

Updates for Treatment of COVID-19 in Hospitalized Patients

DATE: Sept, 2021 Ellie Sukerman, MD

Disclosures

- I have no disclosures

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Objectives

- Review current NIH and IDSA COVID-19 treatment guidelines with focus on immunomodulatory therapies

- Provide update on COVID-19 monoclonal antibodies

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COVID-19 Treatment in Hospitalized Adults

- Updates for immunomodulatory therapies
- No significant updates in antiviral therapies
- Treatment options guided by disease severity
  - Oxygen requirements
  - Evidence of systemic inflammation

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Hospitalized but not Requiring O2	• Panel recommends AGAINST use of dexamethasone (AIIa) or other corticosteroids (AIII) • Insufficient evidence to recommend for or against routine use of remdesivir. For patients at high risk of progression, remdesivir may be appropriate
Hospitalized and Requiring O2	• Use one of the following options: • Remdesivir (BIIa) • Dexamethasone plus remdesivir (BIII) • Dexamethasone (when combination with remdesivir can't be used or is not available)
Hospitalized on High-Flow Device or Noninvasive Ventilation	• Use one of the following options: • Dexamethasone (AI) • Dexamethasone plus remdesivir (BIII) • For recently hospitalized pts with rapidly increasing O2 needs and systemic inflammation: add baricitinib (BIIa) OR IV tocilizumab (BIIa) to 1 of the 2 options above. Tofacitinib can be used instead of baricitinib or IV sarilumab can be used instead of IV tocilizumab.
Hospitalized on Invasive Mechanical Ventilation or ECMO	• Dexamethasone (AI) • For patients who are within 24h of ICU admission: • Dexamethasone plus IV tocilizumab (BIIa) • If IV tocilizumab is not available or not feasible, IV sarilumab can be used (BIIa)

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Adapted from NIH COVID-19 Treatment Guidelines. covid19treatment guidelines.nih.gov. Accessed 9/6/21.

Updates in Immunomodulatory Therapies

Tocilizumab

- Anti-IL-6-receptor monoclonal antibody
- Studies with mixed results
- RECOVERY and REMAP CAP trials reported benefit

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Tocilizumab – Current Recommendations

- **IDSA**: Among hospitalized adults with progressive severe* or critical** illness due to COVID-19 who have elevated markers of systemic inflammation, IDSA *suggests* tocilizumab in addition to standard of care rather than standard of care alone (conditional rec, low certainty of evidence)

*SpO2 ≤ 94% on room air including patients in supplemental O2
**mechanical ventilation and ECMO, end organ dysfunction as seen in sepsis/septic shock

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 9/10/21.

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Tocilizumab – Current Recommendations

- **NIH**: Recommends tocilizumab **in combination with dexamethasone** in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19
  - Recently hospitalized patients (ie, within first 3d of admission) admitted to ICU within past 24h and who require invasive mechanical ventilation, noninvasive ventilation or high-flow nasal canula (HFNC) (>0.4 FiO2/30L/min) (BIIa) **OR**
  - Recently hospitalized patients (i.e., within first 3d of admission) not admitted to ICU who have rapidly increasing O2 needs and require noninvasive ventilation or HFNC and who have significantly increased markers of inflammation (CRP ≥ 75mg/L) (BIIa)

https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/. Accessed 9/10/21.

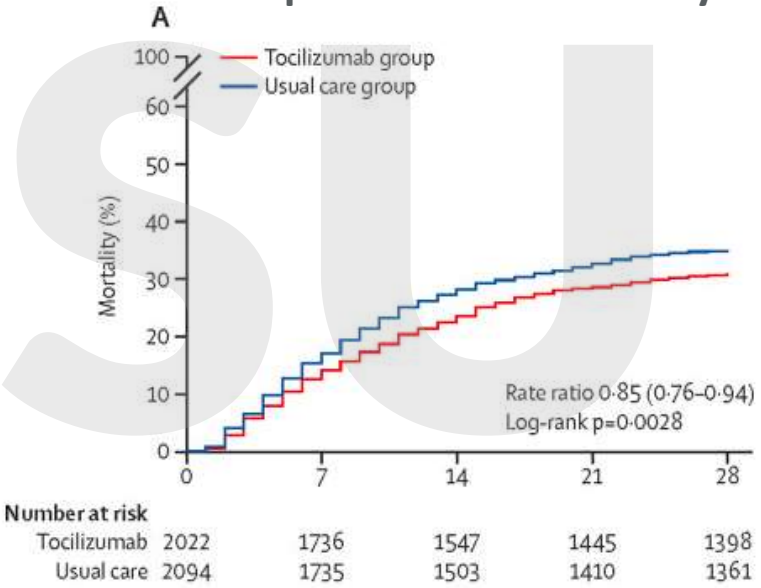
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RECOVERY Trial - tocilizumab

- Significant reduction in 28d mortality, greater probability of discharge from hospital within 28d compared to usual care alone in hospitalized patients with hypoxia **and** systemic inflammation (CRP ≥ 75 mg/L)

- Decreased risk of progression to invasive mechanical ventilation including ECMO compared to usual care alone in patients not on invasive mechanical ventilation at randomization

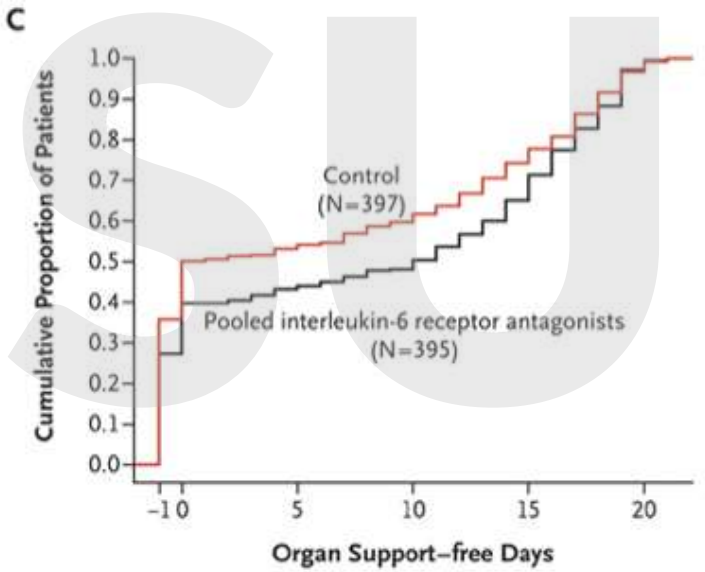
Impact on 28d Mortality



Group RC. *Lancet.* 2021.

REMAP CAP - tocilizumab

- Adults with COVID-19 within 24h of starting organ support in ICU
- Greater median organ support-free days in IL-6 receptor antagonist group vs standard care
- Improved survival in pooled IL-6 receptor antagonist groups



Investigators R-C, Gordon AC, Mouncey PR, et al. *N Engl J Med.* 2021.

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Tocilizumab

- Single dose of 8mg/kg actual body weight IV
- Dose should NOT exceed 800mg
- **Only in patients who have received or are receiving steroids for COVID-19**

Tocilizumab

- Avoid in following patients:
  - Significantly immunosuppressed
  - ALT >5x ULN
  - Uncontrolled serious bacterial, fungal or non-SARS-CoV-2 viral infection
  - ANC <500 or Plt <50k
  - High risk of GI perforation
  - Hypersensitivity to tocilizumab
  - Lack of data in pregnancy; shared decision making recommended and use only if potential benefit felt to outweigh risk in discussion with OB

https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/. Accessed 9/2/21.

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Tocilizumab Shortage as of 9/3/21

Estimated Resupply Dates

- Genentech has stocked out Actemra 20 mg/mL 4 mL, 10 mL and 20 mL vials and the company cannot estimate a release date. All current orders have been cancelled and no orders are being accepted at this time.
- The Actemra ACTPen is on allocation.

- Sarilumab may be used as an alternative if tocilizumab is not available or not feasible; sarilumab for IV administration is not an approved formulation in the U.S.

https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=744&loginreturnUrl=SSOCheckOnly. Accessed 9/3/21.

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Baricitinib

- Janus kinase (JAK) inhibitor
- Should only be used in combination with steroids

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Baricitinib – Current Recommendations

IDSA: Among hospitalized adults with severe COVID-19 having elevated inflammatory markers but not on invasive mechanical ventilation, the IDSA suggest baricitinib rather than no baricitinib

Baricitinib – Current Recommendations

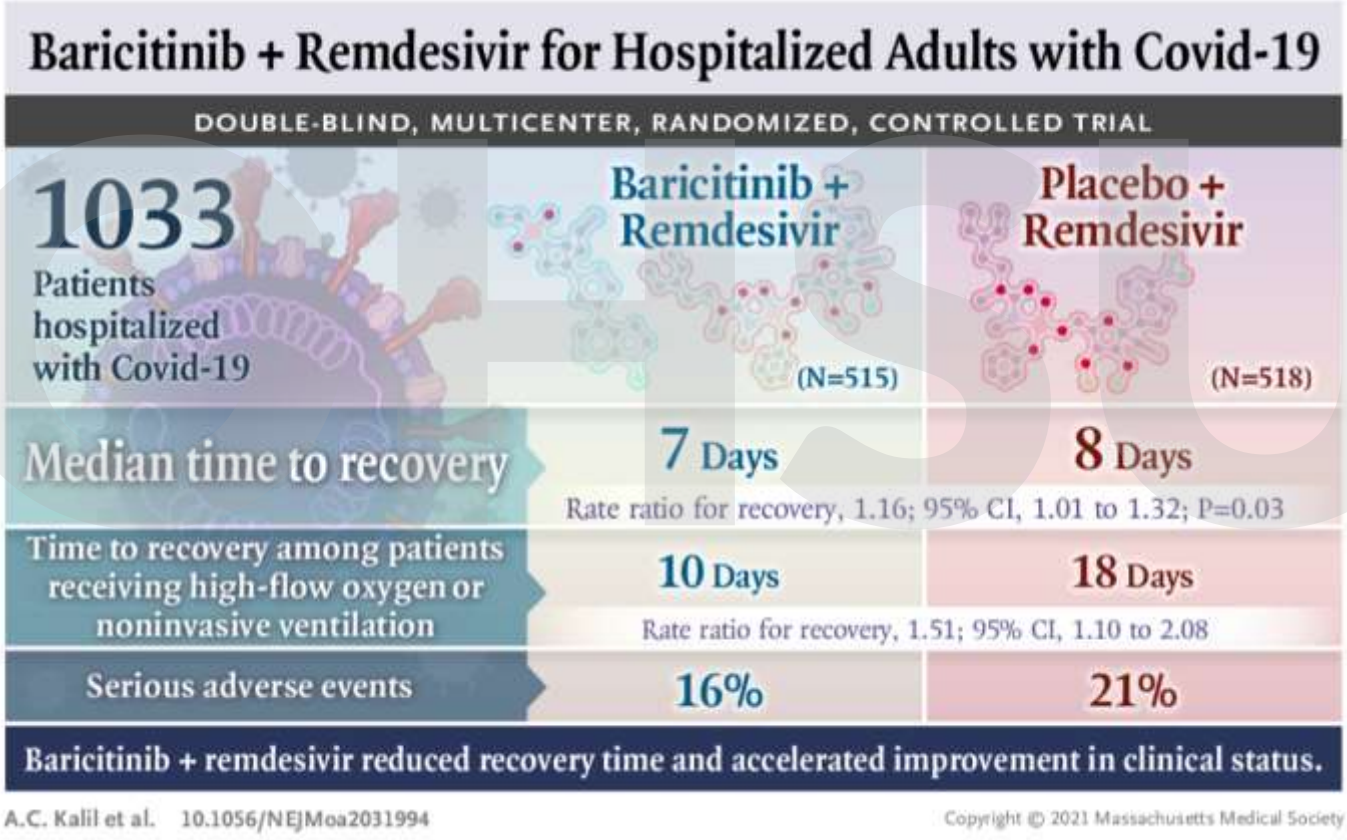
- **NIH**: for recently hospitalized patients with rapidly increasing O2 requirements and systemic inflammation, add baricitinib to one of following:
  - Dexamethasone (AI)
  - Dexamethasone plus remdesivir (BIII)

- NIH guidelines do not include baricitinib in regimen for patients requiring invasive mechanical ventilation or ECMO

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/. Accessed 9/10/21.

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ACTT-2 – remdesivir +/- baricitinib



Baricitinib

- Duration is up to 14d or hospital discharge, whichever comes 1st
- Dose is dependent on eGFR
  - eGFR ≥60 -> 4mg PO daily
  - eGFR 30 to <60 -> 2mg PO daily
  - eGFR 15 to <30 -> 1mg PO daily
  - eGFR <15 -> baricitinib is NOT recommended
- Tofacitinib may be used as an alternative if baricitinib not available or not feasible

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/. Accessed 9/3/21.

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Note on Immunomodulatory Tx

- NIH recommends **AGAINST** use of combination of tocilizumab plus baricitinib except in a clinical trial

- Both are immunosuppressive and results may be additive

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Agents Not Recommended

Ivermectin

- NOT recommended or approved for tx or prevention of COVID-19
- NIH and IDSA guidelines do not recommend ivermectin and/or suggest *against* use outside of a clinical trial
- Pharmacologic studies suggest that to achieve the concentrations necessary for the antiviral efficacy detected in in vitro studies, this would require administration of doses up to 100-fold higher than those approved for use in humans

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Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19



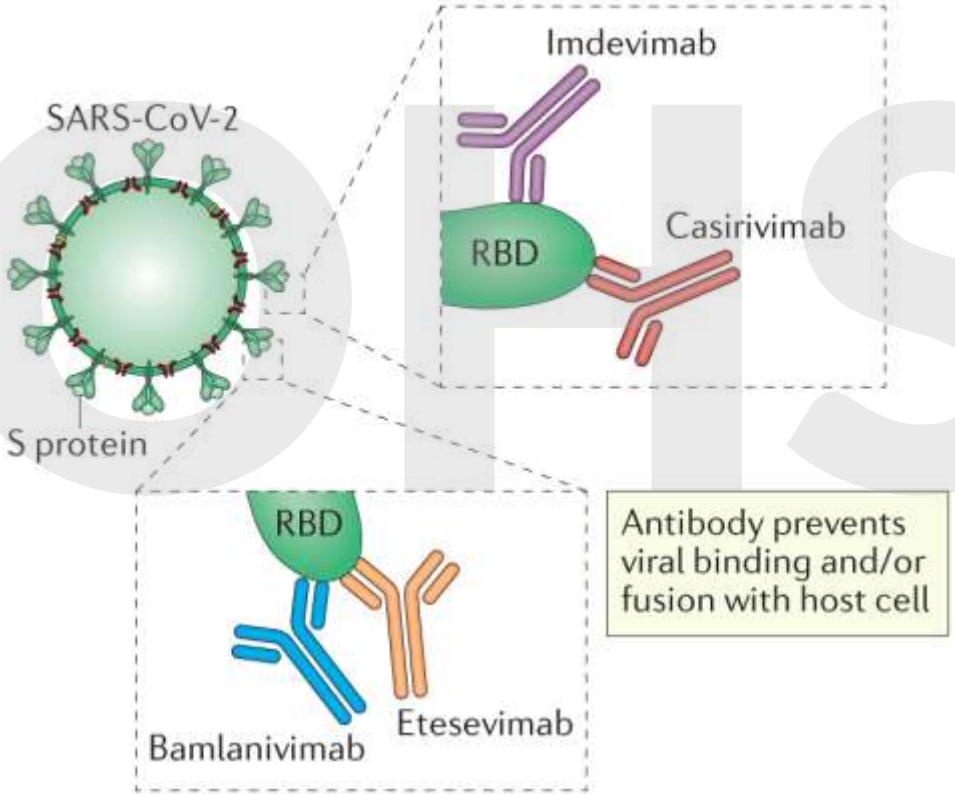


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COVID-19 Monoclonal Antibodies

Monoclonal Antibody Therapy



- Targeted at receptor binding domain (RBD) of viral spike (S) protein
- Prevents binding of S protein to host cell target

Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. *Nat Rev Immunol.* 2021.

Monoclonal Antibody Therapy

- Consider monoclonal antibodies for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they would otherwise meet EUA criteria for outpatient tx

https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/. Accessed 9/12/21.

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Monoclonal Antibody Therapy

- NIH recommends using one of the following anti-SARS-CoV-2 monoclonal antibodies to tx **non-hospitalized** patients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the FDA EUA
  - Casirivimab + imdevimab
  - Sotrovimab

- Tx should be started ASAP after positive NAAT/Ag test and within 10d of sx onset

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/. Accessed 9/3/21.

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REGEN-COV EUA Criteria - Treatment

- NOT authorized for use in patients:
  - Who are hospitalized due to COVID-19, OR
  - Who require O2 therapy due to COVID-19, OR
  - Who require an increase in baseline O2 due to COVID-19 in those on chronic O2 due to underlying non-COVID-19 related comorbidity

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REGEN-COV EUA Criteria – Post-Exposure Prophylaxis

Patients ≥12yo and ≥40kg in individuals who are at high risk of progression to severe COVID-19 and are:

- Not fully vaccinated, **OR**
- Who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, **AND**
- Have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC, **OR**
- Who are at high risk of exposure to an infected individual with SARS-CoV-2 because of SARS-CoV-2 infection in others in the same institutional setting

O'Brien MP, Forleo-Neto E, Musser BJ, et al. *N Engl J Med.* 2021.

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EUA Criteria for Identifying High-Risk Individuals

- Older age (e.g., ≥65yo)
- Obesity or overweight
- Pregnancy
- CKD
- DM
- Immunosuppressive disease or tx
- Cardiovascular disease or htn
- Chronic lung diseases
- Sickle cell disease
- Neurodevelopmental disorders or other conditions that confer medical complexity
- Having a medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))
- Other medical conditions or factors (e.g., race or ethnicity) may also place individual patients at high risk for progression

https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf. Accessed 9/8/21.

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Regeneron Administration and Dosing

- Dose is 600mg casirivimab and 600mg imdevimab for both tx and post-exposure prophylaxis
- IV administration is strongly recommended for tx
- IV or subcutaneous administration appropriate for post-exposure prophylaxis

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Prioritization of Monoclonals

- Logistics may limit ability to offer monoclonal antibody to all individuals who meet EUA eligibility criteria

- If triaging is necessary, NIH recommends prioritizing:
  - Treatment over post-exposure prophylaxis
  - Vaccinated individuals who are not expected to mount an adequate immune response (e.g., immune compromise)
  - Unvaccinated or incompletely vaccinated individuals at high risk of progressing to severe COVID-19

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-the-prioritization-of-anti-sars-cov-2-monoclonal-antibodies/. Accessed 9/12/21.

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Stay tuned…

- RECOVERY Trial pre-print comparing usual care vs usual care plus high-dose REGEN-COV in adults hospitalized with COVID-19

- In patients **seronegative at baseline**, REGN-COV reduced 28d mortality (24% vs 30%; rate ratio 0.80; 95% CI 0.70-0.91; p=0.0010)

- There is **not** currently FDA EUA for this indication

https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1. Accessed 9/12/21.

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Update on Bamlanivimab/Etesevimab

- This monoclonal Ab combination is NOT authorized in states/territories/jurisdictions in which frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%

- Based on most currently available data, bamlanivimab and etesevimab are now authorized in all states which do not exceed this threshold

https://www.fda.gov/media/151719/download. Accessed 9/12/21.

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Take-Home Points

- IL-6 inhibitor or JAK inhibitor may be included in tx regimen for select patients dependent on oxygen requirements and presence of systemic inflammation but should not be used in combination
- Ivermectin should NOT be used for tx or prevention of COVID-19 outside the setting of a clinical trial
- Monoclonal antibody therapy may be considered for patients hospitalized for reasons other than COVID-19 who otherwise meet the ambulatory EUA criteria
- Monoclonal therapy for patients hospitalized due to COVID-19 may be coming but does not have EUA at this time

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Thank You