## Ontario Critical Care Clinical Practice Rounds (OC3PR)

April 15, 2021 From 2:00 PM - 3:00 PM EDT

Evidence-based therapies for COVID-19

Presenter: Dr. Bram Rochwerg Chaired by Dr. Dave Neilipovitz

#### Meeting Etiquette



 Due to attendee numbers, participants will be muted and will be able to submit questions to the panelist
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World Health Organization MAGIC app

# Evidence Based Therapies for Covid-19



Bram Rochwerg Associate Professor McMaster University



Hosted by

CCSO SMPCO

## Declarations

- I treat patients with critical illness from covid-19
- I was methods chair for the WHO guidelines
- I am a member of the GRADE working group
- No other academic or financial conflicts

## Plan for next 25 mins

- How are trustworthy guidelines developed?
- What works and what doesn't work based on the data?
- What's on the horizon?





## Repurposed Meds

Drug	ug Current use	
Chloroquine	Antimalarial	Heme polymerase inhibitor
Kaletra (ritonavir + lopinavir)	HIV	Protease inhibitor
Interferon alfa-2b	Hepatitis-C	Immune modulator
Remdesivir	Experimental	Nucleotide analogue
Favipiravir	Influenza	RNA polymerase inhibitor
Actemra (tocilizumab)	Rheumatoid arthritis; covid-19	Anti-inflammatory
Kevzara (sarilumab)	Rheumatoid arthritis	Anti-inflammatory

Source: WHO, adapted from landscape analysis, 17th February 2020

\*For use on covid-19

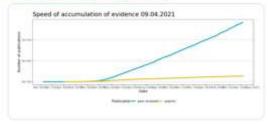


## Information Explosion

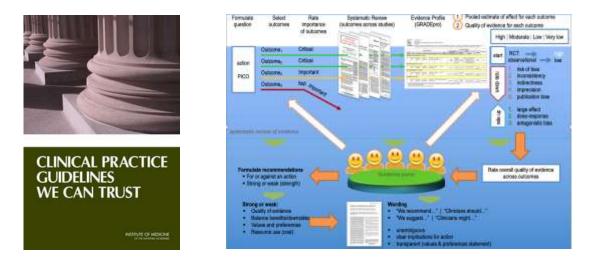
COVID-19 Living Evidence

New milestone reached: 150,000 publications indexed!

As of 09.04.2021, we have indexed 156017 publications: \*13814 pre-prints \*142203 peer-reviewed publications Pre-prints: BioRxiv, MedRxiv Peer-reviewed: PubMed, EMBASE, PsycINFO zika.ispm.unibe.ch/assets/data/pu...



## Trustworthy Clinical Practice Guidelines



## Making Healthcare Decisions in a Pandemic

Nar			

**Emerges From Noise** 

Critical Care Explorations

### Misinformation During the Coronavirus Disease 2019 Outbreak: How Knowledge

Branckieweg, MID<sup>11</sup>, Balland Palas, PhD<sup>11</sup>, Mateman MacDig, MD<sup>11</sup>, Hannman M. Demander, MD<sup>11</sup> Immune Temmer (edg), PhD<sup>11</sup>, Mrin Markall, MD<sup>11</sup>, Seil, K. J., Aldakar, MD<sup>111</sup>, Kirmen Faurt, PKD<sup>111</sup>, Koh Festler, MD<sup>11</sup>, Dampini Lamoningka, MD<sup>111</sup>, Isaaliare E. Ierrenolog, MD<sup>11</sup>

#### TABLE 1. Healthcare Decisions During Pandemic Illness

Factors	Normal Healthcare Doctations	During Pandorsk (Bease
Evalurate quality	Usually high-quality randomized controllosi	Indext data from other populations/pathogene
	Bisto Gathanigh Hot always)	Case even or case reports, even clinical observations from colleagues
Guilarce available	Bely an truthworthy clinical practice	Expert drivery
	gudelines	What works in other jurisdictions/hospitals
Timeles	Often have time to make doctations including all standors	May be forced into nonlinel, high intensity decisions without considering all vantagepoints
Consideration of costs/resources	At least in high-income nations, less of a concern if benefit clear	Decisions must contailer triage and resources expectable if large mandees affected

Crit Care Expl 2020; 2:e0098

## Rapid Recommendations







Rapid Recommendations process step by step (with target times)



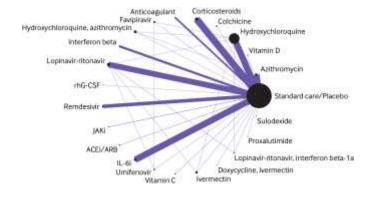
## Birth of the WHO Living Guideline



## Guideline Development

- Guideline development done under auspices of WHO
- Guideline panel (GDG) developed with input from SC but representative of all 6 WHO regions, diversity in all areas key
- GDG members subject to strict COI process including academic and financial COI
- Follow GRADE methods
- Involve patient partners

## The Network Meta-analysis





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BMJ 2020;370:m2980



## Recommendations Addressed So Far

- Corticosteroids (September 2)
- Remdesivir (November 20)
- Lopinavir/ritonavir (December 17)
- Hydroxychloroquine (December 17)
- Ivermectin (March 31)
- Others we need to discuss:
  - Tocilizumab/IL-6 inhibitors
  - Baricitinib
  - Monoclonal antibodies
  - Convalescent Plasma

## Corticosteroids

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 the panel judged that almost all fully informed patients with severe covid-19 would choose to take corticosteroids

## Corticosteroids Reduce Mortality in ARDS

	Corticest	eroids	Cont			Rink Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight.	TV, Random, 95% Cl	IV, Random, 95% CI
121.1 COVID 19 using		eria		1111	1000		To have a second
0E0A-COM019 2020	0000030	100			0.0%	171011.840	
Tomazwi 2020	85	151	- 91		14.4%		+
Subtoral (95% CI)		158		160	15.0%	0.82 (0.76, 1.11)	•
Total events	- 37		93		W		
Hererspicety Tau <sup>2</sup> = 1			1+1P-	+ 2.48	计子语		
Test for overall effect 2	(十文),84 (学)	+ 10.406					
1212 COVID 19 1944	ting DVV						
fright 2020	18	458	30	. 49	2,231	1.10(0.66) 2.561	
COND STEPRED 2000	1.2	1.3	1	-6	0.4%		
Dedun 2020	10	-61	127	59			
Hartey 2020	35	324	293	683	14.5%		+
enanana 2020	58	71		70	26.2%	0.95 (0.82, I.10)	+
Thereids-SAR1 2020	1.9	-13	3	14	5.3%	1.3010.71, 1.962	
Subnoral (95% CE)		542		met	43.5%	0.89 (0.71, 1.12)	•
Yotal events	195		380				1000
Hataropineity Tau <sup>1</sup> + 0 Test for overall effect 2			4-50	+ 0.05	11 17 + 50	28	
1213 Nos Cavid 19 A	IDS.						
Averana 2006	45	305	82	. 92	12.75	0.8610.68.1.08T	
Us 2012	2	12	- 2	14	1.0%	0.33 (0.08, 1.31)	
Metheri 5508	2	.10	5		1.0%	0.20(0.05, 0.61)	
Wedkin 2007	15	-63	12	- 28	4.0%	8.5610.30, 1.033	the second se
fiez# 2013	- 0	- 10	1	. 9			•
Steinberg 2006	-26	89	2.6	1.16	6.3%	1.0210.68, 1.625	
Tongyes 2016		- 94	-40				
Vilur 2026	- 29	139					the second se
Subtotal (95% CI)		1220		+79	43,6%	0.71 (0.54, 0.02)	•
Total events	197		205				
Heterageneity: Tas <sup>1</sup> + I Test for overall effect. 2				+ 0.0	0( ) <sup>4</sup> + 47	TX .	
Total (95% CB		1220		1520	100.0%	0.82 30.72, 0.950	•
Total events	417		078				
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COVID ARDS	RR 0.89 (0.76 to 1.05)
Non-COVID ARDS	RR 0.71 (0.54 to 0.92)

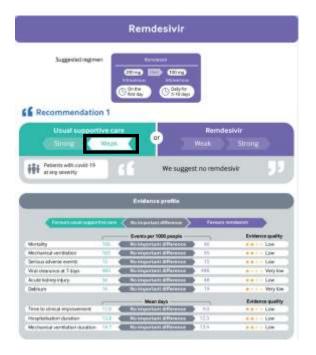


Chaudhuri et al. ICM (accepted for publication)

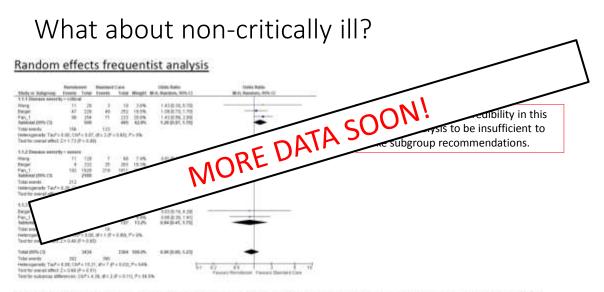
## Remdesivir

- Novel monophosphoramidate adenosine analogue prodrug that once metabolized inhibits RNA synthesis
- In vitro activity against a number of viruses including SARS-CoV-2

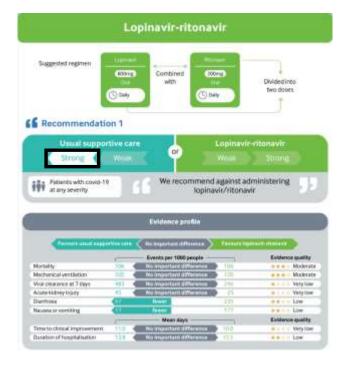
Study	N	Country	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)
Biegel (ACTT-1)	1063	United States, Europe, Asia	58.9	Non-severe (11.3%) Severe <sup>a</sup> (88.7%)	44.1%
Spinner (SIMPLE MODERATE)*	596	United States, Europe, Asia	56-58	Non-severe (100%)	0%
Pan (SOLIDARITY)	5451	Worldwide	< 50 35% 5070 47% > 70 18%	Non-severe (24%) Severe <sup>b</sup> (67%) Critical (9%)	8.9%
Wang	237	China	65	Severe* (100%)	16.1%



 the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it does improve patient-important outcomes.



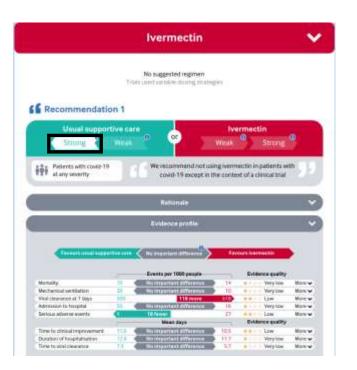
Study-independent (3 group) subgroup analysis with test for subgroup differences p-value = 0.11



- no evidence of benefit on patient-important outcomes
- May increase risk of diarrhea and nausea or vomiting

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Suggested regime			(001.000) (0.11.00)	
Recommendatio	an 1			
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- no benefit on patient important outcomes
- may increase risk of diarrhea and vomiting
- no evidence that the addition of azithromycin modified the effect for any outcome

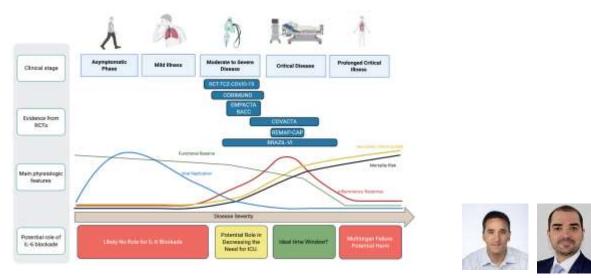


- Assessed for treatment, not prophylaxis
- Mortality numbers look promising but data VERY LOW certainty
- Recommend further trial enrolment but not yet ready for clinical treatment

## IL-6 inhibitors

Trial	Main intervention	Inclusion criteria	Number of participants	Comments
EMPACTA	Tocilizumab 8mg/kg vs Placebo	COVID-19 pneumonia; not receiving IMV; with supplemental O <sub>2</sub> .	389	Most patients received Dex
BACC Bay	Tocilizumab 8mg/kg vs Placebo	Confirmed COVID-19; supplemental O <sub>2</sub> < 10 lpm; inflammatory state (e.g., fever)	243	None on Dexamethasone Not critically ill
BRAZIL VI Investigators	Tocilizumab 8mg/kg vs Standard of Care	Hospitalized with severe COVID-19 + high inflammatory markers	129	70% with steroids 30% with NIV; 15% IMV.
CORIMUNO-19	Tocilizumab 8mg/Kg vs. Usual Care	COVID-19 moderate to severe pneumonia; O <sub>2</sub> >3 L/min.	131	30% on steroids Not critically ill
RCT-TCZ-COVID-19	Tocilizumab 8mg/Kg vs. Standard of Care Second dose at 12 hs	COVID-19 pneumonia; PaFiO <sub>2</sub> between 200-300 without mechanical ventilation at baseline	126	No data on steroid use Not critically ill
COVACTA	Tocilizumab 8 mg/kg vs. placebo	Severe COVID-19 pneumonia; blood oxygen saturation ≤93% or PaFiO <sub>2</sub>	452	30% - 50% with steroids Nearly 40% with invasive mechanical ventilation
REMAP-CAP	Tocilizumab 8mg/kg vs Sarilumab 400mg vs Standard of Care Second dose at 12-24hs	Critically ill within 24 hours of life- support	865	Most patients on steroids Critically ill patients
RECOVERY	Tocilizumab 400 or 800mg vs standard of care Second dose at 12-24 hrs	Severe COVID with sats <92% and CRP >75mg/L	4116	Most patients on steroids 50% critically ill

## IL-6 inhibitors



Lancet Resp Med. (accepted for publication)

## Pooled results – Tocilizumab vs. standard of care

	Pooled relative effect	Certainty
Clinical Improvement	RR 1.06 (1.00 to 1.13)	Moderate
Mortality at 28 days	RR 0.89 (0.82 to 0.97)	High
Serious adverse events	RR 0.89 (0.75 to 1.06)	Moderate

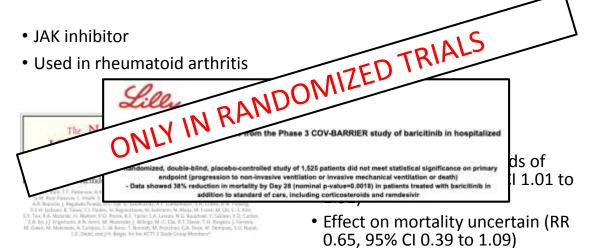
Cochrane Database of Systematic Reviews 2021, Issue 3. Art. No.: CD013881.

- · WHO prospective meta-analysis is coming including new data
- · Evidence suggests toci reduces mortality in combo with steroids

Corticosteroids	NNT = 11.5
tocilizumab	NNT = 31

- Timing matters
- · Availability concerns force triage decisions

## Baricitinib



## Monoclonal antibodies

- Bamlanivimab
- Regeneron casirivimab + imdevimab



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...but no data yet they improve patient outcomes.

## **Convalescent Plasma**

- Most recent meta-analysis published in JAMA February
- 10 RCTs 11,782 patients
- CONCOR-1 stopped for futility

٠	Most recent meta-analysis published in JAMA February				
•	• 10 RCTs – 11,782 patients				
•	CONCOR-1 stopped f	or futility	ZEDTI		
		For futility NRANDOMI oz (0.92 to 1.12)	Certainty		
	ONLY	oz (0.92 to 1.12)	Moderate		
	ar stay	HR 1.07 (0.79 to 1.45)	Low		
L	Need for mechanical ventilation	RR 0.81 (0.42 to 1.58)	Low		
	Some adverse events in plasma group but generally not severe.				

## What's coming next?

### **REMAP-CAP**

Domain	COVID-19	
Antibiotics	Empiric va None	
Macrolide duration		
Antivirals	HCQ/3/R	
Immunoglobulins	Corwalescent -	
Immune Modulation 1	Textilizensels Serifymerk	
Immune Modulation 2	Eritoren, Apremilan	
Corticosteroids	Angebenertiteren	
Anticoagulants	lingaria 🔤	
Anti-platelet Agents	ASA: Clepidogrel	
ACE2/RAS	ACE; ARBs; DMX-200	
Vitamin C	Vitamin C 🚺	
Statins	Seventatio	
Mechanical Ventilation	Protocolized	

### **RECOVERY**

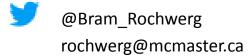
- Immunoglobulin
- Monoclonal antibodies
- Aspirin
- Colchicine
- Barcitinib
- Anikinra
- Dimethyl fumarate

## WHO Guideline Dissemination

- BMJ <u>https://www.bmj.com/content/370/bmj.m3379</u>
- WHO <u>https://www.who.int/publications/i/item/therapeutics-and-</u>covid-19-living-guideline
- MAGICApp https://app.magicapp.org/#/guideline/nBkO1E

## Thank you





# **Tocilizumab Logistics**

Jin-Hyeun Huh Senior Director of Pharmacy , UHN ICU Drug Task Force Lead

## Tocilizumab Supply & Distribution

- Globally increased demand
- Federal PHAC contracted month to month supply with Roche
  - PHAC provides allocation to Provinces/Territories based on patient metrics
  - Can include "out of country supply" + Canadian supply
  - Protected supply for on-label indications
- This month supply (April 8<sup>th</sup> May 6<sup>th</sup>)
  - 200mg vials (Canadian and "out of country" supply)
- Utilize regular distribution channels: order through CPDN/Roche

## Tocilizumab Allocation & Management

- Governance : Critical Care Command table
- Allocation based on COVID hospital admissions (including ICU)
- 73 hospitals identified for allocation
- Weekly drug dashboards identify local supply at hospitals that can be redistributed
- Access for hospitals without allocation
  - Email jin-hyeun.huh@uhn.ca

