-10) by day 14</td>
<td>-0.27 points (95% CI = -0.61 to 0.07)</td>
<td>No benefit of HCQ</td>
</tr>
<tr>
<td>Mitjà et al. (n=293)</td>
<td>Outpatient within five days of symptom onset</td>
<td>Reduction in RNA load of NP swab by day 7</td>
<td>0.07 log (95% CI = -0.29 to 0.44)</td>
<td>No benefit of HCQ (no benefit in clinical secondary outcomes either)</td>
</tr>
<tr>
<td>Cavalcanti et al. (n=667)</td>
<td>Inpatient up to four liters of oxygen; +/- azithromycin</td>
<td>Proportion with improved clinical status (1-7) on day 15</td>
<td>HCQ: OR 1.21 (95% CI = 0.69 to 2.11)</td>
<td>No benefit of HCQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HCQ+azithro: OR 0.99 (95% CI = 0.57 to 1.73)</td>
<td></td>
</tr>
<tr>
<td>Horby et al. (pre-print)</td>
<td>Inpatient</td>
<td>28 day mortality</td>
<td>Rate Ratio 1.09 (95% CI = 0.96 to 1.23)</td>
<td>No benefit of HCQ</td>
</tr>
</tbody>
</table>

CI: confidence interval; HCQ: hydroxychloroquine; NP: nasopharyngeal; OR: odds ratio; RCT: randomized controlled trial; RNA: ribonucleic acid
HCQ - Post Exposure Prophylaxis

• Mitjà et al. (pre-print)
  • 2314 individuals with exposure to confirmed COVID-19
  • Measured symptomatic, PCR-confirmed COVID-19 within 14 days
  • Placebo 6.2% vs. HCQ 5.7%
  • Risk ratio: 0.89 (95% CI = 0.54-1.46)
  • Adverse events: placebo=5.9% vs. HCQ=51.6% (P = <0.001)

• Boulware et al.
  • 821 individuals with household or occupational exposure
  • Measured laboratory confirmed or clinical COVID-19 within 14 days
  • Placebo 14.3% vs. HCQ 11.8%
  • Difference: -2.4% (95% CI = -7.0 to 2.2)
  • Adverse events: placebo=16.8% vs. HCQ 40.1% (P <0.001)
When is antiviral therapy expected to be the most beneficial for COVID-19?

A. Early, during the viral response phase
B. Early, during the hyper-inflammatory phase
C. Late, during the viral response phase
D. Late, during the hyper-inflammatory phase
What would be the most appropriate recommendation for HCQ in regards to COVID-19?

A. It should be used only for therapy
B. It should be used only for prevention
C. It should be used for both
D. Would not recommend for either
Subgroup Analyses

- Often used to identify patient groups who benefit more/less than entire trial population

- Usually only appropriate under stratified randomization

- Hugely problematic
  - Destroy the randomization process
  - Create underpowered subgroups
  - Should be considered hypothesis-generating only
Subgroup Analyses: ISIS-2

- RCT of over 17,000 cases of myocardial infarction
  - Aspirin vs. aspirin+streptokinase vs. neither
  - Significant reduction of 5-week mortality

- *The Lancet* asked for a subgroup analysis

- Subgroup analysis by astrological sign
  - For patients who were Gemini or Libra there was no benefit
  - Nonsignificant, 9% relative increase in mortality

Remdesivir (RDV)

- *In vitro/in vivo* activity against SARS-CoV-2 (also SARS-CoV, MERS-CoV, Ebola)

- Pending FDA approval
  - New Drug Application (NDA) submitted on 8/10/2020
  - Currently available via Emergency Use Authorization (EUA) from the FDA

- Mechanism
  - Phosphoramidate prodrug activated by intracellular esterases
  - Phosphorylated by intracellular kinases
  - Nucleotide analog is incorporated into viral RNA by RNA-dependent RNA polymerase
  - Results in delayed chain termination
Putative COVID-19 Therapy Mechanisms
Remdesivir: Early Clinical Data

Wang et al.
- Double-blind, placebo-controlled RCT in the Hubei province of China
- 239 adults with confirmed COVID-19, < 12 days of symptoms and SpO₂ < 94% on room air
- RDV 200 mg IV x1 followed by 100 mg IV daily for 9 days
- ~80% requiring supplemental O₂; ~65% concomitant corticosteroids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Remdesivir n=158</th>
<th>Placebo n=78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement, days (IQR)</td>
<td>21.0 (13.0-28.0)</td>
<td>23.0 (15.0-28.0)</td>
</tr>
<tr>
<td>28 day mortality, n</td>
<td>22 (14%)</td>
<td>10 (13%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement</td>
<td>1.23 (0.87 - 1.75)</td>
</tr>
<tr>
<td>Subgroup: symptoms &lt; 10 days</td>
<td>1.52 (0.95 – 2.43)</td>
</tr>
</tbody>
</table>

CI: confidence interval; IQR: interquartile range

Remdesivir: ACTT-1

• Double-blind, placebo-controlled, international RCT sponsored by National Institute of Allergy and Infectious Diseases (NIAID)

• 1063 adults with clinical COVID-19 and positive PCR within last 72 hours

• Stratified randomization based on O₂ requirement and study site

• RDV 200 mg IV x1 followed by 100 mg IV daily for 9 days

• Data safety monitoring board reviewed results after enrollment completed
  • Recommended preliminary data be unblinded and reported
  • Final data for the study (including mortality data) are not yet available

Remdesivir: ACTT-1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Remdesivir n=538</th>
<th>Placebo n=521</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to recovery, days (95% CI)</td>
<td>11 (9-12)</td>
<td>15 (13-19)</td>
<td>1.32 (1.12-1.55)</td>
</tr>
<tr>
<td>Baseline 4 (n=67/60)</td>
<td>5 (4-6)</td>
<td>6 (4-8)</td>
<td>1.38 (0.94-2.03)</td>
</tr>
<tr>
<td>Baseline 5 (n=222/199)</td>
<td>7 (6-8)</td>
<td>9 (7-11)</td>
<td>1.47 (1.17-1.84)</td>
</tr>
<tr>
<td>Baseline 6 (n=98/99)</td>
<td>16 (NE-10)</td>
<td>22 (NE-12)</td>
<td>1.2 (0.79-1.81)</td>
</tr>
<tr>
<td>Baseline 7 (n=125/147)</td>
<td>--</td>
<td>28 (NE-22)</td>
<td>0.95 (0.64-1.42)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 day mortality</td>
<td>0.70 (0.47-1.04)</td>
</tr>
<tr>
<td>Baseline 4 (n=67/60)</td>
<td>0.46 (0.04-5.08)</td>
</tr>
<tr>
<td>Baseline 5 (n=222/199)</td>
<td>0.22 (0.08-0.58)</td>
</tr>
<tr>
<td>Baseline 6 (n=98/99)</td>
<td>1.12 (0.53-2.38)</td>
</tr>
<tr>
<td>Baseline 7 (n=125/147)</td>
<td>1.06 (0.59-1.92)</td>
</tr>
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Remdesivir: SIMPLE

- SIMPLE trial: open-label, RCT of 5 vs 10 days of remdesivir
- 397 adults with laboratory-confirmed COVID-19 and SpO$_2$ < 94% on RA

<table>
<thead>
<tr>
<th></th>
<th>5-day (n=200)</th>
<th>10-day (n=197)</th>
<th>Adjusted* difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 Day clinical improvement, n</td>
<td>129 (64%)</td>
<td>107 (54%)</td>
<td>-6.5% (-15.7 to 2.8)</td>
</tr>
</tbody>
</table>

*Adjusted on baseline severity

## Remdesivir: Guidelines

<table>
<thead>
<tr>
<th></th>
<th>NIH</th>
<th>IDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplemental $O_2$</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Supplemental $O_2$</td>
<td>5 days (AI)</td>
<td>5 days</td>
</tr>
<tr>
<td>High flow/NIMV</td>
<td>NR</td>
<td>5 or 10 days (weak recommendation for 5)</td>
</tr>
<tr>
<td>MV/ECMO</td>
<td>NR</td>
<td>10 days</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membranous oxygenation; IDSA: Infectious Diseases Society of America; MV: mechanical ventilation; NIMV: non-invasive mechanical ventilation; NIH: National Institutes of Health NR: no recommendation

RDV Adverse Effects

• Well tolerated in clinical trials
  • Serious adverse events in ACTT-1 occurred in 21.1% with RDV vs 27% with placebo

• AST/ALT elevations observed in healthy subjects and clinical trial participants

• *In vitro* antagonism between RDV and HCQ

• Sulfobutylether-β-cyclodextrin

• No robust data in pregnancy yet
According to the ACTT-1 trial, which patient is most likely to benefit from remdesivir administration?

A. 49-year old male diagnosed with COVID-19 three weeks ago now on ECMO
B. 53-year old female diagnosed with COVID-19 two days ago now on 4L O₂
C. 57-year old female diagnosed with COVID-19 four days ago not requiring supplemental oxygen
D. None of the above
Coronavirus Pathophysiology

Stage I
(Early Infection)

Stage II
(Pulmonary Phase)

Stage III
(Hyperinflammation Phase)

Severity of Illness

Viral response phase

Host inflammatory response phase

Time course

Clinical Symptoms
- Mild constitutional symptoms
  - Fever >99.6°F
  - Dry Cough
- Shortness of Breath without
  (IIA) and with Hypoxia (IIB)
  (PaO2/FiO2<300mmHg)
- Lymphopenia
- Abnormal chest imaging
- Transaminitis
- Low-normal procalcitonin
- ARDS
- SIRS/Shock
- Cardiac Failure
- Elevated inflammatory markers
  (CRP, LDH, IL-6, D-dimer, Ferritin)
- Troponin, NT-proBNP elevation

Potential Therapies
- Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
- Reduce immunosuppression
  (avoid excess steroids)
- Careful use of Corticosteroids; statins; human immunoglobulin,
  IL-1/IL-2/IL-6/IL-10 inhibitors/GM-CSF inhibitors

Dexamethasone

• Corticosteroid selective for glucocorticoid receptor with minimal mineralocorticoid activity

• Exerts anti-inflammatory activity via the glucocorticoid receptor
  • Downregulation of pro-inflammatory cytokines
  • Upregulation of anti-inflammatory cytokines

• Potentially beneficial in acute respiratory distress syndrome (ARDS)
Dexamethasone: RECOVERY

- Open-label, placebo-controlled RCT
- 6425 adults with laboratory-confirmed or clinical COVID-19
  - ~90% laboratory confirmed
- Dexamethasone 6 mg IV or PO daily for 10 days vs usual care
- Preliminary report of dexamethasone arm

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (n=2104)</th>
<th>Usual care (n=4321)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>95%</td>
<td>8%</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>&lt;0.5%</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>HCQ</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>Tocilizumab or sarilumab</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

## Dexamethasone: RECOVERY

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone</th>
<th>Usual Care</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>22.9%</td>
<td>25.7%</td>
<td>0.83 (0.75-0.93)</td>
</tr>
<tr>
<td>No O₂</td>
<td>17.8%</td>
<td>14.0%</td>
<td>1.19 (0.91-1.55)</td>
</tr>
<tr>
<td>Supplemental O₂</td>
<td>23.3%</td>
<td>26.2%</td>
<td>0.82 (0.72-0.94)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>29.3%</td>
<td>41.4%</td>
<td>0.64 (0.51-0.81)</td>
</tr>
</tbody>
</table>

Alternative Steroids

- METCOVID trial
  - Double-blind, placebo-controlled, single center RCT
  - 416 adults admitted with clinical COVID-19 (~80% laboratory confirmed)
  - Methylprednisolone 0.5 mg/kg IV vs placebo
  - No difference in 28-day mortality: 37.1% vs 38.2% ($P = 0.629$)

- Trial issues?
  - Duration
  - Underpowered

- Something special about dexamethasone?
  - Mineralocorticoid sparing
  - Duration of action

# Dexamethasone: Guidelines

<table>
<thead>
<tr>
<th></th>
<th>NIH*</th>
<th>IDSA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplemental O₂</td>
<td>Against (AI)</td>
<td>Against (weak recommendation)</td>
</tr>
<tr>
<td>Supplemental O₂</td>
<td>10 days (BI)</td>
<td>10 days or DC</td>
</tr>
<tr>
<td>High flow/NIMV</td>
<td>10 days (BI)</td>
<td>10 days or DC</td>
</tr>
<tr>
<td>MV/ECMO</td>
<td>10 days (AI)</td>
<td>10 days or DC</td>
</tr>
</tbody>
</table>

*Prednisone, methylprednisone, or hydrocortisone suggested as alternatives if dexamethasone not available (AIII)

ECMO: extracorporeal membranous oxygenation; IDSA: Infectious Diseases Society of America; MV: mechanical ventilation; NIMV: non-invasive mechanical ventilation; NIH: National Institutes of Health NR: no recommendation
Steroid Adverse Effects

• Considerations in pregnancy
  • Potential association with decreased birth weight in first trimester use
  • NIH guidelines: maternal mortality benefit felt to outweigh risk
    • Mechanical ventilation (AIII)
    • Supplemental oxygen (BIII)

• Safety analysis not reported in preliminary data for RECOVERY
  • RECOVERY may underestimate adverse effects as providers could opt out

• Hyperglycemia

• Secondary infections

• Gastrointestinal perforation/bleeding

Which patient is least likely to benefit from dexamethasone?

A. 44-year old diagnosed with COVID-19 on high-flow oxygen
B. 54-year old diagnosed with COVID-19 requiring 1L O₂
C. 28-year old diagnosed with COVID-19 requiring mechanical ventilation
D. 35-year old diagnosed with COVID-19 with no respiratory symptoms admitted for diabetic ketoacidosis
Wrapping Up

• Dexamethasone and remdesivir are both likely beneficial for COVID-19
  • Unclear if remdesivir has a mortality benefit
  • Unclear if dexamethasone is appropriate for all levels of disease severity
  • Confirmatory trials needed

• 5 days of remdesivir appears similarly effective to 10 days

• Dexamethasone may be preferred over other steroids when possible until we know more
Future Directions

- Future trials
  - Remdesivir: ACTT-2, ACTT-3, SIMPLE-2, SOLIDARITY, DISCOVERY

- Combination therapies

- IL-6 inhibitors
  - Phase III trials of tocilizumab and sarilumab did not meet primary/key secondary endpoints

- Other endpoints
  - Loss of taste/smell
  - Chronic fatigue
  - Joint pain
  - Confusion
  - Myocarditis

- Role for biomarkers

Artificially Acquired Immunity

CONVALESCENT PLASMA, MONOCLONAL ANTIBODIES, VACCINES
Adaptive immunity is “the ability of the body to defend itself against **specific** invading agents,” in contrast to non-specific innate immunity (e.g., fever).

Ways to acquire adaptive immunity
- Naturally-acquired active immunity: follows exposure to a microbe
- Naturally-acquired passive immunity: transfer of IgG antibodies from mother to fetus
- Artificially-acquired active immunity: follows vaccination to a microbe
- Artificially-acquired passive immunity: IV injection of immunoglobulins (antibodies)
Immune Basics

R cells make antibodies that activate T-helper cells.

**Vaccine Basics: How We Develop Immunity**
The body’s adaptive immune system can learn to recognize new, invading pathogens, such as the coronavirus SARS-CoV-2.

1. Virus enters the body

**Coronavirus Infection**
The virus uses its surface spike protein to lock onto ACE2 receptors on the surface of human cells. Once inside, these cells translate the virus’s RNA to produce more viruses.

https://www.nature.com/articles/d41586-020-01221-y
Passive Immunity

ARTIFICIALLY ACQUIRED
Intro to Convalescent Plasma (CP)

Not a new idea!

What is it? Passive polyclonal antibodies administered to provide immediate immunity

What’s the biologic plausibility?
- Sharing neutralizing antibodies from one patient may help those who have not yet mounted an adequate antibody response or those whose antibodies are non-neutralizing

Theoretical use for prophylaxis, but the focus today will be on treatment

Recently granted Emergency Use Authorization by the FDA

Convalescent Plasma Donation

Timing of serologic IgG conversion: median 11 days (range 8 to 16 days)

Process: apheresis

Criteria for donation:
- Proven disease
- Recovery at least 14 days
- Eligible to donate blood products
- HLA-antibody negative
- Optimally, neutralizing antibody titers >1:80 (cannot be obtained easily)
- 300-1000 mL of plasma per donation / may donate every 28 days

For more information visit the Red Cross website or go to ccpp19.org


Largest CP Study

Prospective, non-randomized, observational trial of 35,322 hospitalized adults

Inclusion: hospitalized patients with laboratory-confirmed SARS-CoV2 and severe disease (or at risk for severe disease) who received at least one unit (~200 mL) of COVID-19 convalescent plasma

Outcomes: differences found in unadjusted, but very minimally in adjusted analyses

<table>
<thead>
<tr>
<th></th>
<th>Transfused ≤ 3 days of diagnosis</th>
<th>Transfusion 4 days or greater</th>
<th>p value</th>
<th>Low IgG plasma (&lt;4.62 S/Co)*</th>
<th>High IgG plasma (&gt;18.45 S/Co)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-day mortality</td>
<td>8.7%</td>
<td>11.9%</td>
<td>&lt;0.001</td>
<td>13.7%</td>
<td>8.9%</td>
<td>0.048</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>21.6%</td>
<td>26.7%</td>
<td>&lt;0.0001</td>
<td>29.6%</td>
<td>22.3%</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Limitation: time bias whereby both 7-day crude mortality and time to transfusion decreased (e.g., June 04 – July 04 30-day mortality difference early vs late transfusion 18.4% vs 20.2%)

*In a subset of 3,082 transfused patients who received only a single unit of plasma
S/Co: signal-to-cut-off ratio by Ortho-Clinical IgG CLIA qualitative assay – high = ~80th percentile

Only RCT for CP

Open-label, multicenter, RCT

Inclusion: hospitalized patients with symptomatic, confirmed COVID-19

Exclusion: immunoglobulin allergy, IgA deficiency, comorbidity that increases the risk of thromboembolism, disseminated intravascular coagulation, severe congestive heart failure, or detection of high titer of S protein-RBD-specific IgG antibody (≥ 1:640)

Intervention group: 4-13 mL per kg matched ABO type and crossmatched RBCs.

Control group: standard of care per Chinese national COVID-19 treatment guidelines

<table>
<thead>
<tr>
<th></th>
<th>Plasma (n=52)</th>
<th>Standard of Care (n=51)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical improvement by day 28*</td>
<td>27 (52%)</td>
<td>22 (43%)</td>
<td>0.26</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>8 (16%)</td>
<td>12 (24%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Negative SARS-CoV-2 PCR at 72 h**</td>
<td>41/47 (87%)</td>
<td>15/40 (38%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Post-hoc analysis suggested greater effect in severe patients (less effect in life-threatening disease)

**Time between symptom onset and randomization was 30 days.

## Cochrane Review of CP for COVID-19

20 studies, 5443 patients, high risk for bias.

<table>
<thead>
<tr>
<th>Outcome and Study Design</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Group</td>
<td>Plasma Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality at hospital discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C, NR studies</td>
<td>933 per 1000</td>
<td>830 per 1000</td>
<td>0.89 (0.61-1.31)</td>
<td>21 (1 study)</td>
</tr>
</tbody>
</table>

| Improvement of clinical symptoms, assessed by need for respiratory support, 15 day follow up | | | | |
| RCT at day 14            | 176 per 1000 | 326 per 1000 | 1.85 (0.91-3.77) | 103 (1 study) | Very low |
| C, NR studies            | 756 per 1000 | 817 per 1000 | 1.08 (0.91-1.29) | 195 (1 study) | Very low |

C=controlled, NR=non-randomized, RCT = randomized controlled trial
If there is a benefit with convalescent plasma, those most likely to benefit include:

- Those early in the course of infection
- Prior to progression to life-threatening illness
Potential Risks of CP

Transfusion-related reactions
- Transfusion-related acute lung injury (TRALI) (0.22%)
- Transfusion associated circulatory overload (TACO) (0.14%)
- Allergic reaction (0.06%)

Reduction in INR for patients on warfarin (monitor INR)

Theoretical antibody-dependent enhancement

Infection risks from donor

Monoclonal Antibodies Rationale

Targets the surface spike glycoprotein that mediates viral entry into the host cell

Avoids challenges of CP
- Collection challenges
- Unpredictable antibody titers
- Traditional transfusion risks

Could we *manufacture* the antibodies we are trying to capture from recovered patients?

Other examples of this approach in infectious diseases:
- Palivuzumab for respiratory syncytial virus (RSV)
- Raxibacumab for anthrax
- Bevacizumab for *C. difficile*

Has potential for both prophylaxis and treatment
Leading two in development in the United States:

- **REGN-COV-2**: binds to two points on the SARS-CoV-2 spike protein to prevent cell entry
  - NCT04452318: asymptomatic household contacts
  - NCT04425629: symptomatic non-hospitalized adults
  - NCT04426695: hospitalized adults

- **LY-CoV**: potent, neutralizing IgG1 mAb directed against the spike protein of SARS-CoV-2
  - NCT04497987 (LY-CoV555) (BLAZE-2): high risk of exposure due to residing or working in SNFs
  - NCT04427501 (LY-CoV555 with LY-CoV016) (BLAZE-1): symptomatic non-hospitalized adults
  - NCT04501978 (using LY3819253) (ACTIV-3): hospitalized adults

**SNF**: skilled nursing facility

**ACTIV-3**: Accelerating COVID-19 Therapeutic Interventions and Vaccines 3

What are the potential benefits of monoclonal antibodies (select all that apply):

A. Evidence of better efficacy against COVID-19 compared with convalescent plasma
B. Increased odds of getting a product with high antibody concentrations
C. Ensures the antibodies administered to the patient have neutralizing ability
D. Avoids the infectious risk associated with donated blood products
E. A better tolerability profile than convalescent plasma
Vaccines
Operation Warp Speed

Goal: produce and deliver 300 million doses of safe and effective vaccines with initial doses available by January 2021, as part of a broader strategy…

Usual **73-month** process → Aggressive **14-month** process

Led by HHS Secretary Alex Azar and Defense Secretary Mark Esper

Partners: HHS, CDC, FDA, NIH, BARDA, DoD

Funding: $10 million directed by Congress

Example supportive actions:

- Awarded funds to support the development of vaccine candidates with terms that require a certain amount of said vaccine be available to the U.S. Government in return (at a cost)
- Invested in early manufacturing of necessary supplies, including syringes and vials
- Coordinating distribution with McKesson Corporation as a central distributor

**HHS**: Department of Health and Human Serviced, **CDC**: Centers for Disease Control and Prevention; **FDA**: Food and Drug Administration; **NIH**: National Institutes of Health; **BARDA**: Biomedical Advanced Research and Development Authority; **DoD**: Department of Defense

Why Vaccine Development is Crucial

The best vaccine candidate would be safe, offer a high level of protection, have extended duration of immunity, adequate stability, and convenient administration.

<table>
<thead>
<tr>
<th>Near Term</th>
<th>Mid Term</th>
<th>Future Term</th>
</tr>
</thead>
</table>
| • Prevent infection and death  
  • Controlled utilization of healthcare resources  
  • Control outbreak  
  • Develop herd immunity  
  • Gradual economic recovery | • Facilitate periodic COVID-19 vaccinations to prevent outbreaks  
  • Address potential viral mutations | • Strengthen global response to future pandemics |
Vaccine Basics

B cells make antibodies that can block the virus from infecting cells, as well as mark the virus for destruction. Cytotoxic T cells identify and destroy virus-infected cells.

Prevents virus from binding, or tags it for destruction

Long-lived ‘memory’ B and T cells that recognize the virus can patrol the body for months or years, providing immunity

https://www.nature.com/articles/d41586-020-01221-y
The Current Vaccine Landscape


**Coronavirus Vaccine Tracker**

By Jonathan Corum, Denise Grady, Sui-Lee Wee and Carl Zimmer  Updated August 27, 2020

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>LIMITED</th>
<th>APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>14</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

- Vaccines testing safety and dosage
- Vaccines in expanded safety trials
- Vaccines in large-scale efficacy tests
- Vaccines approved for early or limited use
- Vaccines approved for full use

# Vaccines in Phase 3 Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Vaccine Type</th>
<th>Key Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna/NIH (USA)</td>
<td>mRNA vaccine (mRNA-1273)</td>
<td>2-dose vaccine schedule phase I</td>
</tr>
<tr>
<td>BioNTech/Pfizer/FosunPharma (German/USA/China)</td>
<td>mRNA vaccine (BNT162b2)</td>
<td>2-dose vaccine schedule phase I</td>
</tr>
<tr>
<td>CanSino Biologics (China)</td>
<td>Adenovirus type-5-vectored</td>
<td>Single dose (1st phase I report)</td>
</tr>
<tr>
<td>AstraZeneca/ U of Oxford (Sweden/England)</td>
<td>Chimpanzee adenovirus (ChAdOx1 nCoV-19)</td>
<td>2-dose vaccine schedule phase I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylactic acetaminophen</td>
</tr>
<tr>
<td>Wuhan Institute of Biological Products/Sinopharm (China)</td>
<td>Inactivated virus</td>
<td>3-dose vaccine schedule phase I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-dose vaccine schedule phase 2</td>
</tr>
<tr>
<td>Beijing Institute of Biological Products/Sinopharm (China)</td>
<td>Inactivated virus</td>
<td></td>
</tr>
<tr>
<td>Sinovac Biotech (China)</td>
<td>Inactivated virus (CoronaVac)</td>
<td>2-dose vaccine schedule phase I</td>
</tr>
<tr>
<td>Murdoch Children’s Research Institute (Australia)</td>
<td>Re-purposed BCG vaccine</td>
<td>Single dose (BRACE trial)</td>
</tr>
</tbody>
</table>

The New Kid on the Block: mRNA Vaccines

No successful mRNA vaccine FDA-approved to date

Technically categorized as gene therapy

Challenges:
- Efficient intracellular delivery of large, negatively-charged molecule
- Naked mRNA is rapidly degraded by extracellular RNAses (thus the nanoparticle encapsulation)
- Risk of autoimmune reactions; free RNA can cause edema and clotting, local and systemic inflammation, including severe injection site reactions

Benefits:
- Avoids potential risk of genomic integration associated with DNA vaccines
- Efficacious in both mitotic and non-mitotic cells unlike DNA vaccines
- Avoids common risks associated with cell culture vaccines
- Short manufacturing time
# Early Trial Data: mRNA Vaccine

Phase I, dose-escalation, open-label trial, n = 45 healthy adults

Doses: 25-mcg, 100-mcg, and 250-mcg x2 doses given on days 1 and 29

<table>
<thead>
<tr>
<th>Antibody Response</th>
<th>T-Cell Response</th>
<th>Safety Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-mcg and 250-mcg dose groups were similar to the median magnitude of convalescent serum specimens after the 1st dose, and the upper quartile after the 2nd dose</td>
<td>Th1 response &gt; Th2 CD4 response with a low CD8 response with 25-mcg and 100-mcg doses</td>
<td>Systemic reactions (fever, myalgia, headache, etc.) in 67% (1st) and 100% (2nd) doses*</td>
</tr>
<tr>
<td>Neutralizing activity low until after the 2nd vaccination, similar 100-mcg and 250 mcg doses</td>
<td></td>
<td>Local reactions (pain, swelling, induration) occurred in nearly 100% of participants*</td>
</tr>
</tbody>
</table>

*100-mcg dose

Early Trial Data: Adenoviral Vector

Phase I/II, participant-blinded, multicenter, RCT

Doses: \(5 \times 10^{10}\) viral particles or MenACWY (Phase I) as a single IM dose

Two of five sites protocol amendment for prophylactic acetaminophen

<table>
<thead>
<tr>
<th>Antibody Response</th>
<th>T-Cell Response</th>
<th>Safety Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various assays performed differently, neutralizing ability was 62-100% (up to 100% with booster)</td>
<td>Marked increase in effector T-cell responses occurred (limited details provided)</td>
<td>Solicited systemic reactions: feeling feverish in 51% without and 36% with acetaminophen, most common reaction was fatigue at 70% regardless of concomitant acetaminophen</td>
</tr>
<tr>
<td>No negative impacts of acetaminophen</td>
<td></td>
<td>Solicited local reactions: pain in 50% without and 32% with acetaminophen</td>
</tr>
</tbody>
</table>

Folegatti PM, et al. Lancet 2020; Published online July 20, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31604-4
### Early Trial Data: Inactivated Virus

Double-blind, randomized, placebo-controlled phase 1 and 2 trials in 96 and 224 healthy adults

Doses: 2.5-mcg, 5-mcg, and 10-mcg given on days 0, 28 and 56 or control (phase 1)  
5-mcg on days 0 and 14 or days 0 and 21 (phase 2)

<table>
<thead>
<tr>
<th>Antibody Response</th>
<th>T-Cell Response</th>
<th>Safety Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific IgG Ab seroconversion occurred in 100% (42/42) with days 0 and 21 and 86% (36/42) with days 0 and 14 schedule</td>
<td>No notable changes in Th2 cell-related cytokines (key because alum-adjuvanted)</td>
<td>Solicited systemic reactions (fever, myalgia, headache, etc.) in 5% of participants*</td>
</tr>
<tr>
<td>Neutralizing activity low until after the 2nd vaccination, and occurred in 82/84 (98%) in Phase 2</td>
<td>T-cell-mediated immune responses were not measured</td>
<td>Solicited local reactions (pain, swelling, induration) occurred in as many as 16% of participants*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No participants withdrew</td>
</tr>
</tbody>
</table>

*5-mcg dose

Challenges for COVID-19 Vaccination

**Safety:** vaccines have the potential risk of excess side effects and possible rare antibody dependent enhancement of disease

**Demonstrating efficacy:** will require adaptable enrollment in high-prevalence locations or novel approaches

**Mutation:** low to moderate mutation rate could impact select vaccine candidates

**Uptake:** recent vaccine hesitancy and known low rates of influenza vaccination – recent surveys suggest only 3 in 4 people would get vaccinated if a COVID-19 vaccine were available, and only 30% would want to receive the vaccine soon after it becomes available

**How you can help:** be transparent about vaccine effectiveness and adverse effects, take care to avoid unintentionally overemphasizing the risk of rare adverse events
Which description below best describes Operation Warp Speed?

A. A focused strategy designed by the U.S. Government to bring the one best SARS-CoV-2 vaccine to market by Spring of 2021

B. A collaborative of pharmaceutical companies to share knowledge and facilitate the faster development of a SARS-CoV-2 vaccine

C. A broad strategy by the U.S. Government to support the development, manufacture and distribution of 300 million doses of safe and effective vaccines by January 2021

D. A competitive group of vaccine development companies all racing to finish phase 3 vaccine clinical trials the fastest
Which of the following is true regarding mRNA vaccines?

A. mRNA vaccines are a well-established method of vaccination in humans and are currently approved for a variety of infectious diseases

B. Potential risk of mRNA vaccines include autoimmune reactions, edema, clotting, and severe injection site reactions

C. mRNA vaccines are considered gene therapy and are challenged with long production times using cell cultures

D. mRNA vaccines, unlike other vaccine strategies, have a higher odds of inducing antibody-dependent enhancement
Conclusions

Best available data support the use of dexamethasone and remdesivir in patients with COVID-19 with greater benefit to remdesivir earlier in the disease course and dexamethasone later in the disease course.

Hydroxychloroquine is no longer recommended for COVID-19.

Two strategies to provide passively-acquired immunity include convalescent plasma and monoclonal antibodies.

Several promising vaccine candidates are in Phase III clinical trials, many of which have significant systemic and local reactions.
References


References (cont.)


19. Folegatti PM, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trialLancet 2020; Published online July 20, 2020. DOI:https://doi.org/10.1016/S0140-6736(20)31604-4