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

Coronavirus Life Cycle

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 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

Medications to Treat COVID-19

**ANTIVIRALS AND IMMUNE-TARGETING THERAPIES**

**ANTIVIRALS**
- Baricitinib
- Chloroquine
- Favipiravir
- Ivermectin
- Merimepodib
- Remdesivir
- Ruxolitinib

**IMMUNE-TARGETING THERAPIES**
- Baricitinib
- Chloroquine/Hydroxychloroquine (HCQ)
- Colchicine
- Dexamethasone
- Famotidine
- Interleukin-6 (IL-6) inhibitors
- Ivermectin
- Losartan
- Lopinavir
- Merimepodib
- Nitazoxanide
- 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

Putative COVID-19 Therapy Mechanisms
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  
  - Non-significant, 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**

![Image of putative COVID-19 therapy mechanisms](image)

**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

**Outcome**

<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>

**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

**Outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Remdesivir n=538</th>
<th>Placebo n=521</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to recovery, days (95% CI)</td>
<td>11 (9-12)</td>
<td>15 (13-19)</td>
</tr>
<tr>
<td>14 day mortality, n (%)</td>
<td>129 (64%)</td>
<td>107 (64%)</td>
</tr>
</tbody>
</table>

**Remdesivir: SIMPLE**

- SIMPLE trial: open-label, RCT of 5 vs 10 days of remdesivir
  - 397 adults with laboratory-confirmed COVID-19 and SpO₂ < 94% on RA
  - 5-day (n=200) vs 10-day (n=197)
  - Adjusted difference (95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>5-day (n=200)</th>
<th>10-day (n=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 Day Clinical improvement, n</td>
<td>129 (64%)</td>
<td>107 (64%)</td>
</tr>
</tbody>
</table>

*Adjusted on baseline severity*
Remdesivir: Guidelines

<table>
<thead>
<tr>
<th>No supplemental O₂</th>
<th>NR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemental O₂</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

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
Dexamethasone: RECOVERY

<table>
<thead>
<tr>
<th>28-Day Mortality</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>24.0%</td>
<td>1.33 (0.93-1.92)</td>
</tr>
<tr>
<td>Supplemental O2</td>
<td>23.3%</td>
<td>28.2%</td>
<td>0.83 (0.72-0.94)</td>
</tr>
<tr>
<td>Mechanical</td>
<td>20.3%</td>
<td>41.4%</td>
<td>0.49 (0.31-0.78)</td>
</tr>
</tbody>
</table>


- 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% ($P = 0.620$)

**Trial issues?**
- Duration
- Underpowered

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

Alternative Steroids


Dexamethasone: Guidelines

<table>
<thead>
<tr>
<th>NIH</th>
<th>CSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplemental O2</td>
<td>Against (AI)</td>
</tr>
<tr>
<td>Supplemental O2</td>
<td>10 days (BII)</td>
</tr>
<tr>
<td>High-flow/NIMV</td>
<td>10 days (BII)</td>
</tr>
<tr>
<td>MV/ECMO</td>
<td>10 days (AI)</td>
</tr>
</tbody>
</table>

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


- 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

Steroid Adverse Effects


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

- 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

Some Immunology Terminology

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

ARTIFICIALLY ACQUIRED

Passive Immunity

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)

Criteria for donation:
- Proven disease
- Recovery at least 14 days
- Eligible to donate blood products
- HLA-antibody negative
- Optimally, neutralizing antibody titer >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

https://www.grifolsplasma.com/en/plasma

[Only RCT for CP]

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

Cochrane Review of CP for COVID-19

20 studies, 5443 patients, high risk for bias.

Outcome and Study Design | Anticipated absolute effects | Relative risk (95% CI) | No. of participants (studies) | Certainty of the evidence
--- | --- | --- | --- | ---
All-cause mortality at hospital discharge | C: NR studies 938 per 1000 vs NR studies 850 per 1000 | 0.89 (0.81-0.97) | 21 (5 studies) | Very low
Improvement of clinical symptoms, assessed by need for respiratory support, 35 day follow up | C: NR studies 176 per 1000 vs NR studies 326 per 1000 | 1.85 (1.92-3.77) | 100 (3 studies) | Very low
RCT at day 14 | C: NR studies 716 per 1000 vs NR studies 837 per 1000 | 1.08 (0.95-1.22) | 215 (5 studies) | Very low

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

Infusion risks from donor
Monoclonal Antibodies Rationale

Targets the surface spike glycoprotein that mediates viral entry into the host cell
- Aids in the development of a successful vaccine
- Minimizes viral replication

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

Other examples of this approach in infectious diseases:
- Palivizumab for respiratory syncytial virus (RSV)
- Bevacizumab for COVID-19
- Rituximab for rheumatoid arthritis

Has potential for both prophylaxis and treatment

Monoclonal Antibodies in Trials

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
- Bamlanivimab: neutralizing IgG1 mAb directed against the spike protein of SARS-CoV-2

Other examples of this approach in infectious diseases:
- Raxibacumab for anthrax
- Palivizumab for respiratory syncytial virus (RSV)

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

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

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

Vaccines

- Preven 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

- a virus-antibody complex that can block the virus from entering the cell.
- Neutralizing activity is low until after the 2nd dosage.
- The upper quartile after the 2nd dose was the 2nd vaccination, similar to 100-mcg and 250 mcg doses.
- Antibody responses occurred (limited details provided).

The Current Vaccine Landscape

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

- **Company Vaccine**
- mRNA Vaccine: Moderna/MGH (USA), mRNA vaccine (mRNA-1273).
- Biontech/Pfizer/Fosun Pharma (Germany/USA/China), mRNA vaccine (BNT162b2).
- AstraZeneca (UK), adenovirus vaccine (ChAdOx1 nCoV-19).
- Nanobiotix/Vaccitech, adenovirus vaccine.
- CanSino Biologics (China), adenovirus vaccine.
- BioNTech/Pfizer/Fosun Pharma (Sweden/England).
- Sinovac Biotech (China), inactivated virus vaccine (CoronaVac).
- Oxford University (UK), inactivated virus vaccine (AstraZeneca).
- Moderna/NIH (Australia), mRNA vaccine (mRNA-1273).
- AstraZeneca (UK), adenovirus vaccine.
- Sanofi Pasteur (France), inactivated virus vaccine (MenACWY).
- GlaxoSmithKline (USA), inactivated virus vaccine (MenACWY).
- Johnson & Johnson (USA), adenovirus vaccine (Janssen).

Vaccines in Phase 3 Development

- **Company**
- Moderna/MGH (USA)
- Biontech/Pfizer/Fosun Pharma (Germany/USA/China)
- AstraZeneca (UK)
- Nanobiotix/Vaccitech
- CanSino Biologics (China)
- BioNTech/Pfizer/Fosun Pharma (Sweden/England)
- Sinovac Biotech (China)
- Moderna Children's Research Institute (Australia)

<table>
<thead>
<tr>
<th>Company</th>
<th>Vaccine Type</th>
<th>Key Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna/MGH</td>
<td>mRNA vaccine (mRNA-1273)</td>
<td>2-dose vaccine schedule phase 1</td>
</tr>
<tr>
<td>Biontech/Pfizer</td>
<td>mRNA vaccine (BNT162b2)</td>
<td>2-dose vaccine schedule phase 1</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>adenovirus vaccine</td>
<td>Adjuvanted type-5 restorated</td>
</tr>
<tr>
<td>Nanobiotix/Vaccitech</td>
<td>inactivated virus</td>
<td>Inactivated virus in 3-25 dose schedule phase 2</td>
</tr>
<tr>
<td>CanSino Biologics</td>
<td>inactivated virus (Coronavac)</td>
<td>2-dose vaccine schedule phase 1</td>
</tr>
<tr>
<td>BioNTech/Pfizer</td>
<td>inactivated virus</td>
<td>2-dose vaccine schedule phase 2</td>
</tr>
<tr>
<td>Sinovac Biotech</td>
<td>inactivated virus</td>
<td>2-dose vaccine schedule phase 1</td>
</tr>
<tr>
<td>Moderna Children's Research Institute</td>
<td>re-purposed BCG vaccine</td>
<td>Single dose (BCG)</td>
</tr>
</tbody>
</table>

Early Trial Data: mRNA Vaccine

- **Trial Design**
  - Phase I: dose-escalation, open-label trial, n = 45 healthy adults.
  - Doses: 25-mcg, 100-mcg, and 250-mcg x 2 doses given on days 1 and 29.

- **Endpoints**
  - Safety: No negative impacts of prophylactic acetaminophen.
  - Efficacy: 62-100% (up to 100% with booster).

- **Adverse Events**
  - Solicited local reactions: pain in 62-70% and 89%.
  - Solicited systemic reactions: headache, fatigue, and chills.

- **Clinical Observations**
  - One participant withdrew because of transient urticaria.

Early Trial Data: Adenoviral Vector

- **Trial Design**
  - Phase III, participant-blinded, multicenter, RCT.
  - Doses: 5x10^11 viral particles or MenACWY (Phase I) as a single IM dose.
  - Two of five sites protocol amendment for prophylactic acetaminophen.

- **Adverse Events**
  - Acetaminophen: 50% without and 32% with acetaminophen.
  - Common reaction was fatigue at 36% with acetaminophen, most common reaction was sweating.
  - Most common reactions were headache and feeling feverish.

- **Clinical Observations**
  - Marked increase in effector T-cell responses occurred (limited details provided).
  - No negative impacts of acetaminophen.
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>Antigenic Coverage</th>
<th>Cell Response</th>
<th>Safety Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific IgG Ab.</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</td>
<td>No local reactions (pain, swelling, induration) occurred in as many as 10% of participants*</td>
<td>No participants withdrew</td>
</tr>
</tbody>
</table>

Notes:
*5-mcg dose

References
63 64

Challenges for COVID-19 Vaccination

Safety: vaccines have the potential risk of excess side effects and possible 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 10 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

References
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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
10. Lee et al. Safety and efficacy of COVID-19 convalescent plasma in patients with COVID-19: a randomized controlled trial. Available at: https://www.jama.com/jama/fulltext/2020/690933/1802020
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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 trial Lancet 2020; Published online July 20, 2020. DOI:https://doi.org/10.1016/S0140-6736(20)31604-4