COVID-19 Therapeutics Update

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Disclosures

• Dr. Davis has served as a consultant to Spero Therapeutics, Entasis Therapeutics and Summit.
• This presentation includes discussion of non-FDA approved medications
• Remdesivir (Veklury) is FDA approved for COVID-19. Monoclonal antibodies, convalescent plasma, and tocilizumab (in combination with remdesivir) have emergency use authorization (EUA) with specific approved criteria.

• The information disseminated in this presentation is given in my personal capacity and does not necessarily reflect the view of the NIH COVID-19 Treatment Guideline Panel.

Learning Objectives

2. Recognize proposed COVID-19 treatments that lack evidence of efficacy.
3. Discuss current knowledge gaps and unmet needs in COVID-19 management.

Question:
What is your main source of information for the management of COVID-19?

a. NIH guidelines
b. IDSA guidelines
c. Local institutional guidelines
d. Social media/personal network
e. Primary literature

Key Guidelines

NIH Guidelines

IDSA Guidelines

WHO Guidelines

Spectrum of Disease and Therapy
Drugs not recommended or insufficient evidence for COVID-19 treatment

**Antibody & antibody-based**
- Convalescent plasma
- Neutralizing antibodies

**Artificial**
- Hydroxychloroquine
- Protease inhibitors
- Vitamin C
- Zinc

**Miscellaneous**
- Famotidine
- Vitamin D
- ACEIs/ARBs
- Antibacterials
- Ribavirin
- Ivermectin
- Antiviral
- Antibody & immune-based

**Convalescent plasma**
- Not reviewed
- Recommend against; moderate evidence

**Corticosteroids**
- Not reviewed
- Suggest against; very low evidence

**Tocilizumab**
- Not reviewed
- Suggest against routine use; low evidence

**Remdesivir**
- Not reviewed
- Suggest against routine use; low evidence

**Bamlanivimab +/ Etesevimab**
- Suggest use; low evidence

**Bamlanivimab monotherapy**
- Not reviewed
- Recommend against; moderate evidence

**Baracitinib**
- With remdesivir + steroids – only in the context of a clinical trial
- Not reviewed
- With remdesivir; suggests use; low evidence

**Ivermectin**
- Not reviewed
- Suggest against except in a trial; very low evidence

NIH Guideline

https://www.covid19treatmentguidelines.nih.gov/
As of Feb 11, 2021

Abbreviated from IDSA Guideline

<table>
<thead>
<tr>
<th>Agent/Treatment</th>
<th>Severity</th>
<th>NIH Guideline</th>
<th>IDSA Guideline</th>
<th>Other Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>Ambulatory (mild - moderate)</td>
<td>Not reviewed</td>
<td>Recommend against; moderate evidence</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Hospitalized, mild - moderate (not on O2)</td>
<td>Not reviewed</td>
<td>Suggest against; very low evidence</td>
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<tr>
<td>Tocilizumab</td>
<td>Hospitalized, severe (SpO2 &lt; 94%, on O2)</td>
<td>Not reviewed</td>
<td>Suggest against routine use; low evidence</td>
<td></td>
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<tr>
<td>Remdesivir</td>
<td>Hospitalized, critically ill (MV/ECMO)</td>
<td>Not reviewed</td>
<td>Suggest against routine use; low evidence</td>
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<td>Bamlanivimab + Etesevimab</td>
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Management of Inpatients

Hospitalized, Not Critically Ill

The NIH recommends against the use of dexamethasone (0.5 mg/kg of body weight) or other corticosteroids in the treatment of COVID-19. There is insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.

Hospinalized and Requires Supplemental Oxygen

- Use one of the following options:
  - Remdesivir (e.g., for patients who require minimal supplemental oxygen (B5a))
  - Dexamethasone (plus remdesivir) (e.g., for patients who require increasing amounts of supplemental oxygen (B5b))
  - Dexamethasone (plus remdesivir and ventilator support) (B5c), when combined therapy with remdesivir cannot be used or is not available (B5)
Remaining Questions

- Should therapy be continued at discharge?
- Management of special populations (e.g. pediatrics, cancer, transplant, HIV, pregnancy)?
- Inpatient monoclonal antibody therapy?

Hospitalized, Severe and Critically Ill

- Hospitalized and Require Ozone Delivery Through a High-Flow Device or Noninvasive Ventilation?
- Use one of the following options:
  - Suvorexstat® (40 mg)
  - Suvorexstat® (50 mg) and Remdesivir

Hospitalized and Require Invasive Mechanical Ventilation (MV)

- Dexamethasone® (4 mg)

Toxicity statement added March 5th

My favorite twitter response to the REMAP-CAP Publication

I already don’t enjoy pretending to understand frequentist statistics, and I am definitely not going to like the Bayesian stuff.

8:01 PM - Feb 25, 2021 - Twitter for iPhone

We’re going to take a little diversion here for a mini Journal Club...

Good References on Bayesian Statistics (for beginners, myself included)

- JAMA Guide to Statistics and Methods, chapters:
  - Bayesian Hierarchical Models
  - Bayesian Analysis: Using Prior Information to Interpret the Results of Clinical Trials
- Why clinicians are natural Bayesians; BMJ 2005;330:1080–3
- Bays for clinicians who need to know but don’t like math. JAMA clinical review podcast. https://www.ama-assn.org/jr-learning/audio-player/1707408

HF = High flow oxygen; NIMV = non-invasive mechanical ventilation; MV = mechanical ventilation; ECMO = extracorporeal membrane oxygenation

Beigel JG et al. NEJM 2020. DOI: 10.1056/NEJMoa2007764
Kalil AC et al. NEJM 2020. DOI: 10.1056/NEJMoa2031994
WHO Solidarity Trial Consortium, NEJM 2020. DOI: 10.1056/NEJMoa2023184

RECOVERY – survival benefit in MV/ECMO subset
ACTT-1 Noninferiority trial 30 day mortality
ACTT-2 (RECOVERY: Remdesivir plus Baricitinib or Placebo) shorter time to recovery in MV/ECMO subset
Suvorexstat – trend toward increased mortality in MV subset

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REMAP-CAP: Eligibility for Tocilizumab / Sarilumab Domain

- **Toci/Sari Inclusion:**
  - Severe disease state, defined by receipt of respiratory support (HVNO, CPAP/NIV, IMV) or cardiovascular organ failure support in ICU

- **Toci/Sari Exclusion:**
  - > 24 hours since ICU admission/organ support
  - Immune suppressed, already receiving any of the immune modulating drugs for an underlying condition, hypersensitivity, pregnancy, AST/ALT > 5x ULN, platelets < 50, or "not in patient’s best interest"
  - Per the investigators: “eligible for inclusion as long as not actively dying”

Treatment & Endpoints

- **Tocilizumab**
  - 8 mg/kg actual body weight (min 70mg) IV over 1 hour
  - Could be repeated 12-24 hours later

- **Sarilumab**
  - 400mg IV over 1 hour
  - **NOTE:** sarilumab has a higher binding affinity to IL-6r and a longer half life than tocilizumab, so they aren’t pharmacologically equivalent. But in rheum studies they seem to have similar efficacy… maybe this doesn’t matter?

Primary Outcome Measure

- ICU free days
- ICU respiratory and cardiovascular organ support free days
- Ordinal scale composite of in hospital death (assigned worst outcome, -1) and number of days alive and not requiring organ support

A Note on Statistical Approaches

**FREQUENTIST (WHAT YOU’RE USED TO READING)**

- Test a hypothesis
- Calculates the probability of an event (if experiment repeated)
- Assumes randomness
- Fixed p-value/confidence interval thresholds;
  - p-values and CI highly dependent on sample size
  - CI are not probability distributions

**BAYESIAN**

- Applies probability distributions based on prior belief... update that belief based on new data
- Uses “conditional probabilities” — when probability distribution of an event depends on another factor/set of factors
- FREQUENTIST – probability distribution based on presenting data/trials
  - Frequentist “nullhypothesis” (belief intervention is superior)
  - Frequentist “nullhypothesis” (belief intervention not effective) or “excess” (belief intervention ineffective)
  - If previous data doesn’t exist, prior will not be informative, that data will be done impactful

Probability distributions

- **Prior**
- **Likelihood**
- **Posterior**

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<thead>
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<th>Initial consult, history, your expectations</th>
<th>Posterior</th>
<th>Likelihood</th>
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<td>Reviewing results of lab, x-ray, imaging</td>
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<tr>
<td>Clinical reasoning</td>
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The most common criticism of Bayesian models: you can manipulate the results through choice of prior distribution. But in reality it would be pretty hard to get away with that.

You already think like a Bayesian

- **Prior**
- **Posterior**
- **Likelihood**

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Key questions to ask in evaluating clinical trials with Bayesian approach

- Assess the prior
  - Is it pre-specified and defined?
  - What data is it based on? How informative is it?

- Analysis
  - Posterior probability is calculated from the observed evidence and the prior probability
  - Are statistical models and assumptions specified?
  - If you’re a statistician, assess algorithm convergence, borrowing, shrinkage

- Assess data presentation
  - All the usual questions about data summary still apply
  - Bayesian statistics are presented as the credible interval (CrI), interpreted as 95% probability that the true value lies within that range
  - If multiple priors are available, see models shown
Bring this back to REMAP-CAP

- Assess the prior
  - Defined, neutral
- Based on intensive care national audit and research center (details in appendix, clinically relevant and robust)

- Data from patients enrolled before the change in the strata can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new strata into the model.

Analysis

- Models and methods described; convergence/shrinkage/borrowing not explicitly stated but presumed
- Data summarized in table
- Median adjusted OR was presented with credible interval (CrI)

Treatments

- Enrollment was mostly post RECOVERY due to nearly all receiving steroids (93% of those after June, 80% overall)
- 32.8% received remdesivir
- Of those assigned to Toci, 92% received tocilizumab, 29% received second dose
- 90% of sarilumab received sarilumab
- Reasons patients didn't get the drug after randomization: deterioration, clinician thought they were improving, clinician changed mind, drug not available

Major Results

- Don’t let the Bayesian approach intimidate you. The event numbers and %s are still there. You can still directly observe the effect size, ARR. This is just a different way to determine statistical significance.

RCTs with Toci

| Study | n (mITT) | Steroids | Progression/treatment | Duration in ICU | Mortality | Disease Modification
<table>
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<tbody>
<tr>
<td>RECOVERY</td>
<td>4116</td>
<td>82%</td>
<td>33% vs 38%</td>
<td>1.43 (aHR)</td>
<td>28%</td>
<td>1.19 (0.8 – 1.76)</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>865</td>
<td>80%</td>
<td>28% vs 36%</td>
<td>OR 1.19 (0.8 – 1.76)</td>
<td>28%</td>
<td>1.19 (0.8 – 1.76)</td>
</tr>
<tr>
<td>COVACTA</td>
<td>438</td>
<td>42%</td>
<td>19.7% vs 19.4%</td>
<td>1.2 (aHR)</td>
<td>19.7%</td>
<td>1.2 (aHR)</td>
</tr>
<tr>
<td>TOCIBRAS</td>
<td>129</td>
<td>86%</td>
<td>21% vs 9%</td>
<td>1.54 (aHR)</td>
<td>21%</td>
<td>1.54 (aHR)</td>
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<tr>
<td>EMPACTA</td>
<td>389</td>
<td>80%</td>
<td>10% vs 8.6%</td>
<td>1.54 (aHR)</td>
<td>10%</td>
<td>1.54 (aHR)</td>
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<tr>
<td>BACC</td>
<td>243</td>
<td>9%</td>
<td>5.6% vs 4.9%</td>
<td>1.6 (aHR)</td>
<td>5.6%</td>
<td>1.6 (aHR)</td>
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<tr>
<td>CORIMUNO</td>
<td>131</td>
<td>47%</td>
<td>11.1% vs 8.9%</td>
<td>1.54 (aHR)</td>
<td>11.1%</td>
<td>1.54 (aHR)</td>
</tr>
<tr>
<td>TCZ-C19</td>
<td>126</td>
<td>10%</td>
<td>3.3% vs 1.6%</td>
<td>1.54 (aHR)</td>
<td>3.3%</td>
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</tbody>
</table>
Highlights of RECOVERY

- Preprint with preliminary analysis: https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1
- Subject of Twitter ID Journal Club on Feb 15: https://twitter.com/IDJClub/status/1361497274254303234

- Large UK study, open-label, multiple arms, including Toci vs Usual Care
- Weight-based dose: 2° dose allowed 12-24 hours later at clinician discretion

- Primary outcome: all-cause mortality at day 28
- Secondary outcomes: time to discharge, composite of mechanical ventilation or death
- Minimal safety endpoints collected/reported

More RECOVERY highlights

- 79% with completed data (follow-up forms)
- 83% confirmed to actually receive tocilizumab
- Mortality endpoint: 28-day mortality - Toci 29% vs SOC 33% (p=0.007)

TIMING: An exploratory analysis showed that the effects of tocilizumab on mortality were very similar for those randomized <=2 or > 2 days since admission (interaction p = 0.86)

STEROIDS: 82% received steroids, benefit not seen in those who did NOT receive steroids... who are those people? All pre RECOVERY-Dex?

Question: Which of these is your biggest inpatient challenge in therapy of COVID-19?

a. Appropriate use of remdesivir
b. Appropriate use of tocilizumab
c. Inpatient use of monoclonal antibodies
d. Appropriate anti-thrombotic therapy
e. Concerns about treatment of variants
Management of Outpatients

The studies that got us here

PLAZA-1: Phase 2/3 trial, bamlanivimab vs placebo, outpatient setting
Change in viral load
Lower risk of hospitalization/ED visit/death
Unprompted: 65% vs 9% absolute reduction (97% relative) hospitalizations or death
R10933-10987: (press release) Phase 1 & 2 trial of casirivimab/imdevimab vs placebo; outpatient setting
Change in viral load
Small reduction in hospitalizations/ED visit
Additional data via press release at larger sample

Mild to Moderate Illness: Can we prevent progression and need for hospitalization?

Outpatients: What CAN we do?

• Symptomatic relief – talk with your pharmacist!
• Hydration, analgesics, antipyretics, antitussives
• Careful follow-up
• Telehealth vs ED vs face to face
• Pulse oximeter and appropriate instructions/counseling if sent home with supplemental oxygen
• Monoclonal antibodies in patients at high risk for progression according to EUA criteria
Variants: we are learning what we don’t know

- The data updates FREQUENTLY
- The models of antibody resistance are challenging to interpret
- Lack of clinical correlation
- Based on assumptions from other viral models
- Follow the data from CDC

- Follow the fact sheets from FDA:

Lessons learned and moving forward

Best Practice is a moving target

<table>
<thead>
<tr>
<th>NH Recommendations by Month</th>
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<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Remdesivir</td>
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<tr>
<td>Ivermectin</td>
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<td>Anti-SARS-CoV2 Antibody</td>
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Patterns of medication use in pandemic setting: The Cautionary Tale of HCQ

Scientific Literature in a Pandemic: Proceed with Caution

INCREASING COMPLEXITY

- Adaptive trial platforms
- Conflicting results
- Conflicting guidelines
- Subset analyses

SUBVERSION OF PEER REVIEW

- Preprint servers
  - Not peer-reviewed
  - May differ from final publication
- Press releases
  - Sponsor/investigator-selected information
- Public debate
  - Social media (scientists vs personalities)
- Twitter

A good reference on dealing with conflicting data: Maves RC. Clin Infect Dis 2021. https://doi.org/10.1093/cid/ciab012


Preparing for the next pandemic: Leveraging antimicrobial stewardship

- Development of treatment guidelines
- Enhancing compliance with recommendations
- Antibiotic optimization
  - Short-course, routine, and pre-emptive

Antimicrobial Stewardship

- Education and awareness
- Adverse event monitoring
- Diagnostic stewardship
- Drug shortage and supply management

Slide credit: Adapted from Emily Heil for the Society of Infectious Diseases Pharmacists