Abordaje clínico y terapéutico en casos leves/moderados de COVID-19

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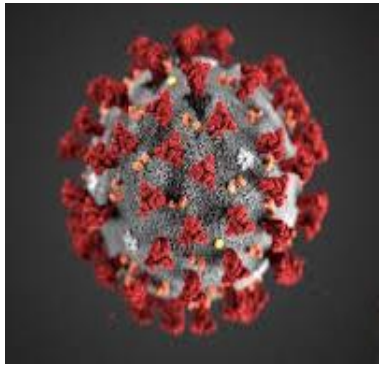
Medicina Interna y Enfermedades Infecciosas

Miérocoles 22 de abril



Objetivos de la charla

- Puesta al día COVID-19
- Contexto Clínico del caso
- Exámenes complementarios útiles en el diagnóstico y seguimiento
- Tratamiento de pacientes COVID-19 leves y moderados.

Puesta al día COVID-19

SHORT VIEW SUMMARY

Definition

- The coronaviruses (CoVs) commonly cause mild but occasionally more severe community-acquired acute respiratory infections in humans. CoVs also infect a wide variety of animals, and several CoVs (e.g., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]) have crossed the species barrier, producing outbreaks of severe respiratory disease. As of May 11, 2014, 537 cases of laboratory-confirmed MERS were reported to WHO with 145 deaths.

Epidemiology

- Community-acquired CoV infections cause about 15% of common colds. They are typically epidemic in the winter months. MERS has occurred in patients in the Arabian peninsula and those who recently traveled from this locale.

Microbiology

- CoVs are members of the Nidovirales order, single-stranded, positive-sense RNA viruses with a large genome. They mutate and also recombine frequently.

Diagnosis

- Laboratory diagnosis is best accomplished by finding viral RNA through polymerase chain reaction.

Therapy

- There are no accepted effective antiviral drugs for CoVs.

Prevention

- Prevention is through epidemiologic methods. The SARS epidemic was halted through careful case finding, quarantine, and use of barrier precautions.

Mandell, Douglas y Bennet. Enfermedades Infecciosas,Principios y Práctica. 8a Edicicón Volumen 2

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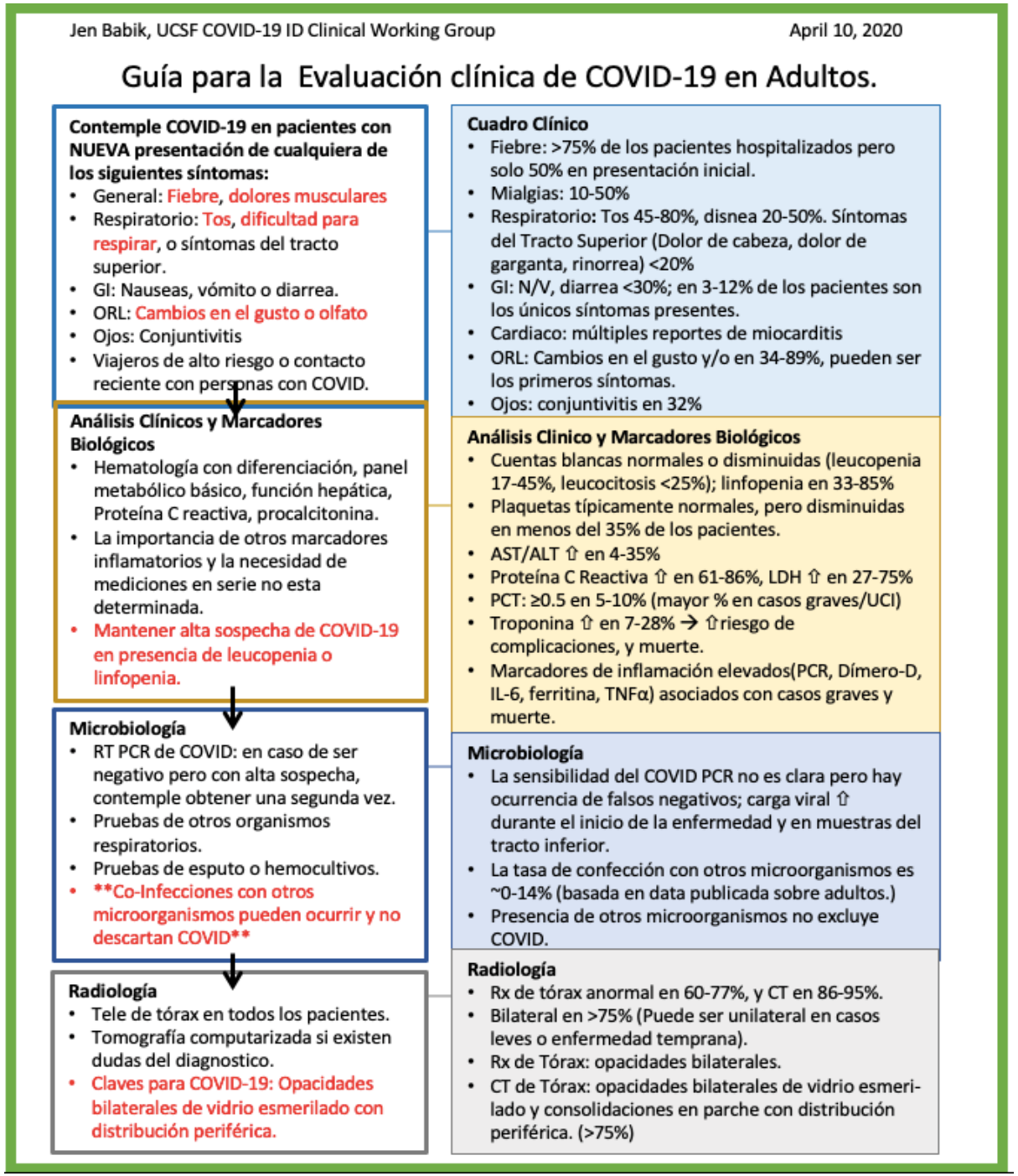
Review Article

Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic

Amin Gasmi [a], Sadaf Noor [b], Torsak Tippairote [c, d], Maryam Dadar [e], Alain Menzel [a], Geir Bjørklund [f]

- Una cantidad significativa de la población mundial contraerá la infección por COVID-19.
- **La evaluación individual de riesgos y las estrategias de gestión son cruciales**.
- El estado metabólico determina la gravedad clínica de COVID-19, desde asintomática hasta muerte.
- Los factores importantes incluyen **dieta, nutrición, edad, sexo, salud, estilo de vida y medio ambiente.**



- **Definición del caso**

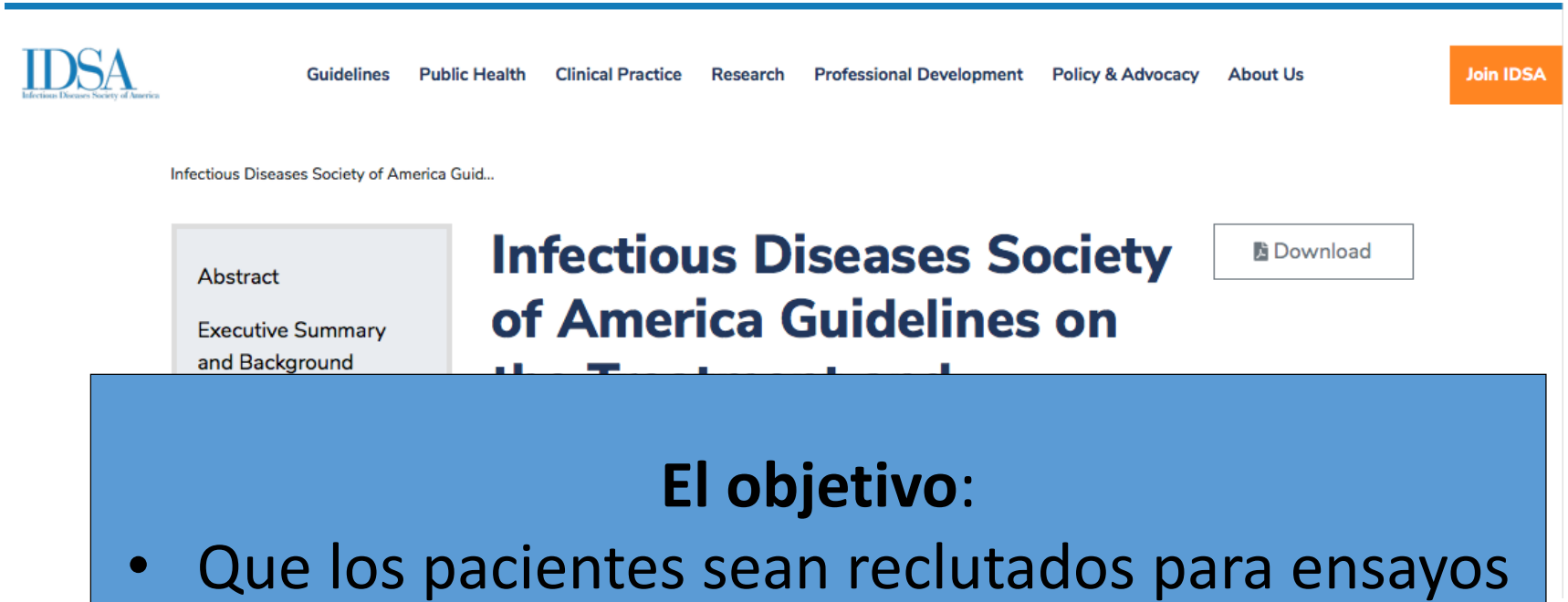
SI - NO *duda clínica válida

- **¿Qué exámenes le realizo y orientan Dx y seguimiento?**

Hematología completa y fórmula (🡻GB 🡻linfos, PFH, reactantes de fase aguda y coagulación

- **Confirmar Dx**

PCR, cultivo de esputo, hemocultivos, Rx Tórax, TAC Torácica

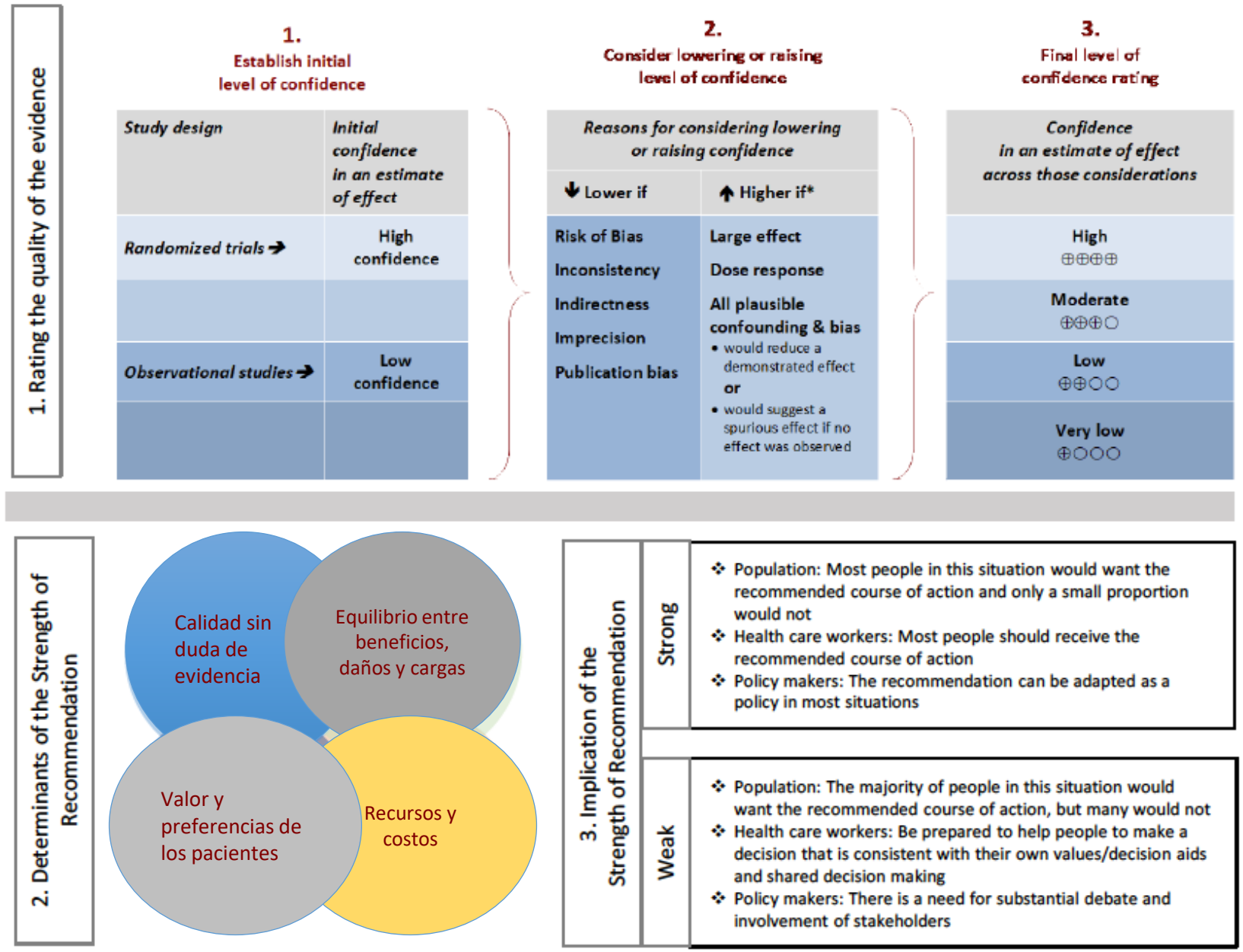


El objetivo:

- Que los pacientes sean reclutados para ensayos en curso, lo que proporcionaría evidencia muy necesaria sobre la eficacia y seguridad de varias terapias para COVID-19.

- IDSA fo ólogos de enferm ción para generar
- Se usó ación de calificación de recomendaciones (**GRADE**) para evaluar la certeza de la evidencia y hacer recomendaciones.

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)



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- **Recomendación 1,2,3** Entre pacientes hospitalizados con COVID-19, el panel de directrices IDSA recomienda hidroxicloroquina / cloroquina, hidroxicloroquina / cloroquina más azitromicina, lopinavir / ritonavir sólo en contexto de un ensayo clínico. (Brecha de conocimiento).

- **Recomendación 4 y 5** Entre pacientes hospitalizados con neumonía por COVID-19**, el panel de pautas IDSA se posiciona en contra del uso de corticosteroides.** (Recomendación condicional, muy baja certeza de evidencia). En *SDRA debido a COVID-19* **IDSA recomienda uso de corticosteroides en contexto de un ensayo clínico.** (Brecha de conocimiento).

- **Recomendación 6**. Entre pacientes hospitzalizados con COVID-19, el panel de directrices IDSA recomienda tocilizumab solo en contexto de un ensayo clínico. (Brecha de conocimiento).

- **Recomendación 7.** Entre pacientes hospitalizados con COVID-19, el panel de directrices IDSA recomienda plasma convaleciente COVID-19 en contexto de un ensayo clínico. (Brecha de conocimiento)

Cunningham et al. Critical Care (2020) 24:91
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Critical Care

EDITORIAL Open Access

Treatment of COVID-19: old tricks for new challenges

Anne Catherine Cunningham[1*], Hui Poh Goh[1] and David Koh[1,2]

- Señalan que el tratamiento con inmunoglobulina humana se ha asociado con un riesgo significativamente mayor de eventos trombóticos en el mismo día (0.04 a 14.9%).

- Falta de conocimiento sobre biología básica del SARS-CoV-2, incluida la variabilidad y mutación del virus, el **plasma recolectado localmente puede reflejar mejor el virus circulante en la población y podría ser una opción de tratamiento válida**.

- Algunos de los tratamientos pueden haberse probado por desesperación, y entre estos, algunos muestran una promesa inicial.

- Es demasiado pronto para ver los resultados publicados de ensayos clínicos rigurosos.

"La respuesta agresiva del presidente Trump y las acciones audaces para mantener a los estadounidenses a salvo de COVID-19 nos dieron un tiempo preciso para avanzar en la terapéutica y otras herramientas necesarias"

Si bien no existen terapias o medicamentos aprobados por la FDA para tratar, curar o prevenir COVID-19, existen varios tratamientos aprobados por la FDA que pueden ayudar a aliviar los síntomas desde una perspectiva de atención de apoyo.

*Sin embargo, 03.04.20 emitió una autorización de uso de emergencia para distribuir los dos medicamentos de la reserva nacional para el tratamiento de pacientes hospitalizados con COVID-19.

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A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19

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- Cloroquina bloquea la I por virus al aumentar la presión endosómica interfiriendo con la glucosilación del receptor celular del SARS.
- **Seis artículos** (una carta narrativa, un estudio in vitro, un editorial, un consenso de expertos, dos documentos de pautas nacionales) y 23 ensayos clínicos en curso en China.
- Existe ***evidencia preclínica de efectividad y evidencia de seguridad del uso clínico a largo plazo para otros indicaciones para justificar la investigación clínica sobre cloroquina en pacientes con COVID-19*.**
- Se necesitan con urgencia datos de seguridad y datos de ensayos clínicos de alta calidad.

AGENTS UNDER INVESTIGATION FOR SARS-CoV-2

This table lists agents that are being investigated and/or theoretically considered for the management of SARS-CoV-2-infected patients. At this time no recommendation can be made for any of these agents. In general, they should be avoided without additional supporting evidence.

Agent	Comments
Anakinra	Interleukin-1 (IL-1) receptor antagonist hypothesized to quell cytokine storming. No data for use as adjunctive therapy for COVID-19 currently. No clinical trials are enrolling in China or the United States exploring this agent.
Arbidol (Umifenovir)	Antiviral used in Russia and China for influenza, being studied in Chinese clinical trials (200mg by mouth three times daily for no more than 10 days) for COVID-19 claiming potent *in vitro* activity. No clinical data exist currently; not available in the United States.
Baricitinib	A Janus kinase family (JAK) enzyme inhibitor, suggested as a COVID-19 treatment from artificial intelligence.[58] No clinical data exist.
Bevacizumab	Recombinant humanized monoclonal antibody which prevents vascular endothelial growth factor (VEGF) association with endothelial receptors Flt-1 and KDR approved for multiple cancers in the United States. Is on critical, national shortage. Being evaluated in a clinical trial in China for COVID-19 (NCT04275414), no data exist at this time to support use.
Brilacidin	A host defense peptide mimetic in clinical development by Innovation Pharmaceuticals. The company recently announced they will begin testing the molecule against SARS-CoV-2 beginning the week of March 16, 2020.
Convalescent plasma	Convalescent plasma from patients who have recovered from viral infections has been used previously for SARS-CoV-1, Middle East respiratory syndrome, Ebola, and H1N1 influenza with reported success.[59] The safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients has not been established and no protocols exist currently in the United States. Protocols are reportedly being developed at The Johns Hopkins University Hospital.
Darunavir/cobicistat	HIV-1 protease inhibitor currently being evaluated in a clinical trial (NCT04252274), but no *in vitro* or human data exist to support use at this time.
Disulfiram	Thiuram derivative which blocks alcohol oxidation. Demonstrated ability to competitively inhibit the papain-like proteases of SARS; however, no clinical data exist.[60] No *in vitro* or clinical data exist for COVID-19.
Eculizumab	Humanized, monoclonal IgG antibody that binds to complement protein C5 and prevents formation of membrane attack complex (MAC). Being evaluated in a clinical trial (NCT04288713) for COVID-19 to quell immune response, no data exist at this time to support use.
Favipiravir	RNA-dependent RNA polymerase inhibitor with broad-spectrum antiviral activity, however, demonstrated high EC_{50} (decreased potency) against SARS-CoV-2 but was effective in protecting mice against Ebola virus despite similarly high EC_{50} values.[3] Currently being evaluated in Clinical Trial NCT04273763 for patients with COVID-19. This agent is not FDA approved or available in the United States.
Galidesivir (BCX4430)	Nucleoside RNA polymerase inhibitor with reported wide spectrum of antiviral activity, currently in pipeline of Biocryst Pharma and previously evaluated for Ebola and other hemorrhagic fever virus infections.
Griffithsin	Algae-derived lectin and potent HIV entry inhibitor agent which demonstrated *in vitro* activity against SARS-COV-1.[61]
IVIG	IVIG remains on critical national shortage in the United States. The benefit in patients with COVID-19 is unclear.
Nelfinavir	Nelfinavir, an HIV-1 protease inhibitor, might be active against SARS-CoV-2 based on a pre-print publication that utilized homology modeling.[62] No clinical data exist.
Niclosamide	Anthelminthic drug with *in vitro* efficacy against SARS-COV-1, however, low absorption and oral bioavailability resulting in a wide range of serum concentrations in healthy volunteers following a single dose may limit utility as antiviral treatment.[63]
REGN3048	Human monoclonal antibody discovered by Regeneron that reportedly binds to the S protein of MERS-CoV. Currently in phase 1 trial in healthy volunteers (NCT03301090). The company reportedly announced recruitment for phase 2 and 3 trials for SARS-CoV-2, however, these are not registered on ClinicalTrials.gov.
Sarilumab	IL-6 receptor antagonist FDA-approved for rheumatoid arthritis. Recently announced a US-based trial will begin enrolling at medical centers in New York for patients with severe COVID-19 disease.
Sofosbuvir	Antiviral used to treat hepatitis C, *in vitro* activity against SARS-COV-1, no clinical data exist.[64]
TZLS-501	A novel, fully human anti-interleukin-6 receptor (anti-IL6R) by Tiziana Life Sciences. The company recently announced they are moving forward with clinical development for patient use in patients with COVID-19 and excessive IL-6 production.
Vitamin C	There is an ongoing clinical trial of 12g IV BID Vitamin C in China for treatment of COVID-19 (NCT04264533). Use of this agent is not recommended at this time.
XueBiJing	Chinese herbal medicine extract infusion formulation given at 100mL IV twice daily, suggested as a "may consider" treatment for severe and critical cases in the National Health Commission of the People's Republic of China: the COVID-19 Diagnosis and Treatment Guide, 7th Edition. This previously demonstrated improved mortality in patients with severe community acquired pneumonia in China.[65]

pharmaceuticals

MDPI

Opinion

COVID-19: A Brief Overview of the Discovery Clinical Trial

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Abstract: The outbreak of COVID-19 is leading to a tremendous search for curative treatments. The urgency of the situation favors a repurposing of active drugs but not only antivirals. This short communication focuses on four treatments recommended by WHO and included in the first clinical trial of the European Discovery project.

Keywords: chloroquine; COVID-19; hydroxychloroquine; lopinavir/ritonavir; remdesivir; repurposing; SARS-CoV-2

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Table 1. Most cited monoclonal antibodies, antiviral drugs, and other small molecules in COVID-19 clinical trials.

Monoclonal antibodies				
Name	**Number of trials as of April 8 (as of March 28)**	**FDA-Approved**	**Brand name**	**Manufacturer(s)**
Tocilizumab	15 (6)	01/08/2010	Actemra	Roche
Sarilumab	5 (4)	05/22/2017	Kevzara	Sanofi and Regeneron
Bevacizumab	2 (2)	02/26/2004	Avastin	Roche
Antiviral drugs				
Name	**Number of trials**	**FDA-Approved**	**Brand name**	**Manufacturer(s)**
Lopinavir + Ritonavir	22 (14)	09/15/2000	Kaletra, Aluvia	AbbVie
Umifenovir	10 (9)	investigational	Arbidol, Abidol	Available in China and Russia
Remdesivir	9 (9)	investigational		Gilead Sciences
Oseltamivir	6 (4)	10/27/1999	Tamiflu	Gilead Sciences, Roche
ASC09 or TMC-310911	5 (3)	investigational		Janssen
Favipiravir	4 (2)	Approved in Japan (2014)	Avigan	Toyama Chem
Other small molecules				
Name	**Number of trials**	**FDA-Approved**	**Brand name**	**Manufacturer(s)**
Hydroxychloroquine	58 (19)	04/18/1955	Plaquenil	Sanofi
Chloroquine	23 (12)	04/18/1955	Aralen	Sanofi
Methylprednisolone	6 (5)	10/24/1957	Depo-Medrol, Solu-Medrol	several
Losartan	5 (2)	04/14/1995	Act Losartan Cozaar	Actavis Pharma several
Colchicine	4 (2)	07/27/1961	Colchicine	several
Thalidomide	2 (2)	07/16/1998*	Thalidomid *	Celgene
Baricitinib	2 (2)	05/31/2018	Olumiant	Eli Lilly & Co

* The product has been reintroduced in the market after it was withdrawn in 1961 due to its teratogenic effects (scandal of the Softenon babies).

Vaccine Platforms, Their Attributes, and the Status of Vaccine Candidates.*

Technology	Attributes				Candidates in Preclinical Development	Candidates in Phase 1
	Single Dose	Licensed Platform	Speed	Current Scale		
DNA	No	No	Fast	Medium	Inovio Pharmaceuticals Takis/Applied DNA Sciences/Evvivax Zydus Cadila	
Inactivated	No	Yes	Medium	Medium to high	Sinovac	
Live attenuated	Yes	Yes	Slow	High	Codagenix/Serum Institute of India	
Nonreplicating vector	Yes	No	Medium	High	GeoVax/BravoVax Janssen Pharmaceutical Companies University of Oxford Altimmune Greffex Vaxart ExpreS2ion	CanSino Biologics (ChiCTR20000 30906)
Protein subunit	No	Yes	Medium to fast	High	WRAIR/U.S. Army Medical Research Institute of Infectious Diseases Clover Biopharmaceuticals Inc/GSK Vaxil Bio AJ Vaccines Genrex/EpiVax/University of Georgia Sanofi Pasteur Novavax Heat Biologics/University of Miami University of Queensland/GSK/ Baylor College of Medicine iBio/CC-Pharming	
Replicating viral vector	Yes	Yes	Medium	High	Zydus Cadila Institut Pasteur/Themis Tonix Pharma/Southern Research	
RNA	No	No	Fast	Low to medium	Fudan University/Shanghai JiaoTong University/RNACure Biopharma China CDC/Tongji University/Stermina Arcturus/Duke-NUS Imperial College London Curevac BioNTech/Pfizer	Moderna/NIAID (NCT04283461)
Uncertain					University of Pittsburgh University of Saskatchewan ImmunoPrecise MIGAL Galilee Research Institute Doherty Institute Tulane University	

* Attributes refer to general attributes of the platform, and assessments are not intended as inferences about a particular candidate. NIAID denotes National Institute of Allergy and Infectious Diseases, and WRAIR Walter Reed Army Institute of Research.

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Developing Covid-19 Vaccines at Pandemic Speed

Nicole Lurie, M.D., M.S.P.H., Melanie Saville, M.D., Richard Hatchett, M.D., and Jane Halton, A.O., P.S.M.

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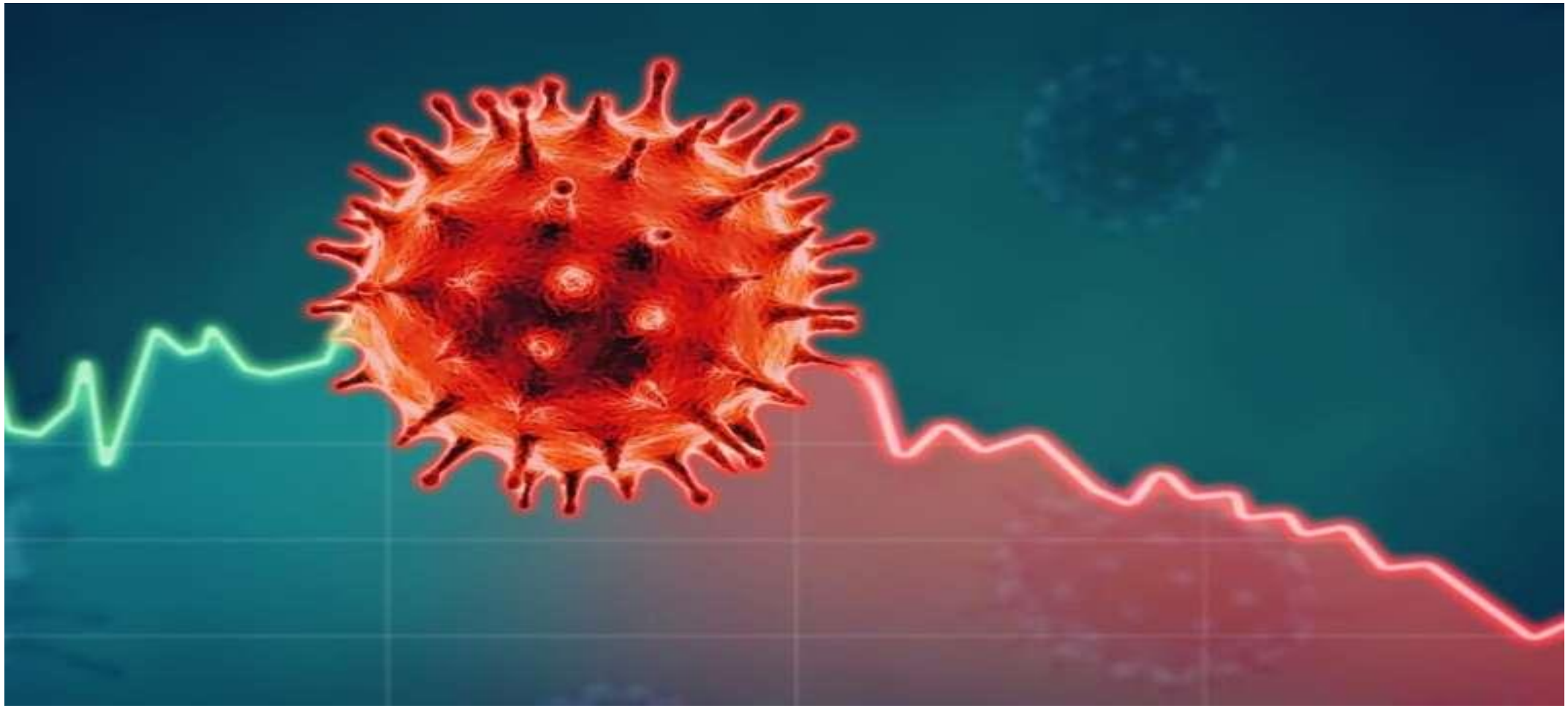

¡Gracias por su atención!