

# Real World Antivirals

鄭琬琳

Aristine Cheng

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## Outline

### Today's Objectives

- Introduce oral antivirals in the landscape of SARS-CoV-2 treatment
- Nirmatrelvir/ritonavir vs. Molnupiravir – the most important things to remember
- Real world experience using antiviral agents



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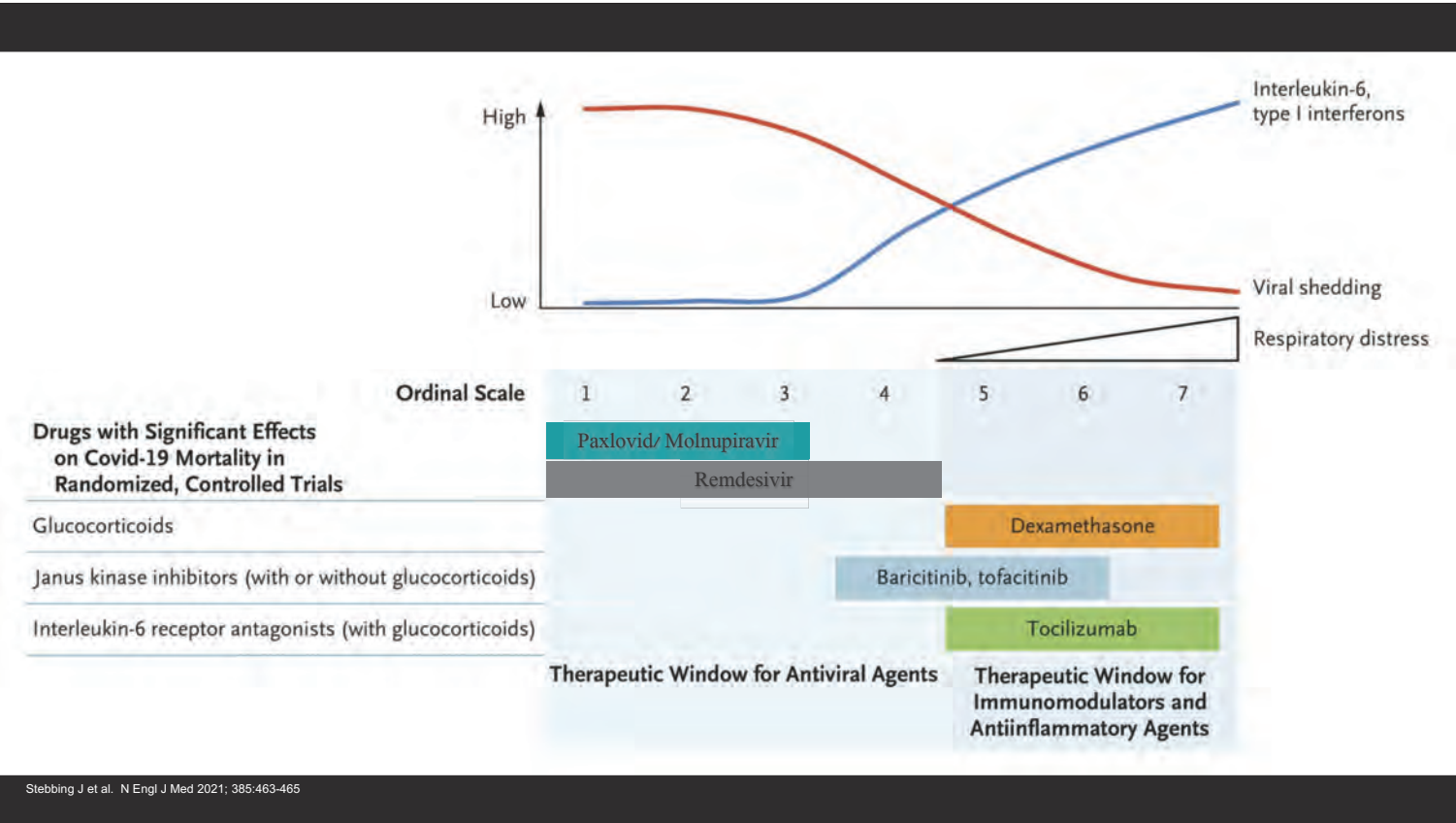
台灣臨床處置指引<sup>1</sup>

- ✓ 未住院病患建議優先選擇口服藥物治療, Paxlovid為優先治療選項
- ✓ 同一欄內藥物必要時可合併使用

	不需用氧且具重症風險因子者	需吸氧治療	高流量氧或NIV	插管
可降低死亡率，建議使用	下列藥物任一 Remdesivir · Nirmatrelvir + ritonavir Casirivimab+imdevimab* · Bamlanivimab+etesevimab* · Molnupiravir#	Dexamethasone	Dexamethasone	Dexamethasone
		+Tocilizumab	+ Baricitinib或tocilizumab	+Tocilizumab
加速臨床改善，考慮使用		+ Remdesivir		

\* 體外試驗顯示對 Omicron 變異株中和能力大幅下降，可能影響臨床效果  
# 若上述藥物均不適用，可使用 Molnupiravir

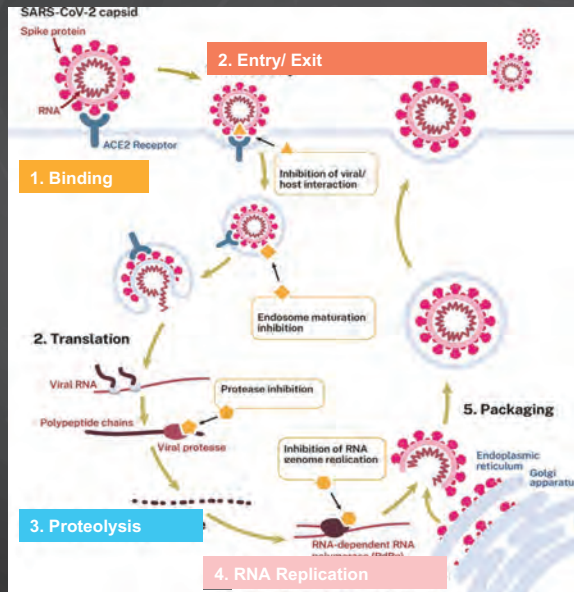
1. 新型冠狀病毒臨床處置指引第十八版 (Accessed May 11, 2022)



# Targeting SARS-CoV-2

## 1. Binding

Vaccines  
Monoclonal Ab cocktail  
Convalescent plasma



Eastman RT, et al. ACS Central Science. 2020;6:672-83

## 2. Entry/Exit

Ensovibep

## 3. Proteolysis

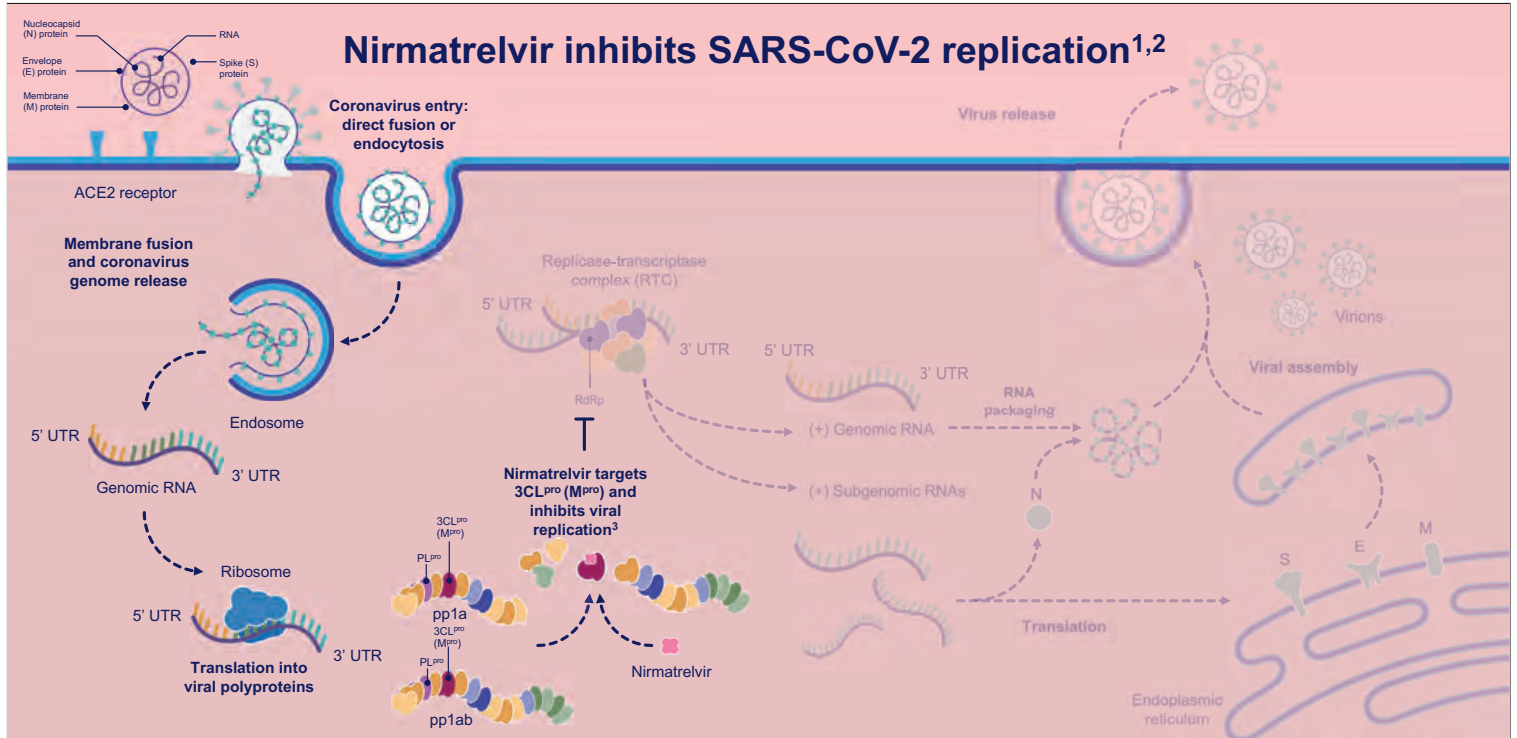
Paxlovid

## 4. RNA Replication

Remdesivir

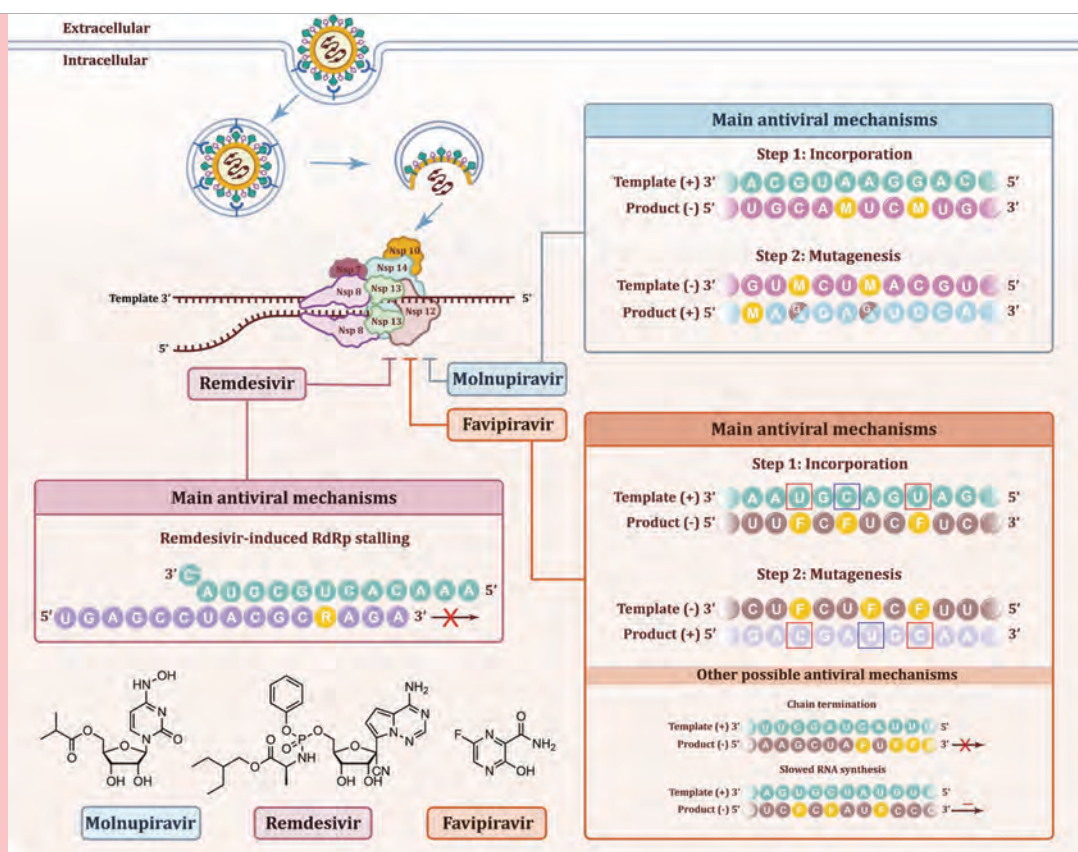
Molnupiravir

## Nirmatrelvir inhibits SARS-CoV-2 replication<sup>1,2</sup>



3CL<sup>pro</sup>, 3-chymotrypsin-like protease; ACE2, angiotensin-converting enzyme 2; M<sup>pro</sup>, main protease; nsp, non-structural protein; PL<sup>pro</sup>, Papain-like protease; pp1a, polyprotein 1a; pp1ab, polyprotein 1ab; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; RTC, replicase-transcriptase complex; UTR, untranslated region.

1. Pluskota-Karwatka D, et al. *J Pharm Anal* 2021;11:383-397;  
2. V Kovski P, et al. *Nat Rev Microbiol* 2021;19:155-170;  
3. Owen DR, et al. *Science* 2021;374:1586-1593.



1. Zhao Y et al. Sig Transduct Target Ther 6, 410 (2021).

	Nirmatrelvir/ritonavir	Molnupiravir
Manufacturer	Pfizer	Merck (MSD)
Brand name	Paxlovid	Lagevrio
FDA EUA Date	12/22/2021	12/23/2021
Mechanism of Action	Inhibits mPRO protease	Viral lethal mutagenesis
Age Limit	12 years	18 years
Weight Limit	40kg	None
Pill Burden	3 tablets q12h	4 capsules q12h
Dose	300mg nirmatrelvir + 100mg ritonavir	800mg molnupiravir
Duration of Therapy	5 days	5 days
With Food?	With or without, high fat meal increases absorption by 15%	With or without
Ok to Crush?	No	No can dissolve powder in water



	Nirmatrelvir/ritonavir	Molnupiravir
Ok for CKD?	eGFR <60ml/min → take 1# nirmatrelvir instead of 2# with ritonavir eGFR <30ml/min → avoid	Yes
Ok for Child C cirrhosis?	No	Yes
Ok for Pregnant Women	Maybe	No
Efficacy in Clinical Trials	89%	50%
Hospitalization placebo vs. drug (D28)	6.5% vs 0.1%	9.7% vs 6.8%
Deaths placebo vs. drug (D28)	9/682 (1.3%) vs 0/697 (0%)	9/699 (1.3%) vs 1/709 (0.1%)
Adverse effects	22.6%	30.4%
Severe adverse effects	1.6%	0%
Common AEs	Dysguesia, diarrhea, hypertension, myalgia	Diarrhea, nausea, dizziness

1. Hammond J et al. N Engl J Med Apr 2022; 386:1397-1408    2. Bernal AJ et al., N Engl J Med Feb 2022; 386:509-520

## 適應症及適用條件<sup>1,2</sup>

適應症	適用於發病 5 天內、具有重症風險因子的輕度至中度新型冠狀病毒疾病(COVID-19，嚴重特殊傳染性肺炎)確診者。
適用條件	具任一重症風險因子，未使用氧氣且於發病 5 天內之≥12 歲且體重≥40 公斤病人。
風險因子	<ol style="list-style-type: none"> <li>1. 年齡≥65 歲</li> <li>2. 癌症</li> <li>3. 糖尿病</li> <li>4. 慢性腎病</li> <li>5. 心血管疾病 (不含高血壓)</li> <li>6. 孕婦與產後 6 週內婦女</li> <li>7. 慢性肺疾 (間質性肺病、肺栓塞、肺高壓、氣管擴張、慢性阻塞性肺病)</li> <li>8. 結核病</li> <li>9. 慢性肝病 (肝硬化、非酒精性脂肪性肝炎、酒精性肝病與免疫性肝炎)</li> <li>10. 失能 (注意力不足及過動症、腦性麻痺、先天性缺陷、發展或學習障礙、脊髓損傷)</li> <li>11. 精神疾病 (情緒障礙、思覺失調症)</li> <li>12. 失智症</li> <li>13. BMI≥30 (或 12-17 歲兒童青少年 BMI 超過同齡第 95 百分位)</li> <li>14. 影響免疫功能之疾病 (HIV 感染、先天性免疫不全、實體器官或血液幹細胞移植、使用類固醇或其他免疫抑制劑)</li> </ol>

## Paxlovid適應症及適用條件<sup>1,2</sup>

### Nirmatrelvir

3CL 蛋白酶抑制劑，抑制新冠病毒的 Mpro 複製<sup>1</sup>

適應症<sup>3</sup>



### Ritonavir

CYP3A4 抑制劑，減緩 Nirmatrelvir 被降解，增強其抗病毒作用<sup>2</sup>

藥物交互作用管理可參照

台灣感染症醫學會  
藥物交互作用管理建議



Liverpool  
Interaction Checker



成人或  $\geq 12$  歲且體重  $\geq 40$  公斤輕症病患

### 具任一重症風險因子<sup>4</sup>

年齡  $\geq 65$  歲、癌症、糖尿病、慢性腎病、心血管疾病、慢性肺疾、結核病、慢性肝病、失能、精神疾病、失智症、BMI  $\geq 30$ 、懷孕、影響免疫功能之疾病



未使用氧氣



發病五天內



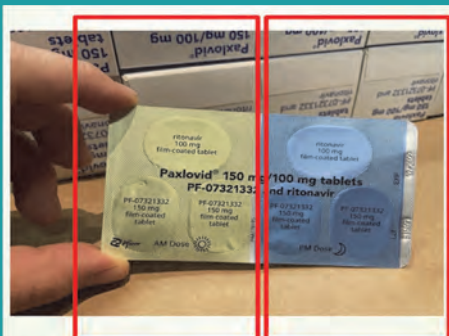
1. V'kovski P, et al. Nat Rev Microbiol. 2021;19(3):155-170. 2. Owen DR, et al. Science 2021;374:1586-93. 3. Paxlovid 中文仿單說明書 (Access date: May-04-2022). 4. 公費 COVID-19 治療用口服抗病毒藥物領用方案 (20220527版)

## Paxlovid用法用量<sup>1</sup>

Nirmatrelvir 2# + ritonavir 1# BID x 5天<sup>1</sup>

早上劑量

下午劑量



(每盒有5片泡殼卡 for 5日劑量)

### 忘記服藥的處理方式

超時  
長度 0 小時

儘快服藥並恢復正常的給藥時程

8 小時

按照常規用藥時間服用下一劑

### 其他注意事項

1. 錠劑需整顆吞服  
不得咀嚼、分開或壓碎



2. 應確實完成完整 5 天治療療程

# Molnupiravir用法用量

Molnupiravir 4# BID x 5天<sup>1</sup>



## 忘記服藥的處理方式

超時  
長度 0 小時

儘快服藥並恢復正常的給藥時程

10 小時

按照常規用藥時間服用下一劑

## 其他注意事項

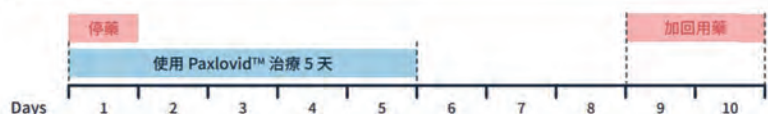
1. 膠囊劑需整顆吞服
2. 可以分解並溶於水 (OK for NG feeding)



2. 應確實完成完整 5 天治療療程

## Paxlovid™ (倍拉維) 與常見用藥交互作用管理建議

若患者目前使用以下藥物，建議停藥或使用替代藥物。無法停藥或使用其他替代用藥時，建議改用其他 COVID-19 抗病毒藥物<sup>1,4-6</sup>



抗心律不整	抗凝血劑	抗血小板	降血脂	肺高壓	
Amiodarone (CORDARONE®) Dronedarone (Multaq®) Propafenone (RYTMONORM®) Flecainide (TAMBOCOR®) Quinidine (QUINIDEX®)	Rivaroxaban (Xarelto®)  Apixaban (Eliquis®)	Ticagrelor (BRILINTA®)  Clopidogrel (PLAVIX®)*	Statins (Fluvastatin (LESCOL®) 除外)	Sildenafil (VIAGRA®, RevaTio®)	
抗癲癇藥	偏頭痛	鎮靜安眠	抗精神病	抗微生物	
Carbamazepine (Tegretol®) Phenytoin (DILANTIN®) Phenobarbital	Ergotamine (DIHYDERGOT®)	Midazolam (DORMICUM®)	Clozapine (CLOZARIL®)	Rifampin (RIFAMPICIN®) Glecaprevir/pibrentasvir (MAVIRET®)	
免疫調節劑	痛風	腸胃用藥	支氣管擴張劑	前列腺肥大	草藥
Cyclosporine (SANDIMMUN®) Tacrolimus (PROGRAF®) Sirolimus (RAPAMUNE®) Everolimus (Certeican®)	Colchicine (COLCHICINE®)	Domperidone (MOTILIUM®)	Salmeterol (SERETIDE® 成份之一)	Alfuzosin (XATRAL®)	St. John's Wort

\$ 由於半生期長，所以考慮直接使用其他 COVID-19 抗病毒用藥<sup>4,6</sup>

\* 放置冠狀動脈支架六週內避免併用，若長期使用 Clopidogrel 則可以併用<sup>5</sup>



1. Asthma/COPD (Seretide)
2. Atrial fibrillation (DOAC/rhythm)
3. BPH (Alfuzosin)
4. CAD (Plavix / Statin / Viagra)
5. Delirium / dementia (BZD)
6. Epilepsy
7. Gout (colchicine)
8. HIV/HCV (Cobicistat/PI)
9. Transplant recipient

#### Medications Without Clinically Relevant Interactions

These commonly prescribed medications may be coadministered without dose adjustment and without increased monitoring.<sup>8</sup> This list is not inclusive of all noninteracting medications within each drug category.

##### Acid reducing agents

- Famotidine
- Omeprazole
- Pantoprazole

##### Allergy medications

- Cetirizine
- Diphenhydramine
- Loratadine

##### Anti-infective agents

- Azithromycin
- Hydroxychloroquine

##### Cardiovascular agents

- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide Dinitrate
- Lisinopril
- Losartan
- Metoprolol
- Prasugrel

##### Diabetes medications

- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

##### Immunosuppressants

- Methotrexate
- Mycophenolate
- Prednisone

##### Lipid-modifying agents

- Ezetimibe
- Pitavastatin
- Pravastatin

##### Neuropsychiatric agents

- Amitriptyline
- Bupropion
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline
- Venlafaxine

##### Pain medications

- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Naproxen

##### Respiratory medications

- Corticosteroids (inhaled)
- Formoterol
- Montelukast

##### Miscellaneous

- Allopurinol
- Contraceptives (oral)<sup>8</sup>
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine
- Ondansetron

## The safe list

### A few caveats to the published data that we cannot apply to real world

- Median age 45-46 yr for Paxlovid trial, and 42-44 yr for Molnupiravir trial
- Omicron BA.2 variants not circulating then
- We are detecting the virus much earlier due to rapid availability of rapid antigen tests



## Pre-print real world data

- Hong-Kong hospitalized patients
- Retrospective analysis (Feb- Apr 2022)
- 2,359 receiving molnupiravir; 1,000 receiving nirmatrelvir/ritonavir; 19,064 controls

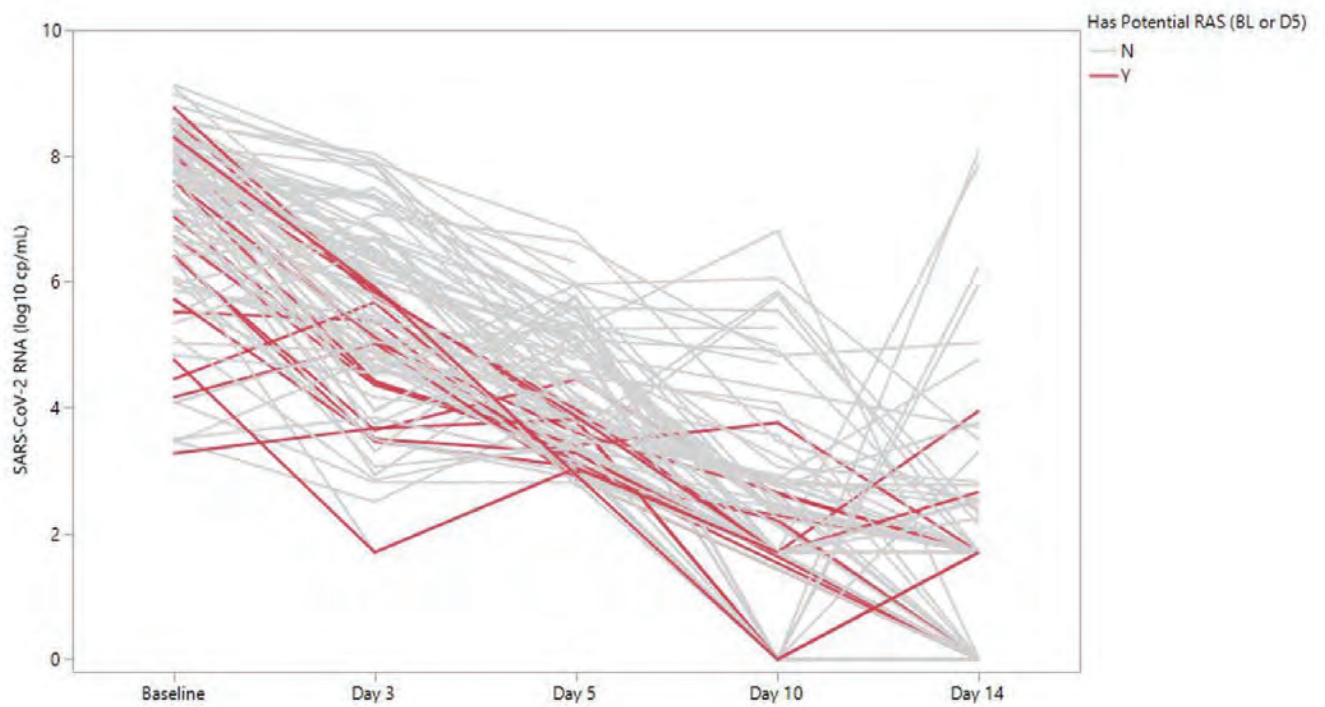
Table 3. Hazard ratios of clinical and virologic outcomes for molnupiravir users versus nirmatrelvir-ritonavir users, and differences in hospital length of stay between the groups amongst discharged survivors

Outcomes	Molnupiravir (N=967)		Nirmatrelvir- ritonavir (N=967)		Molnupiravir vs Nirmatrelvir- ritonavir		
	Cumulative incidence		Cumulative incidence				
	New events	Rate	New events	Rate	HR†	95% CI	P-value
Composite progression outcome*	58	6.0%	38	3.9%	1.44	(0.96, 2.18)	0.078
All-cause mortality	58	6.0%	36	3.7%	1.53	(1.01, 2.31)	0.047
Invasive mechanical ventilation	1	0.1%	5	0.5%	NA	NA	NA
Intensive care unit admission	0	0.0%	0	0.0%	NA	NA	NA
Lower viral load (cycle threshold value $\geq 30$ cycles)	132	16.5%	140	17.9%	0.88	(0.69, 1.11)	0.281
Hospital length of stay, days					Diff	95% CI	P-value
					0.83	(0.07, 1.58)	0.032

Wong CK, et al. medRxiv pre-print 2022 doi: 10.1101/2022.05.19.22275291

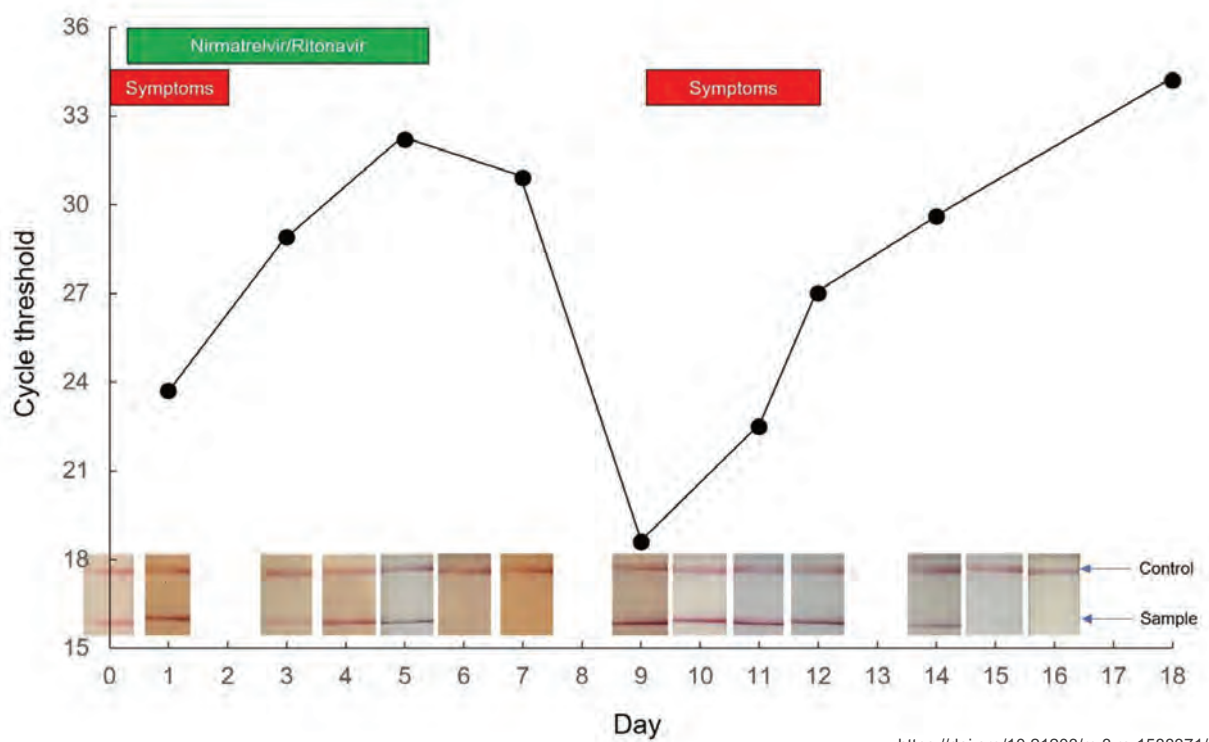
Yes, we see rebounds with all three!

Here is a published example



Paxlovid FDA report

71-year-old man with asthma, fully vaccinated



<https://doi.org/10.21203/rs.3.rs-1588371/v1>

# Summary



## COVID-19 Treatment Guidelines

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

### PATIENT DISPOSITION

Does Not Require  
Hospitalization or  
Supplemental Oxygen

### PANEL'S RECOMMENDATIONS

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

For patients who are at high risk of progressing to severe COVID-19,<sup>a</sup> use 1 of the following treatment options:

#### Preferred Therapies

*Listed in order of preference:*

- Ritonavir-boosted nirmatrelvir (Paxlovid)<sup>b,c</sup> (**AIIa**)
- Remdesivir<sup>c,d</sup> (**BIIa**)

#### Alternative Therapies

*For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:*

- Bebtelovimab<sup>e</sup> (**CIII**)
- Molnupiravir<sup>c,f</sup> (**CIIa**)

The Panel **recommends against** the use of dexamethasone<sup>g</sup> or other systemic corticosteroids in the absence of another indication (**AIII**).

## Paxlovid



Fast

1<sup>st</sup> line  
Preferred if no  
contraindications



Teen

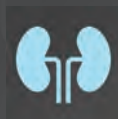
12-18 yr  
>40kg



Pregnant?

No data  
Non-teratogenic

## Molnupiravir



ESRD

No renal dose  
adjustments



Child C

No hepatic dose  
adjustments



Polypharmacy

AF, BPH, Epilepsy,  
Gout, HIV/HCV



#### 4 stages of quarantine:



# Thanks!

Have questions?  
aristine@hotmail.com



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