COVID-19 Therapeutics: Chaos to Evidence in a Pandemic

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Director of Stewardship Innovation, UPMC and Infectious Disease Connect
COVID-19 Therapeutics

How it started

Donald J. Trump
@realDonaldTrump

HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine. The FDA has moved mountains - Thank You! Hopefully they will BOTH (H works better with A, International Journal of Antimicrobial Agents).....

10:13 PM · Mar 21, 2020 · Twitter for iPhone

132.6K Retweets 384.1K Likes
COVID-19 MEDICATION ALERT

This drug **SHOULD NOT** be ordered for **treatment** of COVID-19.

This medication **CAN** be ordered for other, **non-COVID-19 treatment indications**, in a PUI or with confirmed COVID-19.

Do **NOT** use with hydroxychloroquine due to potential for additive QTC prolongation.

Consider doxycycline for treatment of CAP if patient is also receiving hydroxychloroquine.

Medication: azithromycin

**Alert Action:**
- [x] Cancel azithromycin

[Continue]
COVID-19 Therapeutics

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How it’s going

Modern & Pfizer & Johnson & Johnson
First things first...

The vaccines are incredible, amazing, advances in the art and science of medicine and everyone should get vaccinated if you haven’t already (please) + encourage everyone around you to get vaccinated.
Hi, Erin

Physician Services Division
Pharmacy

COVID-19 Clinical Care Protocols

COVID-19 Home Health and Family Hospice Protocols
COVID-19 Inpatient Protocols
COVID-19 Long-Term Care Protocols
COVID-19 Outpatient Protocols

COVID-19 Inpatient Clinical Treatment

COVID-19 Anticoagulation
COVID-19 Antimicrobial Stewardship
COVID-19 Blood Handling
COVID-19 Coding Guidelines
COVID-19 Dragon Medical One Dictation

COVID-19 Inpatient Admission PowerPlan
COVID-19 Inpatient Capacity Resources
COVID-19 Inpatient Clinical Care Delivery for Service Lines and Units
COVID-19 Laboratory Information
COVID-19 REMAP Trial and Treatment Guidelines
COVID-19 Inpatient Pharmacological Treatment Options

Updated April 7:
This information is updated frequently during this evolving situation. Refer to infonet often for the latest information and communications.

Starting Thursday, April 9, providers will complete the COVID-19 Intake Form for all adult (18 years or older) patients admitted to UPMC hospitals using Cerner as the EHR. Note: UPMC Pinnacle patients are not included in this trial. Hydroxychloroquine approval will be via locally designed pathways.

This form will assess all patients for eligibility for the REMAP-COVID clinical trial, where patients may be randomized to receive:
- Hydroxychloroquine versus nothing (all inpatients)
- Hydrocortisone standard dose versus hydrocortisone medium dose versus nothing (ICU patients)

UPMC does NOT recommend:
- Prophylaxis against COVID-19. Prescribers should NOT prescribe for this indication and pharmacists should NOT verify for this indication.
- Treatment for inpatients outside of randomized, controlled trials. For questions about patients who are ineligible for a trial, email covid19therapeutics@upmc.edu.

No provider is required to prescribe antiviral agents for inpatients with COVID-19 outside of a clinical trial given the absence of convincing data for efficacy and outcomes.
### Severity of Illness

<table>
<thead>
<tr>
<th>Mild to Moderate, Not Hospitalized</th>
<th>Defining Characteristics</th>
<th>Remdesivir (see page 2)</th>
<th>Steroids (see page 3)</th>
<th>Monoclonal Antibodies (see page 6-7)</th>
<th>Empiric Therapeutic Anticoagulation (see page 7)</th>
<th>Tocilizumab, Sarilumab, Baricitinib (see page 3-5)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| • Outpatient or Emergency Department  
• Not requiring supplemental oxygen above baseline needs | Not recommended. | Patients breathing ambient air should not receive systemic corticosteroids. | Monoclonal antibody combination treatment is recommended for all patients meeting EUA criteria. | Not recommended outside the context of a clinical trial. | | | Inhaled budesonide: Neither recommend for nor against (see page 9). |

### Moderate-Severe

<table>
<thead>
<tr>
<th>Defining Characteristics</th>
<th>Remdesivir (see page 2)</th>
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<th>Tocilizumab, Sarilumab, Baricitinib (see page 3-5)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| • Hospitalized  
• Breathing ambient air  
• Radiographic evidence of pneumonia  
  • SpO2 > 94%: High risk patients only (see notes).  
  • SpO2 ≤ 94%: 200mg x 1 day, then 100mg daily until back to room air or baseline oxygenation support, not to exceed 5 days. | Not recommended. | Patients breathing ambient air should not receive systemic corticosteroids. | | Consider therapeutic anticoagulation if no contraindication based on benefit observed in the REMAP-Cap trial. | Not recommended. | High risk patients:  
• Solid organ transplant  
• HCT within 100 days of transplant or with ongoing immunosuppression for GVHD  
• Receipt of rituximab, tocilizumab, or olaratumab within previous 60 days  
• Receipt of CAR T within 2 years or with ongoing neutropenia  
• Receipt of chemotherapy for malignancy within 60 days, active leukaemia, or MDS  
| Discontinue remdesivir at time of discharge. Patients should not be kept inpatient to complete 5 days of therapy if they are otherwise medically ready for discharge. |

### Severe: Low-flow oxygen

<table>
<thead>
<tr>
<th>Defining Characteristics</th>
<th>Remdesivir (see page 2)</th>
<th>Steroids (see page 3)</th>
<th>Monoclonal Antibodies (see page 6-7)</th>
<th>Empiric Therapeutic Anticoagulation (see page 7)</th>
<th>Tocilizumab, Sarilumab, Baricitinib (see page 3-5)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| • Hospitalized  
• Requiring low-flow supplemental oxygen  
  • 200mg x 1 day, then 100mg daily until back to room air or baseline oxygenation support, but not to exceed 5 days. | Not recommended. | Dexamethasone 6mg PO/IV for up to 10 days. | | | | Discontinue remdesivir at time of discharge. Patients should not be kept inpatient to complete 5 days of therapy if they are otherwise medically ready for discharge. |

### Severe: High-flow or noninvasive ventilation

<table>
<thead>
<tr>
<th>Defining Characteristics</th>
<th>Remdesivir (see page 2)</th>
<th>Steroids (see page 3)</th>
<th>Monoclonal Antibodies (see page 6-7)</th>
<th>Empiric Therapeutic Anticoagulation (see page 7)</th>
<th>Tocilizumab, Sarilumab, Baricitinib (see page 3-5)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| • Hospitalized  
• Requiring high-flow nasal cannula or noninvasive ventilation  
  • 200mg x 1 day, then 100mg daily until back to room air or baseline oxygenation support, but not to exceed 5 days. | Not recommended. | Dexamethasone 6mg PO/IV for up to 10 days. | | | | Consider remdesivir discontinuation if patient is not immunocompromised and progresses to require high-flow oxygen support or worse. |

### Severe-Critical

<table>
<thead>
<tr>
<th>Defining Characteristics</th>
<th>Remdesivir (see page 2)</th>
<th>Steroids (see page 3)</th>
<th>Monoclonal Antibodies (see page 6-7)</th>
<th>Empiric Therapeutic Anticoagulation (see page 7)</th>
<th>Tocilizumab, Sarilumab, Baricitinib (see page 3-5)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| • Hospitalized  
• Mechanically ventilated and/or ECMO | Not recommended. | Dexamethasone 6mg PO/IV for up to 10 days. | | | | | Large, randomized trials demonstrated no benefit of remdesivir or therapeutic anticoagulation in patients requiring mechanical ventilation. |

Discontinue steroids if supplemental oxygen no longer required. For patients requiring oxygen on discharge, see steroid section below.
Learning While Doing

- There is no magic bullet
- Not intervening is not “doing nothing”
- EHR-integration of clinical trials
- The only way to find an answer is to find an answer

Angus DC. JAMA. 2020.
Table 1. Thirty-Day Mortality Rate of Test Positive and Hospitalized Cases by Wave

<table>
<thead>
<tr>
<th>Wave</th>
<th>Patient Time Period</th>
<th>All Test Positives</th>
<th>Hospitalized Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>March 19 – June 16, 2020</td>
<td>1369</td>
<td>358</td>
</tr>
<tr>
<td>2</td>
<td>June 17 – September 19, 2020</td>
<td>3926</td>
<td>859</td>
</tr>
<tr>
<td>3a</td>
<td>September 20 – December 13, 2020</td>
<td>21471</td>
<td>3925</td>
</tr>
<tr>
<td>3b</td>
<td>December 14, 2020 – March 10, 2021</td>
<td>18637</td>
<td>4174</td>
</tr>
<tr>
<td>4</td>
<td>March 11 – May 7, 2021</td>
<td>6378</td>
<td>1674</td>
</tr>
</tbody>
</table>

Factors associated with 30-day mortality:
Date of hospital admission (per month) aOR: 0.95 (95% CI 0.92 – 0.97, p <.001)

Outpatient Management
Mild-Moderate Disease

• Outpatient or Emergency Department
• Hospitalized, SpO2 >94% breathing ambient air, no radiographic evidence of pneumonia
  • “It’s not about the dry wall”
• Not requiring supplemental oxygen above baseline needs
• Symptom management!!!

Y = Recommended
N = Not recommended
T = Clinical trial only

- Remdesivir
- Systemic steroids
- Monoclonal Antibodies
- Convalescent Plasma
- Therapeutic Anticoagulation
- Immunomodulators
Monoclonal antibodies (mAb) work 😊

<table>
<thead>
<tr>
<th>Study</th>
<th>mAb treated</th>
<th>Placebo</th>
<th>Relative risk</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Bamlanivimab-**etesevimab (Lilly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0/518 (0.0%)</td>
<td>10/517 (1.9%)</td>
<td>0.05 (0.0-0.8)</td>
<td>19 fewer per 1000 (-31 to -7)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>11/517 (2.1%)</td>
<td>36/517 (7%)</td>
<td>0.30 (0.16-0.59)</td>
<td>49 fewer per 1000 (-58 to -29)</td>
</tr>
<tr>
<td><strong>Casirivimab-imdevimab (Regeneron)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>1/736 (0.1%)</td>
<td>1/738 (0.1%)</td>
<td>1.02 (0.06-16.2)</td>
<td>0 fewer per 1000 (-4 to -4)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>6/736 (0.8%)</td>
<td>23/738 (3.1%)</td>
<td>0.27 (0.11-0.65)</td>
<td>22 fewer per 1000 (-27 to -11)</td>
</tr>
<tr>
<td><strong>Sotrovimab (GSK/Vir)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0/291 (0.0%)</td>
<td>1/292 (0.3%)</td>
<td>0.33 (0.01-8.18)</td>
<td>3 fewer per 1000 (-10 to 3)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3/291 (1%)</td>
<td>21/292 (7.2%)</td>
<td>0.11 (0.02-0.45)</td>
<td>62 fewer per 1000 (-69 to -37)</td>
</tr>
</tbody>
</table>
This is true locally, too.
mAbs and SARS-CoV-2 variants

<table>
<thead>
<tr>
<th>Current nomenclature</th>
<th>Former nomenclature</th>
<th>What you may have heard it referred to as</th>
<th>Bamlanivimab-etesevimab neutralizing ability</th>
<th>Casirivimab-imdevimab neutralizing ability</th>
<th>Sotrovimab neutralizing ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>B.1.1.7</td>
<td>UK</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Beta</td>
<td>B.1.351</td>
<td>South Africa</td>
<td>Inactive</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Gamma</td>
<td>P.1</td>
<td>Brazil</td>
<td>Inactive</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Delta</strong></td>
<td><strong>B.1.617.2</strong></td>
<td><strong>India</strong></td>
<td><strong>No change</strong></td>
<td><strong>No change</strong></td>
<td><strong>No change</strong></td>
</tr>
<tr>
<td>Epsilon</td>
<td>B.1.427/429</td>
<td>California</td>
<td>Decreased</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Iota</td>
<td>B.1.526</td>
<td>New York</td>
<td>Decreased</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

As of September 21, 2021, all variants have been downgraded to “variant being monitored” status except for Delta, which is the only current variant of concern.
Data from 8/2/2021

Data from 9/20/2021

Total VOC proportions

Variants in PA

Proportion of cases

Time (weeks)
Learning while doing continues: The OPTIMISE-C19 Trial

<table>
<thead>
<tr>
<th>Table 2. Primary Outcomes and Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome/analysis</strong></td>
</tr>
<tr>
<td>Primary outcome, hospital-free days, median (IQR)</td>
</tr>
<tr>
<td>Patients with 28 hospital-free days, n (%)</td>
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<tr>
<td>Subcomponents of hospital-free days</td>
</tr>
<tr>
<td>Hospitalized patients, median days (IQR)</td>
</tr>
<tr>
<td>Hospitalized, n (%)</td>
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<tr>
<td>After mAb infusion in emergency department</td>
</tr>
<tr>
<td>After mAb infusion in infusion center</td>
</tr>
</tbody>
</table>
Eligibility criteria are:

- Test positive for COVID-19 (PCR or antigen test), **AND:**
- Have had mild-moderate symptoms for 10 days or less (must still be symptomatic), **AND:**
- Age ≥ 65 years **OR**
- Age 12 years and older weighing at least 40 kg with at least one high risk criterion:
  - BMI > 25 kg/m², or if age 12-17, have BMI ≥ 85th percentile for their age and gender based on CDC growth charts
  - Pregnancy
  - Chronic kidney disease
  - Cardiovascular disease (including congenital heart disease, hypertension)
  - Diabetes
  - Down syndrome
  - Dementia
  - Liver disease
  - Current or former smoker
  - Current or history of substance abuse
  - Immunosuppressive disease or immunosuppressive treatment
  - History of stroke or cerebrovascular disease
  - Chronic lung disease
  - Sickle cell disease
  - Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity
  - Having a medical-related technological dependence (e.g., tracheostomy, gastrostomy)
COVID-19

UPMC is staying informed of developments in the COVID-19 (previously known as 2019 Novel Coronavirus or 2019-nCoV) outbreak and taking proper precautions to ensure our facilities and staff are well-equipped to properly care for patients with contagious diseases without exposing other patients, staff, or visitors.

Updated Sept. 16:

- Read the latest COVID-19 Update. This edition includes information about federal and state vaccine mandates, third dose availability, barrier-free on-site testing for staff, serious illness care conversations, and more.

- Read the Aug. 20 COVID-19 Update.

COVID-19 Statistics

COVID-19 Clinical Care Protocols

- COVID-19 Home Health and Family Hospice Protocols
- COVID-19 Inpatient Protocols
- COVID-19 Long-Term Care Protocols
- COVID-19 Outpatient Protocols

COVID-19 Operations

- COVID-19 Facility Entrance Screening
  - COVID-19 Monoclonal Antibodies
- COVID-19 Vaccine
- Returning Students
Update: Distribution and Administration of COVID-19 Therapeutics

- HHS continues to take steps to better manage COVID-19 mAb supply to meet both current and anticipated COVID-19 caseloads
- The increase in the Delta variant of SARS-CoV-2, coupled with low vaccination rates in certain areas of the country has caused a substantial surge in the utilization of monoclonal antibody drugs over the July-August 2021 timeframe
- Beginning Monday, September 13, HHS transitioned to a state/territory-coordinated distribution system similar to the system used in the Nov 2020-Feb 2021 timeframe

Pause in direct ordering; shift to state-territory coordinated distribution system
<table>
<thead>
<tr>
<th>Location</th>
<th>IV Sotrovimab</th>
<th>IV Bamlanivimab-Etesevimab</th>
<th>SUBQ Casirivimab-imdevimab</th>
<th>IV Casirivimab-imdevimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altoona ED</td>
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<tr>
<td>Altoona Outpatient</td>
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<tr>
<td>Bedford ED</td>
<td></td>
<td></td>
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<td>Don’t order more once stock depleted</td>
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<tr>
<td>Chartwell</td>
<td></td>
<td>plan to change to B+E when out of C+I</td>
<td>Able to convert if trouble placing IV</td>
<td>Primary treatment</td>
</tr>
<tr>
<td>Chautauqua ED</td>
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<tr>
<td>Chautauqua Outpatient</td>
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<tr>
<td>Childrens ED</td>
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<tr>
<td>Childrens Outpatient</td>
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<td>Cole Outpatient and ED</td>
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<tr>
<td>East ED</td>
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<td>East Outpatient</td>
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<td>Hamot ED</td>
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<tr>
<td>Hamot Outpatient</td>
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<td>Horizon Greenville ED</td>
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<td>Horizon Shenango ED</td>
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<tr>
<td>Inpatients - ALL SITES</td>
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<tr>
<td>Jameson ED</td>
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<tr>
<td>Jameson Outpatient</td>
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<td>Lock Haven ED</td>
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<td>Magee ED</td>
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<td>Magee Outpatient</td>
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<tr>
<td>McKeesport ED</td>
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<td>Don’t order more once stock depleted</td>
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<tr>
<td>Mercy ED</td>
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<tr>
<td>Location</td>
<td>IV Sotrovimab</td>
<td>IV Bamlanivimab-Etesevimab</td>
<td>SUBQ Casirivimab-imdevimab</td>
<td>IV Casirivimab-imdevimab</td>
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<tr>
<td>Muncy ED</td>
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<td>Don’t order more once stock depleted</td>
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<tr>
<td>Northwest ED</td>
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<tr>
<td>Observation status - ALL SITES</td>
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<td>Passavant Cranberry ED</td>
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<tr>
<td>Passavant McCandless ED</td>
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<tr>
<td>Passavant McCandless Outpatient</td>
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<tr>
<td>Pinnacle ALL SITES</td>
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<tr>
<td>Presbyterian ED</td>
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<tr>
<td>Presbyterian Outpatient (FALK)</td>
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<tr>
<td>Senior Communities</td>
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<td>change to B+E for treatment and PEP once stock depleted</td>
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<tr>
<td>Shadyside ED</td>
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<td>Shadyside Outpatient</td>
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<td>South Side Outpatient</td>
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<td>Don’t order more once stock depleted</td>
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<td>Western Psych</td>
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<tr>
<td>Wellsboro ED</td>
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<tr>
<td>Williamsport Outpatient</td>
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</tbody>
</table>
And we haven’t yet touched on post-exposure prophylaxis

Currently offering IV B+E in senior communities, inpatient settings for unit outbreaks, and case-by-case high risk outpatient basis
Figure 2: Effect of allocation to REGEN–COV on 28-day mortality in: a) seronegative vs seropositive participants; and b) all participants.

### a) Seronegative vs seropositive

- **Seronegative**
  - REGEN–COV: 1633, 1429, 1325, 1260, 1224
  - Usual Care: 1520, 1308, 1173, 1088, 1059

- **Seropositive**
  - REGEN–COV: 2636, 2452, 2322, 2252, 2201
  - Usual Care: 2636, 2503, 2375, 2292, 2243

- **Rate ratio**: Seronegative: 0.60 (0.70–0.91) **P=0.0010 by log-rank test**
- **Rate ratio**: Seropositive: 1.09 (0.95–1.26)

### b) All participants

- **Rate ratio**: 0.94 (0.86–1.03) **P=0.17 by log-rank test**

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Other Outpatient “Therapies”

Colchicine
- COLCORONA Trial
- RECOVERY Trial
- PRINCIPLE Trial

Fluvoxamine
- TOGETHER Trial
- STOP COVID 2 Trial

Ivermectin
- Lopez-Medina et al

Lenze EJ, et al. JAMA. 2020
Inpatient Management
REMAP Trial

**IM-2**
- Eritoran (IV infusion) or placebo → moderate disease only
- Exclusion: received another immunomodulator, pregnancy, chemo within 3 months, ANC < 1000, CD4 < 50, EF < 35%, Child Pugh Class C liver disease, Weight > 150kg

**ACE/ARB**
- Lisinopril or losartan or standard care → moderate or severe disease
- Exclusion: ≥ 96h (Floor) or ≥ 48h (ICU) since admission, hyperkalemia, pregnancy, CrCl < 30 mL/min

**Vit C**
- Vitamin C (50 mg/kg IV q6h x 16 doses) or standard care → moderate or severe disease
- Exclusion: ≥ 24h of organ support, G6PD deficiency, symptomatic kidney stones within 1yr

**P2Y12**
- Ticagrelor or standard care AND/OR prophylactic dosing anticoagulation or enhanced dosing → severe disease only
- Exclusion: contraindication to anticoagulation, platelets < 50, Hgb < 8, aspirin > 162mg daily

**Enrollment via COVID-19 Intake Form in EHR**

For any questions: covidcrc@upmc.edu
REMAP Trial: Answers

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP–CAP COVID–19 Corticosteroid Domain Randomized Clinical Trial

Lopinavir–ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP–CAP randomized controlled trial
Moderate Disease

- Hospitalized
- Requiring low-flow supplemental oxygen above baseline needs
In 2020, remdesivir was the #1 drug expenditure for the entire United States despite it only being included in the data set from Oct-Dec (!!!!!!!)
The Remdesivir Journey Continues

Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

Florence Ader, Maude Boescambert-Duchamp, Maya Hites, Nathan Peffer-Smadja, Julien Poissy, Drifa Belhadi, Alpha Diallo, Minh-Patrick Lê, Gilles Peytavin, Thérèse Staub, Richard Grell, Jérémie Guedj, Jose-Artur Peha, Dominique Costagliola, Yazdan Yazdanpanah, Charles Burdet, France Mentré, and the DisCoVeRy Study Group

Summary
Background The antiviral efficacy of remdesivir against SARS-CoV-2 is still clinical efficacy of remdesivir plus standard of care compared with standard hospital with COVID-19, with indication of oxygen or ventilator support.

“No clinical benefit was observed from the use of remdesivir in patients who were admitted to the hospital for COVID-19”
A  All Participants (N=6425)

Rate ratio, 0.83 (95% CI, 0.75–0.93)
P<0.001

Days since Randomization

Mortality (%)

Usual care
Dexamethasone

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group

The NEW ENGLAND JOURNAL of MEDICINE
In-Hospital Use of Dexamethasone (n=7,588)

Patients who received Oxygen

B. (7/17/2020) Results of RECOVERY trial published online in NEJM
C. (2/25/2021) RECOVERY trial results published in print in NEJM

Figure 2
### Table 1. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
<th>DEXA COVID19</th>
<th>CoDEX</th>
<th>RECOVERY</th>
<th>CAPE COVID</th>
<th>COVID STEROID</th>
<th>REMAP-CAP</th>
<th>Steroids-SARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04325061</td>
<td>NCT04327401</td>
<td>NCT04381936</td>
<td>NCT02517489</td>
<td>NCT04348305</td>
<td>NCT02735707</td>
<td>NCT04244591</td>
<td></td>
</tr>
<tr>
<td>Planned sample size</td>
<td>200</td>
<td>350</td>
<td>NA</td>
<td>290</td>
<td>1000</td>
<td>NA</td>
<td>80</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria • Confirmed COVID-19</td>
<td>• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria • Onset of ARDS &lt; 48 h before randomization • Probable or confirmed COVID-19</td>
<td>Criteria used for this meta-analysis: • Intubation • Suspected or confirmed COVID-19</td>
<td>• Minimal severity • Admitted to ICU or intermediate care unit • Oxygen (≥ 6 L/min) • Probable or confirmed COVID-19</td>
<td>• Oxygen (≥ 10 L/min) • Confirmed COVID-19</td>
<td>• Admitted to ICU receiving high-flow nasal oxygen with FiO₂ ≥ 0.4 at ≥ 30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors • Probable or confirmed COVID-19</td>
<td>• Admitted to ICU with PaO₂:FIO₂ &lt; 200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal cannulae &gt; 45 L/min • Confirmed COVID-19</td>
</tr>
<tr>
<td>Corticosteroid dosage and administration</td>
<td>Dexamethasone 20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d</td>
<td>Dexamethasone 20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d</td>
<td>Dexamethasone 6 mg/d orally or intravenously</td>
<td>Hydrocortisone Continuous intravenous infusion × 8 d or 14 d (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d)</td>
<td>Hydrocortisone 200 mg/d intravenously × 7 d (continuous or bolus dosing every 6 h)</td>
<td>Hydrocortisone 50 mg intravenously every 6 h × 7 d²</td>
<td>Methylprednisolone 40 mg intravenously every 12 h × 5 d</td>
</tr>
</tbody>
</table>

- **DEXA COVID19**: Dex 20mg x 5 days, Dex 10mg x 5 days
- **CoDEX**: Dex 20mg x 5 days, Dex 10mg x 5 days
- **RECOVERY**: Dex 6mg
- **CAPE COVID**: Dex 7.5mg
- **COVID STEROID**: Dex 7.5mg
- **REMAP-CAP**: Dex 7.5mg
- **Steroids-SARI**: Dex 15mg
So where are we at with steroids?

- High-dose dexamethasone (i.e., 20mg x 5 days followed by 10mg x 5 days) was studied in small, randomized clinical trials for patients with advanced acute respiratory distress syndrome; trials were terminated early.

- Other randomized, clinical trials evaluating dexamethasone 12-15mg compared to 6mg found no or minimal difference.

- The addition of immunomodulatory therapy with a different mechanism of action (i.e., tocilizumab, sarilumab, baricitinib) to low-dose dexamethasone has demonstrated a mortality benefit in multiple randomized, clinical trials and is preferred over escalating doses of corticosteroids.

- If tocilizumab, sarilumab, and baricitinib are all unavailable due to supply constraints and/or the patient has a contraindication to all three agents, clinical judgement should be used on a case-by-case basis regarding corticosteroid management in patients who clinically worsen while receiving dexamethasone 6mg IV/PO daily.

- Patients receiving only low-flow supplemental oxygen for COVID-19 should not receive more than 6 mg of dexamethasone and do not require additional immunomodulatory therapy.
Therapeutic Anticoagulation – Moderately Ill
Severe Disease – HFNC/NIV

- Hospitalized
- Requiring high-flow nasal canula or noninvasive ventilation

Y = Recommended
N = Not recommended
T = Clinical trial only

- Remdesivir
- Systemic steroids
- Monoclonal Antibodies
- Convalescent Plasma
- Therapeutic Anticoagulation
- Immunomodulators
Severe Disease – MV

- Hospitalized
- Requiring mechanical ventilation

Y = Recommended
N = Not recommended
T = Clinical trial only

- Remdesivir: N
- Systemic steroids: Y
- Monoclonal Antibodies: N
- Convalescent Plasma: N
- Therapeutic Anticoagulation: N
- Immunomodulators (but give early!): Y
Therapeutic Anticoagulation – Critically Ill

REMAP-CAP. NEJM. 2021.
Tocilizumab and sarilumab

- IL-6 Domain, REMAP-CAP RECOVERY Trial

Graphs showing mortality and organ support-free days for different treatments.

- RR 0.88 (0.77-0.96)
- Log-rank p=0.0006

- Usual care
- Tocilizumab
- Control (N=397)
- Sarilumab (N=45)
- Tocilizumab (N=350)
Hi all,

Tocilizumab is in critical, national shortage. As of Wednesday, August 25th, tocilizumab is no longer permitted for use in patients with COVID-19 at any UPMC facility in order to conserve supply. Use is restricted to non-COVID-19 indications (i.e., CART, RA, etc.).

- A MedCall will go out tomorrow (Tuesday) morning to all prescribers
- A new, alternative option PowerPlan will be turned on view tomorrow (Tuesday) morning
  - A huge thank you to the eRecord team for building this PowerPlan today – you all are amazing
- The current tocilizumab for COVID-19 PowerPlan will be turned off view on Wednesday morning
- An alert will pop-up for prescribers when ordering tocilizumab on COVID-19 positive or COVID-19 PUI patients to direct them to the alternative PowerPlan
- We have secured some supply of baricitinib and sarilumab; these should be prioritized over high-dose dexamethasone based on national guidelines and RCT data
Baricitinib

Inclusion for tocilizumab, baricitinib, and sarilumab

- Confirmed SARS-CoV-2 AND
- Receiving high-flow nasal cannula (>6L), non-rebreather, invasive or non-invasive mechanical ventilation for less than 48 hrs AND
- Receiving systemic corticosteroids (i.e., dexamethasone 6mg daily) AND
- CRP > 7.5 mg/dL (75 mg/L) AND
- *Baricitinib only*: Provide patient fact sheet (https://www.fda.gov/media/143824/download)

Exclusion for tocilizumab and sarilumab

- High concern for or presence of systemic bacterial or fungal co-infection
- ALT or AST > 10x ULN
- Treatment with anakinra, tocilizumab, or sarilumab in past 30 days
- Known hypersensitivity to tocilizumab
- Death is deemed to be imminent and inevitable within 24 hours
- More than 14 days have elapsed since admitted to hospital with symptoms of an acute illness due to suspected or proven COVID-19
Exclusion for baricitinib

- Pregnancy unless given in consultation with critical care, infectious diseases, and OB/GYN/MFM
- High concern for or presence of systemic bacterial or fungal co-infection
- Active tuberculosis
- Hemodialysis or eGFR < 15 mL/min/1.73m²
- Absolute lymphocyte count (ALC) < 200 cells/µL
- Absolute neutrophil count (ANC) < 500 cells/µL
- ALT or AST >5x ULN or if drug-induced liver injury is suspected
- Prior receipt of certain immune suppressive treatments:
  - JAK-inhibitors in last 7 days
  - TNF inhibitors in last 14 days
  - Cytotoxic therapies, T-cell targeted therapies, interferon treatment in last 4 weeks
  - Anakinra, tocilizumab, or sarilumab in last 4 weeks
- Known hypersensitivity to baricitinib
- History of recurrent VTE or diagnosed with VTE within last 12 weeks
- History of a live or live attenuated vaccine within last 4 weeks
- Death is deemed to be imminent and inevitable within 24 hours
- More than 14 days have elapsed since admitted to hospital with symptoms of an acute illness due to suspected or proven COVID-19
Additional considerations

- Combination of tocilizumab or sarilumab + baricitinib has not been studied and both the safety and efficacy of this combination is unclear. Cases in which patients are initiated on baricitinib but develop contraindications for use prior to completion of treatment course may arise, and case-by-case considerations will determine subsequent recommendations.

- Decision to resume baricitinib after an interruption due to decrease lymphocyte count, neutrophil count, or VTE must be made on a case-by-case basis.

- Tocilizumab OR sarilumab is preferred in pregnant patients over baricitinib.
  - Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. Consistent with the mechanism of action, embryo-fetal toxicities including skeletal anomalies and reduced fertility have been observed in animals dosed in excess of the maximum human exposure. The limited human data on use of baricitinib in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage.
Medications Not Recommended

- Acalabrutinib
- Anakinra
- Azithromycin
- Epoprostenol (inhaled) and nitric oxide (inhaled)
- Famotidine
- Hydroxychloroquine
- Ibrutinib
- Interferon
- Ivermectin
- IVIG

- Lopinavir/ritonavir
- Nintedanib
- Nitazoxanide
- Oseltamivir
- Pirfenidone
- Ribavirin
- Ruxolitinib
- Vitamin D
- Zinc
- And more....
Future Directions

• AstraZeneca mAb (AZD7442)
  • Long-active (6-12 months)
  • PROVENT Trial: 77% reduced risk of developing symptomatic COVID-19 through day 183 (non peer reviewed) when given for pre-exposure prophylaxis
  • STORM CHASER Trial: not effective as post-exposure prophylaxis
  • ACTIV-3: Enrolling hospitalized patients

• Long Covid
  • Increasing requests for complex, off-label therapies
  • Direct patients to clinic: UPMCCovidClinic@upmc.edu
    • Coordinated by Dr. Alison Morris
COVID-19 Therapeutics: Chaos to Evidence in a Pandemic

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Director of Stewardship Innovation, UPMC and Infectious Disease Connect

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