STANDARDS OF CARE AND PULMONARY PROTOCOLS IN THE MANAGEMENT OF COVID

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ACOI SPRING SUBSPECIALITY CONFERENCE

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DISCLOSURES

- Currently a member of the speakers bureau for Grifols and Mylan Speciality.

OBJECTIVES

- Understand that the treatment of COVID-19 varies depending on disease severity. Be able to identify the appropriate treatment based on this severity.
- Know what treatments are currently recommended for COVID-19 and the appropriate monitoring for these patients.
- Know what treatments are not indicated for the treatment of Covid 19.

THIS INFORMATION IS WHAT IS KNOWN TODAY.
THIS COULD ALL CHANGE TOMORROW.

THE NUMBERS

- As of February 22nd, of this year there have been more than 426 million cases of confirmed covid reported globally.
- As of February 22nd, of this year there have been more than 5.8 million deaths attributed to covid globally.

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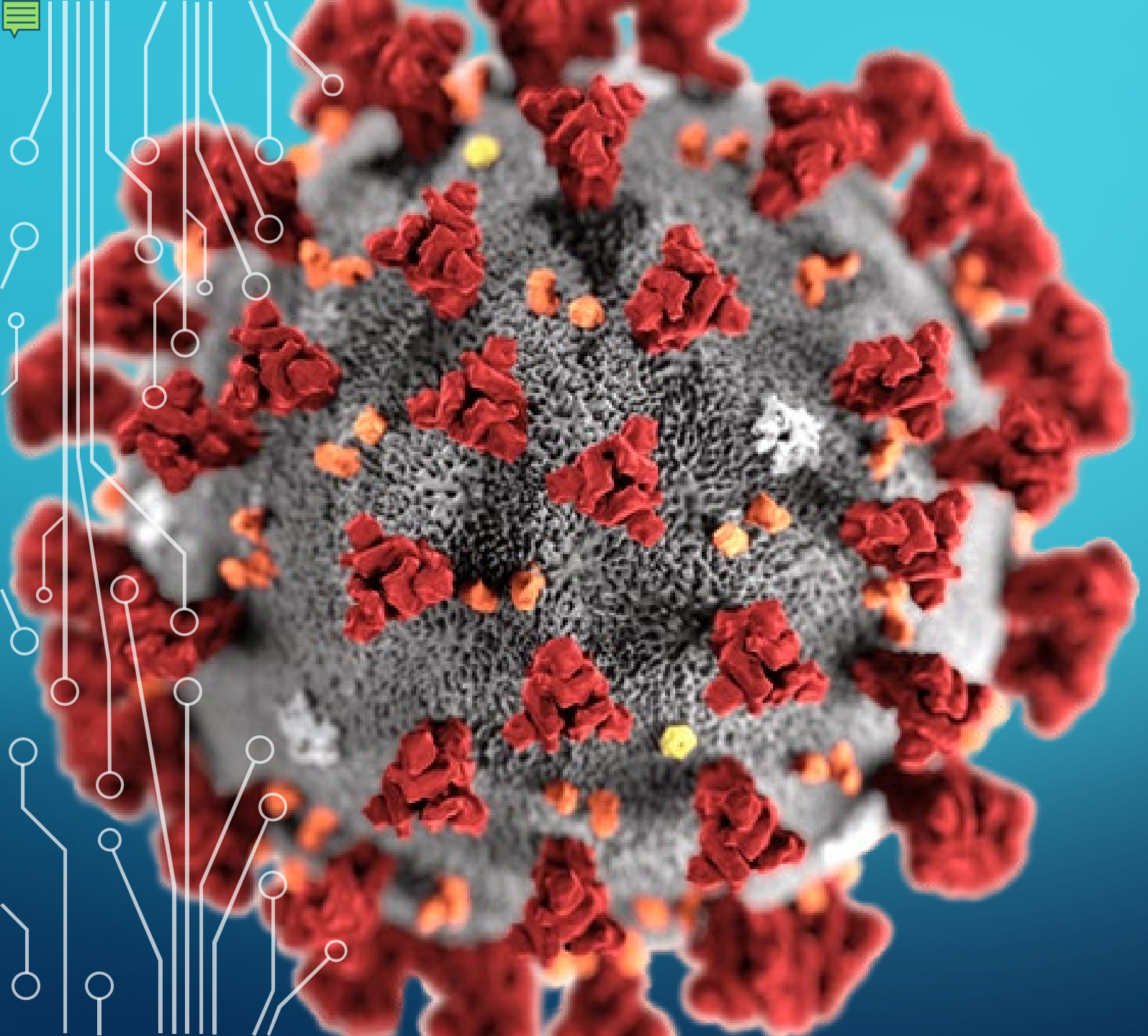

COVID-19

- Single strand positive-sense RNA virus.
- Composed of 4 main structural proteins
  - Spike (S)
  - Small envelope
  - Membrane glycoproteins
  - Nucleocapsid protein

CYTOKINE STORM

- This is a term that has been used in medical literature as well as lay press.
- Refers to the dysregulation of the immune system. This leads to a significant release of pro-inflammatory cytokines. This can lead to severe and overwhelming tissue damage.

- Some of the key players
  - Interferon's (INF)
  - Cytokines – includes IL-6, IL-1β, IL-17, IL-8
  - Chemokines
  - Tumor necrosis factor – α(TNF-α)

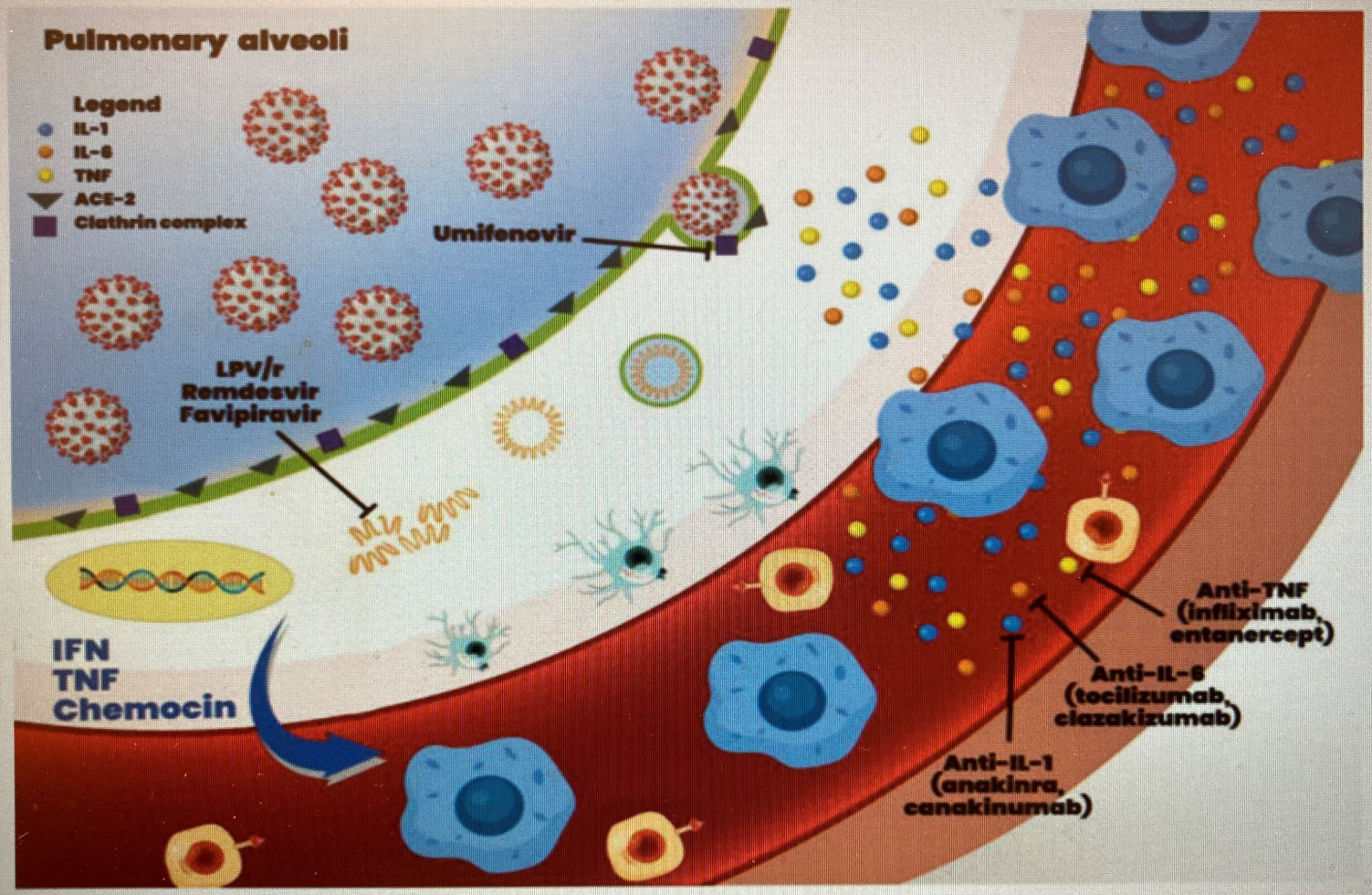

Figure 1 Cytokine storm. Figure shows SARS-CoV-2 contacting, invading and releasing genetic material in an alveolar pulmonary type 2 cell. This may induce cell death, but also leads to exposition of pathogen-associated molecular patterns, which is recognised by leucocyte pattern recognition receptors, both activate innate immunity and cause interferon (IFN), tumour necrosis factor (TNF)-α and chemokines release. This attracts leukocytes that release cytokines (notably IL-1, IL-6 and TNF) and induce tissue damage and cell death, which leads to a vicious cycle of inflammation (cytokine storm) and tissue damage. Some drugs have been studied as therapeutic targets (block to viral entry or to cytokine storm) and are listed in the figure. For further details, see the text. IL, interleukin; LPV/r, lopinavir and ritonavir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

KALFA G, VENETI S, POLYCHRONOPOULOS G, ET AL. REVIEW OF THE THERAPEUTIC TARGETS FOR COVID-19: INSIGHTS FROM CYTOKINE STORM. POSTGRAD MED J 2021; 97:391-398

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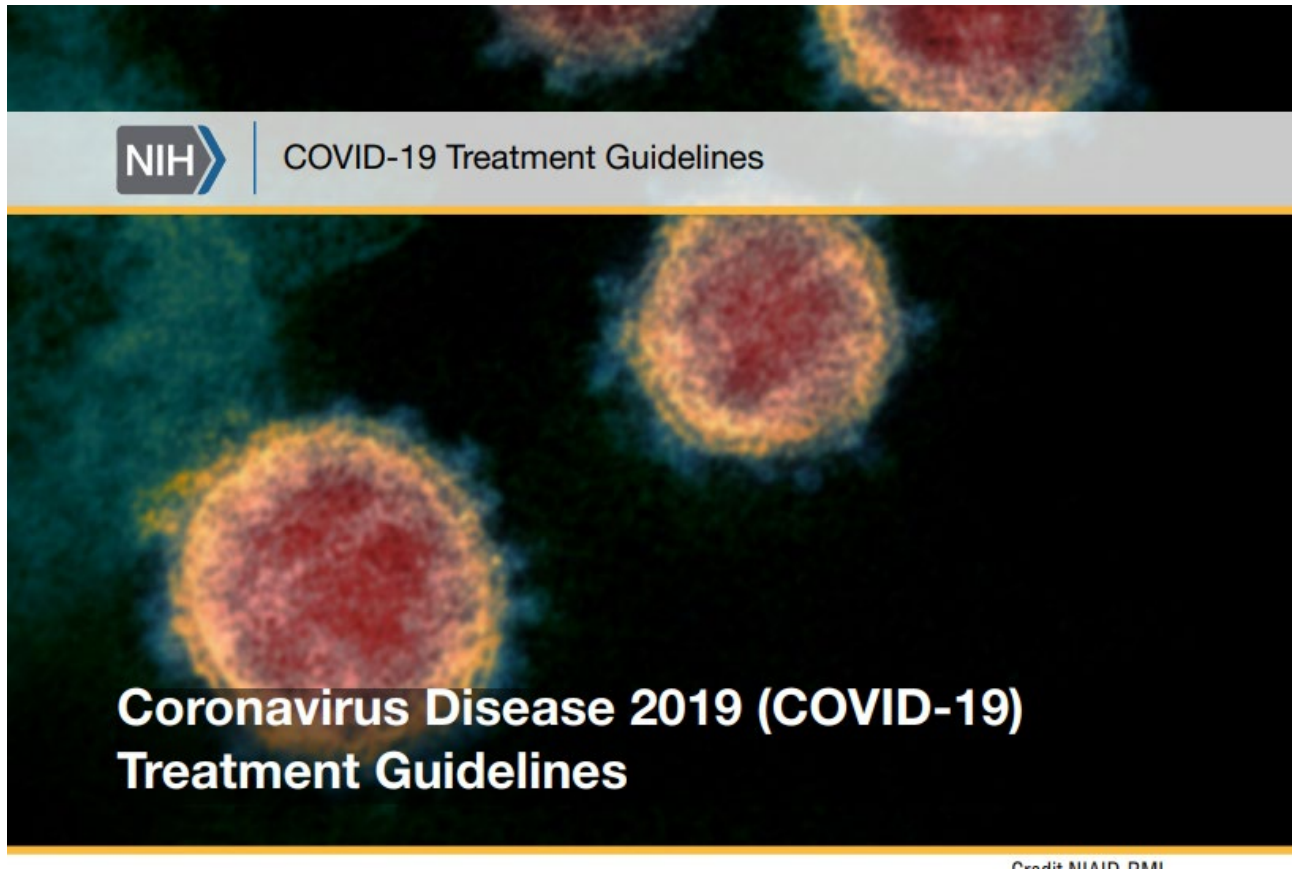

- https://www.covid19treatmentguidelines.nih.gov/

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NIH COVID TREATMENT PANEL

- American Association of Critical-Care Nurses
- American Association for Respiratory Care
- American College of Chest Physicians
- American College of Clinical Pharmacy
- American College of Emergency Physicians
- American College of Obstetricians and Gynecologists
- American Society of Hematology
- American Thoracic Society
- Biomedical Advanced Research and Development Authority
- Centers for Disease Control and Prevention
- Department of Defense
- Department of Veterans Affairs
- Food and Drug Administration
- Infectious Diseases Society of America
- National Institutes of Health
- Pediatric Infectious Diseases Society
- Society of Critical Care Medicine
- Society of Infectious Diseases Pharmacists

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MEDICATIONS THAT ARE APPROVED, AUTHORIZED OR UNDER INVESTIGATION FOR THE TREATMENT OF COVID

- Remdesivir*
- Rotonavir-boosted nirmatrelvir
- Sotrovimab
- Molnupiravir
- Dexamethasone
- Barcitinib
- Heparin
- Tofacitinib
- Tocilizumab
- Sarilumab

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NIH GUIDELINES FOR THE TREATMENT OF THE NONHOSPITALIZED PATIENT

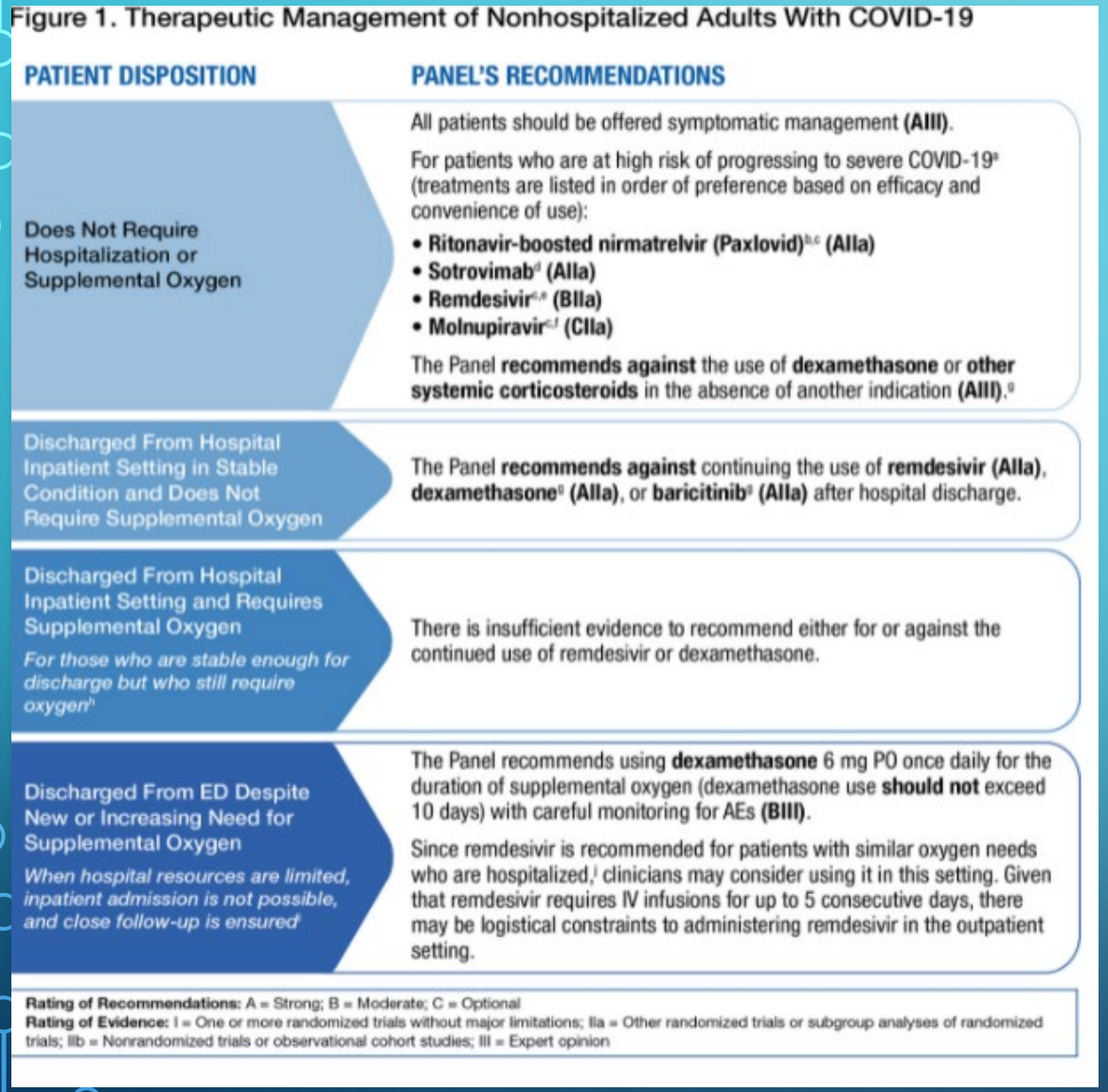

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19[a] (treatments are listed in order of preference based on efficacy and convenience of use): • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[b,c] **(AIIa)** • **Sotrovimab**[d] **(AIIa)** • **Remdesivir**[e,f] **(BIIa)** • **Molnupiravir**[c,f] **(CIIa)** The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.[g]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone**[g] **(AIIa)**, or **baricitinib**[g] **(AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[h]	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[i]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII)**. Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[i] clinicians may consider using it in this setting. Given that remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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Does Not Require Hospitalization or Supplemental Oxygen

All patients should be offered symptomatic management **(AIII)**.

For patients who are at high risk of progressing to severe COVID-19[a] (treatments are listed in order of preference based on efficacy and convenience of use):

- **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)**
- **Sotrovimab[d] (AIIa)**
- **Remdesivir[e,f] (BIIa)**
- **Molnupiravir[c,f] (CIIa)**

The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.[g]

HIGH RISK PATIENTS

- The NIH guidelines references the CDC guidelines regarding high-risk patients. These are individuals that are moderately or severely immunocompromised.
- This list is quite extensive
- https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

SYMPTOM MANAGEMENT

- This includes treatment for symptoms including fever, myalgias, cough and headache.
- This is with over-the-counter medications.
- Patients may benefit from resting in the prone position.
- This would include managing expectations and educating patients regarding the variability in symptom resolution and recovery.

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SELF PRONING INSTRUCTIONS

- These instructions were developed in New York City during the beginning of the pandemic.
- They have been utilized at many facilities in the United States.

nstructions for patients with cough or trouble breathing:

Please try to not spend a lot of time lying flat on your back! Laying on your stomach and in different positions will help your body to get air into all areas of your lung. You may notice improvement in breathing immediately or several minutes after positioning change. Please do not stay in any position that causes discomfort or pain; skip such positions in the rotation. It is most important you do not just lay flat in bed and this guide is designed to help you change positions in bed.

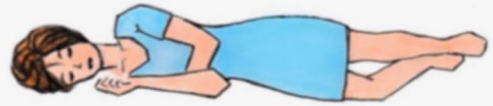
Your healthcare team recommends trying to change your position every 30 minutes to 2 hours and even sitting up is better than laying on your back. **If you are able to, please try this:**

1. 30 minutes – 2 hours: lying on your belly
2. 30 minutes – 2 hours: lying on your right side
3. 30 minutes – 2 hours: sitting up
4. 30 minutes – 2 hours: lying on your left side; then back to position #1.

PHOTOS BELOW TO DEMONSTRATE THIS:

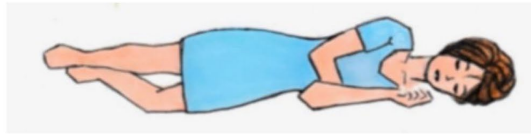
1. 30 minutes – 2 hours: laying on your belly

2. 30 minutes – 2 hours: laying on your right side



3. 30 minutes – 2 hours: sitting up

4. 30 minutes – 2 hours: laying on your left side



Then back to Position 1. Lying on your belly!

Self- positioning Guide/instructions by Suzanne Bentley MD MPH, Laura Iavicoli MD, David Cherkas MD, Rikki Lane MD. Illustrated by Sarah Lin. New York City Health + Hospital/ Elmhurst. English, Last updated May 8, 2020.

DRUGS AND DOSING REGIMENS RECOMMENDED FOR HIGH-RISK NONHOSPITALIZED PATIENTS

Drug Name	Dosing Regimen	Time From Symptom Onset
Ritonavir-Boosted Nirmatrelvir (Paxlovid)	GFR ≥60 Nirmatrelvir 300 mg with Ritonavir 100 mg po BID for 5 days GFR 30-59 Nirmatrelvir 150 mg with Ritonavir 100 mg BID for 5 days Not recommended GFR < 30 Severe hepatic impairment	Within 5 days
Sotrovimab	500 mg as a single IV infusion	Within 10 days
Remdesivir	200 mg IV the first day and 100 mg IV on days 2 and 3	Within 7 days
Molnupiravir	800 mg po BID for 5 days	Within 5 days

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RITONAVIR-BOOSTED NIRMATRELVIR

- The panel recommends 300mg nirmatrelvir + 100mg of ritonavir po for 5 days within 5 days of symptom onset.
- There are a significant number of drug interactions.
- This is based on EPIC-HR trial. Showed reduced risk of death or hospitalization by 88% compared to placebo.
- This drug is expected to be effective against the Omicron variant.

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ANTI-SARS-CoV-2 mAB PRODUCTS

- There are currently 3 that have FDA emergency use authorization.
  - Bamlanivimab + etesevimab
  - Casirivimab + imdevimab
  - Sotrovimab
- In clinical trials these drugs have reduced the risk of death or hospitalization by 70-85%
- The panel is recommending against using bamlanivimab + etesevimab and casirivimab + imdevimab as they are not effective against Omicron which is currently the dominant variant. Sotrovimab has in vitro studies that indicate it is effective against Omicron.
- the Panel recommends Sotrovimab with level AIIa evidence

REMDESIVIR

- Currently approved by the FDA for the treatment of hospitalized patients with COVID-19 as well as nonhospitalized patients with COVID-19 who have a high-risk of disease progression.
- The is based on the PINETREE trial.

MOLNUPIRAVIR

- The Panel recommends this ONLY be used if other medications are not available or cannot be used.
- Emergency use authorization(EUA) was given based on the MOVe-OUT trial.

DEXAMETHASONE

- The Panel recommends against the use of dexamethasone and other corticosteroids for treating patients that do not require hospitalization or oxygen.

Discharged From ED Despite New or Increasing Need for Supplemental Oxygen

When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured

The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII)**.

Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[1] clinicians may consider using it in this setting. Given that remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

DEXAMETHASONE

- In patients who are discharged from the emergency room with covid and are requiring oxygen the Panel recommends dexamethasone 6 mg daily until oxygen needs are better or 10 days.

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OTHER AGENTS

- Drugs with insufficient evidence to support a recommendation
  - Ivermectin
- The Panel recommends against the use of anticoagulants or other antiplatelet therapies for the prevention of VTE
- Drugs the panel recommends against
  - Interferon alfa or lambda
  - Systemic interferon beta
  - Chloroquine
  - Hydroxychloriquine
  - Azithromycin
  - Lopinavir/ritonavir and other protease inhibitors

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NIH GUIDELINES FOR THE TREATMENT OF THE HOSPITALIZED PATIENT

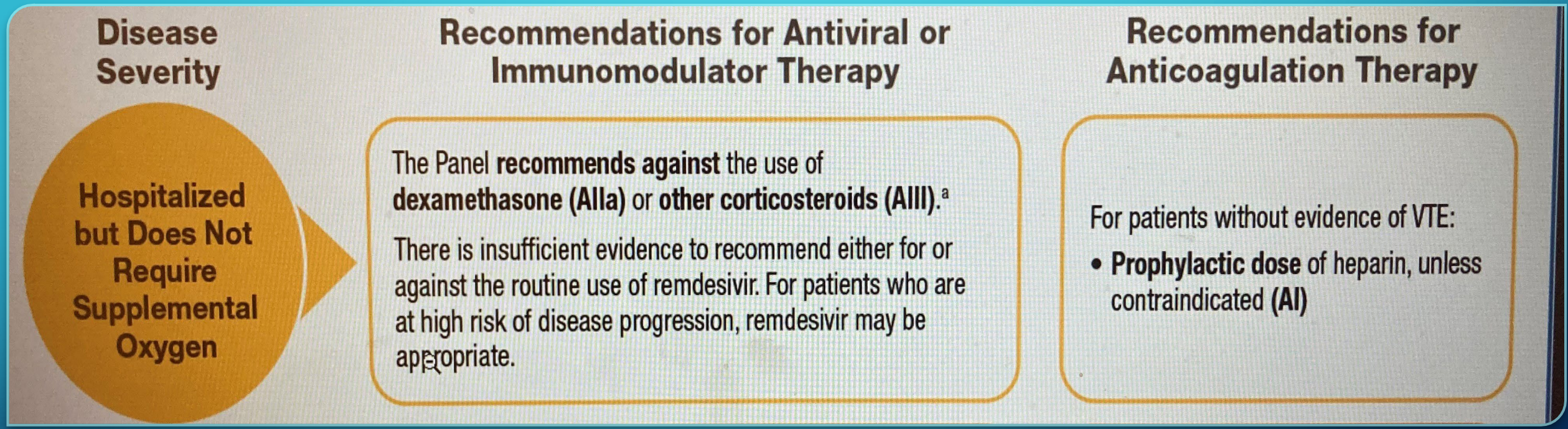
Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Drug	Dosing	comments
Remdesivir	200 mg IV once daily then 100 mg IV daily for 4 additional days or until discharge	Recommended to check GFR, LFT's and PT prior to starting therapy May need to be d/c'd if ALT >10x ULN Should be d/c'd if ALT increasing and there is evidence of liver inflammation Not studied in patients with GFR <50 Recommend not using in patients with GFR <30
Dexamethasone	6 mg IV or po once daily for up to 10 days or until hospital discharge	If dexamethasone is not available can use the equivalent dose of another corticosteroid
Barcitinib	Depends on GFR GFR > 60 4 mg once daily GFR 30-59 2 mg once daily GFR 15-29 1 mg daily GFR <15 not recommended All regimens are 14 days or until hospital discharge	

Drug	Dosing	Comments
Tofacitinib	10 mg po twice daily for 14 days or until discharge	This is to be used if Barcitinib is not available If GFR < 60 dose is reduced to 5 mg po bid
Tocilizumab	8 mg/kg IBW up to 800 mg as a one time IV dose	Some clinical trials gave a second dose 8 hours later if no improvement
Sarilumab	Single-dose prefilled syringe for SQ injection	This is used as an alternative if Tocilizumab is not available



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MILD DISEASE - REMDESIVIR

- There is insufficient data currently to recommend for or against Remdesivir in this patient population.
- Patients at high risk of disease progression may benefit.

There have been multiple trials with conflicting data including ACTT-1, Solidarity trial and PINETREE trial.

The NIH panel states not enough evidence either for or against Remdesivir in this patient population based on the conflicting data of these trials.

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MILD DISEASE - STEROIDS

- The RECOVERY trial found no survival benefit in patients not requiring oxygen that were given dexamethasone .
- It is based on this data that the NIH panel recommended against the use of dexamethasone in this patient population

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ANTICOAGULATION

- All patients should be placed on DVT prophylaxis unless contraindicated.
- Should be placed on therapeutic anticoagulation if there is documented need for this.

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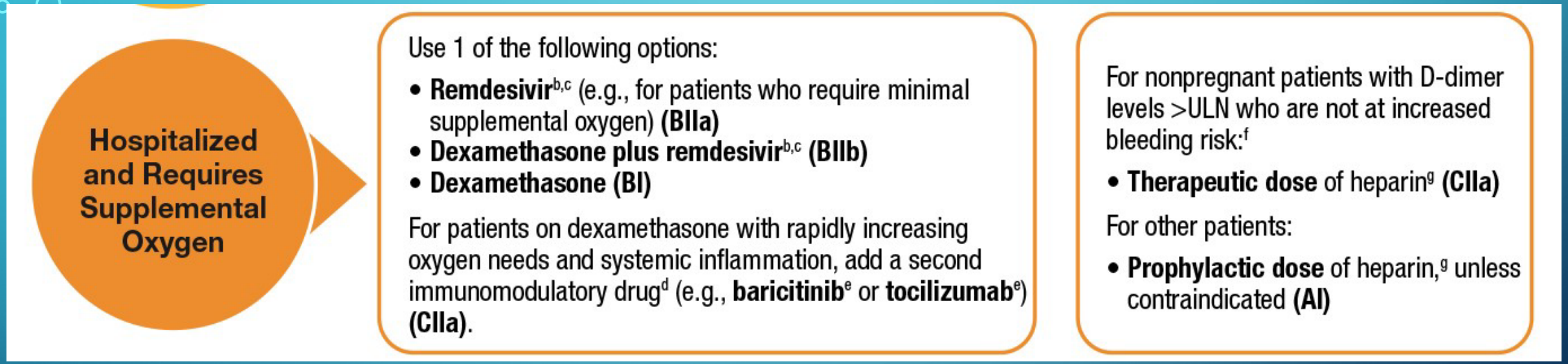

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MILD HYPOXEMIA - REMDESIVIR

- The panel recommends Remdesivir as a treatment option for some patients with COVID 19 on low dose supplemental oxygen and are early in the course of the disease.
- A 5 day course was shown to be comparable to 10 days.
- Based on multiple trials including ACTT-1, Solidarity trial, DisCoVeRy trial, PINETREE trial.
- Solidarity and DisCoVeRy did not show mortality benefit, but ACTT-1 did. PINETREE and ACTT-1 suggested that Remsedivir would have the most impact given early.

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MILD HYPOXEMIA – REMDESIVIR PLUS DEXAMETHASONE

- The combination of Remdesivir and Dexamethasone has not been directly compared to Dexamethasone alone.
- The panel recommends this combination based on a theoretical combined benefit.

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MILD HYPOXEMIA - DEXAMETHASONE

- If dexamethasone is not available an alternative can be used (prednisone, methylprednisolone or hydrocortisone)
- For patients already on Dexamethasone that have rapidly increasing oxygen needs as well as systemic inflammation can add a second immunomodulatory drug. This would be Tocilizumab or Barcitinib

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ADDITIONAL IMMUNOMODULATORY THERAPY

- As there is uncertainty in this patient population on which patients would benefit the Panel recommends considering these medications on a case-by-case basis in patients with have rapidly increasing oxygen requirements and evidence of systemic inflammation – level CIIa
- This is based on trials including the RECOVERY trial, COV-BARRIER and STOP-COVID trial.

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ADDITIONAL THOUGHTS ON IMMUNOMODULATORY THERAPIES

- Barcitinib or tocilizumab should only be given with dexamethasone.
- There are no studies comparing one of these drugs to another. The use of these medications may increase the risk of opportunistic infections..
- If barcitinib or tocilizumab are not available can consider using tofacitinib instead of barcitinib – level BIIa. Could consider using sarilumab if tociluzimab is not available – level BII a.
- The panel recommends against using these drug in combination.

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ANTICOAGULATION

- The Panel recommends using therapeutic heparin for patients with covid who have D-dimer levels about the ULN, are requiring low flow oxygen and have no increased risk of bleeding. Level of evidence CIIa.
- Patients who do not have elevated D-dimer levels and have no contraindications should be placed on prophylactic doses of anticoagulation.

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Hospitalized and Requires Oxygen Through a High-Flow Device or NIV

Use 1 of the following options:

- **Dexamethasone (AI)**
- **Dexamethasone plus remdesivir**[b] **(BII)**

For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]

For patients without evidence of VTE:

- **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**

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DEXAMETHASONE

- The Panel recommends the use of dexamethasone in this patient population. Level of evidence AI.
- Based on RECOVERY trial. This showed a survival benefit in this patient group.
- In patients already receiving corticosteroids and have increasing oxygen demands or signs of systemic inflammation can consider the addition of a second immunomodulator.

REMDESIVIR

- This is NOT recommended as monotherapy in this patient group. There is not data at this point to suggest that this subgroup would benefit.
- If patients on low-flow oxygen and monotherapy with remdesivir clinically worsen and require high-flow or NIV remdesivir course should be completed and dexamethasone added.

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REMDESIVIR PLUS DEXAMETHASONE

- The Panel recommends this combination based on theoretical benefit of having an antiviral medication combined with anti-inflammatory medications.
- Level of evidence is BIIb
- This is recommended over remdesivir alone

ADDITIONAL IMMUNOMODULATORY THERAPY

- Barcitinib or Tocilizumab should be considered in patients already receiving dexamethasone whose oxygen requirements remain high, worsen or have evidence of severe inflammatory response.
- There are no studies that directly compare either of these medications.
- Can use tofacitinib if barcitinib not available and sarilumab if tocilizumab is not available.

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ANTICOAGULATION

- The Panel recommends the use of a prophylactic dose of anticoagulation unless patients have a contraindication or other indication for therapeutic anticoagulation.

AWAKE PRONE POSITIONING

- Prone positioning not a new concept for ARDS. Initially used in the 1970's to treat severe ARDS.
- There have been multiple observational and retrospective studies.
- Large international study was done April 2, 2020 through January 26, 2021. This study of 1121 COVID positive patients "found that awake prone positioning reduced the incidence of treatment failure and the need for intubation without signs of harm."
  - Awake Prone Positioning for COVID-19 acute hypoxaemic respiratory failure: a randomized, controlled, multinational, open-label meta-trial. Lancet Respir Med:2021:9:1387-95

SPECIAL CONSIDERATIONS
COVID IN THE PREGNANT PATIENT

The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine have guidance for these patients.

Generally, recommend care to be provided in a facility that can do maternal as well as fetal monitoring, if appropriate.

TREATMENT OF PREGNANT PATIENTS

- Recommend having a multidisciplinary treatment team. This team may include obstetrics, maternal-fetal medicine, infectious diseases, pulmonary and critical care.
- In general the treatment of the pregnant patient is the same as the non pregnant patient – level of evidence AIII
- One difference is the goal oxygen saturation of 95% in these patients
- Use of shared decision making when considering medications with emergency use authorization or experimental status.

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Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone**[g] **(AIIa)**, or **baricitinib**[g] **(AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[h]	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.

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ADDITIONAL THOUGHTS

- Goals of care
- Code status
- Vaccination

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