Overview of COVID-19 Antivirals and Treatment Updates

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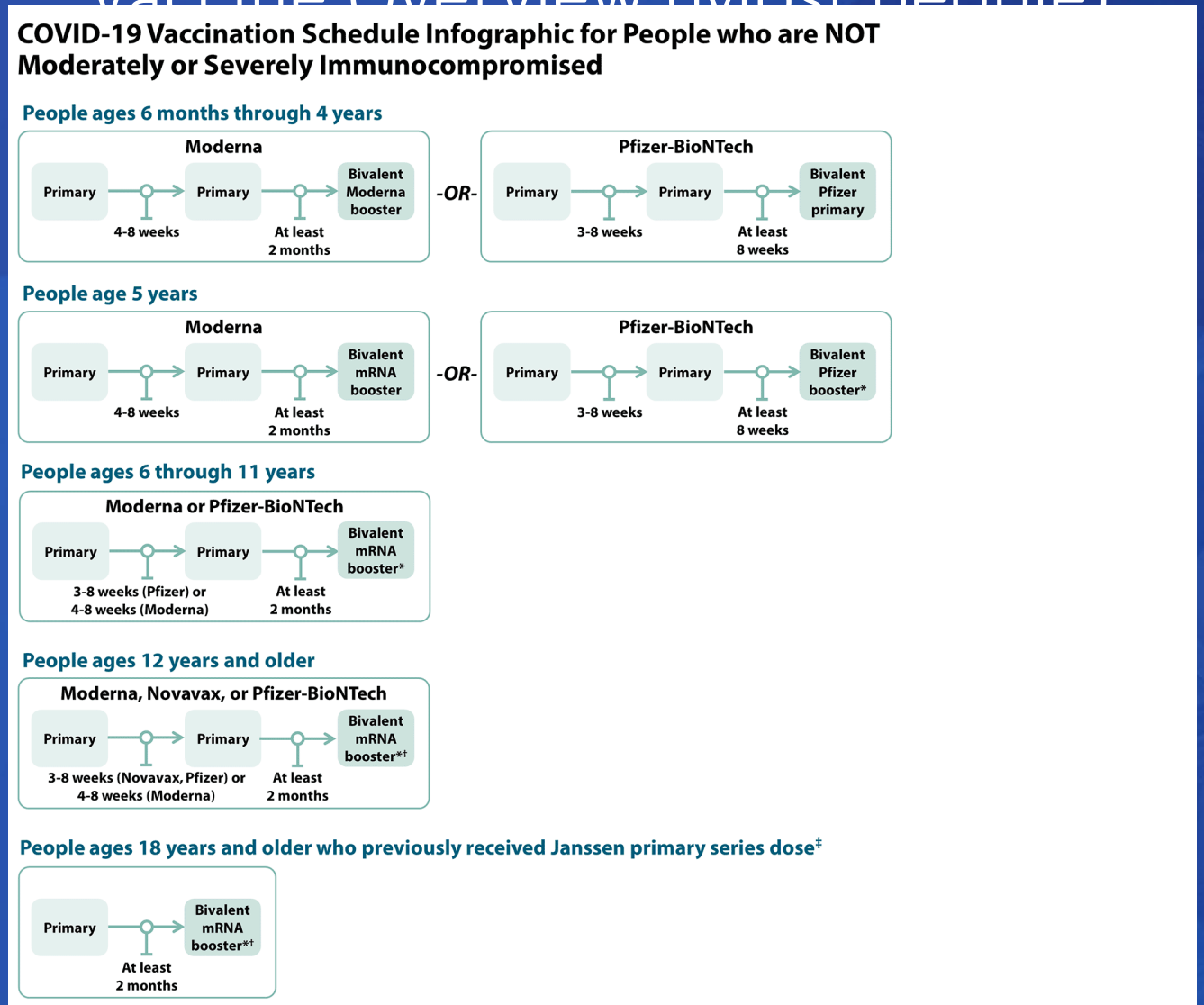
Objectives

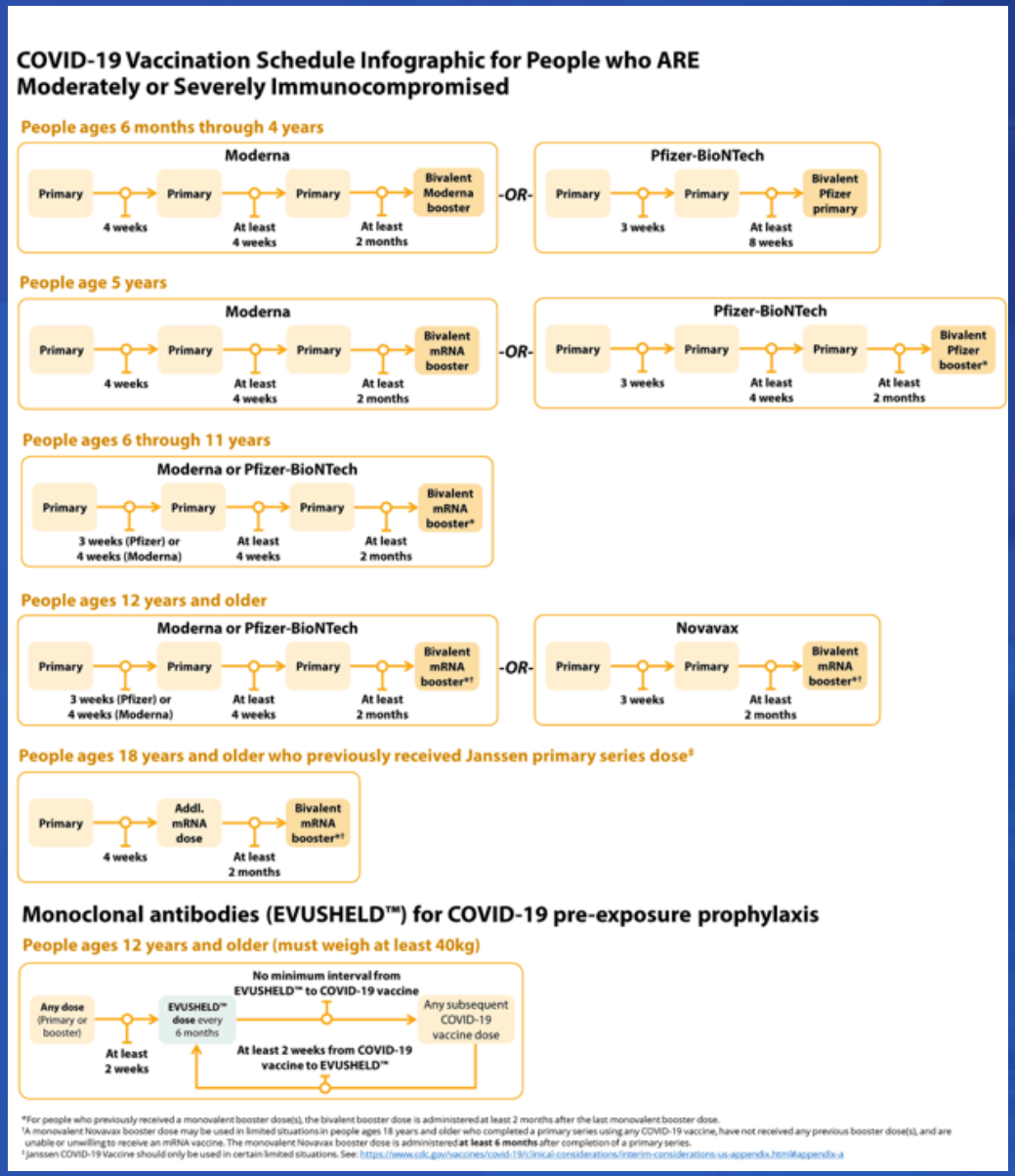
- Define current treatment guidelines for COVID-19
- Describe appropriate use of each medication for COVID-19
- Evaluate use of COVID-19 antiviral treatments considering other medications and conditions

Vaccine Overview (Most people)



https://www.cdc.gov/vaccines/covid-19/images/COVID19-vaccination-schedule-most people.png

Vaccine Overview (Immunocompromised)



https://www.cdc.gov/vaccines/covid-19/images/COVID19-vaccination-schedule-immunocompromised.png

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What drives COVID-19 pathogenesis?

Replication of SARS-CoV-2

Dysregulation of the immune/inflammatory response to SARS-CoV-2 leading to tissue damage

Who is at increased risk of disease progression?

1. Older age
2. Prolonged amount of time since the most recent vaccine dose (e.g., >6 months)
3. Decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications

Therapeutic Management of Nonhospitalized Patients with COVID-19

Table 2a. Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: December 28, 2022

Patient Disposition	Panel's Recommendations
All Patients	• All patients should be offered symptom management (AIII). • The Panel **recommends against** the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication (AIIb).
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] (AIIa) • **Remdesivir**[d,e] (BIIa) *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] (CIIa)

https://www.covid19treatmentguidelines.nih.gov/tables/management-of-nonhospitalized-adults-summary/

Non-hospitalized Patients

- Dexamethasone:
  - There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm

https://www.covid19treatmentguidelines.nih.gov/tables/management-of-nonhospitalized-adults-summary/

Paxlovid (nirmatrelvir tablets; ritonavir tablets)

- Authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death
- Must be started within 5 days of start of symptoms or positive test, whichever is sooner
- STANDARD DOSING: [no known or suspected renal impairment or mild renal impairment eGFR ≥ 60mL/min to < 90mL/min]
  - 2 nirmatrelvir 150mg tablets (300mg) and 1 ritonavir 100mg tablet, taken together, twice daily, with or without food, for five days
- RENAL DOSING:[eGFR ≥30mL/min to < 60mL/min]
  - 1 nirmatrelvir 150mg tablet and 1 ritonavir 100mg tablet, taken together, twice daily, with or without food, for five days

Managing Paxlovid Drug interactions

- Web-based drug-drug interaction checker: The Liverpool COVID-19 Drug Interactions website
- Tables with guidance on managing specific drug-drug interactions: The University of Waterloo/University of Toronto drug interaction guide

Managing Paxlovid Drug interactions

- Increasing monitoring for potential adverse reactions to the concomitant medication.
- Adjusting the dose of the concomitant medication.
- Temporarily withholding the concomitant medication.
- Using an alternative to the concomitant medication.
- Using alternative COVID-19 therapies

Paxlovid Drug Contraindications

- Potent CYP3A4 inducers
  - Anticancer drugs: apalutamide
  - Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
  - Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
  - Antimycobacterials: rifampin
  - Herbal Products: St. John's Wort (hypericum perforatum)

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

Paxlovid interactions, where it may be appropriate to temporarily withhold the concomitant medication

- Generally, withhold during treatment and 2-3 days after completion. May need to withhold longer in elderly.

- **Anticoagulants**
- Rivaroxaban[d]
- **Anti-infectives**
- Erythromycin
- **BPH**
- Alfuzosin
- Silodosin
- **Cardiovascular**
- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

- **Immunosuppressants**[e]
- Everolimus
- Sirolimus
- Tacrolimus
- **Lipid-modifiers**
- Atorvastatin[f]
- Lomitapide
- Lovastatin[f]
- Rosuvastatin[f]
- Simvastatin[f]
- **Migraine**
- Eletriptan
- Rimegepant
- Ubrogepant

- **Neuropsychiatric**
- Suvorexant
- Triazolam[g]
- **Erectile dysfunction**
- Avanafil
- **Respiratory**
- Salmeterol
- **Miscellaneous**
- Certain chemotherapeutic agents[c]
- Colchicine[h]
- Finerenone
- Flibanserin
- Naloxegol

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

Paxlovid treatment: Adjust concomitant dose and monitor for adverse effects

Evaluate the specific adjustments to make at Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide

- **Anticoagulants**
- Apixaban
- Dabigatran
- Edoxaban
- **Anti-infectives**
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin
- **BPH**
- Tamsulosin
- **Cardiovascular**
- Cilostazol
- Digoxin
- Mexiletine
- **Diabetes**
- Saxagliptin
- **Erectile dysfunction**
- Sildenafil
- Tadalafil
- Vardenafil

- **Immunosuppressants**
- Cyclosporine[e]
- Dexamethasone[j]
- Fedratinib
- Ruxolitinib
- Tofacitinib
- Upadacitinib
- **Migraine**
- Almotriptan[h]
- **Neuropsychiatric**
- Alprazolam[g]
- Aripiprazole
- Brexpiprazole
- Buspirone
- Cariprazine
- Chlordiazepoxide[g]
- Clobazam[g]
- Clonazepam[g]
- Clorazepate[g]
- Diazepam[g]
- Estazolam[g]
- Flurazepam[g]
- Iloperidone
- Lumateperone
- Pimavanserin
- Quetiapine
- Trazodone

- **Pain**
- Fentanyl
- Hydrocodone
- Oxycodone
- **Pulmonary hypertension**
- Riociguat
- **Miscellaneous**
- Certain chemotherapeutic agents[c]
- Darifenacin
- Elexacaftor/ tezacaftor/ivacaftor
- Eluxadoline
- Ivacaftor
- Solifenacin
- Tezacaftor/ivacaftor

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

Taking Paxlovid where you can Continue Concomitant Medication and Monitor for Adverse Effects

- **Anticoagulants**
- Warfarin
- **Anti-infectives**
- Brincidofovir[k]
- Cobicistat- or ritonavir-boosted antiretrovirals
- Isavuconazole
- Posaconazole
- Voriconazole
- **BPH**
- Doxazosin
- Terazosin
- **Diabetes**
- Glyburide

- **Cardiovascular**
- Amlodipine
- Diltiazem
- Felodipine
- Nifedipine
- Sacubitril
- Valsartan
- Verapamil
- **Migraine**
- Zolmitriptan
- **Neuropsychiatric**
- Haloperidol
- Hydroxyzine
- Mirtazapine
- Risperidone
- Ziprasidone
- Zolpidem

- **Pain**
- Buprenorphine
- Hydromorphone
- Methadone
- Morphine
- Tramadol
- **Miscellaneous**
- Certain chemotherapeutic agents[c]
- Certain conjugated monoclonal antibodies[l]
- Oxybutynin

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

Adverse effects of Paxlovid

- Altered taste
- Diarrhea
- Hypertension
- Myalgia
- Abdominal pain
- Nausea

Paxlovid Rebound

- “rebound” is defined as testing positive 2-8 days after completing a 5-day course of Paxlovid
- Studies have demonstrated that this is not unique to Paxlovid, monupiravir or even those who did not receive antiviral treatment.
- Rates have been reported to be between 3-5%

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9258292/

Remdesivir

- treatment of COVID-19 in adults and pediatric patients aged ≥28 days and weighing ≥3 kg
- Non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, remdesivir should be started within 7 days of symptom onset and administered for 3 days
- Hospitalized patients should receive remdesivir for 5 days or until hospital discharge, whichever comes first

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/remdesivir/

Remdesivir Monitoring

- recommends performing estimated glomerular filtration rate (eGFR), liver function, and prothrombin time tests as clinically appropriate
- administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed and for 1 hour afterward
- No clinically significant drug-drug interactions
- Can use in renal impairment but must monitor closely
- Adverse effects: increased liver enzymes,
- Can be used in pregnancy

Molnupiravir

- molnupiravir 800 mg orally (PO) twice daily for 5 days as an alternative therapy in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who are at high risk of disease progression ONLY when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 5 days of symptom onset
- Recommendations are to not use in pregnancy
- Males of reproductive ages should use a reliable method of contraception for the duration of treatment and for at least 3 months after the last dose of molnupiravir
- Adverse effects: diarrhea, nausea, and dizziness

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/molnupiravir/

COVID-19 Management in Hospitalized patients

Table 2b. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severit

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Patient Disposition	Recommendations for Antiviral or Immunomodulator Therapy	
	Clinical Scenario	**Recommendation**
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other systemic corticosteroids (AIII)** for the treatment of COVID-19.[b]
	Patients who are at high risk of progressing to severe COVID-19[a]	**Remdesivir**[c] **(BIII)**
Hospitalized and Requires Conventional Oxygen[d]	Patients who require minimal conventional oxygen	**Remdesivir**[e] **(BIIa)**
	Most patients	Use **dexamethasone plus remdesivir**[e] **(BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[f] or **IV tocilizumab**[f] to 1 of the options above **(BIIa)**.
Hospitalized and Requires HFNC Oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[f] **(AI)** • **Dexamethasone plus IV tocilizumab**[f] **(BIIa)** If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: • **Dexamethasone**[h] **(AI)** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**.[i]
Hospitalized and Requires MV or ECMO	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[f] **(BIIa)** • **Dexamethasone plus IV tocilizumab**[f] **(BIIa)** If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: • **Dexamethasone**[h] **(AI)**

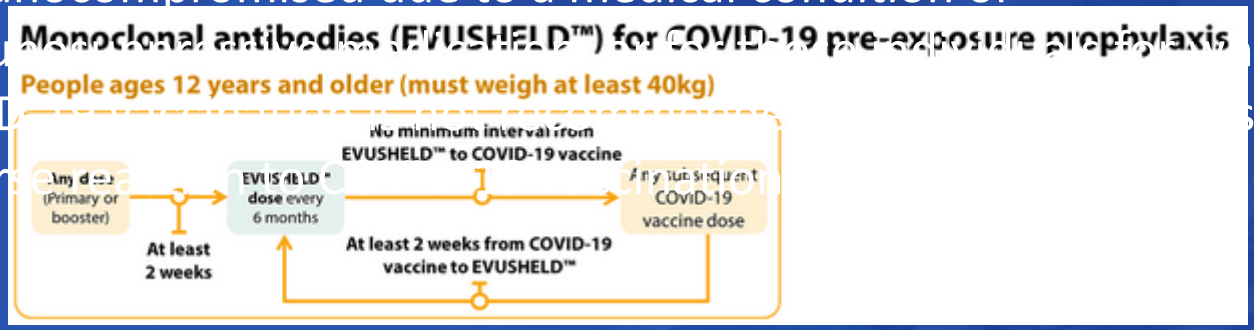
https://www.covid19treatmentguidelines.nih.gov/tables/management-of-hospitalized-adults-summary/

New just authroized for COVID:

- VERY limited indication: Actemra (Tocilizumab)
- Patient must:
  - Be hospitalized AND be receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation
  - CANNOT be used in non-hospitalized treatment of COVID-19

Remaining preventative: Evusheld

- a combination of two monoclonal antibodies, is authorized as pre-exposure prophylaxis to prevent COVID-19 in people who have moderate to severe immune compromise
- can provide protection for those not expected to mount an adequate immune response following vaccination, including those who are immunocompromised due to a medical condition or immu… …om COVID… …severe adver…



https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/pre-exposure-prophylaxis.html

Summary

- Our BEST tools remain vaccination and booster. Evusheld® should also used for those who are moderate to severely immunocompromised.
- Non-hospitalized COVID-19 patients first line of treatment is Paxlovid®, followed by remdesivir for those who do not qualify. There are interactions with Paxlovid®, but many can be managed readily.