World Health Organization

MAGIC app

Evidence Based Therapies for Covid-19

thebmj

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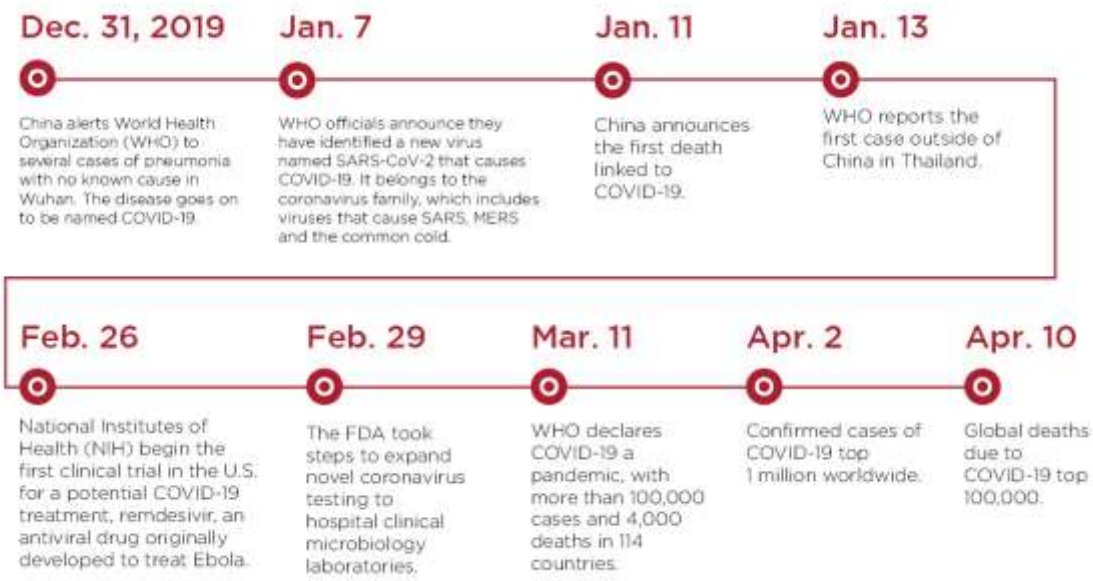
Declarations

- 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?

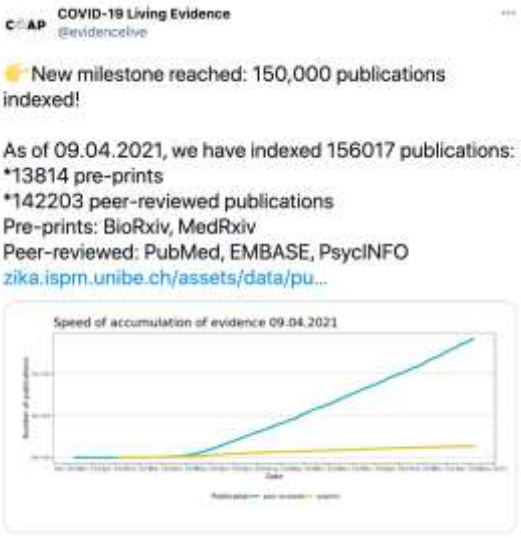


Repurposed Meds

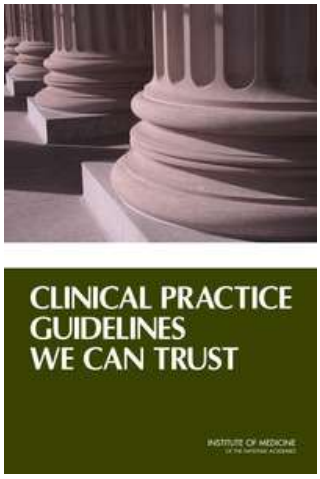
Drug	Current use	Original mode of action
Chloroquine	Antimalarial	Heme polymerase inhibitor
Kaletra (ritonavir + lopinavir)	HIV	Protease inhibitor
Interferon alfa-2b	Hepatitis-C	Immune modulator
Remdesivir	Experimental	Nucleotide analogue
Favipiravir	Influenza	RNA polymerase inhibitor
Actemra (tocilizumab)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

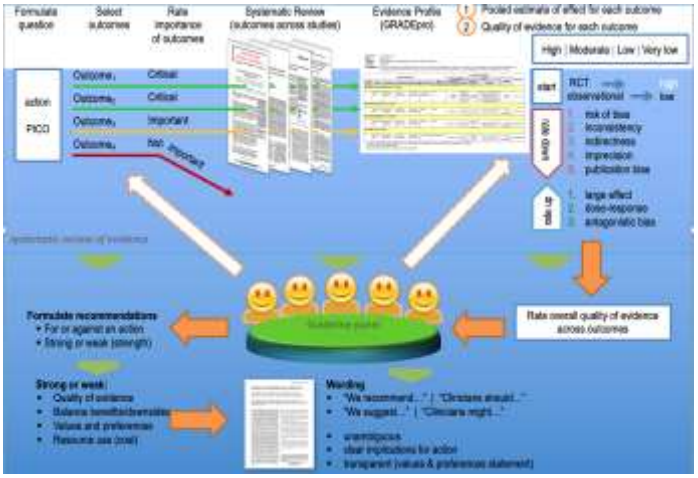
Source: WHO, adapted from landscape analysis, 17th February 2020 *For use on covid-19

Information Explosion



Trustworthy Clinical Practice Guidelines





Making Healthcare Decisions in a Pandemic

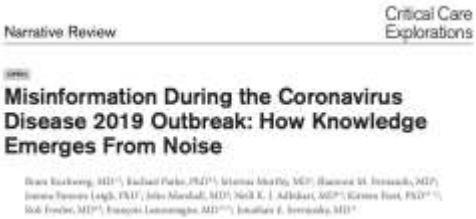


TABLE 1. Healthcare Decisions During Pandemic Illness

Factors	Normal Healthcare Decisions	During Pandemic Illness
Evidence quality	Usually high-quality randomized controlled trials (although not always)	Indirect data from other populations/pathogens Case series or case reports, even clinical observations from colleagues
Guidance available	Rely on trustworthy clinical practice guidelines	Expert driven What works in other jurisdictions/hospitals
Timelines	Often have time to make decisions including all stakeholders	May be forced into rushed, 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 consider triage and resources especially if large numbers affected

Crit Care Expl 2020; 2:e0098

Rapid Recommendations

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Rapid Recommendations process step by step (with target times)

- Step 1: Monitor and identify potentially practice changing evidence
- Step 2: Executive + chair triggers process and RapidRecs panel (day 7)
- Step 3: Systematic reviews created by separate teams (day 45)
- Step 4: RapidRecs created in MAGICapp and as synopsis paper (day 60)
- Step 5: RapidRecs + reviews submitted for peer review (day 60)
- Step 6: RapidRecs and reviews disseminated globally (day 90)

Birth of the WHO Living Guideline

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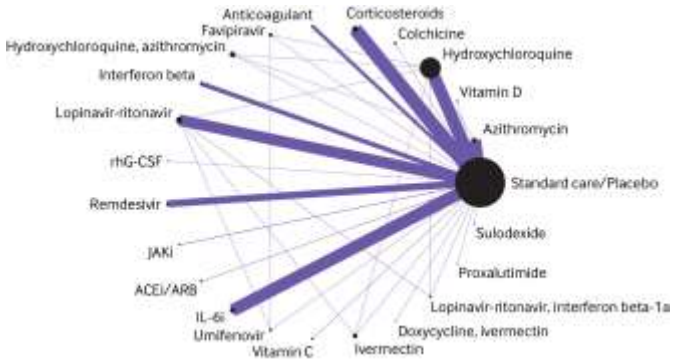
Random Collaborative Canadians interested in Clinical Practice Guidelines

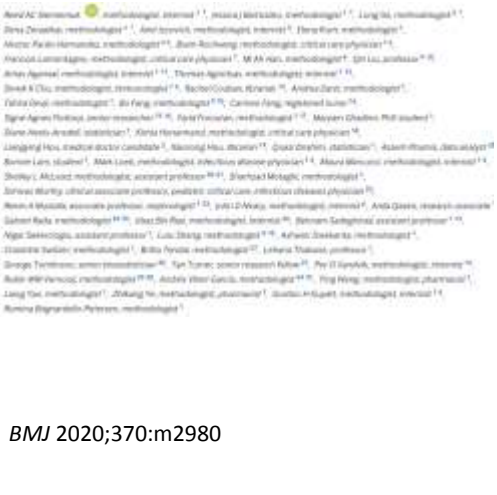


Guideline Development

- 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





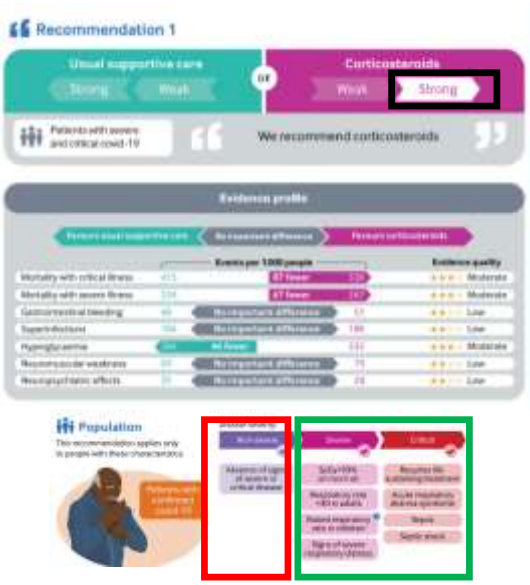
BMJ 2020;370:m2980

Recommendations Addressed So Far

- Corticosteroids (September 2)
- Remdesivir (November 20)
- Lopinavir/ritonavir (December 17)
- Hydroxychloroquine (December 17)
- Ivermectin (March 31)

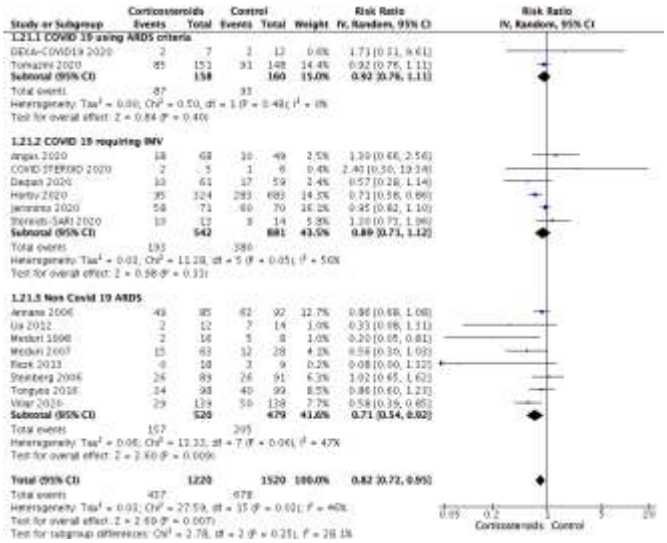
- Others we need to discuss:
  - Tocilizumab/IL-6 inhibitors
  - Baricitinib
  - Monoclonal antibodies
  - Convalescent Plasma

Corticosteroids



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

Corticosteroids Reduce Mortality in ARDS



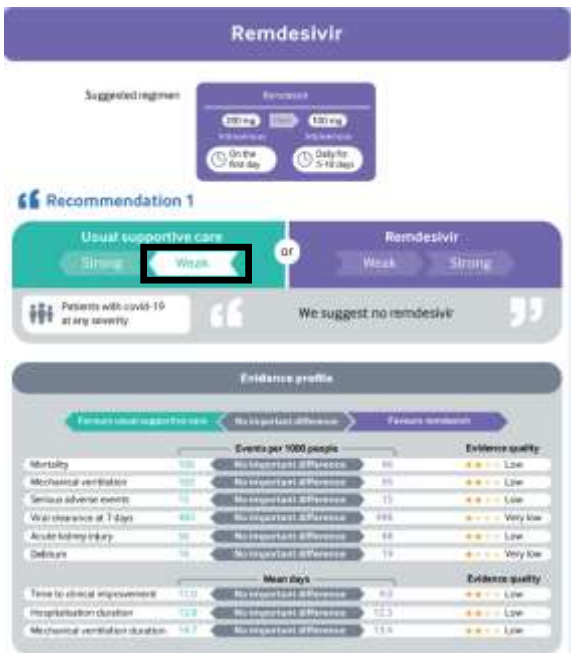
COVID ARDS	RR 0.89 (0.76 to 1.05)
Non-COVID ARDS	RR 0.71 (0.54 to 0.92)

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

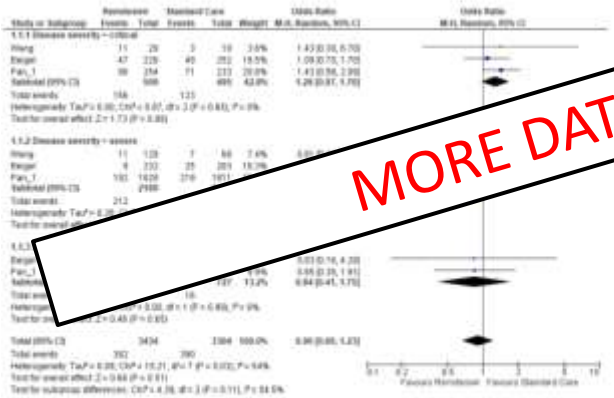
Study	N	Country	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)
Biegel (ACTT-1)	1063	United States, Europe, Asia	58.9	Non-severe (11.3%) Severe[a] (88.7%)	44.1%
Spinner (SIMPLE MODERATE)*	596	United States, Europe, Asia	56–58	Non-severe (100%)	0%
Pan (SOLIDARITY)	5451	Worldwide	<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

What about non-critically ill?

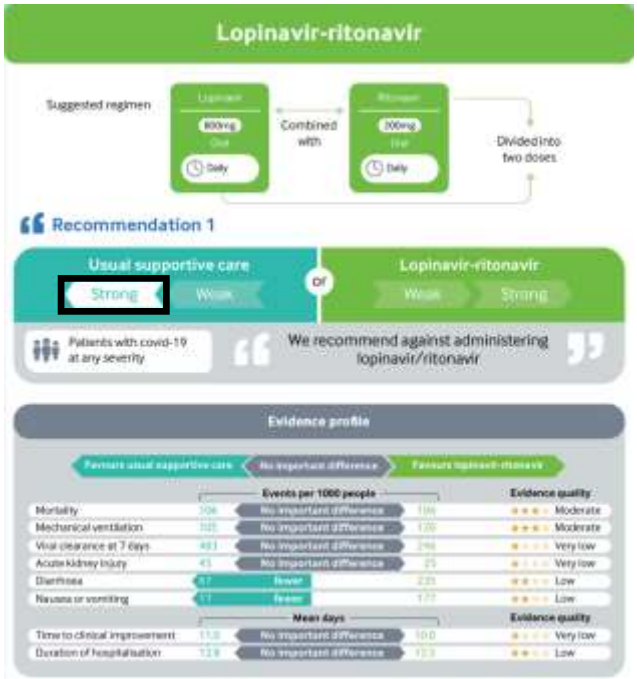
Random effects frequentist analysis



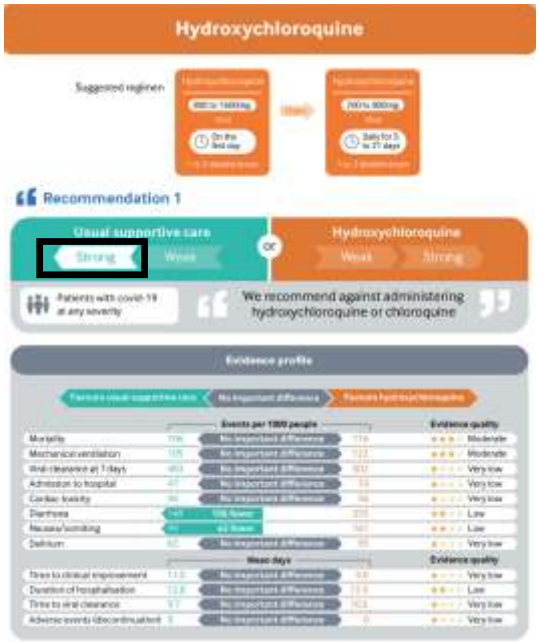
MORE DATA SOON!

…edibility in this …ysis to be insufficient to …e subgroup recommendations.

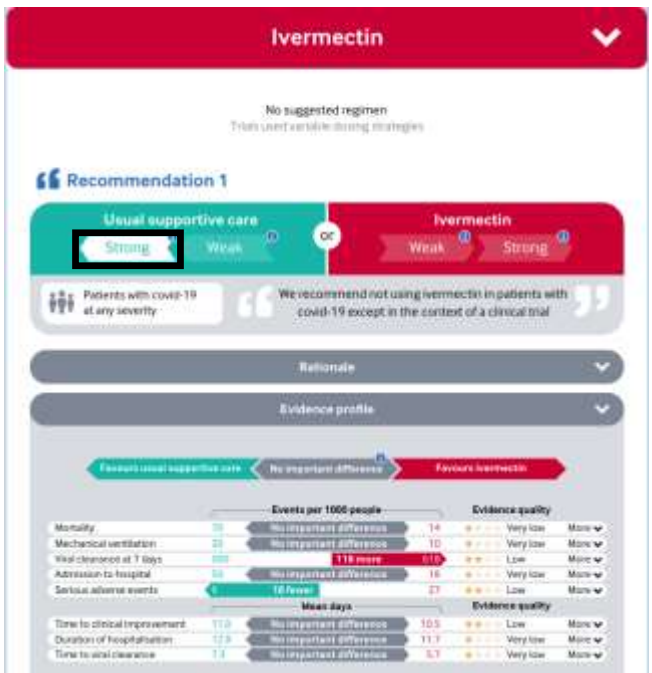
Study-independent (3 group) subgroup analysis with test for subgroup differences p-value = 0.11



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



- 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

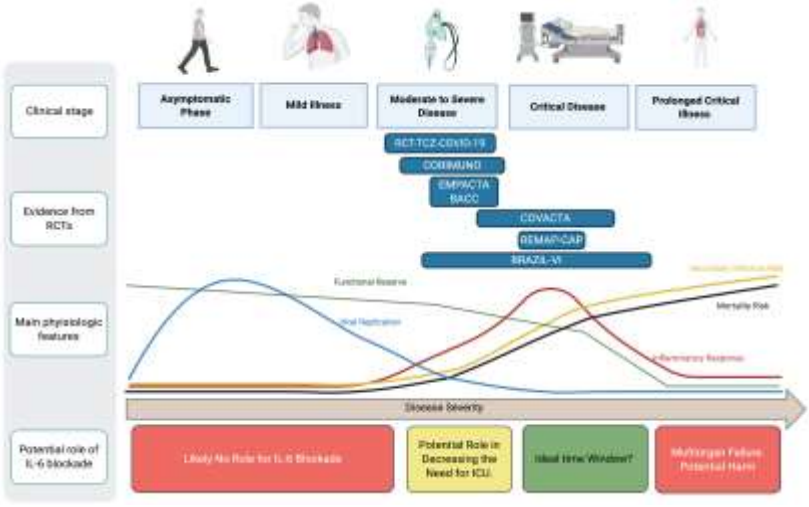


- Assessed for treatment, not prophylaxis
- Mortality numbers look promising but data VERY LOW certainty
- Recommend further trial enrolment but not yet ready for clinical treatment

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_2.	389	Most patients received Dex
BACC Bay	Tocilizumab 8mg/kg vs Placebo	Confirmed COVID-19; supplemental O_2 < 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_2 >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; $PaFiO_2$ 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 $PaFiO_2$	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.

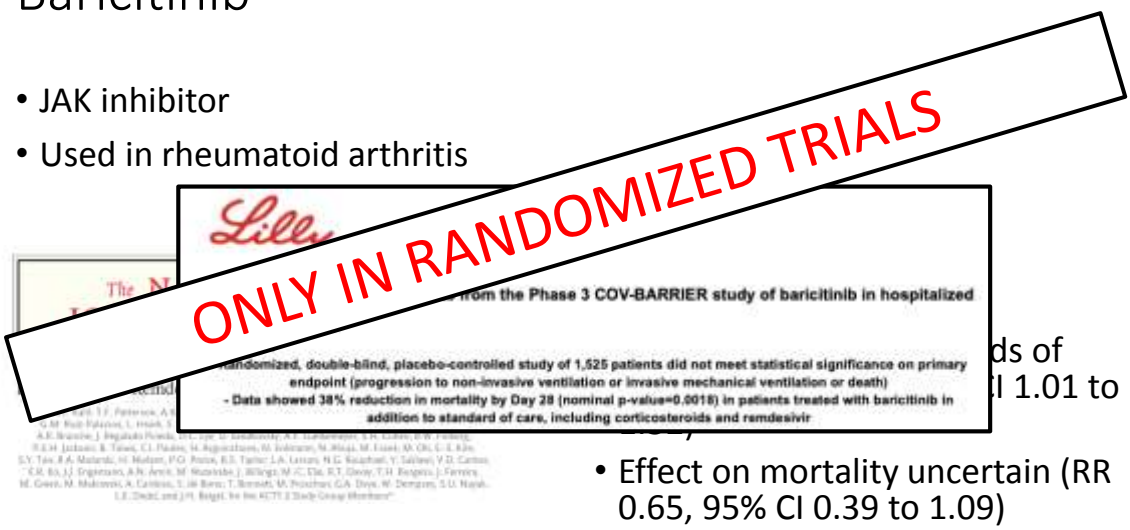
- WHO prospective meta-analysis is coming including new data
- Evidence suggests toci reduces mortality in combo with steroids

Corticosteroids	NNT = 11.5
tocilizumab	NNT = 31

- Timing matters
- Availability concerns force triage decisions

Baricitinib

- JAK inhibitor
- Used in rheumatoid arthritis



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l 1.01 to

- Effect on mortality uncertain (RR 0.65, 95% CI 0.39 to 1.09)

Monoclonal antibodies

- Bamlanivimab
- Regeneron – casirivimab + imdevimab

Monoclonals may decrease viral load…

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

…mab as Monotherapy or in …tion With Etesevimab on Viral Load in …atients With Mild to Moderate COVID-19
A Randomized Clinical Trial

ONLY IN RANDOMIZED TRIALS

…but no data yet they improve patient outcomes.

Convalescent Plasma

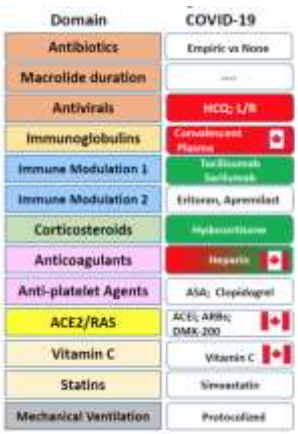
- Most recent meta-analysis published in JAMA February 2[illegible]
- 10 RCTs – 11,782 patients
- CONCOR-1 stopped for futility

ONLY IN RANDOMIZED TRIALS

		Certainty
Mortali[illegible]	[illegible]02 (0.92 to 1.12)	Moderate
[illegible]al stay	HR 1.07 (0.79 to 1.45)	Low
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



RECOVERY

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

WHO Guideline Dissemination

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

Thank you

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Tocilizumab Logistics

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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 8th – May 6th)
  - 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