Outpatient Dexamethasone use in Patients with COVID-19 without Respiratory Support

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May 8th, 2023

Objectives

- Perform an in-depth review of a patient case including CC, PMH, and labs
- Review the current COVID-19 clinical practice guidelines
- Perform a primary literature review of two relevant studies
- Formulate an evidence-based answer to the proposed clinical question

Patient Information

Chief complaint	• Dyspnea
Urgent Care	• Diagnosed with COVID-19 • Not on supplemental oxygen • Ambulatory
Community pharmacy	• Picking up Paxlovid® and dexamethasone

Patient Information

PMH

- GAD
- ADHD
- MDD (self-harm)
- Mild persistent asthma
  ↑ risk: severe COVID-19
- Hyperlipidemia
- HTN

Vitals 04/03/2023

- T: 100.4 ◦F
- P: 80 bmp
- R: 24 BPM
- BP: 124/75 mmHg
- Pulse Ox: 95%
- eGFR: 90 mL/min

Respiratory Assessment Scoring Grid 04/03/2023

- Respiratory rate: 2 – Moderate Dyspnea
- Accessory Muscle Use: 2 – Moderate Retractions (intercostal, sub-costal, Increased WOB)
- HR: 80
- Total Score: 5

Medication List

Medication	Dose	Dose/Frequency
Albuterol Inhaler	0.9 mg/actuation	1 to 2 puffs by mouth every 4-6 hours as needed
Symbicort Inhaler	160 mcg/4.5 mcg	2 puffs by mouth daily
Amlodipine/benazepril	10 mg/20 mg	1 capsule by mouth daily
Dextroamphetamine ER	10 mg	1 capsule by mouth daily
Valacyclovir HCL	500 mg	1 tablet by mouth daily
Escitalopram	20 mg	1 tablet by mouth daily
Naltrexone HCl	50 mg	1 tablet by mouth daily
Paxlovid	100 mg / 300 mg	2 capsules by mouth BID for 5 days
Dexamethasone	4 mg	1 tablet by mouth daily
Acetaminophen	325 mg	1 tablet by mouth every 4 hours as needed
Atorvastatin	40 mg	1 tablet by mouth daily

Clinical Question

Is there a clinical benefit for outpatient use of dexamethasone without supplemental oxygen for a COVID -19 infection?

Coronavirus Disease (COVID – 19)[1]

Cause	• SARS-CoV-2 virus
Presentation	• Loss of taste/smell, fever, cough, fatigue • May appear up to 14 days after exposure (5-6 days on average)
Severe Symptoms	• Dyspnea, chest pain, AMS
High Risk of hospitalization/death	• Diabetes, chronic respiratory diseases, CV diseases, cancer • Most patients with respiratory conditions recover without special treatment

Dexamethasone[2]

Classification	• Long-acting corticosteroid
Warnings	• Hypertension, CHF, GI disease
ADEs	• Psychiatric disturbances, GI symptoms, hyperglycemia

Paxlovid®[3]

Classification	• Antiviral
Warnings	• SJS, HTN, hepatoxicity
ADEs	• GI discomfort, hypertension, myalgia

2021 IDSA Guidelines[4]

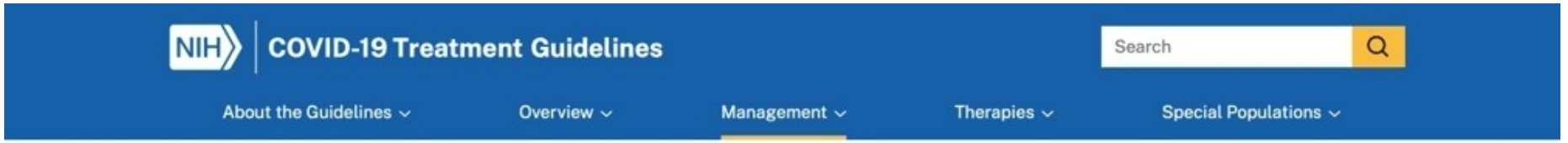
Overview of IDSA COVID-19 Treatment Guidelines

Version 10.2.1

	Pre- and post-exposure prophylaxis: *healthy people w/o symptoms or diagnosis*	***Ambulatory care:*** *mild-to-moderate disease*	***Hospitalized:*** *mild-to-moderate disease without need for suppl. oxygen*	***Hospitalized:*** *severe but non-critical disease (SpO_2 ≤94% on room air)*	***Hospitalized:*** *critical disease (e.g., in ICU needing MV, or septic shock, ECMO)*
Hydroxy-chloroquine[a]	NA	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
Hydroxy-chloroquine[a] *+ azithromycin*	NA	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
Post-exposure hydroxy-chloroquine	**Recommend against use** ⊕⊕⊕◯	NA	NA	NA	NA
Lopinavir + ritonavir	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
Corticosteroids	NA	NA	**Suggest against use††** ⊕⊕◯◯	**Suggest use†** ⊕⊕⊕◯ **R:** If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used. Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable.[b]	**Recommend use** ⊕⊕⊕◯ **R:** If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.[b]

Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Disease Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America. Version 10.2.1. Available at: https:www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Published May 27, 2021. Updated April 11, 2023. Accessed April 15, 2023.

NIH Guidelines[1]



Home / Management / Clinical Management of Adults / Nonhospitalized Adults: Therapeutic Management / Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

Last Updated: December 28, 2022

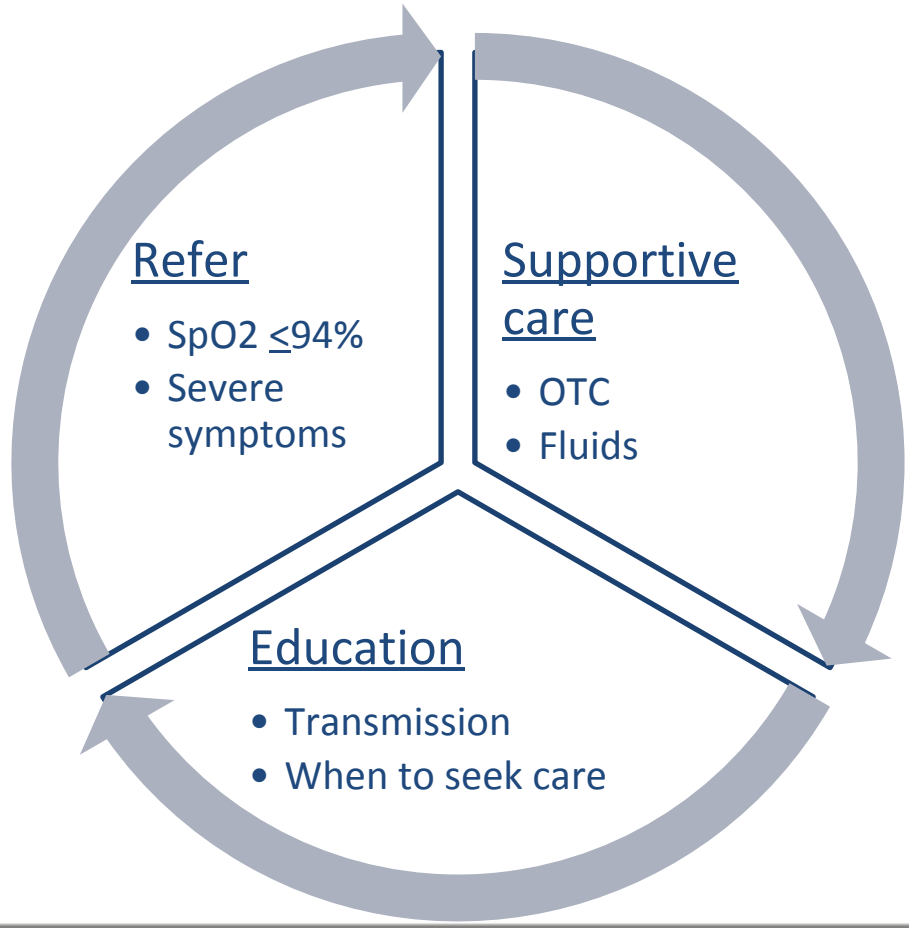
Patient Disposition	Panel's Recommendations
All Patients	• All patients should be offered symptom management (**AIII**). • The Panel **recommends against** the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication (**AIIb**).
Patients Who Are at High Risk 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**)

[a] 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.

COVID-19 Treatment Guidelines Panel. Coronavirus Disease (COVID-19) Treatment Guidelines. National Institutes for Health. Available at: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults-general-management/. Updated September 26, 2022. Accessed April 15, 2023.

NIH COVID-19 Treatment Guidelines[1]

Non-hospitalized Adults



- OTC
  - Analgesics
  - Antitussives
  - Antipyretics

Study No. 1: The RECOVERY Trial[5]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 25, 2021 VOL. 384 NO. 8

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with COVID-19. *N ENGL J MED* 2021; 384(8): 693-204. doi: 10.1056/NEJMoa2021436.

Endpoints[5]

Primary endpoint

- 28-day mortality (all cause)

Secondary endpoints

- Time until discharge
- Progressed to mechanical ventilation
- Death

Methods[5]

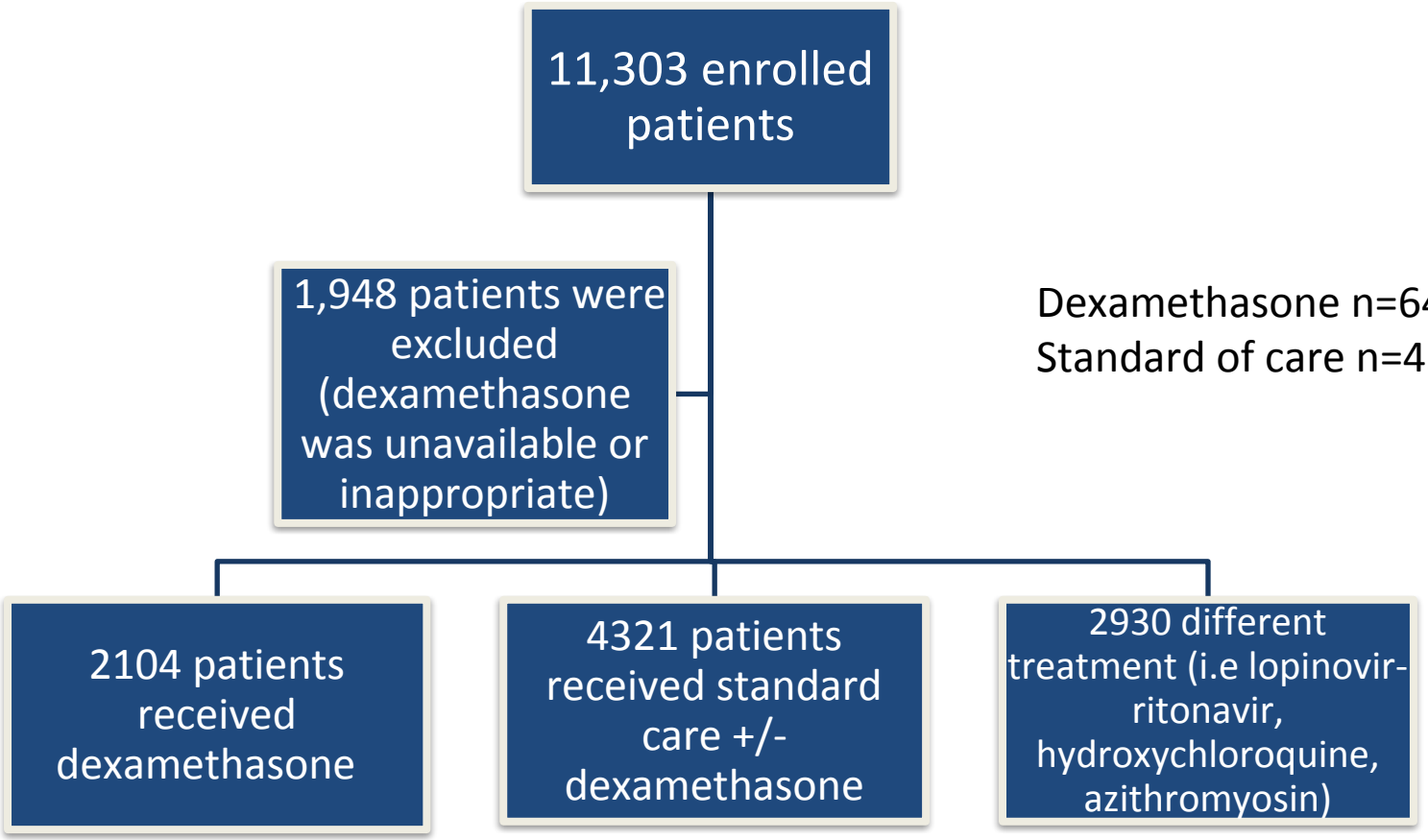
- Controlled
- Open-label
- PO/IV dexamethasone (6mg QD x10 days or until discharge) vs. standard care alone
- Location: UK
- Multi-center: 176 health facilities

Inclusion and Exclusion Criteria[5]

Inclusion	Exclusion

• Positive for COVID-19 (or suspected)
• Hospitalization
	• Active Treatment:
	  • Not available
	  • Contraindicated
	• Allowed to participate:
	  • Pregnant and breastfeeding
	  • Patients <18 years old

Methods continued[5]



Dexamethasone n=6425
Standard of care n=4321

Primary Endpoint Results[5]

Level of respiratory support	Mortality rate (%) dexamethasone group vs. standard of care	RR	95% CI
Invasive mechanical ventilation	29.3% vs. 41.4%	0.64	0.51-0.81
Oxygen without invasive mechanical ventilation	23.3% vs. 26.2%	0.82	0.72-0.94
No respiratory support	17.7% vs 14%	1.19	0.92-1.55

Secondary Endpoint Results[5]

Outcome	Dexamethasone (%)	Standard Care (%)	Rate or Risk Ratio (95% CI)
Discharged (within 28 days)	67.3%	63.6%	1.10 (1.03-1.17)
Progressed to requiring invasive mechanical ventilation	26%	27.6%	0.79 (0.64-0.97)
Death	21.7%	22.7%	0.93 (0.84-1.03)

Strengths[5]

No financial conflict of interest

- The trial sponsors were not involved

Increased external validity

- Age limit of ≥18 was removed
- Pregnant and breastfeeding women were included
- Large sample size
- Multi-center

Limitation[5]

Risk of performance bias

- Open-label trial
  - Patients and clinicians

Risk of detection bias

- Treatment group was assigned by the prescriber

Decreased external validity

- Unavailability of dexamethasone
- Exclusion of many patients

Conclusion[5]

- In patients requiring respiratory support, dexamethasone decreased 28-day mortality rates

- In patients who did not require respiratory support, dexamethasone did not benefit patient

Study No. 2[6]

Observational Study

Medicine

OPEN

Early antiviral and supervisory dexamethasone treatment improve clinical outcomes of nonsevere COVID-19 patients

Tullaya Sitasuwan, MD[a], Pochamana Phisalprapa, MD, PhD[a], Weerachai Srivanichakorn, MD[a], Chaiwat Washirasaksiri, MD[a], Chonticha Auesomwang, MD[a], Rungsima Tinmanee, MD[a], Naruemit Sayabovorn, MD[a], Methee Chayakulkeeree, MD, PhD[b], Pakpoom Phoompoung, MD[b], Korapat Mayurasakorn, MD[c], Nitat Sookrung, PhD[d], Anchalee Tungtrongchitr, MD, PhD[e], Rungsima Wanitphakdeedecha, MD[f], Saipin Muangman, MD[g], Sansnee Senawong, MD[h], Watip Tangjittipokin, PhD[h], Gornmigar Sanpawitayakul, MD[i], Diana Woradetsittichai, BNS[j], Pongpol Nimitpunya, MD[a], Chayanis Kositamongkol, PharmD, MSc[a], Cherdchai Nopmaneejumruslers, MD[a], Visit Vamvanij, MD[k], Thanet Chaisathaphol, MD[a,*]

Manchester University

Sitasuwan T, Phisalprapa P, Srivanichakorn W, et al. Early antiviral and supervisory dexamethasone treatment improve clinical outcomes of nonsevere COVID-19 patients. Medicine 2022; 101 (45):1-9. doi: http://dx.doi.org/10.1097/MD.0000000000021681.

Endpoints[6]

Primary endpoint

- Determine the efficacy of early vs. late favipiravir
  - Asymptomatic or mild symptoms

Secondary endpoint

- Analyze nonsevere COVID-19 management of ambulatory patients

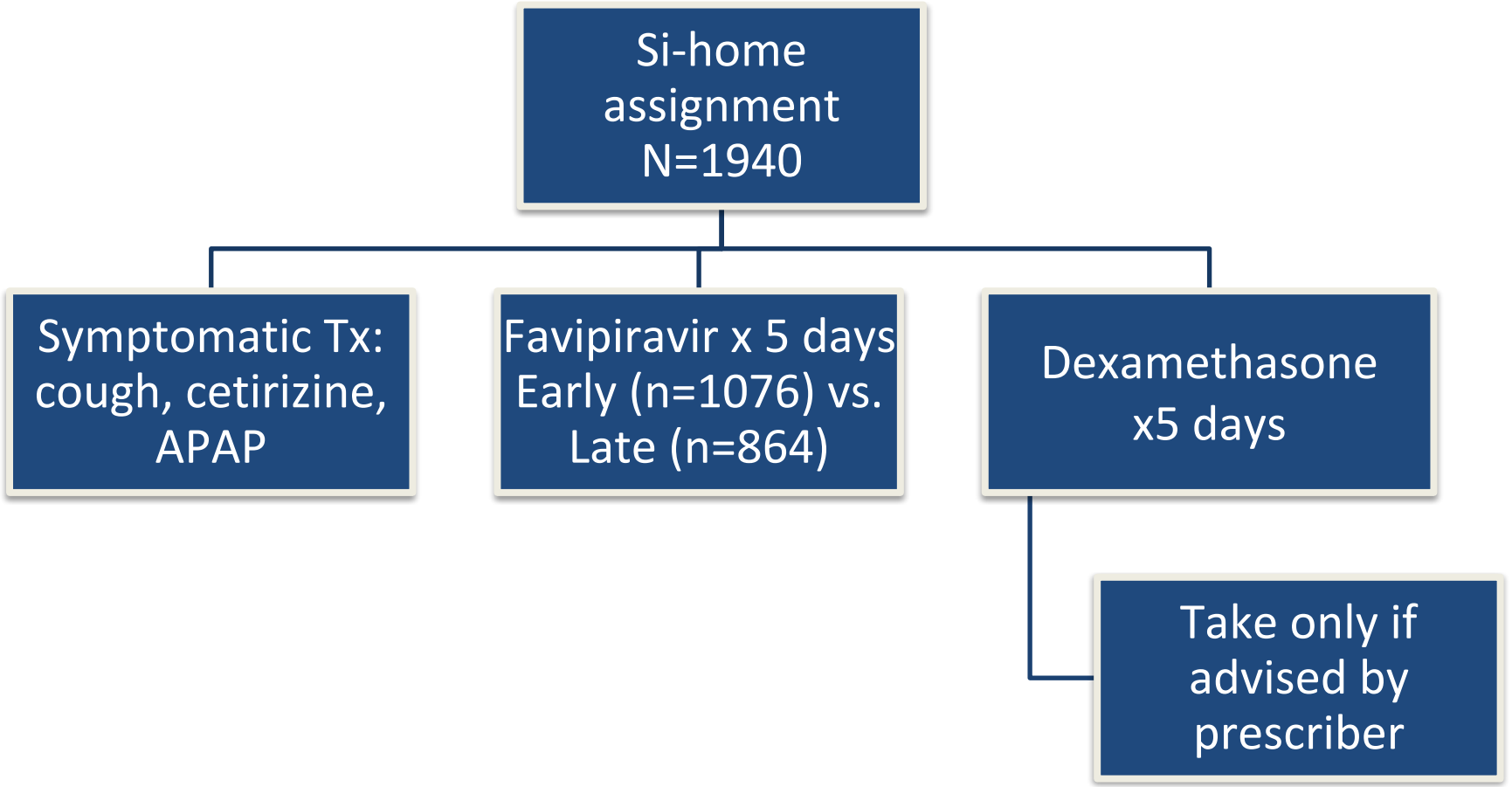
Methods[6]

- Retrospective: EMR
- Treatment: favipiravir +/- dexamethasone
- Location: Siriraj home isolation system, Thailand
- Duration: July 2021-November 2021

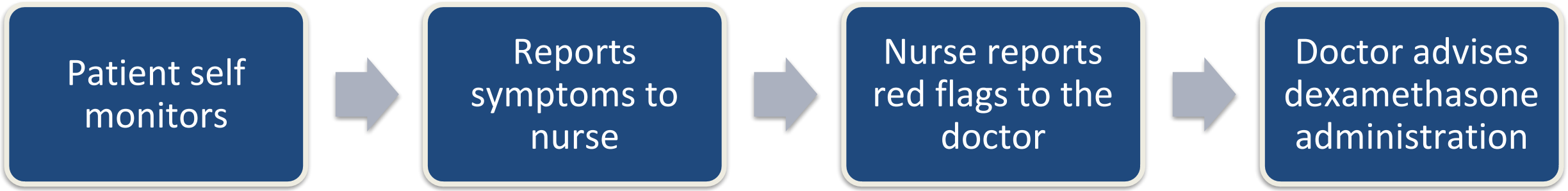
Inclusion and Exclusion Criteria[6]

Inclusion	Exclusion Criteria
• ≥ 18 years • Asymptomatic or mildly symptomatic • Positive COVID-19 test	• Pregnancy • Advanced liver disease • Supplemental oxygen requirements

Methods continued[6]



14-Day Monitoring by Medical Team[6]



If the patient's status deteriorated → Siriraj Hospital transfer

Primary Endpoint Results[6]

	Early favipiravir administration n(%)	Late favipiravir administration n(%)	P value	OR	95% CI
Clinical deterioration	50 (4.6%)	65 (7.5%)	0.008	1.669	1.141-2.441

Outpatient Dexamethasone Treatment Outcomes[6]

Patients with symptomatic deterioration	Improved after dexamethasone	Hospital admission + oxygen supplementation	Death
115	77 (67%)	38 (33%)	8 (0.4%)

Not provided: p-value & 95% CI

Unable to determine statistical and clinical significance

Strengths[6]

- Ambulatory patients
  - Nonsevere COVID-19 patients
    - Asymptomatic
    - Mildly symptomatic
- Active treatment → dexamethasone
  - Prescribing was blinded

Limitations[6]

- Unable to determine statistical and clinical significance
  - Dexamethasone treatment
    - Missing p-values and 95% CI

- Antiviral treatment
  - Favipiravir → main focus of study
  - JS is on Paxlovid®

- Setting: Siriraj homes
  - Not patients' actual home
  - Physician supervision was required

- Decrease external validity
  - Resources (thermometer, pulse oximeter)
  - Study population: single-center

Conclusion[6]

- Favipiravir treatment in field hospitals and via telehealth services allowed for the prevention of clinical deterioration of patients with nonsevere COVID-19
  - Early treatment within 5 days after symptom onset
  - Treatment duration → 5 days
  - Not available in the U.S.
- Per authors, dexamethasone prevented clinical deterioration
  - Impossible to confirm significance due to unreported p-values and 95% CI

Recommendation[2,3]

- Do not fill and dispense:
  - Paxlovid 100mg/300mg 2 capsules by mouth BID for 5 days
    - Incorrect quantity of capsules
  - Dexamethasone 4 mg 1 tablet by mouth daily
    - MDD, history of self-harm

- Fill and dispense
  - Initiate Paxlovid 100 mg/300 mg 3 capsules by mouth BID for 5 days

Monitoring[3]

- Therapeutic efficacy monitoring:
  - Symptom relief (dyspnea)
  - Temperature
  - SpO2%
- Toxicity monitoring:
  - Blood pressure
  - LFTs
  - SCr and eGFR

Follow up in 2 weeks or sooner if symptoms worsen

Paxlovid Counseling Points[3]

- ADE: muscle pain, headache, change in taste, diarrhea
- May take with or without food
- Store at room temperature
- Missed dose
  - May take as soon as you remember
  - If ≥8 hours skip the dose

References

1. COVID-19 Treatment Guidelines Panel. Coronavirus Disease (COVID-19) Treatment Guidelines. National Institutes for Health. Available at: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults-general-management/. Updated September 26, 2022. Accessed April 15, 2023.

2. Dexamethasone. Lexi-Drugs. Lexi-Comp Online. Lexi-Comp, Inc. Hudson, OH. Available at:http://online.lexi.,com/crlonline. Accessed April 15, 2023.

3. Paxlovid®, Lexi-Drugs. Lexi-Comp Online. Lexi-Comp, Inc. Hudson, OH. Available at:http://online.lexi.,com/crlonline. Accessed April 15, 2023.

4. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Disease Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America. Version 10.2.1. Available at: https:www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Published May 27, 2021. Updated April 11, 2023. Accessed April 15, 2023.

5. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with COVID-19. N ENGL J MED 2021; 384(8):693-704. doi: 10.1056/NEJMoa2021436.

6. Sitasuwan T, Phisalprapa P, Srivanichakorn W, et al. Early antiviral and supervisory dexamethasone treatment improve clinical outcomes of nonsevere COVID-199 patients. Medicine 2022; 101(45):1-9. doi: http://dx.doi.org/10.1097/MD.0000000000031681.