Emily G. McDonald MD MSc
Associate Professor of Medicine

Updates on COVID-19

Overview

- Disclosures
- Outpatient treatments
- Hospitalized
  - Noncritical care treatments
  - Critical care treatments
- Will only focus on major updates given time limits

Disclosures

- Investigator and/or site, provincial or national lead on a number of COVID-19 trials of repurposed drugs:
  - CONTAIN (inhaled ciclesonide); STOP COVID 2 (fluvoxamine); ATTACC (LMWH); HCQ trials
- Funding from the CIHR, CABHI, CFN, MI-4
- Jointly own the IP for MedSafer; a software for deprescribing
- Founder of MedSafer Corp

Treatment for COVID-19 by Category

- Antivirals (ex. remdesivir, nirmatrelvir-ritonavir, molnupiravir)
- Anti-inflammatories (ex. dexamethasone; inhaled corticosteroids)
- Anticoagulants (ex. LMWH)
- Immune modulators (tocilizumab, sarilumab, baracitinib)
- Monoclonal antibodies (tixagevimab/cilgavimab, sotrovimab)
- Other (fluvoxamine, colchicine)

Outpatient treatments

Options

- Nirmatrelvir-ritonavir
- Resdesivir
- (Monoclonal antibodies)
- (Molnupiravir)
- Other

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*

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of symptomatic Covid-19 with nirmatrelvir plus ritonavir resulted in a risk of progression to severe Covid-19 that was 89% lower than the risk with placebo

Nirmatrelvir-ritonavir

- **Ritonavir-boosted nirmatrelvir (marketed as Paxlovid) is a Health Canada–approved oral antiviral medication with activity against SARS-CoV-2**
- **Studies recruited primarily unvaccinated participants, and predated the omicron variant**

cmaj
CANADIAN MEDICAL ASSOCIATION JOURNAL

Practice

Nirmatrelvir-ritonavir for COVID-19

Emily G McDonald and Todd C Lee

CMAJ February 14, 2022 194 (6) E218; DOI: https://doi.org/10.1503/cmaj.220081

Nirmatrelvir~ritonavir

- Patients with 5% risk of hospital admission:
  - NNT to prevent 1 hospital admission of 24 (95% CI 22–29)
- Common adverse effects are dysgeusia, diarrhea, vomiting, increased blood pressure and headache
- **The treatment is copackaged as nirmatrelvir (300 mg – two 150 mg tablets) with ritonavir (one 100 mg tablet); the 3 tablets are taken together twice daily for 5 days**
  - Ideally start within 5 days of symptoms
- In moderate renal failure (eGFR 30–60 mL/min): 1 tab nirmatrelvir/1 tab ritonavir twice daily.
  - Contraindicated with eGFR < 30 mL/min.

Numerous drug~drug interactions

- **The ritonavir component boosts nirmatrelvir levels and is a cytochrome P450 3A4 (CYP3A4) inhibitor when taken short term, leading to important drug–drug interactions**
- Particular attention should be paid to high-risk medications:
  - antiarrhythmics (amiodarone, digoxin),
  - oral antithrombotics (apixaban, rivaroxaban, ticagrelor),
  - statins (atorvastatin, lovastatin, simvastatin),
  - benzodiazepines (diazepam),
  - opioids (methadone, fentanyl),
  - anticonvulsants,
  - neuropsychiatric drugs and
  - immunosuppressants

https://www.covid19-druginteractions.org/checker

REF: https://www.cmaj.ca/content/194/6/E218

Remdesivir

ORIGINAL ARTICLE

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

Robert L. Gottlieb, M.D., Ph.D., Carlos E. Vaca, M.D., Roger Paredes, M.D., Ph.D., Jorge Mera, M.D., Brandon J. Webb, M.D., Gilberto Perez, M.D., Godson Oguchi, M.D., Pablo Ryan, M.D., Ph.D., Bibi U. Nielsen, M.D., Michael Brown, Ph.D., F.R.C.P., Ausberto Hidalgo, M.D., Yessica Sachdeva, M.D., et al., for the GS-US-540-9012 (PINETREE) Investigators†

- Among non-hospitalized patients who were at high risk for Covid-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo

Monoclonal antibodies

REGN10933, COV2-2196 (marketed as tixagevimab), and COV2-2130 (marketed as cilgavimab) neutralized omicron/BA.2 (Evusheld);
HC auth Apr 14, 2022

FDA: Sotrovimab no longer authorized where BA.2 subvariant predominates

CORRESPONDENCE

Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2

As of February 2022, omicron variants have been divided into four distinct sublineages: BA.1, BA.1.1, BA.2, and BA.3

Molnupiravir

- Not yet authorized for use in Canada
- $$, especially given the higher NNT
- https://read.idtrials.com/outptcovid

EDITOR'S CHOICE

Outpatient Therapies for COVID-19: How Do We Choose?

Todd C Lee ✉, Andrew M Morris, Steven A Grover, Srinivas Murthy, Emily G McDonald

Open Forum Infectious Diseases, Volume 9, Issue 3, March 2022, ofac008,
https://doi.org/10.1093/ofid/ofac008
Published: 19 January 2022 **Article history** ▾

Molnupiravir	$700.00	49 (36-100)	0.59 (0.44-0.80);I²=0.0 Rand Eff: 0.59 (0.44-0.80)

Other~ inhaled corticosteroids

CONTAIN (BMJ 2021)	1.87 (0.48-7.26)	3.5%
NCT04377711 (JAMA Int Med 2021)	0.44 (0.12-1.68)	3.6%
PRINCIPLE (Lancet 2021)	0.75 (0.56-0.99)	78.7%
STOIC (Lancet Resp 2021)***	0.18 (0.04-0.78)	3.0%
COVERAGE (CMI 2022)	1.36 (0.63-2.93)	11.1%

Inhaled Corticosteroid	$131.60	87 (50-20000)	0.77 (0.60-1.00);I²=51.5 Rand Eff: 0.77 (0.44-1.37)

THE LANCET
Global Health

ARTICLES | VOLUME 10, ISSUE 1, E42-E51, JANUARY 01, 2022

Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial

Other- Fluvoxamine

Study	Drug	Estimated Cost (USD)	NNT @ 5% risk	Meta-Analysis / Single Result	Relative Risk	Weight
Stop Covid 1 (JAMA 2020)					0.18 (0.02-1.50)	1.5%
Stop Covid 2 (NIH Presentation)					0.93 (0.42-2.06)	10.6%
Together (Lancet Global Health 2021)*					0.75 (0.56-0.98)	87.9%
	Fluvoxamine	$14.03	80 (48-667)	0.75 (0.58-0.97);I²=0.2 Rand Eff: 0.75 (0.57-0.97)		

Hospitalized treatments

Options

- Antivirals
- Anti-inflammatories
- Immune modulators
- Anticoagulants
- (Monoclonal antibodies)

Antivirals

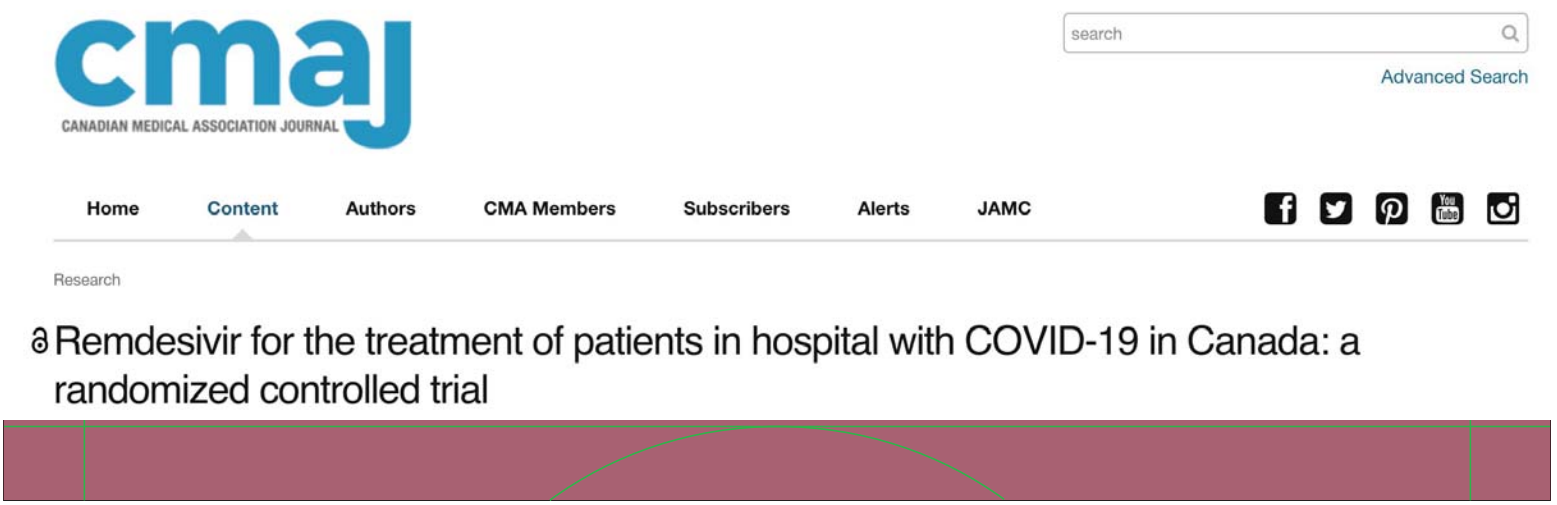
Nirmatrelvir-ritonavir has not been studied in hospitalized patients

It was studied in outpatients to prevent hospitalization

Update for remdesivir

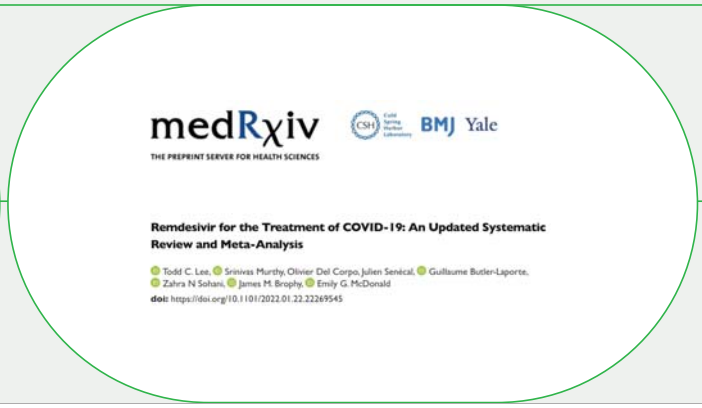
Results of the CATCO trial published in CMAJ	Additional data in patients requiring oxygen

Remdesivir



Remdesivir

- Benefits of remdesivir in hospitalized patients debated:
  - NIH and WHO have contradictory recommendations
- Systematic review and meta-analysis with Bayesian probabilities
- Using neutral priors, the probabilities that remdesivir reduces mortality were 74.7% (no supplemental O2), 96.9% (supplemental O2) and 8.9% (ventilated).
- The probability that remdesivir reduced mortality by ≥1% was 88.1% for nonventilated patients requiring oxygen.



Remdesivir

Then vs Now

We previously concluded that the oxygen only subgroup should be prioritized for future trials.

In our 1st analysis, the certainty of the evidence was low due to imprecision and inconsistency of trial results.

The certainty of the evidence is now moderate based on results of CATCO (not previously included).

Patients who require oxygen but who aren't critically ill **should receive remdesivir.**

Monoclonals

Sotrovimab?	High dose Sotrovimab?	Cannot access tixagevimab/cilgavimab for treatment
• Depends on BA2 prevalence • High in Quebec/predominant)	• No evidence for this. The FDA removed the EAU for Sotrovimab for BA2	• Marketed for pre-exposure prophylaxis

Immune modulators

Few to no head-to-head trials

In July 2021, a meta-analysis coordinated by WHO on IL-6 inhibitors demonstrated reduced mortality from **tocilizumab** in hospitalized patients with COVID-19

Although **sarilumab**'s effect size was uncertain (OR1.08 [95% CI: 0.86 – 1.36]), it was recommended with the same strength as tocilizumab

On January 14, 2022, WHO guidelines added a new recommendation for use of the Jak 1,2 inhibitor, **baricitinib**, for hospitalized patients with COVID-19, treated with corticosteroids

Baricitinib vs tocilizumab

Depends on availability

Evidence is strongest for tocilizumab

Bari has some advantages (and disadvantages)

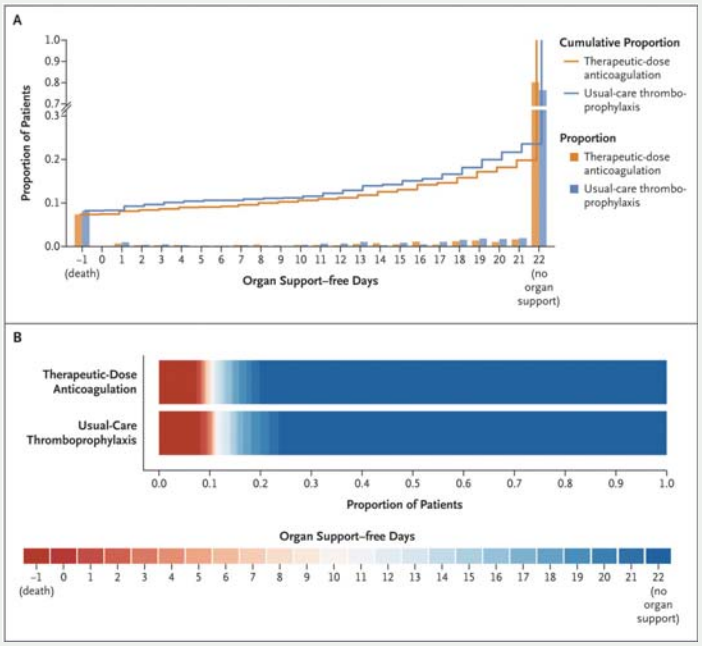
- Shorter half-life (implications for risk of secondary infections)
- Costs less in many jurisdictions
- Only available in pill form
- Not studied in pregnancy or severe renal failure

Always in combination with dexamethasone (for both)

(Sarilumab has greater uncertainty regarding its treatment effect)

Anticoagulants ATTACC trial

- Therapeutic-dose anticoagulation increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis

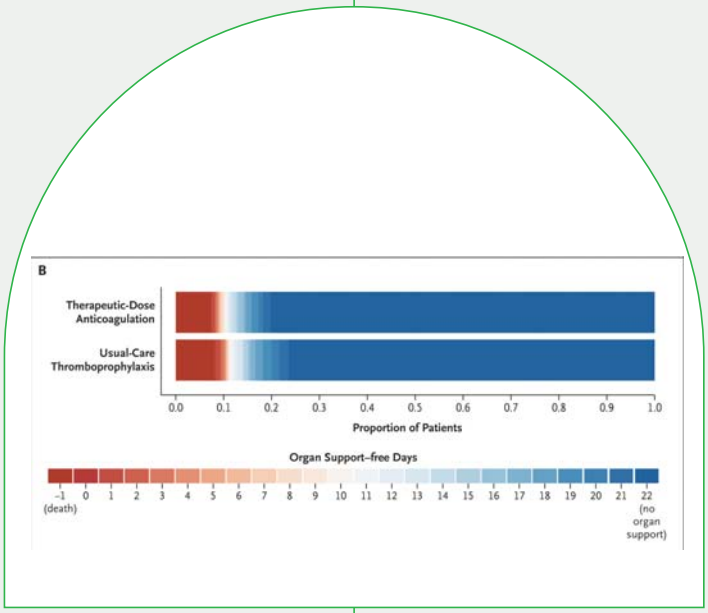


Panel B shows the number of days without organ support as horizontally stacked proportions of patients in the two treatment groups

In-hospital death with or without the receipt of organ support (dark red, the worst possible outcome, corresponding to a score of −1 on the ordinal scale);

Survival with organ support provided in ICU (red-to-blue based on # of days alive without organ support; intermediate outcome, score of 0 to 21 on the ordinal scale);

Survival until hospital discharge without ICU-support (dark blue, best possible outcome, a score of 22 on the ordinal scale).



Questions or Comments

- **@DrEmilyMcD** on Twitter
- emily.mcdonald@mcgill.ca