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 baricitinib (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.

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Learning Objectives

1. State current evidence-based guidelines for the treatment of COVID-19.
2. Recognize proposed COVID-19 treatments that lack evidence of efficacy.
3. Discuss current knowledge gaps and unmet needs in COVID-19 management.

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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

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Key Guidelines

NIH Guideline
COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/.

IDSA Guideline
Bhimraj A, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management.

WHO Guideline
Country and Technical Guidance for COVID-19 documents available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019

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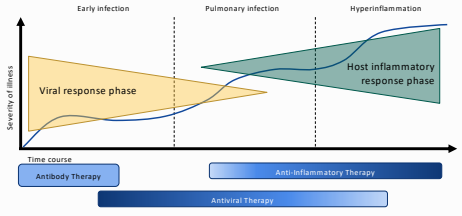
Spectrum of Disease and Therapy



Current therapies (darker gradient used to imply strength of evidence)

Adapted from: Siddiqi HK, https://doi.org/10.1016/j.healun.2020.03.012

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Drugs not recommended or insufficient evidence for COVID-19 treatment

- Antibody & Immune-based
  - Convalescent plasma
  - IVIG
  - Interferons
- Antiviral
  - Hydroxy-chloroquine
  - Protease inhibitors
  - Ribavirin
- Miscellaneous
  - Vitamin C
  - Zinc
  - Famotidine
  - Vitamin D
  - Ivermectin
  - Antibacterials
  - ACEIs/ARBs
  - Colchicine
  - Fluvoxamine

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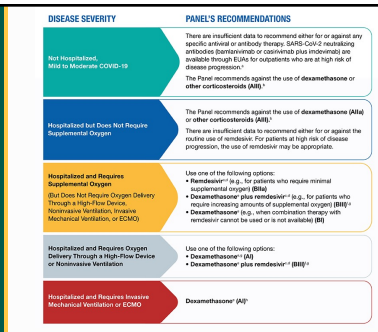
Treatment Recommendations

NIH Guideline



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

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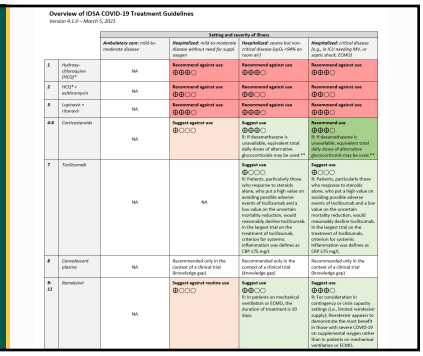
Treatment Recommendations

IDSA Guideline

Last updated March 5

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/



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Abbreviated from IDSA Guideline

Agent/Severity	Ambulatory (mild – moderate)	Hospitalized, mild-moderate (not on O2)	Hospitalized, severe (SpO2 < 94%, on O2)	Hospitalized, critically ill (MV/ECMO)
Hydroxychloroquine +/- azithro	Not reviewed	Recommend against; moderate evidence	Recommend against; moderate evidence	Recommend against; moderate evidence
Corticosteroids	Not reviewed	Suggest against; very low evidence	Suggest use; moderate evidence	Recommend use; moderate evidence
Tocilizumab	Not reviewed	Suggest against routine use; low evidence	Suggest use; very low evidence	Suggest use; very low evidence
Remdesivir	Not reviewed	Suggest against routine use; low evidence	Suggest use; low evidence	Suggest use; moderate evidence; most benefit in those not on MV
Bamlanivimab + Etesevimab	Suggest use; low evidence	Not reviewed	Not reviewed	Not reviewed
Bamlanivimab monotherapy	Not reviewed	Not reviewed	Recommend against; moderate evidence	Not reviewed
Baricitinib	With remdesivir + steroids – only in the context of a clinical trial	Not reviewed	With remdesivir; Suggest use; low evidence	Not reviewed
Ivermectin	Suggest against except in a trial very low evidence	Not reviewed	Suggest against except in a trial very low evidence	Not reviewed

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Management of Inpatients

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Hospitalized, Not Critically Ill

Hospitalized but Does Not Require Supplemental Oxygen

The Panel recommends against the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII).**[b]

There are 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.

Hospitalized and Requires Supplemental Oxygen

(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)

Use one of the following options:
- **Remdesivir**[c,d] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**
- **Dexamethasone**[e] **plus remdesivir**[c,d] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[f,g]
- **Dexamethasone**[e] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**

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Remaining Questions

Not hospitalized → Hospitalized, mild → Hospitalized, O2 → Severe, HF/NIMV → Critical, MV/ECMO

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

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Hospitalized, Severe and Critically Ill

Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[e,n] **(AI)** • **Dexamethasone**[e] **plus remdesivir**[f,o] **(BIII)**[g]
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[e] **(AI)**[h]

Tocilizumab statement added March 5th

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Hospitalized, Severe and Critically Ill

Not hospitalized → Hospitalized, mild → Hospitalized, O2 → Severe, HF/NIMV → Critical, MV/ECMO

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

RECOVERY
Dexamethasone – survival benefit in MV/ECMO subset
ACTT-1
Remdesivir - no difference in time to recovery in HV/NIMV or MV
ACTT-2 (RCT remdesivir plus baricitinib or placebo)
shorter time to recovery in HF/NIMV subset
Solidarity
remdesivir – trend toward increased mortality in MV subset

RECOVERY Collaborative Group, Horby P, et al. NEJM 2020. DOI: 10.1056/NEJMoa2021436

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

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Hospitalized, Severe and Critically Ill

Recommendations

Based on the collective evidence from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Randomized Evaluation of COVID-19 Therapy (RECOVERY) trials, the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:

- The Panel recommends the use of **tocilizumab**[b] (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) **in combination with dexamethasone** (6 mg daily for up to 10 days)[h] in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19.[c] The patients included in this population are:
  - Recently hospitalized patients[d] who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO_2/30 L/min of oxygen flow) **(BIIa)**; or
  - Recently hospitalized patients[d] (not in the ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation **(BIIa)** (**Note**: The RECOVERY trial inclusion criterion for inflammation was C-reactive protein (CRP) ≥75 mg/L; see details below).
- For hospitalized patients with hypoxemia who require conventional oxygen supplementation, the Panel recommends using one of the following options: **remdesivir (BIIa)**, **dexamethasone plus remdesivir (BIII)**, or **dexamethasone alone (BI)** (see Therapeutic Management of Adults With COVID-19).
  - There is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L but who do not yet require NIV or HFNC, as described above.

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My favorite twitter response to the REMAP-CAP Publication

Replying to @GermHunterMD @remap_cap and 2 others

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

8:31 PM · Feb 25, 2021 · Twitter for iPhone

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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
- Bayes for clinicians who need to know but don't like math. JAMA clinical review podcast. https://edhub.ama-assn.org/jn-learning/audio-player/17071468

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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"

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Treatment & Endpoints

- Tocilizumab
  - 8 mg/kg actual body weight (max 800mg) 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 toci, 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

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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 CIs highly dependent on sample size
  - CIs 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
- PRIORs – probability distribution based on pre-existing data/trials
  - Terms: "enthusiastic" (believe intervention is superior) and "skeptical" (believe intervention not effective) or "neutral" (between those)
  - If previous data doesn't exist, prior will not be informative, trial data will be more impactful

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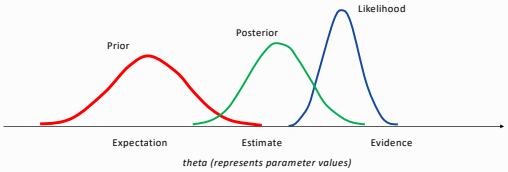
Probability distributions



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.

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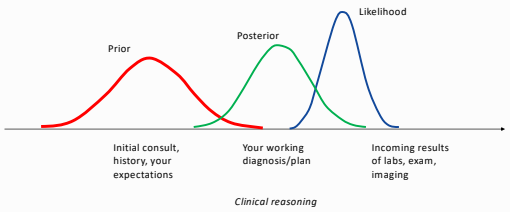
You already think like a Bayesian



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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 is 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, are all models shown

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Bring this back to REMAP-CAP

- Assess the prior
  - Defined, neutral
  - Based on data from intensive care national audit and research center; detail 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
- Assess data presentation
  - Data summarized in table
  - Median adjusted OR was presented with credible interval (CrI)
  - Multiple priors not used; secondary analyses and subsets evaluated

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Table 1. Baseline Characteristics of Participants in the Immune Modulation Therapy domain*

	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)	All participants in the IMT domain (N=865)
Age - mean (SD), years	61.5 (12.5)	63.4 (13.4)	61.1 (12.8)	61.4 (12.7)
Male Sex - n (%)	261 (73.9)	39 (81.3)	283 (70.4)	629 (72.7)
BMI- median (IQR), kg/m²	30.5 (26.9-34.9) (n=342)	29.2 (26.0-33.8) (n=39)	30.9 (27.1-34.9) (n=377)	30.5 (26.8-34.9) (n=815)
APACHE II score - median (IQR)	13 (8-19) (n=337)	10 (7-16) (n=42)	12 (8-18) (n=381)	12.5 (8-19) (n=820)
Confirmed infection – n/N (%)	284/345 (82.3)	44/47 (93.6)	334/394 (84.8)	715/847 (84.4)

Typical of an ICU population. APACHE a little low. Investigators presume that this is because these patients present with single organ (respiratory) failure and don't score much on the multisystem organ failure

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Treatments

- Enrollment was mostly post RECOVERY-dex so nearly all received steroids (93% of those after June; ~80% overall)
- 32.8% received remdesivir
- Of those assigned to Toci, 92% received toci, 29% received second dose
  - Would love to know more about who/why 2nd doses given
- 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

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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.

	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
Organ support-free days (OSFDs)			
Median (IQR)	**10 (-1 to 16)**	**11 (0 to 16)**	**0 (-1 to 15)**
Median adjusted OR (95% CrI)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control, %	>99.9	99.5	-
Subcomponents of OSFDs			
In-hospital deaths, n (%) *	**98/350 (28.0)**	**10/45 (22.2)**	**142/397 (35.8)**
OSFDs in survivors, median (IQR)	14 (7 to 17)	15 (6.5 to 17)	13 (4 to 17)
Primary Hospital Survival			
Median adjusted OR (95% CrI)	1.64 (1.14 to 2.35)	2.01 (1.18 to 4.71)	1
Probability of superiority to control, %	99.6	99.5	-

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Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline

	Tocilizumab	Sarilumab	Control
Free of invasive mechanical ventilation at baseline, n	242	37	273
Progression to intubation, ECMO or death, n (%)	100/242 (41.3)	13/37 (35.1)	144/273 (52.7)
Adjusted OR median (95% CrI)	1.69 (1.17 to 2.42)	1.74 (1.01 to 3.14)	1
Probability of superiority to control, %	99.8	97.7	-

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RCTs with Toci

Want to have some fun with numbers? calculate ARR (difference) and NNT (1/ARR) for mortality…

Then do the same thing for remdesivir…

Study (, N)	Conv O2; HF/NIMV; MV/ECMO (%/%/%)	Steroids %	Progression/Recovery	Mortality
RECOVERY N=4116	45 / 41 / 14	82%	Time to discharge: 20d vs >28d MV or death by d28: 33% vs 38%	**29% (Toci) vs 33%**
REMAP CAP N=865	<1 / 70 / 29	80%	Organ free support: 10d vs 0d Time to ICU Discharge: aHR 1.43	**28% (Toci) vs 36%**
COVACTA n=438 mITT	28 / 30 / 38	42%	Ordinal scale day 28: OR 1.19 (0.8—1.76) Time to discharge: 20 vs 28d (p=.04) Duration in ICU: 9.8 vs 15.5d (p=.05)	19.7% (toci) vs 19.4%
TOCIBRAS n=129	52 / 32 / 16	86%	MV or death by 15d: 28% vs 20% (p=.32) Vent-free days within 29d: 19% vs 21% (p=.53)	21% (toci) vs 9%
EMPACTA n=389	64 / 27 / NA	80%	MV or death by 28d: 12% vs 19.3% (p=.04) Time to discharge: 6 vs 7 d	10.% (toci) vs 8.6%
BACC-Bay N=243	80 / 4 / <1	9%	MV or death: 10.6 vs 12.5% Clinical worsening (ordinal): HR 1.1 (0.6-2.1) Duration of supplemental oxygen: 5 vs 4.9d	5.6% (toci) vs 4.9%
CORIMUNO N=131	All conventional O2	47%	WHO-CPS < 5 at day 4: 19% vs 28% MV/Death by day 14: 24% vs 36%	11.1% vs 8.9%
TCZ-C19 N=126	All conventional O2	10%	Clinical prog (ICU/MV/hypoxia/death) d 14: 28% vs 27% ICU admission at day 14: 10% vs 7.9%	3.3% (toci) vs 1.6%

Bold/green = statistically favoring toci

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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 toci dose; 2nd dose allowed 12-24 hours later at clinician discretion
  - *DOES THIS MAKE SENSE WITH THE HALF LIFE? NO. NO IT DOES NOT. Why does this bother me so much?*
- Primary outcome: all cause mortality at day 28
- Secondary outcomes: time to discharge, composite of mechanical ventilation or death
- Minimal safety endpoints collected/reported

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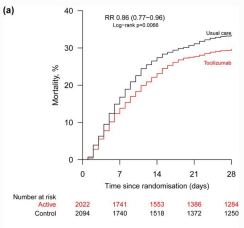
More RECOVERY highlights



Interim analysis:

- 79% with completed data (follow-up forms)
  - 83% confirmed to actually receive toci

Mortality endpoint:

28-day mortality - Toci 29% vs SOC 33% (p=0.007)

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More RECOVERY highlights

TIMING. "an exploratory analysis showed that the effects of toci 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?

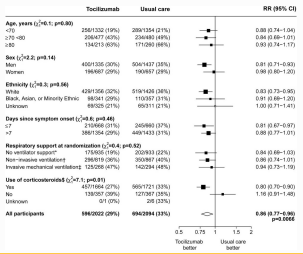

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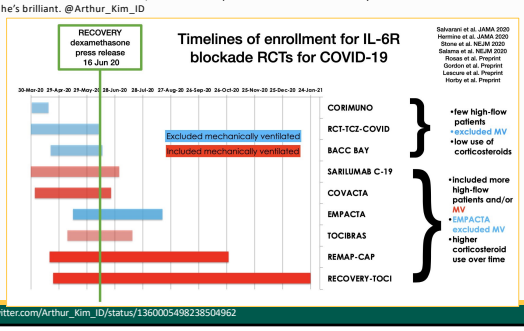
Image stolen from Arthur Kim's tweets, because this is prettier than I could make it myself. Follow him on twitter, he's brilliant. @Arthur_Kim_ID



https://twitter.com/Arthur_Kim_ID/status/1360005498238504962

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Other Inpatient Care:
Antithrombotic therapy (in patients without suspected or confirmed VTE)

For patients requiring ICU level care at initiation	• ASH: suggests **prophylactic-intensity** over intermediate-intensity or therapeutic-intensity anticoagulation • Based on preliminary analysis of pooled trials indicating futility, and potential safety concern
For patients not requiring ICU level care at initiation	• ASH: suggests prophylactic-intensity over intermediate-intensity or therapeutic-intensity; Use clinical judgment and assess individual risk • Preliminary analysis of multiplatform trial suggests full dose anticoag may be superior in reducing the need for organ support and mortality in moderately ill

ASH FAQs: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation
December 2020 NIH Press release: https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients
January 2021 NIH Press release: https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients

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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

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Management of Outpatients

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Mild to Moderate, Not Hospitalized

- Dexamethasone or other corticosteroids are NOT recommended
- **Feb 11:** There are currently insufficient data for the Panel to recommend either for or against the use of the following anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with mild to moderate COVID-19:
  - Bamlanivimab
  - The combination of casirivimab plus imdevimab
- **March 2:** The Panel recommends the use of **bamlanivimab 700 mg plus etesevimab 1,400 mg** for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the EUA criteria (see below) **(BIIa)**.
  - Treatment should be started as soon as possible after the patient has received a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset

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The studies that got us here

Not hospitalized → Hospitalized, mild → Hospitalized, O2 → Severe, HF/NIMV → Critical, MV/ECMO

BLAZE-1:
- Phase 2/3 trial, bamlanivimab vs placebo; outpatient setting
- Change in viral load
- Lower rate of hospitalization/ED visit/death
- **UPDATE**: BAM vs BAM + Etesevimab, 5% absolute reduction (70% relative) hospitalizations or death

R10933-10987-COV-2067: (press release)
- Phase 1&2 trial of casirivimab/imdevimab vs placebo; outpatient setting
- Change in viral load
- Small reduction in hospitalization/ED visit
- Additional data via press release on larger sample

Chen P, Nirula A, Heller B, et al. *N Engl J Med*. 2020

Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: https://www.fda.gov/media/143892/download.

Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization of bamlanivimab and etesevimab. 2021. Available at https://www.fda.gov/media/145801/download

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

Drug	Mechanism	Current Status
Bam/Etesevimab OR Casi/Imdevimab	SARS-CoV-2 neutralizing antibodies	**Emergency Use Authorization** for Outpatients with COVID-19 at High Risk of progression
Ivermectin	Antiparasitic drug, possible antiviral, inflammatory effects	Insufficient data to draw conclusions https://www.covid19treatmentguidelines.nih.gov/statement-on-ivermectin/
Fluvoxamine	SSRI; possible anti-inflammatory effects	Small RCT published, *JAMA*. 2020;324(22):2292-2300. additional trials in progress
Colchicine	Anti-inflammatory (used for gout, pericarditis, etc)	Two RCTs completed, preliminary results only, awaiting publications

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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

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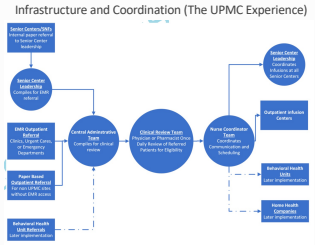
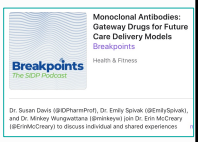
Monoclonal Antibody Therapy: Making it work

Infrastructure and Coordination (The UPMC Experience)





Bariola RJ et al. OFID March 26 2021, https://doi.org/10.1093/ofid/ofab151

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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:
    - https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html
- Follow the fact sheets from FDA:
  - https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-fact-sheets-address-sars-cov-2-variants-monoclonal-antibody-products-under

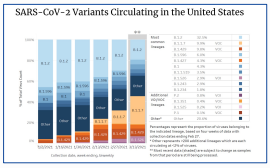

Table 1: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1-2 Molar Ratio)

Lineage with Spike Protein Substitution	Key Substitutions Tested*	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change*
B.1.351 (South Africa origin)	K417N + E484K + N501Y	>45*
P.1 (Brazil origin)	K417T + E484K + N501Y	>51†*
B.1.427/B.1.429 (California origin)	L452R	7.4
B.1.526 (New York origin)#	E484K	17

* For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.
† No change: <3-fold reduction in susceptibility.
‡ No activity observed at highest concentration tested. Bamlanivimab and etesevimab together are not expected to retain activity against variants from this lineage.
# Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

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Lessons learned and moving forward

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Best Practice is a moving target

NIH Recommendations by Month

Gray = insufficient data;
Orange = not recommended except in a clinical trial;
Red = recommend AGAINST;
Blue = recommended for some patients

Drug	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan21	Feb	Mar
Remdesivir												
HCQ (+/-Azithro)												
Ivermectin												
Anti-SARS-CoV2 Antibody												
Convalescent Plasma												
Corticosteroids												
Colchicine												
Fluvoxamine												
Tocilizumab												
(room to add…)												

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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 JCs "we ARE the peer review!"
  - Public pressure

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

A good reference on keeping up with new trials: Robinson J, The Pharmaceutical Journal, https://www.pharmaceutical-journal.com/news-and-analysis/features/everything-you-need-to-know-about-the-covid-19-therapy-trials/

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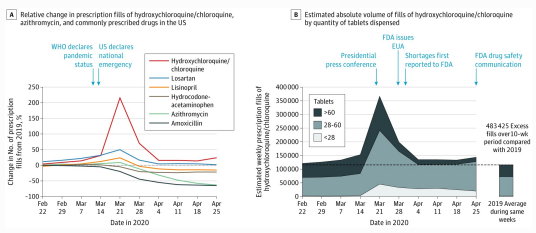
Patterns of medication use in pandemic setting: The Cautionary Tale of HCQ



Vaduganathan M. *JAMA*. 2020;323(24):2524-2526.

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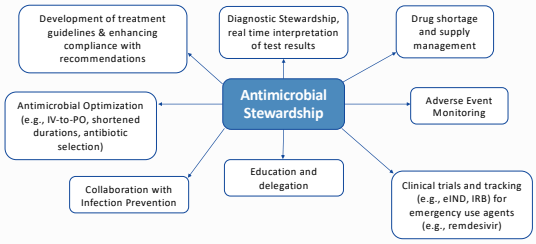
Preparing for the next pandemic: Leveraging antimicrobial stewardship



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

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