Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence

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Objetives

- Collect the best available evidence on pharmacological interventions for patients with COVID-19 or exposed to SARS-COV2

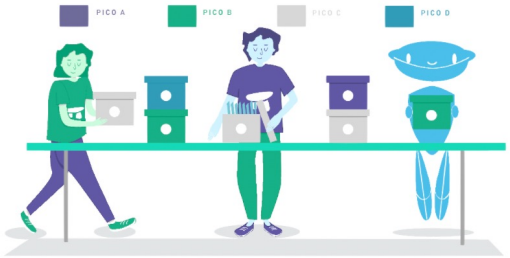
- Sustain a “living” update process in which every new piece of evidence is rapidly incorporated to the review

- Analice aquired evidence using standarized tools

Search

L·OVE repository

- **>300,000** records (articles screened 2 million approximately)
- Any type of article
- Automated: 41 databases + preprint + trial registries
  - Main sources screened hourly (eg. Pubmed, medRxiv)
- Manual: many other sources
- Studies included in systematic reviews (coming from any source)
  → **Largest repository** according to our own estimation

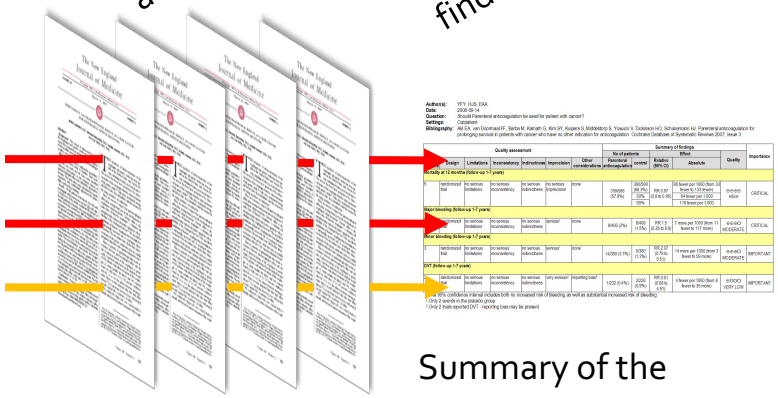


GRADE

Outcomes across studies

Summary of findings tables

Certainty of the evidence assessment



Summary of the estimates of effects for every outcome

- High
- Moderate
- Low
- Very Low

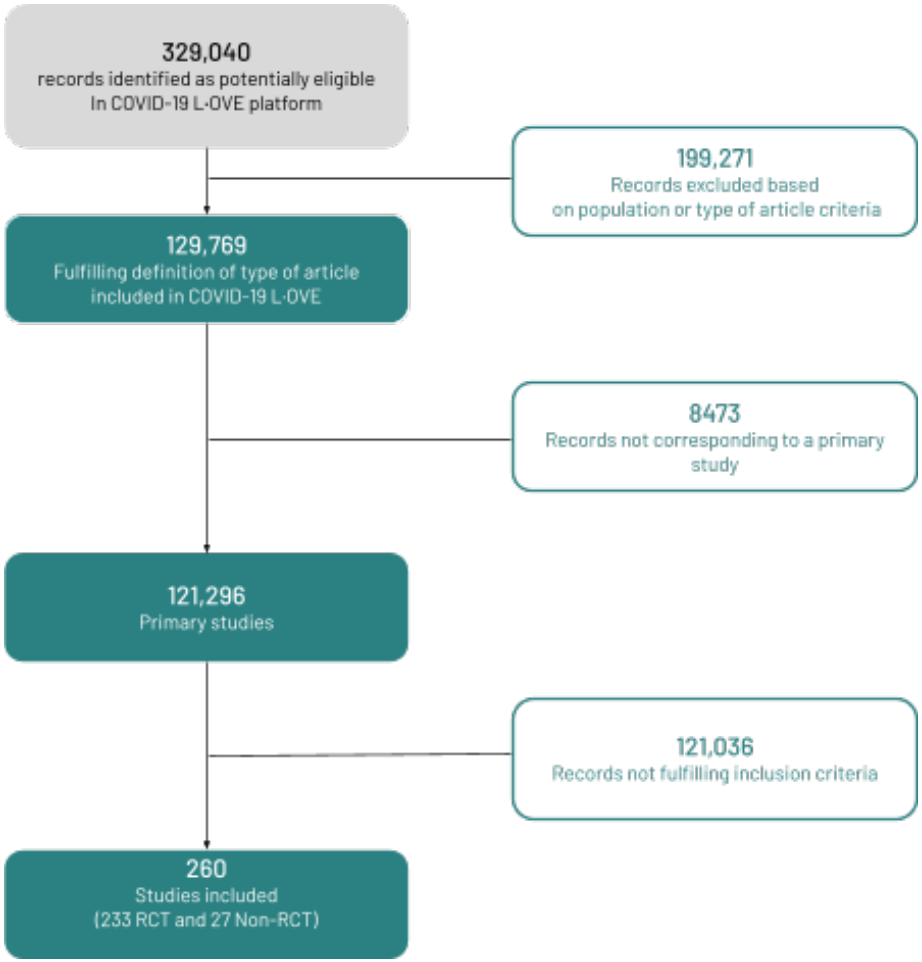
Downgrade

1. RoB
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Upgrade

1. Big effect
2. Dose-response gradient
3. Confounders

Results


329,040
records identified as potentially eligible
In COVID-19 L·OVE platform
199,271
Records excluded based
on population or type of article criteria
129,769
Fulfilling definition of type of article
included in COVID-19 L·OVE
8473
Records not corresponding to a primary
study
121,296
Primary studies
121,036
Records not fulfilling inclusion criteria
260
Studies included
(233 RCT and 27 Non-RCT)

Intervention		Overall number of studies including the intervention, n=218	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)
Hydroxychloroquine or Chloroquine	NEW	35	9	7	6	6	9
Ivermectin		22	7	1	7	3	2
Glucocorticoids		13	11	5	4		6
Convalecent plasma	NEW	12	11	6	4		3
Favipiravir	NEW	11	1		6		1
Lopinavir-Ritonavir	NEW	10	3	3	2		1
Tocilizumab	NEW	10	9	8	5		9
Azithromycin	NEW	6	3	2	2		1
Remdesivir		6	4 (*)	4	3		3
Umifenovir		5					
Colchicine		4	3	2			1
Interferon beta-1a		4	3	3	2		

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmfull effect		
Uncertain effect		
No evidence or no estimable effect		

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Lopinavir-Ritonavir	NEW	10	3	3	2		1
Tocilizumab	NEW	10	9	8	5		9
Azithromycin	NEW	6	3	2	2		1
Remdesivir		6	4 (*)	4	3		3
Umifenovir		5					
Colchicine		4	3	2			1
Interferon beta-1a		4	3	3	2		
Sofosbuvir +/- Daclatasvir		4	2	2	2		
Vitamin C	NEW	4	4	4	2		
Zinc	NEW	4	1	1	2		
Bamlanivimab		3	1		2		3
IVIG		3	3	2			1
Mesenchimal cell tranplantation		3	1		1		1
Vitamin D		3	1	1			1
ACEIs or ARBs (continuation)		2	2	2			
Bromhexine Hydrochloride		2	1	1	1		1
Dutasteride	NEW	2			1		
Leflunomide		2					
Mouthwash (povidone iodine or essential oils)	NEW	2					
Nitazoxanide	NEW	2	1	1	1		1
Ozone		2	2		1		1
Sarilumab	NEW	2	2	1	1		1
99mTc-MDP		1					
ACEIs or ARBs (treatment)	NEW	1	1	1			
Anakinra		1	1	1	1		1
Anticoagulants		1	1				
Aprepitant		1					
Artemisinin	NEW	1			1		1
Auxora		1	1	1			
Azvudine		1					
Baloxavir		1			1		
Bamlanivimab + etesevimab		1	1		1		1
Baricitinib		1	1	1	1		1
BCG		1	1				
Chloroquine nasal drops		1					
Clarithromycin	NEW	1					
CIGB-325		1			1		1
Cofactors		1			1		1
Darunavir-Cobicistat		1					
Electrolyzed saline		1	1		1		
Enisamium		1			1		
Febuxostat		1					
Flebuxamine		1	1	1			1
Helium (inhaled)		1					
Icatibant		1	1				
iC1e/K		1	1				
IFN-alpha2b + IFN-gamma		1					
IFX-1		1	1				1
INM005 (equine antibodies)		1	1	1	1		1
Interferon beta-1b		1	1	1	1		
Interferon beta-1a (inhaled)		1	1	1	1		1
Interferon kappa + TFF2		1	1				1
Itolizumab		1	1	1			1
Levamizole		1					
Lincomecin		1					
Melatonin	NEW	1	1		1		
Metisoprinol	NEW	1					
Molnupiravir		1					1
Mouthwash (hydrogen peroxide)		1	1	1	1		
N-acetylcysteine		1	1	1			1
Nasal hypertonic saline		1			1		
Novaferon		1					
Omega-3 fatty acids		1					
Peg-IFN lambda		1					1
Progesterone		1	1	1			1
Prolectin-M		1	1	1			1
Propolis		1	1	1	1		
Proxalutide		1	1	1			
Quercetin		1	1		1		
Ramipril		1	1			1	
Recombinant Super-Compound IFN		1	1		1		
REGN-COV2 (Regeneron)		1					1
Ribavirin		1					
Ribavirin + Interferon beta-1b		1					
Ruxolitinib		1			1		
rhG-CSF		1	1		1		1
Sofosbuvir/ledipasvir	NEW	1	1	1	1		
Steroids (inhaled)	NEW	1			1		
Sulodexide		1	1	1			1
Telmisartan		1	1	1			
Triazavirin		1	1		1		1
α-Lipoic acid		1	1				

(*) Inconsistent results between included studies. Beigel et al. informed mortality reduction with remdesivir while WHO SOLIDARITY found no significant differences. Pooled estimates show a small non-statitically significant mortality reduction (RR 0.94, 95%CI 0.82 - 1.08).

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Mild patients (ambulatory)

Hydroxychloroquine	→	No benefits (High certainty)
Ivermectin	→	No benefits (Low certainty)
Lopinavir-ritonavir	→	No benefits (Moderate certainty)
Colchicine	→	Small benefits (Low certainty)
Steroids	→	Not assessed
Azithromycin	→	Not assessed

Moderate patients (patients with pneumonia without respiratory failure)

Hydroxychloroquine	No benefits (High certainty)
Ivermectin	No benefits (Low certainty)
Lopinavir-ritonavir	No benefits (Moderate certainty)
Colchicine	No benefits (Moderate certainty)
Steroids	No benefits (Low certainty)
Azithromycin	No benefits (Moderate certainty)
Conv. Plasma	No benefits (Moderate certainty)
Tocilizumab	Not assessed

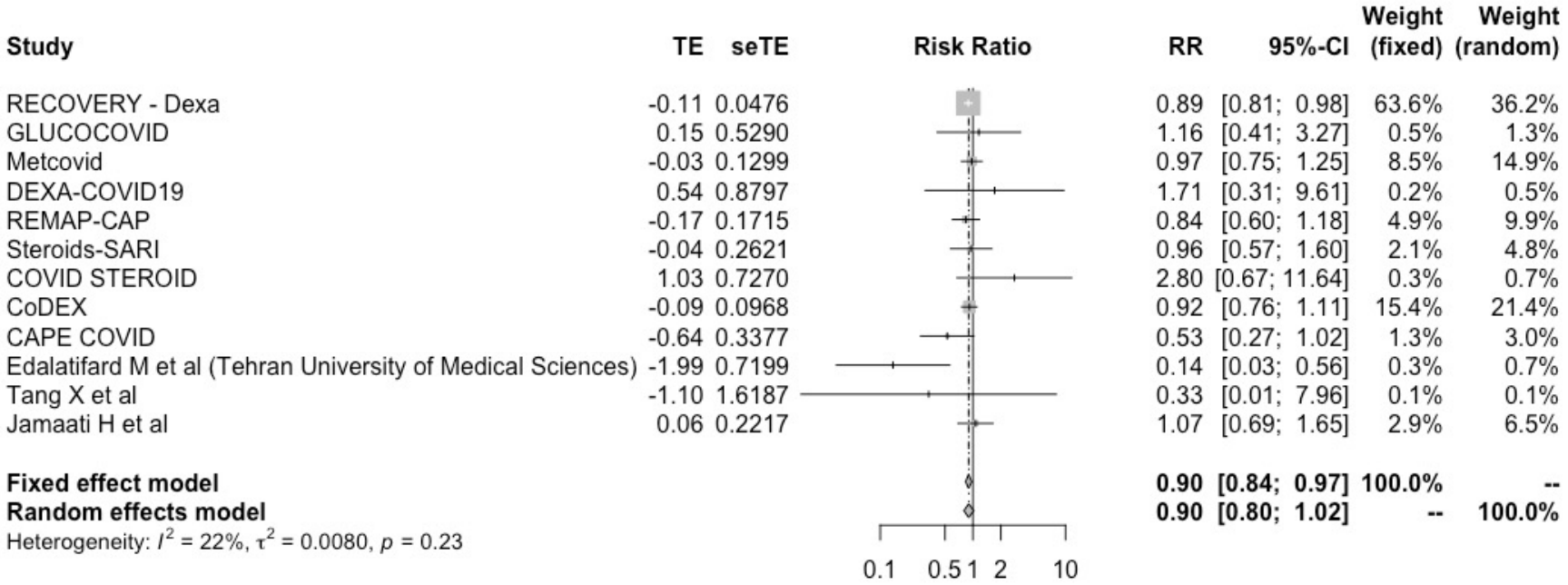
Severe and critical patients (patients with respiratory failure)

Hydroxychloroquine	No benefits (High certainty)
Ivermectin	No benefits (Low certainty)
Lopinavir-ritonavir	No benefits (Moderate certainty)
Colchicine	No benefits (Moderate certainty)
Steroids	Important benefits (Modertate certainty)
Azithromycin	No benefits (Moderate certainty)
Conv. Plasma	No benefits (Moderate certainty)
Tocilizumab	Important benefits (Moderate certainty)

Systemic steroids

- **14 RCTs, 8115 patients**

All cause mortality: Steroids vs. Standard of care



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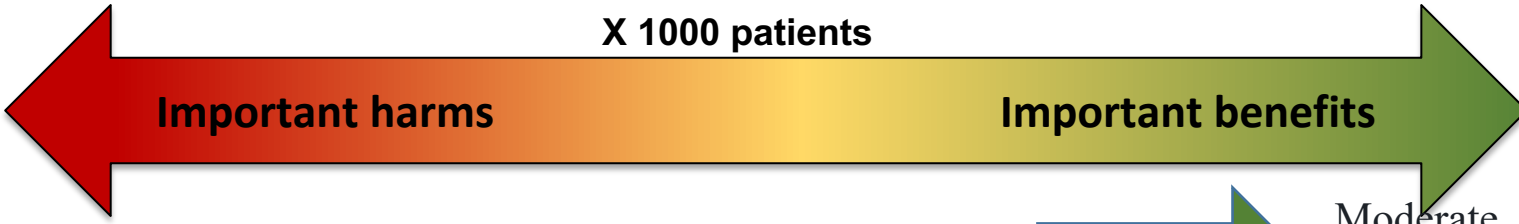
Systemic steroids



Mortality	- 16	Moderate Certainty ⊕⊕⊕◯
Invasive mechanical ventilation	- 22	Moderate Certainty ⊕⊕⊕◯
Time to symptom resolution	163	Low Certainty ⊕⊕◯◯
Symptomatic infection (prophylaxis)	No information	
Severe adverse events	-11	Low Certainty ⊕⊕◯◯

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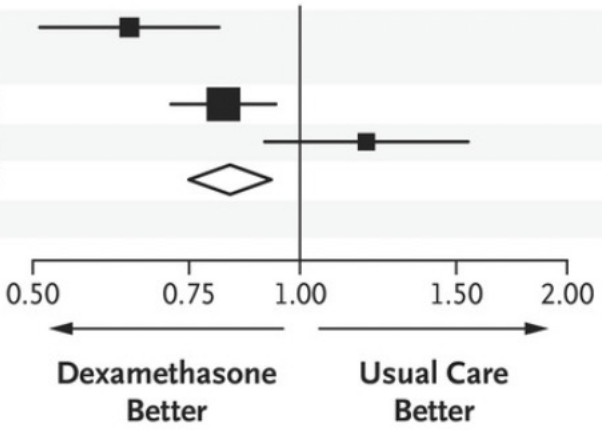
Systemic steroids in RECOVERY trial

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5



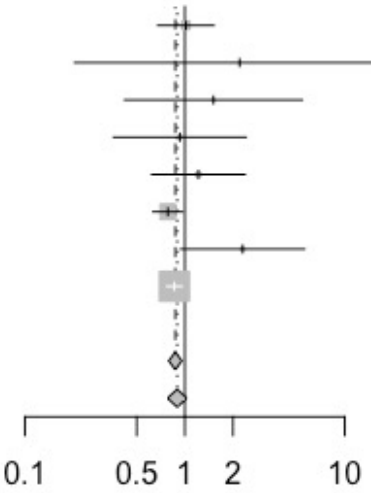
Tocilizumab

- **10 RCT, 6440 patients**

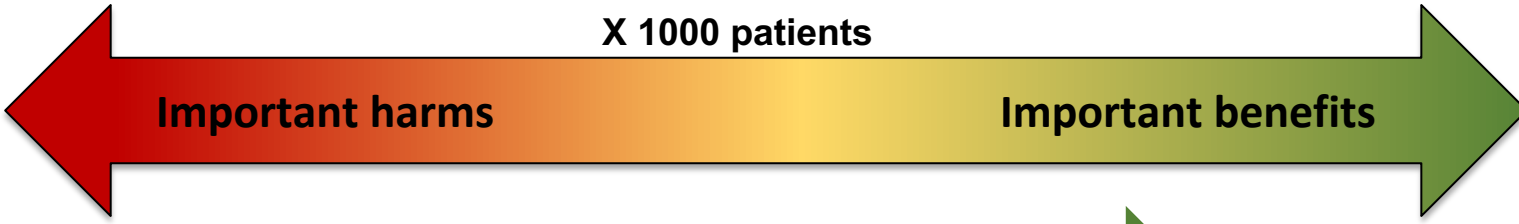
  All cause mortality: Tocilizumab vs. Standard of care

Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
COVACTA	0.01	0.2064	1.01	[0.68; 1.52]	5.3%	10.4%
RCT-TCZ-COVID-19	0.79	1.2117	2.20	[0.20; 23.65]	0.2%	0.3%
BACC Bay Tocilizumab Trial	0.41	0.6526	1.51	[0.42; 5.42]	0.5%	1.2%
CORIMUNO-TOCI 1	-0.07	0.4869	0.93	[0.36; 2.42]	0.9%	2.1%
EMPACTA	0.19	0.3428	1.22	[0.62; 2.38]	1.9%	4.1%
REMAP-CAP - tocilizumab	-0.24	0.1090	0.78	[0.63; 0.97]	19.0%	27.6%
Veiga	0.83	0.4551	2.30	[0.94; 5.61]	1.1%	2.4%
RECOVERY-TCZ	-0.15	0.0563	0.86	[0.77; 0.96]	71.1%	51.9%
Fixed effect model			**0.87**	**[0.79; 0.96]**	**100.0%**	--
Random effects model			**0.90**	**[0.78; 1.03]**	--	**100.0%**

Heterogeneity: I^2 = 16%, τ^2 = 0.0067, p = 0.30



Tociluzumab



Mortality	- 16	Moderate Certainty ⊕⊕⊕◯
Invasive mechanical ventilation	- 35	High Certainty ⊕⊕⊕⊕
Time to symptom resolution	60	Low Certainty ⊕⊕◯◯
Symptomatic infection (prophylaxis)	No information	
Severe adverse events	-11	Moderate Certainty ⊕⊕⊕◯

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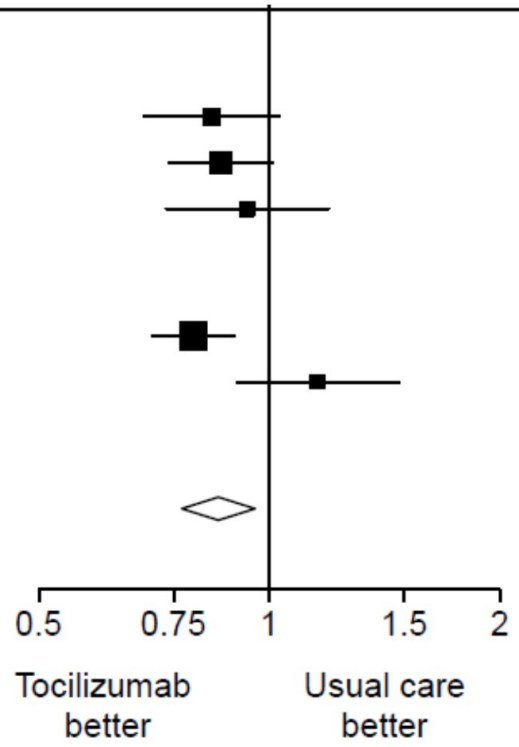
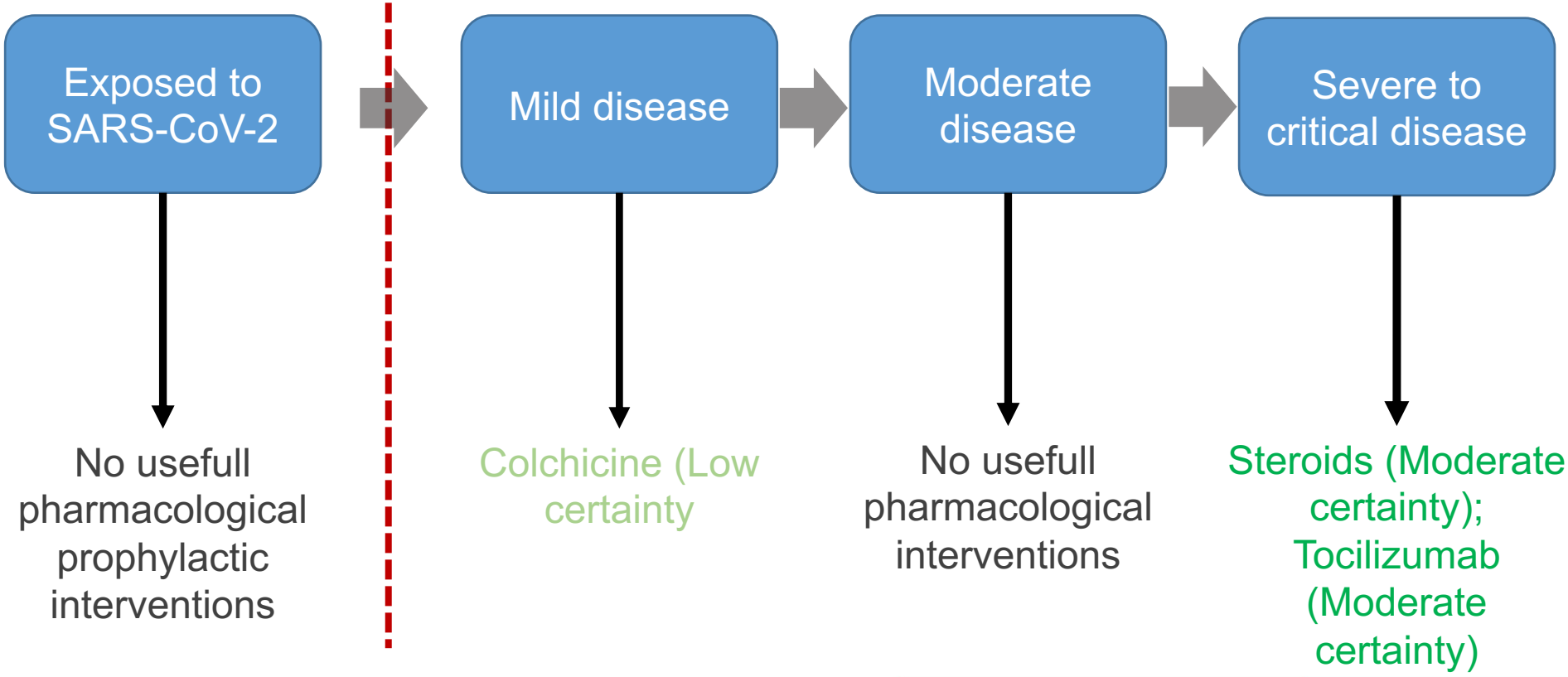
Tociluzumab in RECOVERY trial

	Tocilizumab	Usual care	RR (95% CI)
Respiratory support at randomization (χ^2_1=0.4; p=0.52)			
No ventilator support*	175/935 (19%)	202/933 (22%)	0.84 (0.69–1.03)
Non–invasive ventilation†	296/819 (36%)	350/867 (40%)	0.86 (0.74–1.01)
Invasive mechanical ventilation‡	125/268 (47%)	142/294 (48%)	0.94 (0.73–1.19)
Use of corticosteroids$ (χ^2_1=7.1; p=0.01)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70–0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91–1.48)
Unknown	0/1 (0%)	2/6 (33%)	
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77–0.96) p=0.0066**



Without COVID-19

COVID-19

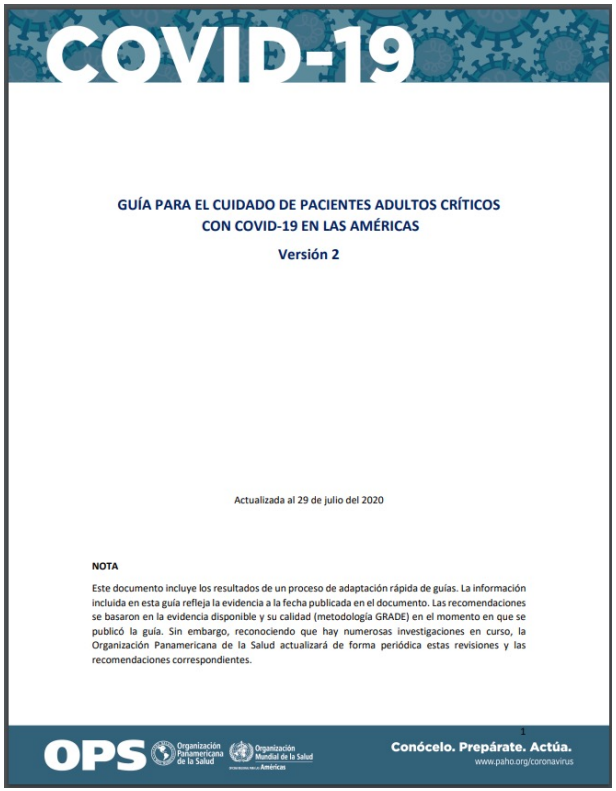


Thromboprophylaxis in hospitalized patients

- **No benefits of intemediate dose** (i.e LMWH 1 mg/kg a day) over standard dose (i.e LMWH 40mg a day) doi:10.1001/jama.2021.4152

- **No benefits of full dose** (i.e LMWH 1m/kg twice a day) over standard dose (i.e LMWH 40mg a day) https://doi.org/10.1101/2021.03.10.21252749

Manejo de los patients con COVID-19


COVID-19

GUÍA PARA EL CUIDADO DE PACIENTES ADULTOS CRÍTICOS CON COVID-19 EN LAS AMÉRICAS

Versión 2

Actualizada al 29 de julio del 2020

NOTA

Este documento incluye los resultados de un proceso de adaptación rápida de guías. La información incluida en esta guía refleja la evidencia a la fecha publicada en el documento. Las recomendaciones se basaron en la evidencia disponible y su calidad (metodología GRADE) en el momento en que se publicó la guía. Sin embargo, reconociendo que hay numerosas investigaciones en curso, la Organización Panamericana de la Salud actualizará de forma periódica estas revisiones y las recomendaciones correspondientes.

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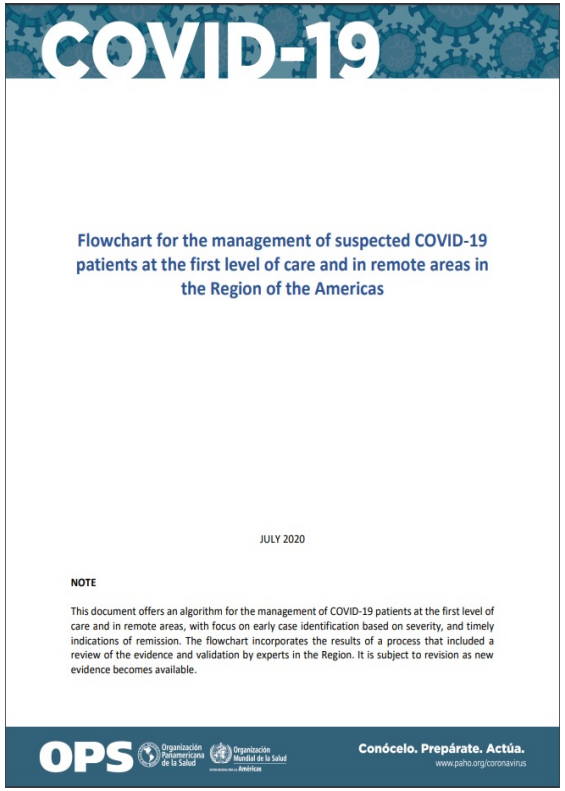
COVID-19

Flowchart for the management of suspected COVID-19 patients at the first level of care and in remote areas in the Region of the Americas

JULY 2020

NOTE

This document offers an algorithm for the management of COVID-19 patients at the first level of care and in remote areas, with focus on early case identification based on severity, and timely indications of remission. The flowchart incorporates the results of a process that included a review of the evidence and validation by experts in the Region. It is subject to revision as new evidence becomes available.

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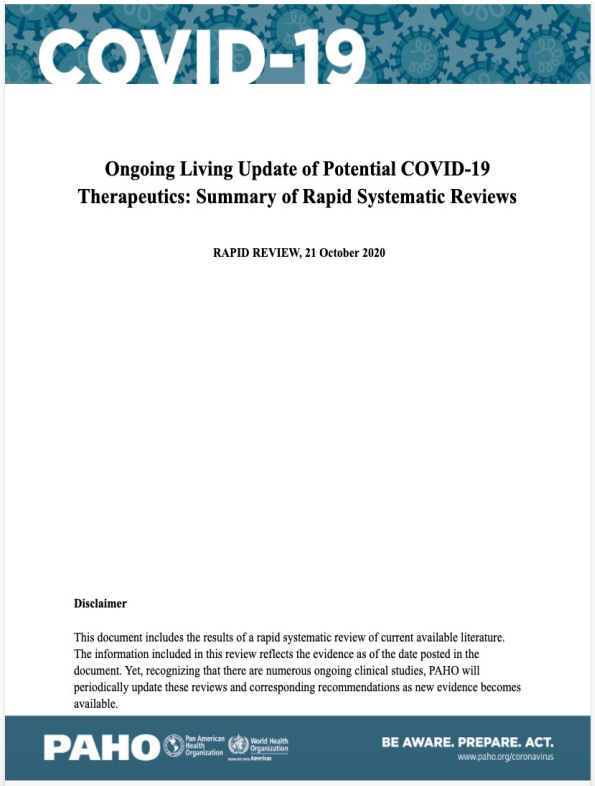
COVID-19

Ongoing Living Update of Potential COVID-19 Therapeutics: Summary of Rapid Systematic Reviews

RAPID REVIEW, 21 October 2020

Disclaimer

This document includes the results of a rapid systematic review of current available literature. The information included in this review reflects the evidence as of the date posted in the document. Yet, recognizing that there are numerous ongoing clinical studies, PAHO will periodically update these reviews and corresponding recommendations as new evidence becomes available.

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BE AWARE. PREPARE. ACT.
www.paho.org/coronavirus

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Thank you!!