Hong Kong Society of Nephrology Newsletter

March 2022 issue

Dr. Chow Kai Ming

THANKS FOR ALL YOUR HARD WORK

On behalf of the Hong Kong Society of Nephrology HKSN, I would like to thank all members who have been working hard during this fifth wave of coronavirus pandemic.

Here are few important things you might wish to know, as our members, about the recently authorized oral antiviral drugs, molnupiravir (from Merck Sharp & Dohme MSD) and nirmatrelvir-ritonavir (under brand name Paxlovid, from Pfizer). We hope this timely update will equip everyone on the knowledge of the two drugs for our renal patients.

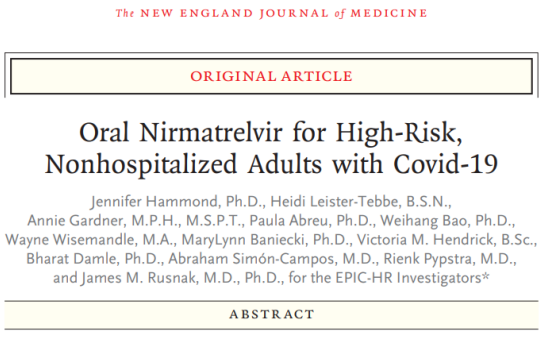
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2022 VOL. 386 NO. 6

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

ABSTRACT



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

ABSTRACT

What You Need to Know about Molnupiravir?

This new drug has been authorized for use under Emergency Use Authorization (EUA) issued by the U.S. Food and Drug Administration (FDA), mostly after the publication of the MOVe-OUT Study in the *New England Journal of Medicine*. In the phase 3 double-blind, parallel-group, randomized, placebo-controlled trial, 1433 nonhospitalized (unvaccinated) patients with mild to moderate Covid-19 with symptom onset 7 days or less before randomization received drug or placebo. Fewer participants were hospitalized or died through day 29 after molnupiravir versus placebo (6.8% vs. 9.7%). The largest clinical

benefit was seen for patients whose treatment began less than 5 days from symptom onset. Among the recruitment criteria for defining increased risk, obesity was the predominant one contributing to 74% of the trial participants; only 6% of them were listed as increased risk as a result of chronic kidney disease. The direction of the estimated treatment effect in the MOVe-OUT trial favored molnupiravir over placebo with respect to all risk factors, except diabetes mellitus.

Q: How does molnupiravir work?
A: This is a small-molecule ribonucleoside prodrug metabolized to the ribonucleoside analogue N-hydroxycytidine (NHC) which is subsequently phosphorylated to the pharmacologically active ribonucleoside triphosphate (NHC-TP), thereby inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication by viral mutagenesis. In brief, the drug works by causing an accumulation of deleterious errors throughout the viral genome, ultimately rendering the virus noninfectious and unable to replicate.

Q: What should we instruct the patient (or nurses administering the drug) to take molnupiravir?
A: The drug is available as 200 mg capsules; the recommended dose is four 200 mg capsules (800 mg) twice daily for 5 days. We should advice patients to take the oral capsules with or without food. The capsules should be swallowed whole with a glass of water and should not be crushed or chewed. If nasogastric tube administration is required, the capsules should be opened and transferred into preparation bottle. Add 40 mL water to the preparation bottle and shake the capsule contents and water for 3 minutes. Reconstituted solution should be administered as soon as possible (and not later than 2 hours after preparation).

Q: Can we prescribe molnupiravir for patients with reduced kidney function or on dialysis?
A: Yes, we can. The drug does not require dose adjustment for kidney function.

What You Need to Know about Paxlovid?

This drug is a combination of oral protease inhibitors, nirmatrelvir and ritonavir. The best evidence for this drug comes from the publication of the EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) trial in the *New England Journal of Medicine*. In the double-blind, placebo-controlled study of 2246 nonhospitalized (unvaccinated) symptomatic patients, there was an 88.9% relative risk reduction in Covid-19–related hospitalization or death from any cause by day 28 among adults at high risk for progression to severe disease who were commenced treatment within 3 days after symptom onset (and 87.8% relative risk reduction if within 5 days). There were no deaths in the group receiving nirmatrelvir plus ritonavir, versus 13 deaths in the placebo group.

Q: Can we prescribe Paxlovid for patients with reduced kidney function or on dialysis?
A: We need to be cautious, and should avoid the drug if the patient has glomerular filtration rate lower than 30 ml/min (or severe hepatic impairment such as Child-Pugh class C). The drug consists of 300 mg nirmatrelvir (two 150 mg tablets) with one 100 mg ritonavir tablet, to be taken together orally twice daily for 5 days. In case our patient has stage 3 chronic kidney disease (glomerular filtration rate between 30 and 60 ml/min), the dose is one 150 mg nirmatrelvir tablet and one 100 mg ritonavir tablet taken together twice daily for five days.

Q: Can we prescribe Paxlovid for patients who have kidney transplantation?
A: We need to be extremely cautious, although transplant recipients belong to the category of patients at high risk of Covid-19 disease. The major concern is the potential for drug interactions with immunosuppression based on the mechanism of action of ritonavir. Ritonavir is actually a protease inhibitor administered to slow down the metabolism and thereby boosting the level of nirmatrelvir. By itself, ritonavir has no activity against SARS-CoV-2. As a potent inhibitor of CYP3A, ritonavir would significantly increase the level of calcineurin inhibitors like cyclosporine and tacrolimus. The same applies to sirolimus and everolimus. Although close therapeutic monitoring (after empirical reduction of cyclosporine, say, to one-fifth of original dose, or holding the drug following the first dose of Paxlovid) can be attempted theoretically, this is technically challenging and cumbersome for transplant recipients managed as outpatients.

Q: How can we avoid high-impact drug interaction for renal patients who might be prescribed Paxlovid?
A: We must be mindful of the dangerous interactions with drugs with which chronic kidney disease patients are frequently given. Examples include HMG-CoA reductase inhibitors (statins), calcium channel blockers (amlodipine, verapamil) and anticoagulants or antiplatelet agents (warfarin, apixaban, clopidogrel), colchicine, and not to mention the immunosuppression drugs. Education to healthcare worker and general public should be provided. Channels include newsletter (such as the one you're reading), grand rounds, lectures, email notifications and information sheets. Furthermore, partnership with pharmacies and system alert from the clinical information system are beneficial.*

In case you want a quick update on the two novel oral antiviral agents with FDA emergency use authorization for outpatient use in mild-to-moderate COVID-19, here is a table for reference. On the other hand, please stay tuned to emerging evidence.

	Molnupiravir	Nirmatrelvir / ritonavir (Paxlovid)
Mechanism	Nucleoside analog targeting viral RNA, introducing fatal errors in replication	Inhibiting the main protease of SARS-CoV-2
Efficacy (high risk population) based on trials	30% for all-cause hospitalization or death when given within 5 days of symptom onset	89% for Covid-19-related hospitalization or death when given within 3 days of symptom onset
Renal function adjustment	No need	GFR 30-60 ml/min: reduce dose GFR < 30 ml/min: not recommended
Drug interaction	Not known	Increase level of drugs metabolized by P450 CYP3A (including sirolimus, everolimus, tacrolimus, cyclosporine)*
Common side effects	Diarrhoea, nausea	Dysgeusia (taste disturbance), diarrhoea
Pregnancy	Contraindicated (potential mutagenicity and genotoxicity)	Potential use (no human data but reduced fetal body weights after high dose nirmatrelvir in animal studies)
Nasogastric tube administration	Possible (see Q&A above)	Not recommended (tablets not for crushing)

* For proper use of Paxlovid, you are encouraged to refer to interaction checker such as the University of Liverpool app: https://www.covid19-druginteractions.org/

Here are the factsheets from FDA for the two drugs molnupiravir and Paxlovid respectively:

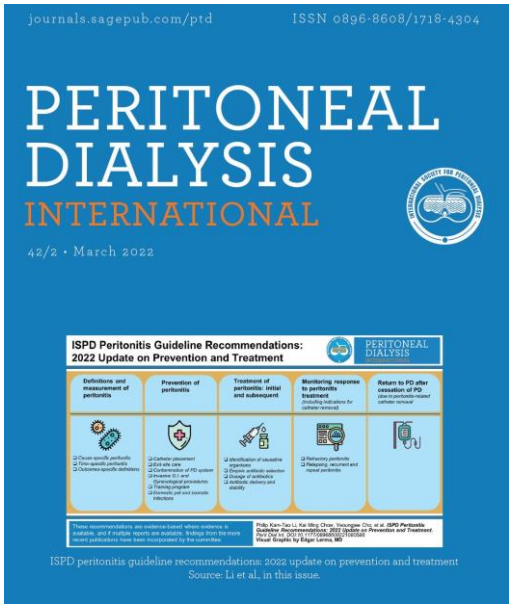
https://www.fda.gov/media/155054/download

https://www.fda.gov/media/155050/download

What's New in Nephrology – ISPD Peritonitis Guideline

In case you haven't read the most recently published "ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment", you should do so. Things have changed since 2016, when the last version of peritonitis management guideline was written.

We are pleased to highlight here the "What's new in the 2022 update" before you have time to go through the full text.



ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment
Source: Li et al., in this issue.

The newly updated guideline is now published in the March issue of *Peritoneal Dialysis International*, under the leadership of Prof. Philip Li and David Johnson.

We fully understand that many of us are tied up with handling the pandemic and at the same time working hard to look after peritoneal dialysis patients. That means you might not have spare time to go through the thirty pages of guideline during this busy period.

As such, we hope the bullet-point summary will give you a quick update.

Special Series/Guidelines

PERITONEAL DIALYSIS INTERNATIONAL

Peritoneal Dialysis International
2022, Vol. 42(2) 110–153

DOI: 10.1177/08968608221080586
journals.sagepub.com/home/ptd
SAGE

ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment

Philip Kam-Tao Li[1,2], Kai Ming Chow[1,2], Yeoungjee Cho[3,4], Stanley Fan[5], Ana E Figueiredo[6], Tess Harris[7], Talerngsak Kanjanabuch[8,9], Yong-Lim Kim[10], Magdalena Madero[11], Jolanta Malyszko[12], Rajnish Mehrotra[13], Ikechi G Okpechi[14], Jeff Perl[15], Beth Piraino[16], Naomi Runnegar[17], Isaac Teitelbaum[18], Jennifer Ka-Wah Wong[19], Xueqing Yu[20,21] and David W Johnson[3,4]

Abstract

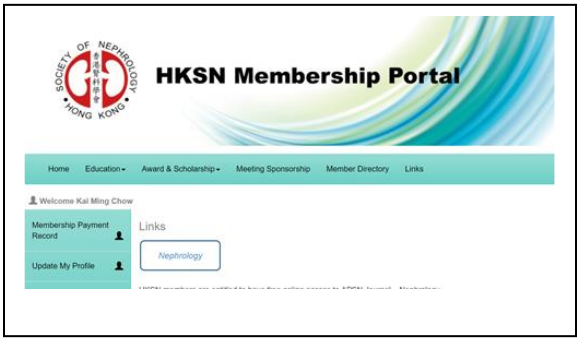
Peritoneal dialysis (PD)-associated peritonitis is a serious complication of PD and prevention and treatment of such is important in reducing patient morbidity and mortality. The ISPD 2022 updated recommendations have revised and clarified definitions for refractory peritonitis, relapsing peritonitis, peritonitis-associated catheter removal, PD-associated haemodialysis transfer, peritonitis-associated death and peritonitis-associated hospitalisation. New peritonitis categories and outcomes including pre-PD peritonitis, enteric peritonitis, catheter-related peritonitis and medical cure are defined. The new targets recommended for overall peritonitis rate should be no more than 0.40 episodes per year at risk and the percentage of patients free of peritonitis per unit time should be targeted at >80% per year. Revised recommendations regarding management of contamination of PD systems, antibiotic prophylaxis for invasive procedures and PD training and reassessment are included. New recommendations regarding management of modifiable peritonitis risk factors like domestic pets, hypokalaemia and histamine-2 receptor antagonists are highlighted. Updated recommendations regarding empirical antibiotic selection and dosage of antibiotics and also treatment of peritonitis due to specific microorganisms are made with new recommendation regarding adjunctive oral N-acetylcysteine therapy for mitigating aminoglycoside ototoxicity. Areas for future research in prevention and treatment of PD-related peritonitis are suggested.

What's new from the 2022 updated guideline?

- There are standardized definitions for outcomes such as medical cure and peritonitis-associated catheter removal, haemodialysis transfer, hospitalization and death.
- There are standardized definitions for peritonitis, including the entity of pre-PD peritonitis, defined as a peritonitis episode occurring after PD catheter insertion and prior to commencement of PD treatment. The date of PD initiation is defined as the day when the first PD exchange is performed with the intention of continuing long-term PD treatment from that day; the intermittent flushing of a PD catheter for the purpose of maintaining catheter patency does not qualify as PD initiation.
- The overall peritonitis rate should be no more than 0.40 episodes per year at risk. This is an improvement from the previously set bench of 0.5 episodes per year at risk (according to the 2016 guideline). From global review of data of reports from registries and studies, this is an achievable standard and should be used in initiative to reduce peritonitis rates.
- The optimal PD training program (how, how long, where, when and by whom) remains uncertain, but the guideline emphasizes on regular reassessment PD exchange technique, especially direct inspection of the PD technique.
- The recommendation for PD patients keeping pets include the precaution not to allow the pets in the room where PD exchange takes place, and where dialysis tubing, equipment and machine are stored.
- There is new recommendation for tackling modifiable risk factors, such as avoidance and treatment of hypokalaemia, avoiding or limiting the use of histamine-2 receptor antagonists to prevent enteric peritonitis.
- Although the recommendation to remove PD catheter in refractory peritonitis (defined as failure of the PD effluent to clear after 5 days of appropriate antibiotics) still holds, the new guideline agrees with observation for antibiotic effect longer than 5 days if PD effluent white cell count is decreasing towards normal (as opposed to mandatory PD catheter removal on day 5). On the other hand, in the event of *Pseudomonas* peritonitis, early catheter removal is suggested if there is no clinical response after 5 days of effective antibiotic treatment, instead of using 3 antibiotics as an attempt to salvage.
- The recommendation for enterococcal peritonitis treatment should be 3 weeks with oral amoxicillin (for ampicillin-susceptible enterococci) or intraperitoneal IP vancomycin.
- Antituberculous therapy, instead of PD catheter removal, is considered the primary treatment of peritonitis caused by *Mycobacterium tuberculosis*. On the other hand, non-tuberculous mycobacterial peritonitis should be treated with both effective antibiotics and catheter removal.
- The 2016 recommendation to avoid prolonged courses of IP aminoglycosides still holds, but there is suggestion for adjunctive oral N-acetylcysteine therapy to prevent aminoglycoside ototoxicity.

For those of you who are full HKSN members, you can simply login our website via the Society membership portal, go to the "Link" on the top right corner. That will link to the *Peritoneal Dialysis International* journal full version.

If you are associate members, please be informed that this guideline will soon be made available as open access to all by ISPD for use around the world.



Congratulations to the New President of the Asian Pacific Society of Nephrology APSN

We are glad to share the good news: Prof. Sydney Tang, our HKSN Council member and previous HSKN Chairman, has been elected the President of the Asian Pacific Society of Nephrology. You might read the full text of his new message from the website
https://www.apsneph.org/web/index.html