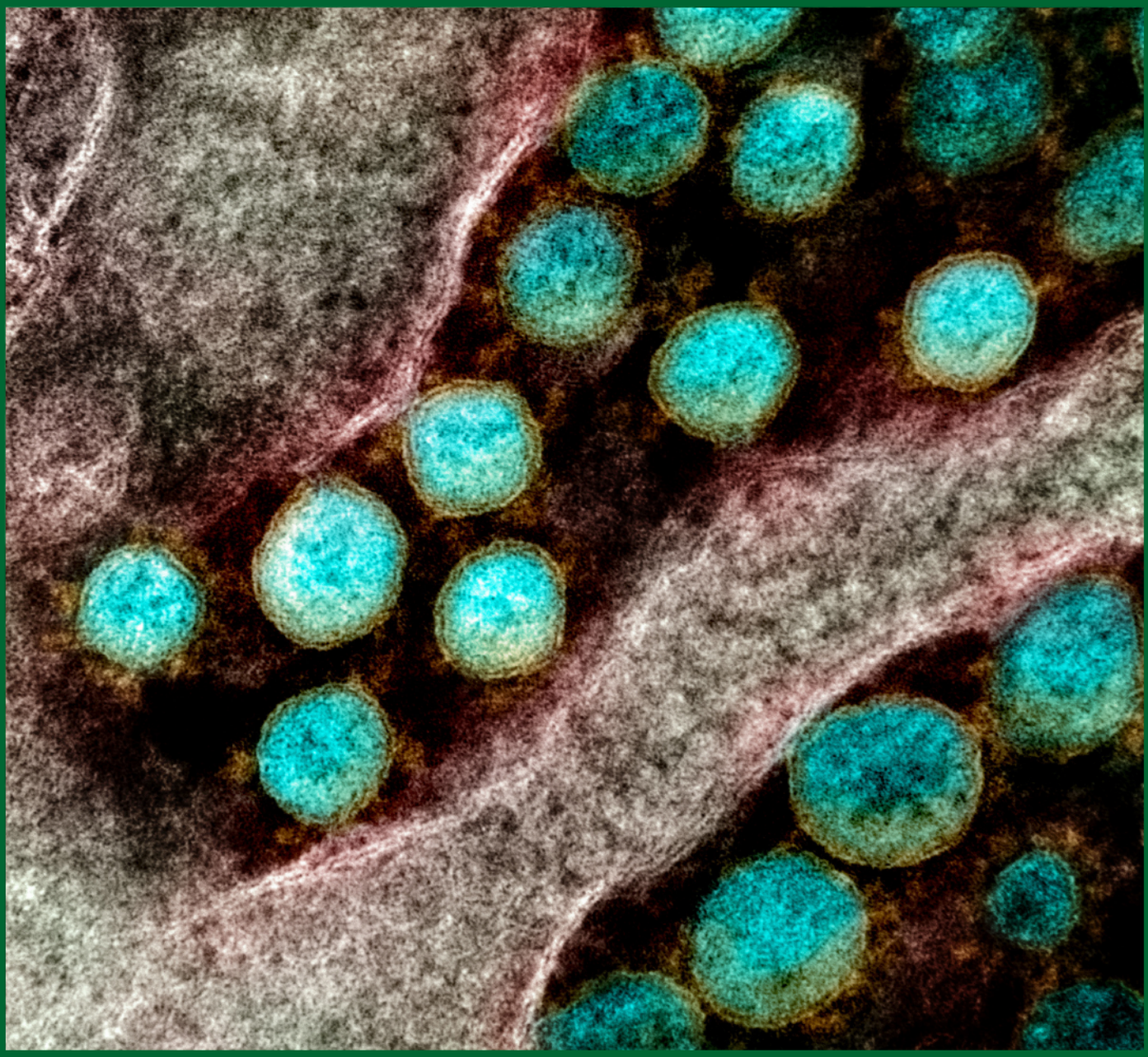
COVID-19
Rush Journal Club- Treatment



NOVEL CORONAVIRUS SARS-COV-2. Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID Available at: https://www.flickr.com/photos/niaid/49597768397/in/album-72157712914621487/. Accessed April 19, 2020.

This document is a collection of efforts from students of Rush University. It provides brief reviews of research articles regarding COVID-19. We hope that this will be helpful to clinicians, students, community leaders, and the general public. This document, however, does not act as a replacement of the original source documents. Please use the DOI on each page to read more.

Student Editors

Alice Burgess, MS3
Joseph Dodson, MS2
Audrey Sung, MS2
John Levinson, MS3
Ayesan Rewane, MSCR

Student Editors in Chief

Joseph deBettencourt, MS4
Lindsay Friedman, MS4
Leah Greenfield, MS3
Danesha Lewis, PhD candidate
Morgan Sturgis, MS3
Travis Tran, MS3
Ashley Wehrheim, MS3
Kaitlyn Wehrheim, MS3
Bijan Zarrabi, MS3

Faculty Editors and Mentors

Frank Cockerill, MD - ***Adjunct Professor of Medicine***
Mete Altintas, PhD - ***Director, Translational and Preclinical Studies***
Rachel Miller, PhD - ***Assistant Professor of Internal Medicine***
Michael Bradaric, PhD - ***Director of Pharmacology, Rush Medical College***
Brinda Bradaric, PhD - ***Assistant Professor, Dept of Health Sciences***
Jitesh Pratap, PhD - ***Assistant Professor, Dept of Cell and Molecular Medicine***
Steve Mangos, PhD - ***Director, Internal Medicine Drug Discovery and Imaging Core***

Graphic design

Sam Auger, MD
Beth Hall, MD
Joseph deBettencourt, MS4

Is there a study you'd like us to review? Do you have questions or feedback?
Please email: Joseph_b_deBettencourt@rush.edu

Reviews are provided by students at Rush University and edited by Rush faculty. Level of evidence in each study, if applicable, was assessed using the Oxford guidelines as presented below. More information can be found at http://www.cebm.net/2016/05/ocebm-levels-of-evidence/

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

Table of Contents: Treatment (1/6)
(Divided by Therapy)

Table of Contents:Treatment (2/6)

Section	Manuscript	Reviewer (Date Posted)
Treatment-Hydroxychloroquine	Chen Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758, 2020.	Joseph B deBettencourt (4/23)
	Ferner, Robin E., and Jeffrey K. Aronson. "Chloroquine and hydroxychloroquine in covid-19." (2020).	Amanda Narkis (5/5)
	Borba M, et. al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. JAMA Netw Open. 2020 Apr 24;3(4):e208857. doi: 10.1001/jamanetworkopen.2020.8857.	Joseph B deBettencourt (4/30)
	Chen Jun LD. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ Med Sci. 2020;49(1):0-0.	Joseph B deBettencourt (4/27)
	Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 2020. doi:10.1056/NEJMoa2012410	Kavya Timmireddy (5/23)
	Mehra MR et al., Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet, Published online May 22, 2020; https://doi.org/10.1016/S0140-6736(20)31180-6	Joseph B deBettencourt (5/30)
	Bessière F et al., Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit. JAMA Cardiol. Published online May 01, 2020. doi:10.1001/jamacardio.2020.1787	Steven Heidt (6/3)
	Mercuro NJ et al., Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. Published online May 01, 2020. doi:10.1001/jamacardio.2020.1834	Steven Heidt (6/4)
	Rosenberg ES et al., Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. Published online May 11, 2020. doi:10.1001/jama.2020.8630	Steven Heidt & Hannah Raff (6/4)
	David R. Boulware et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. The New England Journal of Medicine 2020 [Published online ahead of print, 2020 June 3]	Dallas Kramer (6/26)
	Garcia-Cremades, M. et al. "Optimizing Hydroxychloroquine Dosing for Patients With COVID-19: An Integrative Modeling Approach for Effective Drug Repurposing" Clin Pharmacol Ther. 2020;108(2):253-263. doi:10.1002/cpt.1856	Abigail Bawden (8/12)
	Mahévas M. et al. "Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data" BMJ. 2020;369:m1844. doi:10.1136/bmj.m1844	Carter Do (9/24)
	Self WH et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients with COVID-19: A Randomized Clinical Trial. JAMA . Published online November 9,	Alex Hodakowski (12/1)

Table of Contents: Treatment (3/6)

Table of Contents: Treatment (4/6)

Table of Contents: Treatment (5/6)

Table of Contents: Treatment (6/6)

Reviews from 2022

Section	Manuscript	Reviewer (Date Posted)
Treatment	Mahase, E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. Published online November 8, 2021. DOI: 10.1136/bmj.n2713	Robert Roth (2/23/22)
	Jayk Bernal, Angélica, et al. "Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients." New England Journal of Medicine 386.6 (2022): 509-520. DOI: https://doi.org/10.1056/NEJMoa2116044	Natalie Maltby (2/23/22)
	Gottlieb, Robert L., et al. "Early remdesivir to prevent progression to severe covid-19 in outpatients." New England Journal of Medicine (2021). DOI: 10.1056/NEJMoa2116846	Melissa Porterhouse (2/23/22)

Clinical and microbiological effects of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study

Philippe Gautret et al.

Travel Medicine and Infectious Disease
April 17, 2020
DOI: https://doi.org/10.1016/j.tmaid.2020.101663

Purpose	To determine if a hydroxychloroquine and azithromycin combination provides an effective treatment for COVID-19 patients and can decrease virus carriage.
Study design	Non-controlled, non-comparative observational study (n=80)
Level of evidence	Level 5
Methods	An 80-person inpatient cohort with mild COVID-19 infection were given hydroxychloroquine and azithromycin over a period of 3 or more days. Measurements included clinical outcome, contagiousness via PCR and culture, and length of stay in infectious disease unit (IDU).
Findings	**All cases in this 80-patient cohort showed improvement in outcome measures following administration of combination of hydroxychloroquine and azithromycin except for two patients-** one of which arrived to the hospital in an advanced form, and another patient who was still in intensive care at the time of writing. There was a drop in nasopharyngeal viral load with 83% testing negative on Day 7 and 93% on Day 8. Culture positivity began to decline on Day 2 with viral cultures being completely negative in 97.5% of patients on Day 5. Patients were discharged from the IDU with mean length of stay being 5 days.
Clinical Implications	Combination of hydroxychloroquine and azithromycin shows promise in the treatment for SARS-CoV-2. It is important to intervene in the early stages of disease with a treatment regimen to prevent progression to the irreversible severe respiratory complications.
Limitations	This was an uncontrolled study with a small sample size. The participants had a relatively mild clinical presentation, so the efficacy of this combination was not determined in more severe cases. There was also no analytic approach performed to look for potential confounding variables. Criteria for discharge was altered over the course of the study going from two successive negative nasopharyngeal samples from PCR assay.

Management of COVID-19 Respiratory Distress

John J. Marini et al.

JAMA

April 24, 2020

DOI: 10.1001/jama.2020.6825

Purpose	The purpose of this article is to summarize the current recommendations for ventilation support in COVID-19 patients with ARDS
Study design	Literature Review
Level of evidence	5
Methods	This paper reviewed current literature on the management of COVID-19 ventilation support. The authors describe two patient phenotypes: **Type L** and **Type H**. -Typle L: Scattered ground-glass infiltrates, higher compliance (>50 mL/cm H2O), not PEEP responsive, less dyspnea -Type H: Extensive infiltrates of atelectasis and edema, lower compliance, PEEP responsive, overtly dyspneic
Findings	**-In the early stages of CARDS (COVID-19 with ARDS), the objective should be adequate gas exchange and avoidance of patient self-induced lung injury (P-SILI) from powerful respiratory effort causing lung and vascular stress.** Options include supplemental O2, CPAP, noninvasive ventilation (NIV), high flow nasal cannula (HFNC), prone positioning and target nonvigorous breathing. Early intubation, effective sedation, and/or paralysis may interrupt this cycle. **For Type L patients after intubation, the goal is to minimize pulmonary stress, optimize O2, and avoid VILI (ventilator-induced lung injury) vortex. Use lower PEEP (<10 cm H2O), use more liberal tidal volume (7-9 mL/kg) as needed, and consider prone positioning.** If lung edema increases in the Type L patient (either because of the disease itself and/or P-SILI), Type H phenotype progressively develops. **The goal in Type H patients after intubation is to reduce and evenly distribute lung and vascular stresses, optimize O2, and avoid VILI.** Use higher PEEP (<15 cm H2O), lower tidal volume (5-7 mL/kg), reduce O2 demand and implement prone positioning. Despite the disease type, weaning should be undertaken cautiously. **The goal for the weaning phase is to avoid reversion to previously worsened pulmonary state by causing VILI and worsening edema.**
Clinical Implications	The recommendations described above represent the most current ventilation recommendations in COVID-19 patients with ARDS and could improve outcomes.
Limitations	This paper attempts to categorize COVID patients with respiratory distress into two groups; however, not all patients may conveniently fall into each of these two groups but rather fall along a spectrum of respiratory compromise.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret et al.

Int J Antimicrob Agents
March 20, 2020
DOI: 10.1016/j.ijantimicag.2020.105949

Purpose	This clinical trial aims to assess the effect of hydroxychloroquine +/- azithromycin on respiratory viral loads in SARS-CoV-2-infected patients compared to a control group.
Study design	Open label, non-randomized clinical trial (n=36)
Level of evidence	3
Methods	36 of 42 patients who met inclusion criteria (age >12 and PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission regardless of clinical status) were seen at baseline for enrollment, initial data collection and treatment at day 0, and again for daily follow-up for 14 days. Patients in the study group received oral hydroxychloroquine sulfate 200 mg TID for 10 days. Among hydroxychloroquine-treated patients (n=20), six received azithromycin (500 mg on day 1 followed by 250 mg per day for the next 4 days) to prevent bacterial super-infection. The primary endpoint was virological clearance at day-6 post-inclusion.
Findings	The proportion of patients that had negative PCR results in nasopharyngeal samples was significantly different between treated patients and controls at days 3-4-5 and 6 post-inclusion. **At day 6, 70% of hydroxychloroquine-treated patients were virologicaly cured comparing with 12.5% in the control group (P=0.001). Similarly, the addition of azithromycin led to a statistically significant benefit (100% patients were virologically cured) when compared to the hydroxychloroquine-only treatment group (57.1%, P<0.001) at days 3-4-5 and 6 post-inclusion.** Overall, it is shown that hydroxychloroquine is efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days. **These preliminary results also suggest a synergistic effect of the combination of hydroxychloroquine and azithromycin; however, it is important to note that only six patients were given azithromycin in addition to hydroxychloroquine.**
Clinical Implications	-Hydroxychloroquine alone for the treatment of COVID-19 may be useful in reducing viral loads, but larger randomized trials should be performed -The addition of azithromycin to hydroxychloroquine to treat COVID-19 patients may provide an additional benefit in reducing viral loads but larger randomized trials are required.
Limitations	There were limitations of this study including a small sample size, limited long-term outcome follow-up, and a dropout of six patients from the study. This clinical trial was also not randomized, which could introduce bias into the study.

Pharmacologic treatments for coronavirus disease 2019 (COVID-19)

James M. Sanders
JAMA Network
April 13, 2020
DOI: 10.1001/jama.2020.6019

Purpose	To summarize current evidence regarding major proposed, repurposed or experimental treatments for COVID-19 and to provide a summary of current clinical experience and treatment guidance for COVID-19.
Study design	Literature Review
Level of evidence	N/A
Methods	A literature review was performed using PubMed to identify relevant English-language articles published through March 25th, 2020. Search terms included 'coronavirus', 'severe acute respiratory syndrome coronavirus 2', '2019-nCoV', 'SARS-CoV-2', 'SARS-CoV', 'MERS-CoV', and 'COVID-19' in combination with treatment and pharmacology. Case reports, case series, and review articles were included due to the lack of randomized controlled trials. Currently active clinical trials were also included using the disease search term 'coronavirus infection' on ClinicalTrials.gov and the index of studies of novel coronavirus pneumonia in the Chinese Clinical Trial Registry.
Findings	Treatment recommendations based on clinical treatment experience, descriptive reports, and case series should be interpreted with caution due to lack of clinical trials. There are currently no medical therapies that have been definitively shown to improve outcomes in patients with COVID-19. Several drugs have demonstrated in vitro activity against SARS-CoV-2 virus including hydroxychloroquine, chloroquine, darunavir, ribavirin, baricitinib, imatinib, dasatinib, cyclosporine, nitazoxanide, remdesivir, and favipiravir.
Clinical Implications	There is currently no effective therapy for COVID-19, and therefore there is an urgent need for randomized clinical trials to test the effectiveness of proposed therapies.
Limitations	To date, published data is limited to observational studies and small clinical trials with less than 250 patients. This review focused primarily on adult patients and lacks data on pediatric population infected with SARS-CoV-2. The amount of published literature is rapidly growing, and recommendations are constantly changing.

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Manli Wang et al.

Cell Research, Nature Publishing Group
February 4, 2020
DOI: https://doi.org/10.1038/s41422-020-0282-0

Purpose	To determine which drug is the most effective in treating the 2019-nCov virus.
Study design	Letter to the editor – in vitro lab study
Level of evidence	Level 5
Methods	Seven drugs, Ribavirin, Penciclovir, Nitazoxanide, Nafamostat, Chloroquine, Remdesivir and Favipiravir, were evaluated to determine their efficacy against 2019-nCov in vitro. Vero E6 cells were infected with the COVID virus at a multiplicity of infection of 0.05 with various degrees of concentration of the trial drugs for 48 hours. For the control group, DMSO was used instead. The primary endpoint was to determine the cytotoxicity of these drugs using CCK-8 assays, as well as the viral yield which was determined by quantifying the superna-tant using RT-PCR. This was later confirmed by using immunofluorescence to visualize the virus nucleoprotein expression. The results are listed below showcasing the half-maximal effective concentration used (EC50 in micromoles) and the selectivity index (SI) achieved during testing.
Findings	- Ribavirin (EC50 = 109.50, SI > 3.65), Penciclovir (EC50 = 95.96, SI > 4.17) and Favipiravir (EC50 = 61.88, SI > 6.46), the 3 nucleoside analogs, required high levels of concentration to reduce the viral infection. - Nafamostat (EC50 = 22.50, SI > 4.44) which prevents membrane fusion, was inhibitive against the Covid virus. - Nitazoxanide, (EC50 = 2.12, SI > 16.76) an antiprotozoal agent, was able to inhibit 2019 nCoV at low micro molar concentration. - **Remdesevir (EC50 = 0.77, SI > 129.87) and Cloroquine (EC50 = 1.13, SI > 88.50) were able to block the virus infection at low micro molar concentration and demonstrated high selectivity index.**
Clinical Implications	**Further in vivo studies are required to evaluate the true efficacy of these drugs, however, Remdesevir and Cloroquine appear promising**. Their low micromolar concentration and high selectivity index to block virus infection sets them apart from other drugs.
Limitations	The study was conducted in vitro using Vero E6 cells which are derived from the African green monkey and hence may not be translatable to human trials. As a letter to the editor, it is not clear if this study has been peer-reviewed.

Some Drugs for COVID-19

The Medical Letter on Drugs and Therapeutics
April 6, 2020
Retrieved from: secure.medicalletter.org/w1595a

Purpose	To review current data regarding the efficacy or lack thereof for the use of repurposed drugs in the treatment of COVID-19 in addition to the impact of commonly used daily medications on COVID-19 disease progression.
Study design	Review
Level of evidence	Level 3
Methods	The researchers summarized the clinical evidence related to repurposing of drugs for the treatment of COVID-19. They chose agents that have been widely reported on as potential treatments.
Findings	-**ACE inhibitors and ARBS**: There is no clinical evidence to suggest these agents increase or decrease the severity of COVID-19. Patients who take these drugs and contract COVID-19 should continue their medications as prescribed. -**NSAIDS**: There is no clinical evidence that NSAIDs increase or decrease the severity of COVID-19, however continued fever suppression with NSAIDs can possibly decrease the immune system and increase the duration of viral shedding. Patients who are taking NSAIDs for other indications should not stop taking them. -**Lopinavir/ritonavir (Kaletra)**: When compared to standard care in clinical trial of severely diseased COVID-19 patients, Kaletra was no more effective than the standard of care alone and Society of Critical Care Medicine does not recommend its use in critically ill patients. -**Hydroxychloroquine with Azithromycin**: Open label study in hospitalized COVID-19 patients in France suggests enhanced viral load reduction compared to treatment of hydroxychloroquine alone. These drugs can prolong the QT interval – clinical trials evaluating safety and efficacy are in progress. -**IL-6 inhibitors (ie: tocilizumab, sarilumab)**: Insufficient data, clinical trials are in progress to see if these agents and reduce cytokine induced lung damage in patients with severe disease. -**Convalescent sera**: Passive antibody therapy using serum of recovered patients was both safe and reduced viral load in Chinese patients who were treated early in the course of their infection with COVID-19. There are ongoing studies to examine this effect in critically ill patients.
Clinical Implications	The data summarized in this review helps guide clinicians in the treatment of COVID-19 and helps delineate between evidence-based practice and media publicization of available agents. The authors also advise that until clinical trials clearly establish the safety and efficacy of any drug used for COVID-19 treatment, current standard of practice is supportive treatment and management of COVID-19 complications.
Limitations	This review was unable to adequately synthesize efficacy of the drugs highlighted in this review due to lack of high quality RCTs. Also, little data describing the effect of the drugs in patients with different disease severity; the review findings only commented on limited ranges of disease severity.

Evaluation of Antiviral Therapies for Coronavirus Disease 2019 (COVID-19) Pneumonia in Shanghai, China

Xiudong Shi et al.

J Med Virol.
April 16, 2020
DOI: https://doi.org/10.1002/jmv.25893

Purpose	Evaluate the therapeutic effect of antiviral drugs on COVID-19 pneumonia.
Study design	Single-center, retrospective review (n=184)
Level of evidence	4
Methods	A total of 184 patients seen at the Shanghai Public Health Clinical Center that tested positive for COVID-19 were divided into 7 different groups according to their treatment, which was administered over a 5-day period. The groups were as follows: (1) symptomatic treatment only (2) Arbidol, (3) Lopinavir/Ritonavir, (4) Arbidol and Lopinavir/Ritonavir, (5) Interferon, (6) Interferon and Lopinavir/Ritonavir, and (7) Interferon and Darunavir. Chest CT scans at admission and at day 1 or 2 after treatment were reviewed and the Quantitative Evaluation System of CT for Pneumonia was utilized to calculate pulmonary inflammation volume (pneumonia volume).
Findings	**The average pneumonia volume in all groups increased, except in the Interferon and Lopinavir/Ritonavir combination group. However, differences between groups** (i.e. Lopinavir/Ritonavir treatment alone or in combination with Interferon-α2β or Arbidol) **were not statistically significant**. While there was also no significant difference in pneumonia resolution among the groups, the highest proportion of pneumonia resolution was in the Interferon and Lopinavir/Ritonavir combination group, followed by the Interferon and Darunavir combination group.
Clinical Implications	This study did not find that the addition of antiviral drugs in therapeutic regimens reduced the volume of lung affected by pneumonia in COVID-19 patients, nor did it significantly shorten their hospital stay compared to symptomatic treatment alone. The treatment of COVID-19 pneumonia remains challenging, as there are no specific and effective drugs available.
Limitations	This study set the treatment period of 5 days, which may not have been long enough to see results. Additionally, results of quantitative detection of viral load were not reported as part of this study and CT follow up findings were not included.

Current evidence for directed and supportive investigational therapies against COVID-19

R van Rensburg et al.

African Journal of Thoracic and Critical Care Medicine
April 30, 2020
DOI: https://doi.org/10.7196/AJTCCM.2020.v26i2.072

Purpose	To investigate types of therapies currently being studied for treatment of COVID-19.
Study design	Systematic Review
Level of evidence	Level 3
Methods	Authors used current literature published in peer-reviewed scientific journals to determine current evidence regarding several types of therapeutic interventions for the treatment of COVID-19.
Findings	Two groups of therapies were evaluated, directed therapies and supported therapies. Directed therapies included hydroxychloroquine and chloroquine, lopinavir/ritonavir, remdesivir, and favipiravir. Hydroxychloroquine and chloroquine are immunomodulatory drugs that show in vitro activity against COVID-19, theorized to be due to increasing endosomal pH to inhibit COVID-19 spike protein cleavage, preventing entry. **Studies are showing conflicting evidence of hydroxychloroquine and chloroquine having no effect or being able to reduce viral shedding.** Lopinavir/ritonavir are protease inhibitors that have shown in vitro activity against SARS-CoV. **Case reports show successful management with lopinavir/ritonavir combination.** Remdesivir is a nucleotide analogue developed against the Ebola virus which shows in vitro activity against COVID-19. Supported therapies included tocilizumab and corticosteroids. Tocilizumab is a monoclonal antibody against the IL-6 receptor that is approved for treating cytokine release syndrome. Trials have shown patients improving following inadequate response to standard care. **Corticosteroid trials are inconclusive or showed potential to cause harm.**
Clinical Implications	There is a lack of in vivo and human studies to determine which therapy, if any, is effective in treating COVID-19. Studies for hydroxychloroquine, chloroquine, lopinavir/ritonavir, remdesivir, favipiravir, tocilizumab show promise based on in vitro studies, but there is significant lack of data to conclude what is effective in treating COVID-19. Studies typically started later in the disease course, after organ damage had potentially occurred.
Limitations	There are limited peer-reviewed publications out currently that can further knowledge of therapeutic studies. These studies also are started late in the disease course when it may be too late to prevent irreversible organ damage.

Triple Combination of Interferon beta-1b, Lopinavir–Ritonavir, and Ribavirin in the Treatment of Patients Admitted to Hospital with COVID-19: An Open-label, Randomised, Phase 2 Trial

Ivan Fan-Ngai Hung et al.

The Lancet

May 08, 2020

DOI: https://doi.org/10.1016/S0140-6736(20)31042-4

Purpose	To assess the efficacy and safety of a triple anti-viral therapy consisting of interferon beta-1b, lopinavir-ritonavir, and ribavirin for treatment of patients with COVID-19.
Study design	Multicenter prospective, open-label, randomized, phase 2 trial
Level of evidence	Level 2
Methods	Patients diagnosed with mild to moderate COVID-19 were randomly assigned (2:1) to a 14-day combination therapy consisting of lopinavir (400mg) and ritonavir (100mg) every 12 hours, ribavirin (400mg) every 12 hours, and three doses of 8 million IU of interferon beta-1b on alternate days (combination growth) or 14 days of lopinavir 400mg and ritonavir 100mg every 12 hours (control group). The primary endpoint was the time to RT-PCR negative nasopharyngeal swab for SARS-CoV-2. The secondary endpoint was time to resolution of symptoms defined as a national early warning score of 0 maintained for 24 hours, and length of hospital stay.
Findings	Patients receiving combination therapy demonstrated superior clinical improvement with shorter time to complete symptom resolution (4 days), significantly shorter time from initiation of treatment to negative nasopharyngeal swab (7 days), and shorter mean hospital stay (9 days) when compared to the control group (8, 12, and 14.5 days respectively). Treatment was also shown to be safe with minor and self-limited gastrointestinal adverse events of diarrhea and vomiting with no difference in rate between those receiving combination therapy and the control group. In addition, serum levels of the inflammatory cytokine interleukin 6 (IL-6) were significantly lower in patients treated with combination therapy on treatment days 2, 6, and 8.
Clinical Implications	**Early treatment with triple antiviral therapy was safe and superior to lopinavir-ritonavir in alleviating symptom**s and shortening the duration of viral shedding and hospitalization in patients with mild to moderate COVID-19. Triple antiviral therapy rapidly rendered viral load negative in all patients, thereby reducing infectiousness of the patient.
Limitations	The trial was open label without inclusion of a placebo group. Results were confounded by the subgroup omitting interferon beta-1b within the combination group and were dependent on time of symptom onset. The absence of critically ill patients does not allow for the generalization of findings to severe cases.

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Adarsh Bhimraj et al.

Clinical Infectious Diseases
April 17, 2020
DOI: https://doi.org/10.1093/cid/ciaa478

Purpose	To develop evidence-based rapid guidelines intended to support patients, clinicians, and other health-care professionals in their decision-making regarding treatment and management of patients with COVID-19.
Study design	Systematic Review
Level of evidence	Level 3
Methods	Infectious Diseases Society of America (IDSA) formed a multidisciplinary guideline panel of nine infectious disease clinicians, pharmacists, and methodologists with varied areas of expertise. Clinical questions in PICO format (Population, Intervention, Comparison, Outcomes) were developed and panel members prioritized questions with available evidence meeting minimum acceptable criteria (i.e., body of evidence reported on at least a case-series design, case reports excluded). A systematic review of the peer-reviewed and grey literature from Ovid Medline and Embase was then conducted. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess certainty of evidence and make recommendations. 435 viable references were identified, of which 13 informed the evidence base for the authors' recommendations.
Findings	The IDSA guideline panel recommends that treatment of COVID-19 infected patients with the following agents should be limited to the context of a clinical trial: hydroxychloroquine (HCQ), HCQ + azithromycin combination, lopinavir/ritonavir, tocilizumab, COVID-19 convalescent plasma transfusion, and corticosteroids (based on indirect findings from systematic review of SARS and MERS outbreaks). Of note, if a patient is receiving steroid therapy for another indication (e.g., asthma), the steroid should not be discontinued.
Clinical Implications	Given that the panel could not make a determination whether the benefits outweigh harms for HCQ, azithromycin, steroids, or IL-6 inhibitors, it would be ethical to enroll patients with COVID-19 in clinical trials, rather than use clinically unproven therapies. There are about 100 ongoing clinical trials on COVID-19 in the U.S. alone, which will allow us to understand more about the effects of these treatments and their potential therapeutic benefits within the coming months.
Limitations	Due to the urgency in producing, synthesizing, and disseminating data during the current pandemic, an increase in "fast-tracked" study publication has resulted in issues including circumvention of usual research steps (delay of IRB approval, inclusion of same patients in several studies), a limited peer-review process, and increased potential for publication bias (in the interest of showing promising data). The extent and impact of these considerations were acknowledged in the development of these IDSA guidelines.

Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19

Samia Arshad et al.

International Journal of Infectious Diseases
June 29, 2020
DOI: https://doi.org/10.1016/j.ijid.2020.06.099

Purpose	To evaluate the effectiveness of hydroxychloroquine therapy alone and in combination with azithromycin in treating hospitalized COVID-19 patients.
Study design	Multi-center Retrospective Observational Study (n=2541)
Level of evidence	Level 3
Methods	Retrospective analysis of 2,541 patients with laboratory confirmed SARS-CoV-2 infection from March 10-May 2, 2020 at 6 hospitals in the Henry Ford Health System in Southeast Michigan was completed. All treatments were protocol driven and uniform across hospitals. Hydroxychloroquine was administered as two 400 mg doses on day 1, followed by 200mg twice daily on days 2-5. Azithromycin was used as one 500mg dose on day 1, followed by 250mg once daily on days 2-5. Combination therapy was reserved for patients with severe COVID-19 and minimal cardiac risk factors. Clinical protocols also included adjunctive immunomodulatory therapy with corticosteroids and tocilizumab. Primary endpoint was in-patient hospital mortality.
Findings	The average age of patients was 64 years, 51% were male, 56% were African American, and the mean BMI was 31.7. The most common comorbidities were hypertension (65.4%), chronic lung disease (63.7%), chronic kidney disease (43.3%), and diabetes mellitus (37.6%). Overall mortality rate was 18.1%. Group mortality rates were 13.5% in the hydroxychloroquine alone group, 20.1% in the hydroxychloroquine and azithromycin group, 22.4% in the azithromycin alone group, and 26.4% in the group receiving neither drug, respectively. Primary causes of mortality were respiratory failure (88%), cardiopulmonary arrest and multi-organ failure (8%) and cardiac arrest (4%)(mean QTc interval from last ECG reading 471 ms). Compared to patients who took neither drug, treatment with hydroxychloroquine alone decreased mortality hazard ratio by 66% ($p<0.001$) whereas hydroxychloroquine plus azithromycin decreased mortality hazard ratio by 71% ($p<0.001$).
Clinical Implications	**Treatment with hydroxychloroquine alone and hydroxychloroquine plus azithromycin was associated with a significant reduction in mortality among hospitalized COVID-19 patients.** This therapy is most effective when applied prior to the hyperimmune response associated with COVID-19.
Limitations	This study was non-blinded and non-randomized, limiting its ability to evaluate the effectiveness of hydroxychloroquine therapy in treating hospitalized COVID-19 patients. In addition, **improved patient mortality may be due to corticosteroid treatment.** 78.9% of patients receiving hydroxychloroquine and 74.3% of patients receiving hydroxychloroquine plus azithromycin received adjunct corticosteroid therapy, compared to 35.7% of patients receiving neither therapy and 38.8% receiving only azithromycin. It is also possible that the different dosing used in this study relative to previous studies not showing a benefit of hydroxychloroquine made a difference in the outcome.

Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

Zhaowei Chen et al.

medRxiv

April 10, 2020

DOI: https://doi.org/10.1101/2020.03.22.20040758

Purpose	To investigate the efficacy of hydroxychloroquine in addition to standard treatment in patients hospitalized with confirmed COVID-19
Study design	Randomized double-blind study (n = 62 patients)
Level of evidence	Level 2
Methods	Patients were followed for 6 days. The treatment group received 400mg/day of oral hydroxychloroquine sulfate (HCQ) tablets on days 1-5 plus Standard Treatment (O2 therapy, antiviral agents, antibiotics, and immunoglobulin +/- corticosteroids). The control group was given Standard Treatment only.
Findings	Statistically significant differences were observed favoring the treatment group vs the control group for improvement in Chest CT findings (p=0476), days for resolution in fever (p=0.0008) and days for resolution of cough (p=0016). Only 2 of 31 patients in the treatment group developed side effects that were not "severe".
Clinical Implications	Although this study suggests that hyoxychloroquine treatment for patients with mild COVID-19 disease is beneficial, **auxiliary treatment modalities are unspecified and may have confounded the results, the patients enrolled were relatively young and the observation time was limited.**
Limitations	The results may not be applicable to hospitalized patients in the US due to the exclusion criteria. Patients with cardiac conduction/arrhythmias were excluded which could limit the use of this medication in hospital patients who often are sicker at baseline and with significant cardiac comorbidities. Similarly, patients with renal and liver dysfunction at baseline were excluded, limiting application. Patients were of relatively young age (44.7 yrs), all patients had "mild disease", the observation period was limited to 6 days and most significantly the standard therapy included confounding and unspecified treatments: antiviral agents, antibiotics and immunoglobulin +/- corticosteroids. This standard care is worrisome as we do no know which patients received which antiviral agent or antibiotics and which patients received immuglobulin and in those who received immunoglobulin which also received corticosteroids.

Chloroquine and hydroxychloroquine in COVID-19

Robin E Ferner et al.

BMJ
April 8, 2020
DOI: https://doi.org/10.1136/bmj.m1432

Purpose	To advise on the potential premature use and potential harm of chloroquine and hydroxychloroquine in COVID-19.
Study design	Editorial
Level of evidence	N/A
Methods	Authors report their opinions on how previous lab studies in combination with poor methods and reporting may show that the early use of 4-aminoquinolines, chloroquine and hydroxychloroquine may lead to potential harm.
Findings	In cell cultures and animal studies, the effects of 4-aminoquinolines on viruses from H5N1 to Zika have been variable. For example, in one study of chikungunya virus, chloroquine was active in laboratory studies but worsened the clinical course of infection in monkeys. The disparity between laboratory and clinical experiments may be due to the complex pharmokinetics of 4-aminoquinolines, making it hard to use the correct concentration in culture media to doses in humans. Many studies currently coming out about positive findings of hydroxychloroquine treatment of COVID-19 include poor methods as well as unreliable results. Although advocates have deemed hydroxychloroquine as safe and widely used, that cannot be guaranteed and can expose some patients to rare and potentially fatal reactions. There have been previous medications that have been withdrawn because of adverse reactions after showing clinical promise.
Clinical Implications	· **Many studies have shown that 4-aminoquinolines, such as hydroxychloroquine and chloroquine, are active against a range of viruses, but the translation to clinical use as treatment with multiple other viruses has not proven as useful.** · There is to be more success in COVID-19 treatment via prevention by a vaccine or treatment with drugs that target specific structures in the virus rather than using old drugs that may work in the laboratory, but lack data supporting clinical use. · There needs to be better, properly powered, randomized controlled trials of chloroquine or hydroxychloroquine in order to prove effectiveness. Until then, SARS-CoV-2 is "essentially untreatable" except for supportive measures.
Limitations	The editorial only referred to two studies of 4-aminoquinolines in COVID-19 treatment that had poor study designs, while also citing previous studies in a wide range of viruses, which are not directly compared to the pathogenesis of SARS-Cov-2.

Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

Mayla Gabriela Silva Borba et al.

JAMA Network
April 22, 2020
DOI: 10.1001/jamanetworkopen.2020.8857

Purpose	To assess the safety and efficacy of high and low-dose chloroquine (CQ) for patients with severe COVID-19
Study design	Parallel, double-masked, randomized, phase IIb clinical trial (n= 81)
Level of evidence	Level 2
Methods	Primary outcome was lethality by day 28, secondary outcomes were lethality on day 13, patient clinical status, lab examinations, electrocardiogram (ECG) on days 13 and 28, daily clinical status, duration of mechanical ventilation, supplemental O2 use, and time from treatment to death. Of 131 patients admitted to the hospital with acute respiratory distress syndrome (ARDS) older than 18 years of age, 81 were determined to be positive for COVID-19 by RT-PCR or have a high likelihood of having COVID-19 by epidemiologic data. 41 patients were placed on high dose CQ (600mg BID for 10 days) and 40 were placed on low dose CQ (450mg BID for one day then 450mg daily for 4 days; placebo tablets were used such that low dose patients took equal number of total tablets as high dose patients). The study hypothesized that lethality would be decreased by 50% in the high-dosage versus the low-dosage group.
Findings	**At day 13, lethality was 39.0% (16/41) in the high-dose group and 15.0% (6/40) in the low-dosage group, additionally 86.4% (19/22) of the deceased still had virologic confirmation of SARS-CoV-2 infection antemortem**. These findings showed the opposite of the study's hypothesis and the safety review board recommended the immediate interruption of the study. **This study shows no evidence of benefit or increased viral clearance with use of chloroquine in patients presenting with SARS-CoV-2. High-dose chloroquine was associated with increased mortality over low-dose chloroquine dosing and over historical mortality data of similar patients with SARS-CoV-2.**
Clinical Implications	This trial suggests use of high-dose CQ (12g) given concurrently with azithromycin and oseltamivir is not safe, showed no evidence of benefit, and should not be used to treat patients with severe COVID-19.
Limitations	The study was ended early due to concerns for increased lethality with high-dose regimen, leaving the study underpowered to detect efficacy of either dosages. It also only focuses on critically ill patients and results may not be generalizable to less severe disease. All patients received oseltamivir (for influenza) which is also known to increase the QTc interval. It is possible increased lethality of CQ may have resulted from synergistic cardiotoxic effects. No placebo group was used.

A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)

J Chen et al.

Journal of Zhejiang University (Medical Sciences)
March 6, 2020
DOI: 10.3785/j.issn.1008-9292.2020.03.03

Purpose	To study the efficacy and safety of hydroxychloroquine sulfate treatment in COVID-19
Study design	Single-center, randomized study (n = 30 patients)
Level of evidence	Level 2
Methods	The experimental group received hydroxychloroquine sulfate 400mg once a day for 5 days plus conventional treatment. The control received conventional treatment alone. Conventional treatment included bed rest, oxygen support, symptomatic care, antiviral medications (nebulized IFN-alpha, oral lopinavir/ritonavir), and antibiotics. The primary endpoint of the study was negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on day 7 after randomization or death within 2 weeks. Secondary endpoints were serious adverse effects or deterioration of patient's condition within 2 weeks.
Findings	By day seven, 86.7% (13/15) of the trial group and 93.3% (14/15) of the control group tested negative for SARS-CoV-2 via pharyngeal swab. At two weeks all patients tested negative, and were clinically improved.
Clinical Implications	**This study showed no improvement in clearance or change in mortality with the addition of hydroxychloroquine to the conventional treatment.** This study suggests that hydroxychloroquine is not effective as an adjuvant medication in addition to current standards of care.
Limitations	The study had a small sample size of only 30 patients. It excluded any patients with serious comorbidities. These exclusions make the results difficult to generalize to critically ill patients. The authors also noted that their study was underpowered to determine if HCQ was better or worse than standard care, by their estimates at least 784 subjects would be needed to appropriately power the study.

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris et al.

The New England Journal of Medicine
May 7, 2020
DOI: 10.1056/NEJMoa2012410

Purpose	To investigate the relationship between hydroxychloroquine (HCQ) use and respiratory failure using a composite endpoint of intubation and/or death as major predictors of respiratory failure.
Study design	Observational study (n=1376)
Level of evidence	Level 4
Methods	De-identified data (age, sex, ethnicity, insurance, initial vital signs, arterial partial pressure of O2 to the fraction of inspired oxygen ratio [PaO2/FIO2] at admission, BMI, initial lab tests, smoking status, past medical history, medication administration, HCQ exposure, and outcomes [discharge, death, intubation]) from time of admission to death or discharge (prior to April 25, 2020) of COVID-19 positive patients hospitalized for a minimum of 24 hours between March 7-April 8, 2020 at Columbia University Irving Medical Center (CUIMC) were extracted and analyzed. Treatment with HCQ was at provider discretion and consistent with current hospital guidelines (600 mg twice on day 1, followed by 400 mg daily for 4 additional days). Bivariate frequencies were calculated to evaluate associations between pre-admission variables. Cox proportional hazard regression models were run to analyze association between HCQ exposure and outcomes of death or intubation. Additional models were used to account for demographic, clinical, and laboratory variables. To reduce risk of confounding, propensity scores for receipt of HCQ were calculated and used in inverse probability weighted analysis for Kaplan-Meier curves and Cox models. Additional analyses were completed for patients admitted at least 48 hours.
Findings	1376 patients were followed for a median of 22.5 days, 811 (58.9%) received HCQ. Among patients recieving HCQ, administration began after 24 hours in 45.8% and after 48 hours in 85.9%. Patients receiving HCQ demonstrated lower PaO2:FIO2 at baseline than those who did not (median, 233 vs 360 mmHg). Death or intubation occurred in 346 (262 received HCQ, 84 did not). While crude analysis hazard ratios (HR) showed a significant association between HCQ use and death/intubation (HR: 2.37), no significant association was observed in the multivariable analysis with inverse probability weighting (HR: 1.04). No association was found between death/intubation and azithromycin use (HR: 1.03)
Clinical Implications	This study does not support the routine use of HCQ for COVID-19 patients as they found no association (neither harm nor benefit) between the drug's use and patient outcomes of death or intubation. This study recommends that HCQ should only be used in clinical trials for efficacy. More research is needed to determine the best dose, when to administer (and for how long), and how the risks and benefits of these medications compare when treating COVID-19 patients.
Limitations	This study was observational in nature and used relatively wide confidence intervals, therefore these findings cannot rule out the harms or benefits of HCQ use in patients infected with COVID-19. As an observational study (i.e., the authors only looked at the end results without involving treatment), the analysis is subject to unmeasured confounding and bias, although attempts were made to limit their impact.

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra et al.

The Lancet

May 22, 2020 **[Retracted June 4]**

DOI: https://doi.org/10.1016/S0140-6736(20)31180-6

Purpose	To determine the effects of treatment with chloroquine (CQ) or hydroxychloroquine (HCQ) with or without a macrolide on COVID-19 positive patient outcomes.
Study design	Multinational registry analysis
Level of evidence	Level 2
Methods	SARS-CoV-2 positive patients hospitalized between December 20, 2019-April 14, 2020 from 671 hospitals in 6 continents were placed in a registry. Patients were divided into a control group receiving no treatment, or one of four groups receiving treatment with chloroquine (CQ) or hydroxychloroquine (HCQ) with or without a macrolide. Individuals receiving treatment after 48 hours or while on mechanical ventilation and those receiving remdesivir were excluded. Primary outcome was in-hospital mortality. Secondary outcomes included ventricular arrhythmia frequency, rate of progression to mechanical ventilation, and total length of stay in an intensive care unit. Data were collected on patient baseline characteristics, underlying comorbidities, smoking history, and baseline medications. To determine baseline risk, cox proportional hazards regression analysis was performed and hazard ratios (HR) were obtained.
Findings	98262 patients were reviewed, 2230 were excluded, leaving 96032 patients (mean age: 53.8 years, 46.3% women) for randomization. Of these, 14888 (CQ alone: 1868, CQ w/ macrolide: 3783, HCQ alone: 3016, CQ w/ macrolide: 6221) were placed in the treatment group and 81144 in the control group. When comparing survivors with non-survivors, the latter were more likely to be older, obese, African-American, Hispanic, diabetic, have coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), hyperlipidemia, history of arrhythmias, or history of smoking. Mortality was higher in treatment groups compared to the control population ($p<0.0001$). Control group mortality rate was 7530/81144 (9.3%) versus 307/1868 (16.4%, HR 1.365) in CQ alone, 839/3783 (22.2%, HR 1.368) in CQ w/ macrolide, 543/3016 (18.0%, HR 1.335) in HCQ alone, and 1479/6221 (23.8%, HR 1.447) in HCQ w/ macrolide. All treatment groups showed increased risk for ventricular arrhythmias with hazard ratios ranging from 2.369 (HCQ alone) to 5.106 (for HCQ w/ macrolide).
Clinical Implications	This is the largest and most comprehensive data set thus far evaluating the efficacy of CQ and HCQ. The large number of facilities and patients from multiple geographic regions that participated in this study increases the generalizability of findings. No clinical benefit was observed with use of CQ or HCQ with or without macrolide antibiotics, and use of these agents increased risk of mortality and ventricular arrhythmias. These drugs should not be used for treatment of COVID-19 outside of a controlled trial until a randomized clinical study can be performed.
Limitations	**STUDY RETRACTED** This is an observational study; cause and effect relationship cannot be inferred from this data (i.e., association does not imply causation). While the "n" is large, it does not review controlled trials. Treatment regimens were not uniform between hospitals and these results do not apply to outpatient settings.

Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit

Francis Bessière et al.

Journal of the American Medical Association Cardiology
May 1, 2020
DOI: 10.1001/jamacardio.2020.1787

Purpose	To evaluate changes in corrected QT (QTc) interval among critically ill COVID-19 positive patients receiving therapy with hydroxychloroquine (HCQ) alone or in combination with azithromycin.
Study design	Retrospective case series (n=40)
Level of evidence	Level 4
Methods	COVID-19 positive patients (via PCR analysis of nasopharyngeal swab) admitted to the intensive care unit (ICU) between March 15 and March 29, 2020 were included in the analysis. All patients received HCQ monotherapy (200 mg, twice a day, for 10 days). A subset of patients also received azithromycin (250 mg daily, for 5 days). Patients were not included in the analysis if baseline QTc was greater than 460 ms. Patients underwent daily electrocardiogram (ECG) and continuous monitoring of the QTc interval. Prolonged QTc was the primary endpoint and was classified by one of two parameters: a QTc change (DQTc) of more than 60 ms or a prolonged QTc interval of more than 500 ms.
Findings	The outcomes of 40 COVID-19 patients who received HCQ alone (55%) or in combination with azithromycin (45%) were examined. Of these, the median age was 68 years, 32 (75%) were male, 30 (75%) required intubation, and 25 (63%) required vasoactive medications. Most patients (93%) had an increase in QTc after administration of therapy, regardless of treatment group. 10 patients (25%) demonstrated a DQTc of more than 60 ms and 7 patients (17.5%) demonstrated prolonged QTc intervals of more than 500 ms, with some patients meeting both criteria. By the authors' definition, 14 total patients (36%) demonstrated prolonged QTc. A greater percentage of patients in the combination therapy group (33%), compared to those in the monotherapy group (5%, p=0.03), demonstrated a DQTc of more than 60 ms. No ventricular arrhythmias were seen in either group, but therapy was stopped in 45% of patients due to ECG abnormalities or acute renal failure.
Clinical Implications	HCQ and azithromycin use in COVID-19 positive patients may result in prolongation of the QTc interval, particularly when administered together. Authors suggest that this treatment should only be used when patients can be closely monitored because serious complications may develop. Further research conducted in a larger number of patients may help to clarify the risks and benefits of these therapies.
Limitations	This was a small case series conducted at a single site. In addition to small sample size, generalizability is limited due to all patients receiving ICU level care. ICU patients may require and receive additional medications that contribute to prolongation of the QTc interval.

Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19)

Nicholas J. Mercuro et al.

Journal of the American Medical Association Cardiology
May 1, 2020
DOI: 10.1001/jamacardio.2020.1834

Purpose	To evaluate QTc changes in patients diagnosed with COVID-19 pneumonia treated with hydroxychloroquine (HCQ) monotherapy or in combination with azithromycin.
Study design	Observational, retrospective cohort study at a single center.
Level of evidence	Level 3
Methods	Clinical data were obtained from COVID-19 positive patients diagnosed (via PCR analysis of nasopharyngeal swabs) between March 1 and April 7, 2020. All patients received at least one day of HCQ monotherapy or HCQ with concomitant azithromycin. Data were analyzed at the cohort level and comparisons were made between the monotherapy and combination therapy groups. Primary endpoints of interest included DQTc from baseline, development of prolonged QTc greater than 500ms, and development of adverse drug events.
Findings	The study was comprised of 90 patients with a mean age of 60.1 years, mean BMI of 31.5, and 48.9% female. At the cohort level, median baseline QTc was 455ms, 11% of patients had a DQTc of greater than 60ms, and 20% demonstrated post-treatment QTc of more than 500ms. In the monotherapy group, 3% of patients had a DQTc of more than 60ms and 19% demonstrated a prolonged QTc. In the combination therapy group, 13% had a DQTc of more than 60ms and 21% had a prolonged QTc. The likelihood of a prolonged QTc was greater in those taking loop diuretics (31% vs 12%, p=0.03) and those with a baseline QTc of greater than 450ms (30% vs 8%, p=0.008). Both findings remained independently associated after adjusting for at least two systemic inflammatory response syndrome (SIRS) criteria. One patient ultimately developed torsades de pointes and other ventricular arrhythmias.
Clinical Implications	Patients receiving HCQ therapy alone or in combination with azithromycin for the treatment of COVID-19 pneumonia experience alterations in QTc which may progress to significant arrhythmias. Larger scale research is required to further characterize the risk-benefit ratio of such medications in the treatment of COVID-19 patients.
Limitations	This retrospective, non-randomized study consisted of only 90 patients at a single medical center and did not include a control arm to evaluate potential changes to QTc attributable to COVID-19. Patients in the study were not stratified by illness severity and it is possible that sicker patients may demonstrate more profound changes to QTc due to disease progression and administration of additional medications.

Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Eli S. Rosenberg et al.

Journal of the American Medical Association
May 11, 2020
DOI: 10.1001/jama.2020.8630

Purpose	To evaluate in-patient mortality of COVID-19 positive patients treated with hydroxychloroquine (HCQ) with or without azithromycin as compared to patients treated with neither drug.
Study design	Retrospective cohort study (n=1438 patients)
Level of evidence	Level 3
Methods	Lab confirmed COVID-19 patients admitted across 25 New York hospitals for at least 24 hours between March 15 and March 28, 2020 were randomly selected. Only hospitals with at least 45 COVID-19 discharges or deaths within that time frame were included. Medications, preexisting conditions, clinical measures on admission, outcomes, and adverse events were collected from medical records. The primary outcome was in-hospital mortality. Secondary outcomes included cardiac arrest and abnormal electrocardiogram (ECG) findings (e.g., arrhythmia or QT prolongation). The final date of follow up was April 24, 2020.
Findings	Of 1438 patients included in the study, 735 (51.1%) received HCQ and azithromycin, 271 (18.8%) received HCQ alone, 211 (14.7%) received azithromycin alone, and 221 (15.4%) received neither medication. Adjusted Cox proportional hazard models demonstrated no significant difference in in-hospital mortality in the combination therapy group (hazard ratio, HR: 1.35), HCQ group (HR: 1.08), or azithromycin group (HR: 0.56) when compared to patients receiving neither medication. An unadjusted logistic model demonstrated an elevated risk of cardiac arrest or abnormal ECG findings in patients receiving combination therapy (odds ratio, OR: 2.13), but adjusted models found no significant differences between groups.
Clinical Implications	There was no significant difference in in-patient mortality in COVID-19 positive patients treated with HCQ with or without azithromycin as compared to patients treated with neither drug. While there were no significant differences between groups regarding incidence of cardiac arrest or abnormal ECG findings, a risk-benefit calculation should be made when using these drugs.
Limitations	This observational study did not standardize medication dose among patients under evaluation. Mortality data was limited to in-hospital deaths, which assumes that discharged patients were still alive during the study period.

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

David R. Boulware et al.

The New England Journal of Medicine
June 3, 2020
DOI: 10.1056/NEJMoa2016638

Purpose	Determine whether hydroxychloroquine can prevent symptomatic infection after SARS-CoV-2 exposure.
Study design	Randomized, double-blind, placebo-controlled trial
Level of evidence	Level 2
Methods	A total of 821 asymptomatic patients who had household or occupational exposure to an individual with confirmed Covid-19 were enrolled. Patients were assigned within 4 days after exposure at a 1:1 ratio to receive either placebo or Hydroxychloroquine (800 mg once -> 600 mg 6-8 hours later -> 600 mg daily for 4 days).
Findings	**There was no significant difference in incidence of new Covid-19 illness between those receiving placebo (14.3%) and hydroxychloroquine (11.8%) during the 14 days follow-up (p=0.35)**. Adherence in both groups was moderate, with 75.4% of hydroxychloroquine and 82.6% of placebo reporting 10% adherence to trail interventions. Side effects were more frequent in the hydroxychloroquine group (40.1%) than placebo (16.8%). Nausea, loose stools, and abdominal distension were the most commonly reported, there were no severe adverse events.
Clinical Implications	Hydroxychloroquine did not prevent illness when used as a postexposure prophylaxis within 4 days of moderate-risk or high-risk exposure to Covid-19.
Limitations	An internet recruitment of participants with participant reported data. Additionally, study size limited the power of investigation. The predictive power remains uncertain given the limited availability of PCR testing at the time of investigation.

Optimizing Hydroxychloroquine Dosing for Patients With COVID-19: An Integrative Modeling Approach for Effective Drug Repurposing

Maria Garcia-Cremades et al.

Clinical Pharmacology and Therapeutics
April 14, 2020
DOI: https://doi.org/10.1002/cpt.1856

Purpose	To improve Hydroxychloroquine (HCQ) dosing for effective SARS-CoV-2 viral decline.
Study design	Systematic review with meta-analysis.
Level of evidence	Level 3
Methods	In vivo data was obtained from a published nonrandomized single arm open label study of HCQ 200 mg TID (w/wo azithromycin) for treatment of SARS-CoV-2. HCQ regimens of 200, 400, 600, and 800 mg BID for 5, 7 and 10 days (with and without loading dose) were simulated and evaluated based on externally predicted %PCR-negative patients in each cohort; each simulation included 100 virtual patients and was run 1000 times. PK/PD-corrected QT simulations were used to predict the risk of corrected QT prolongation with each HCQ regimen using a published PK-QTc model; the predicted relationship was validated as it successfully predicted QTc prolongation.
Findings	Each 1 uM increase in plasma HCQ was associated with a 28% decrease in viral load per day with an estimated 4.7. plasma concentration for 50% viral inhibition. Dosing regiments producing plasma concentrations at or above 7.5 uM were associated with >1% of patients having an increase of >60 ms QTc during treatment. **HCQ 800 mg BID for 10 days was predicted to produce the lowest percentage of patients with detectable viral loads (9%), but was predicted to result in a significant probability of QTc prolongation**. Dosing regiments of 400 mg BID for 7 or 10 days, and 600 mg BID for 5, 7 or 10 days were predicted to have lower detectable viral loads than those previously studied. Regimens of 200 mg BID orTID showed modest efficacy. Utilization of higher doses appeared to offer more benefit when compared with extended treatment duration**. PK-QTc models demonstrated that the average patient could receive HCQ doses of 400 mg BID over 5 or 7 days with minimal risk (1.0-2.0%) of QTc prolongation.**
Clinical Implications	Current data and translational modeling indicates that dosing regimens of ~800 mg/day (either loaded or as 400 mg BID) would be safely tolerated and would reduce the time with a detectable SARS-CoV-2 viral load, improving treatment outcomes. Further examination in clinical trials is needed to evaluate safety and efficacy.
Limitations	Clinical HCQ data are limited to nonrandomized studies; no well-defined model for natural rate of viral decline exists. Additionally, drug efficacy at the site of action is determined by the fraction of drug unbound in tissue, which has not been studied for HCQ. Lastly, in vitro viral replication data was obtained from SARS-CoV-1 data and may not accurately represent SARS-CoV-2 replication rates and/or declines.

Clinical Efficacy of Hydroxychloroquine in Patients with Covid-19 Pneumonia Who Require Oxygen- Observational Comparative Study Using Routine Care Data

Mattheiu Mahévas et al.

BMJ

May 14, 2020

DOI: 10.1136/bmj.m1844

Purpose	To determine the efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen.
Study design	Observational, multicenter retrospective cohort study (n=181 patients)
Level of evidence	Level 3
Methods	Patients with COVID-19 pneumonia were recruited from four French tertiary hospitals between March 12 and March 31, 2020. Out of 181 patients, 84 (46%) received hydroxychloroquine (600 mg/day) within 48 hours of admission, 8 (4%) received hydroxychloroquine more than 48 hours after admission, and 89 (49%) did not receive the drug (control group). The primary outcome measure was survival without transfer to ICU on day 21. The secondary outcome measures included survival without acute respiratory distress syndrome; successful weaning from oxygen; and discharge from hospital, to either home or rehabilitation services.
Findings	On day 21, 5% patients in the treatment group had died, and 4% in the control group had died. The rate of survival without transfer to intensive care on day 21 was 76% in the treatment group, versus 75% in the control group. The overall survival rate at 21 days was 89% in the treatment group, versus 91% in the control group. The survival rate without acute respiratory distress syndrome was 69% in the treatment group, and 74% in the control group. For patients weaned off of oxygen, the survival rate in the treatment group was 82%, and in the control group was 76%. Finally, 76% of patients in the treatment group were discharged, compared to 82% in the control group
Clinical Implications	**The results of this study do not support the use of hydroxychloroquine in patients admitted to the hospital with COVID-19 infections who require oxygen. In fact, the control group, who did not receive the drug, had better statistical outcomes overall.**
Limitations	The treatment and control groups were not randomized. Because only patients admitted to the hospital were included, the researchers could not draw any further conclusions about hydroxychloroquine and whether or not it can help to prevent COVID-19 in the general population. **More research is needed to confirm whether Hydroxychloroquine serves any medical purpose during the pandemic, or if it should be avoided entirely due to lack of proven clinical benefit**.

Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients with COVID-19: A Randomized Clinical Trial

Wesley H. Self et al.

Journal of American Medical Association
November 9, 2020
DOI: doi:10.1001/jama.2020.22240

Purpose	To evaluate the hypothesis that in comparison to placebo, hydroxychloroquine improves clinical outcomes for adults hospitalized with COVID-19
Study design	Randomized Clinical Trial
Level of evidence	Level 1a
Methods	Researchers randomized 479 hospitalized adults (median age: 57 years) with laboratory-confirmed SARS-CoV- 2 infection and symptoms of respiratory illness for less than 10 days. Patients were enrolled between April 2 and June 19, 2020 across 34 hospitals within the United States.Any patients that had received more than 1 dose of hydroxychloroquine or chloroquine in the prior 10 days, elevated QTc interval greater than 500 ms, or any prior or planned receipt of medications that prolong QTc interval were excluded from the study. Randomization was double-blinded and performed by a central electronic system in a 1:1 ratio of hydroxychloroquine to placebo. Hydroxychloquine randomized patients received two 400 mg of hydroxychloroquine sulfate on treatment day one and 200 mg in pill form twice a day for next 4 days, for a total of 10 doses over 5 days. Placebo group received matching placebo in same dosing frequency. Primary outcome was clinical status 14 days after randomization assessed with the COVID Outcomes scale consisting of 7 mutually exclusive categories.
Findings	No significant difference in symptoms of acute respiratory infection, COVID Outcomes Scale category at randomization, and laboratory measurements at randomization between the 2 groups were found. **No significant difference at 14 days in COVID Outcomes Scales score between hydroxychloroquine and placebo group were found.** Remdesivir, azithromycin and corticosteroids were received by 104, 91, and 88 patients respectively during the trial. No significant differences in primary outcomes between the hydroxychloroquine group and placebo group for patients treated with these drugs were found. **No significant difference in any of the 12 secondary outcomes between hydroxychloroquine and placebo groups were found.** No significant difference in survival between the hydroxychloroquine group and placebo group in survival or time to discharge were found.
Clinical Implications	**Treatment with hydroxychloroquine did not improve or worsen clinical outcomes for adults hospitalized for respiratory illness from COVID-19.** These findings were consistent across subgroup analysis, as well as all outcomes evaluated. These results are congruent with other open-label trials from the UK and Brazil suggesting that hydroxychloroquine is not beneficial for adults hospitalized with COVID-19.
Limitations	This trial only included hospitalized results so the findings may not be applicable to other populations. Outcome analysis was only limited to 28 days after randomization so it is possible that there may be a change in results if further long-term analysis was performed.

Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial

Yueping Li et al.

medRxiv preprint
April 15, 2020
DOI: https://doi.org/10.1101/2020.03.19.20038984

Purpose	To analyze the safety and efficacy of lopinavir/ritonavir or arbidol monotherapy in the treatment of mild-moderate COVID-19.
Study design	Non-blinded, Randomized Control Trial (n=86)
Level of evidence	Level 2
Methods	This study was a single-center, randomized controlled trial performed at the Guangzhou Eighth People's Hospital. 86 inpatients between the ages of 18 and 80 hospitalized with mild-moderate COVID-19 were enrolled in the study. Patients were randomly assigned in a 2:2:1 ratio into the following three groups: lopinavir/ritonavir 200 mg/50 mg twice daily for 7-14 days (n=34), arbidol 200 mg three times daily for 7-14 days (n=35), and a control group (n=17) who were not given any medication. Groups were followed for 21 days and patients in all groups received supportive care and oxygen therapy, if needed. The primary outcome was the rate of positive to negative conversion of COVID-19 rtPCR testing from the initiation of treatment until day 21 of follow-up. The secondary outcomes were the rate of positive to negative conversion of COVID-19 rtPCR testing from the initiation of treatment until days 7 and 14 of follow-up, the number of days until fever cessation following initiation of treatment, the number of days until cough cessation following initiation of treatment, and the improvement of chest CT imaging at days 7, 14, and 21 of follow-up.
Findings	**There was no statistically significant difference in the mean number of days for positive to negative conversion of COVID-19 rtPCR testing across all three groups (about 9 days for each group).** There was also no statistically significant difference in rates of positive to negative conversion of COVID-19 rtPCR testing at 7, 14, and 21 days of follow-up across all three groups. Furthermore, there was no statistically significant difference in the rates of fever cessation, cough resolution, and improvement on chest CT imaging on follow-up days 7, 14, and 21 across all three groups.
Clinical Implications	Treatment with either lopinavir/ritonavir or arbidol monotherapy in hospitalized patients with mild-moderate COVID-19 appears to provide minimal benefit on clinical outcomes.
Limitations	The sample size in this study is relatively small, limiting the power of the findings. Additionally, critically ill patients and patients with many comorbidities that would likely predispose them to adverse outcomes were excluded from the study, which limits the generalizability of the findings. Also this study has not been peer-reviewed. Lastly, the study was not blinded and took place at only one medical center in China.

Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19

Zhen Zhu et al.

Journal of Infection
March 30, 2020
DOI: https://doi.org/10.1016/j.jinf.2020.03.060

Purpose	To evaluate the antiviral efficacy and safety of lopinavir/ritonavir versus arbidol in the treatment of COVID-19 patients.
Study design	Retrospective cohort review (n=50 patients)
Level of evidence	4
Methods	Fifty patients with RT-PCR-confirmed COVID-19 were divided into two groups: lopinavir/ritonavir group (n=34) and arbidol group (n=16). All patients received standard treatments of oxygen supplementation and inhalation of recombinant human interferon-alpha2b. Patients who were in the lopinavir/ritonavir group (n=34) received a 400 mg/100 mg regimen twice daily for 1 week. Patients who were in the arbidol group (n=16) received 0.2 g three times daily for 1 week. Outcomes measured included duration of fever in days, various laboratory markers including LFTs, CRP, WBCs, D-dimer, CT findings of pneumonia and days testing positive for COVID-19 RNA were recorded and analyzed.
Findings	There was no statistically significant difference in duration of fever, which lasted < 7 days in both groups, ALT, WBC count, and D-dimer. The lopinavir/ritonavir group had statistically significant higher CRP values and neutrophils than the arbidol group in addition to statistically significant lower lymphocyte counts. No patients across either group developed severe pneumonia or ARDS. On day 7 of admission, 50% of patients in the arbidol group had undetectable COVID-19 viral loads compared to 23.5% of patients in the lopinavir/ritonavir group. On day 14, viral load was undetectable in all patients in the arbidol group whereas viral RNA was detected in 44.1% of patients treated with lopinavir/ritonavir. Furthermore, total duration of positive COVID-19 RNA testing in days was shorter to a statistically significant degree in the arbidol group compared to the lopinavir/ritonavir group. No apparent side effects were found in both groups.
Clinical Implications	**The arbidol monotherapy regimen was superior to the lopinavir/ritonavir regimen in the treatment of COVID-19.** A previous study from China suggested that arbidol combined lopinavir/ritonavir was superior to the lopinavir/ritonavir alone, and so this study suggests that arbidol monotherapy may be sufficient for the treatment of COVID-19.
Limitations	This study was a retrospective cohort review without randomization. Furthermore, there was a size discrepancy between the two groups such that there was more than double the number of patients in the lopinavir/ritonavir group compared to the arbidol monotherapy group. This limits the power of the findings associated with the arbidol monotherapy group. Additionally, there was no mention of specific inclusion or exclusion criteria for patients in this study, such as comorbidities or other medications the patients take on a regular basis. Lastly, all patients seemed to have mild disease, as none of the 50 patients in the study had severe pneumonia or ARDS. This limits the generalizability of these findings to other populations of COVID-19 patients with more severe disease.

A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19

Bin Cao et al.

New England Journal of Medicine
March 18, 2020
DOI: 10.1056/NEJMoa2001282

Purpose	Determine the efficacy of Lopinavir-Ritonavir treatment in confirmed SARS-CoV2 infected patients in decreasing time to clinical improvement.
Study design	Open label, randomized control trial. (N=199)
Level of evidence	Level 2
Methods	189 patients were randomly assigned to receive either Lopinavir-Ritonavir (400mg and 100mg) orally or via a nasogastric tube plus standard care; or standard care alone for 14 days. The primary endpoint was time to clinical improvement.
Findings	**Patients assigned to receive Lopinavir-Ritonavir treatment did not have a time to clinical improvement different from that of standard-care group. The 28-day mortality was numerically lower in the Lopinavir-Ritonavir treatment group as compared to the standard-care group** (19.2% vs 25% difference).The percentage of patients with clinical improvement on day 14 was higher in the Lopinavir-Ritonavir treatment group (45.5% vs 30%). Secondary findings included the percentage of patients with clinical improvement on day 14 was higher in the Lopinavir-Ritonavir treatment group (45.5% vs 30%) and detectable viral RNA at various time points was similar in both groups on subsequent sampling days.
Clinical Implications	A 14-day Lopinavir-Ritonavir (400mg-100mg) therapy does not have a time to clinical improvement different from that of patients assigned to standard-of-care alone. Gastrointestinal adverse events (nausea, vomiting, diarrhea) were more common in the Lopinavir-Ritonavir treatment group. The side effect profile observed in this study increases concern that a lengthened course of treatment or a higher dose regimen to improve outcomes might not be feasible.
Limitations	Based on the emergency nature of the trial, placebos were not prepared, thus limiting the ability to blind the participants and researchers. The characteristics of the patients were generally balanced but there was a slightly higher throat viral load in the lopinavir-ritonavir group, raising the possibility that this group has more viral replication, influencing clinical outcomes. Additionally, some patients received additional pharmacological interventions, such as glucocorticoid treatment, which might have acted as a cofounder.

Clinical Efficacy of Lopinavir/Ritonavir in the Treatment of Coronavirus Disease 2019

Xiaoting Ye et al.

European Review for Medical and Pharmacological Sciences
March 2020
DOI: 10.26355/eurrev_202003_20706

Purpose	To investigate whether lopinavir/ritonavir (LPV/R) in combination with pneumonia-associated adjuvant drugs has therapeutic benefits when compared to pneumonia-associated adjuvant treatment alone in the context of COVID-19.
Study design	Retrospective cohort study (n=47)
Level of evidence	Level 3
Methods	47 COVID-19 positive patients (via quantitative PCR) admitted to the same hospital in Rui'an, China were divided into a test group (n=42) or a control group (n=5). The test group consisted of patients treated with LPV/R in addition to pneumonia-associated adjuvant drugs (therapeutic scheme including other antivirals and anti-inflammatory medications) during hospitalization. The control group included patients treated with pneumonia-associated adjuvant drugs alone. Body temperature and laboratory values were measured three times over a ten-day period. The primary endpoint was improvement of clinical symptoms, as measured by fever. Secondary endpoints included improvement in laboratory findings, as measured by blood routine indexes, and the hepatic safety of LPV/R.
Findings	Patients in the test group returned to normal body temperature in a shorter time than the control group (P=0.036). Patients in the test group were also found to have generally lower levels of abnormal proportions of WBC, lymphocytes, CRP, and PLT after three treatments than that in the control group. The number of patients with abnormal AST/ALT measurements in the test group was not significantly increased as compared to the control group, suggesting that LPV/R does not cause significant hepatotoxicity.
Clinical Implications	These findings suggest that LPV/R is safe for clinical use and may **demonstrate efficacy in treating COVID-19 when used with adjuvant drugs**.
Limitations	Large age range of patients from 5-68 years of age. The control group was small (n=5) and mostly female (n=4). Patients in both the test group and the control group received various pneumonia-associated adjuvant drugs. Therefore, results of this study demonstrating the efficacy of LPV/R may be dependent on simultaneously receiving the same therapeutic regimen used in these patients. Additionally, as this was a retrospective cohort study, further randomized double-blinded clinical trials are needed.

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Chenguang Shen et al.

JAMA
March 27, 2020
DOI: 10.1001/jama.2020.4783

Purpose	Investigate the potential benefit of administration of convalescent plasma transfusion for treatment of critically ill patients with SARS-CoV-2 infection.
Study design	Preliminary Uncontrolled Case Series (n= 5)
Level of evidence	Level 4
Methods	Five laboratory-confirmed COVID-19 patients with acute respiratory distress syndrome (ARDS) who also met the following criteria of severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PAO2/FIO2 <300; and mechanical ventilation were given a transfusion with convalescent plasma with a SARS-CoV-2–specific antibody 10-22 days after admission.
Findings	**Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the Sequential Organ Failure Assessment (SOFA) score decreased, and Pao2/Fio2 increased within 12 days. Viral loads decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased.** ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. At the end of the study, 3 patients were discharged from the hospital and 2 were in stable condition.
Clinical Implications	Administration of convalescent plasma with neutralizing antibody lead to improvement in the patients' clinical status. The limited sample size and study design do not allow for a conclusive statement about the potential effectiveness of plasma transfusion therapy.
Limitations	The study was limited by its small sample size and study design that included no controls. It is unclear if patients would have had the same outcome without transfusion of plasma especially since they previously were treated with other agents. The transfusions were also given 10-22 days after admission, so the timing and association of outcomes is unknown.

The feasibility of convalescent plasma therapy in severe COVID- 19 patients: a pilot study

Kai Duan et al.

medRxiv
March 23, 2020
DOI: https://doi.org/10.1101/2020.03.16.20036145

Purpose	To examine the feasibility of providing convalescent plasma (CP) as a potential therapy for patients who have tested positive for COVID-19.
Study design	Safety trial (n=10)
Level of evidence	Level 4
Methods	Ten patients in three Chinese hospitals who had been diagnosed with COVID-19 (by rRT-PCT) and found to be in respiratory distress were identified. Convalescent plasma was donated by patients at the same three hospitals who met criteria for recovery from COVID-19. 200mL convalescent plasma was prepared and transfused according to WHO transfusion protocol. The first study endpoint was evaluating the safety of convalescent plasma transfusion. The second endpoint was improvement of clinical symptoms and laboratory parameters within three days of transfusion.
Findings	There were no serious adverse events in all ten patients. All ten patients in the study experienced an improvement in clinical symptoms within one to three days of transfusion. Furthermore, all ten patients also demonstrated negative RT-PCR testing, increased oxygen saturation, and improved lymphocyte counts, CRP and liver function. Neutralizing antibody levels, compared to those prior to transfusion, increased in five patients, remained the same in four patients and were not measured in one. All ten patients showed variation in reduction of lesions on chest CT after transfusion.
Clinical Implications	These findings suggest that CP appears safe in a small number of patients. Additionally, CP may improve clinical outcomes.
Limitations	Prior to transfusion of CP, patients received varying therapeutic regimens. Some received antivirals, whereas others only supportive care. This lack of standardization of treatment protocol confounds the assessment of the potential benefits of CP alone. Furthermore, the small sample size and lack of a control group, limit the power and subsequent observations of this study.

High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Paients With Coronavirus Disease 2019

Wei Cao et al.

Open Forum Infectious Disease
March 21, 2020
DOI: https://doi.org/10.1093/ofid/ofaa102

Purpose	Evaluate the value of administration of high-dose IVIG for rapidly deteriorating patients with COVID-19 pneumonia.
Study design	Case Observational Study (n= 3)
Level of evidence	Level 4
Methods	Three patients were diagnosed with COVID-19, severe type and administered high-dose IVIg (at 0.3-0.5 g/kg) for 5 days. Computed tomography (CT) scan was documented before and after treatment. All patients were treated at the early stage of clinical deterioration. Testing for COVID-19 was performed through PCR or oropharyngeal swab.
Findings	**Of the 3 patients, all demonstrated clinical improvement shortly after administration of high dose IVIg**. Variables measured include stabilizing temperature within 1-2 days and breathing difficulty alleviated in 3-5 days. CT scans compared before and after treatment demonstrated partial to complete resolution of lesions. **Between 5-6 days after the first dose of treatment, all 3 patients tested negative for COVID-19. No adverse outcomes were reported in any of the 3 patients.**
Clinical Implications	IVIg used early in a patients course after diagnosis with the severe type of COVID-19 could provide clinical use in shortening the duration of symptoms of COVID-19 pneumonia. However, the clinical results require confirmation from a randomized controlled trial (RCT). The study describes 3 clinically relevant phases of COVID-19 including an initial phase, an accelerating phase with potential for an overall inflammatory storm (lab values indicating progressive lymphocytopenia and inflammatory markers) and a recovery phase.
Limitations	The study was limited by its small sample size (n=3) and lack of control cases. Additionally, confounding factors between patients include the use of lopinavir/ritonavir in one patient and moxifloxacin in a one patient and a short course of steroids in the third patient.

Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea

Jin Young Ahn et al.

J Korean Med Sci
April 13, 2020
DOI: 10.3346/jkms.2020.35.e149

Purpose	To describe outcomes of convalescent plasma therapy in acute respiratory distress (ARDS) in two patients.
Study design	Uncontrolled Case Series (n=2)
Level of evidence	Level 4
Methods	Both patients received hydroxychloroquine and lopinavir/ritonavir after initial diagnosis of COVID-19, both progressed to ARDS, and required mechanical ventilation. The patients then received convalescent plasma from donors in their 20s, positive for ELISA IgG test for SARS-CoV-2, with previous presentation of bilateral pneumonia. The donors were determined to have completely recovered. Plasma was divided into two doses and administered at 12-hour intervals with each dose given over course of 1 hour. Both cases involved simultaneous infusion of corticosteroids. Corticosteroids were not given initially (due to the lack of evidence of its clinical efficacy on mortality reduction) but applied when the patients' condition deteriorated to ARDS (methylprednisolone was administered one day and two days before the plasma infusion to patient 1 and 2, respectively).
Findings	**Patient 1**: Previously healthy 71-year-old male -Day 9 of hospitalization (Day 22 of symptom onset), received convalescent plasma. -Day 11, patient's condition improved with fever subsiding, decreased oxygen demand and CRP. Radiograph showed resolution of lung infiltrate. Patient was weaned from ventilator. **Patient 2**: 67-year-old woman with history of hypertension -Day 4, patient was intubated due to increased oxygen demand with intravenous methylprednisolone added and was put into prone position to improve oxygen demand. -Day 6, convalescent plasma was provided. -Day 9, density of bilateral infiltration improved along with decreased CRP and IL-6 levels. -Day 20, negative rRT-PCR for SARS-CoV-2. -Day 24, patient was extubated and discharged.
Clinical Implications	Transfusion of convalescent plasma shows promise for the treatment of severe COVID-19 patients. Following the infusion of convalescent plasma, viral loads rapidly decrease, inflammatory makers decrease, and oxygenation improves.
Limitations	This describes only two patients with similar clinical presentations of ARDS and similar treatment regimens, preventing generalizability to a diverse patient population. Additionally, the timing of administration of plasma varied greatly, and the antibodies provided in the plasma could not be determined if they had high neutralizing titers.

Effectiveness of convalescent plasma therapy in severe COVID-19 patients

Kai Duan et al.

Proc Natl Acad Sci
March 18, 2020
DOI: https://doi.org/10.1073/pnas.2004168117

Purpose	To determine the safety of convalescent plasma (CP) transfusion in patients with COVID-19 and to observe the improvement of clinical symptoms, radiologic findings and laboratory parameters within 3 days after CP transfusion.
Study design	Prospective Cohort Study (n=10)
Level of evidence	Level 3
Methods	Ten COVID-19 patients (confirmed by real-time viral RNA test) in severe condition received one dose of 200 mL of CP derived from recently recovered donors (titers>1:640) transfused ~16.5 days after development of symptoms. CP was given in addition to maximal supportive care and antiviral treatments. Severe classification was defined as patients presenting with severe dyspnea, respiratory distress (tachypnea>30 breaths/min), or hypoxia (SpO2<90%). A historic control group was formed by random selection of 10 patients treated in the same hospital and matched by age, gender, and severity of the diseases.
Findings	Chest CTs showed improvement in different degrees of absorption of pulmonary lesions after CP transfusion in all patients. Lymphocytopenia and SaO2 increased whereas C-reactive protein (CRP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) decreased. An increase in neutralizing antibody titers was found in 5/10 patients, viral load was decreased to an undetectable level in 3/10 patients. Clinical outcome in the CP group improved as compared to the control group. In the CP group, three cases discharged, while the remaining seven cases were given a "much improved status" and were ready for discharge. In the control group, there were three deaths, six cases were classified as "stabilized", and one case classified as "much improved status". No serious adverse reactions or safety events were recorded after CP transfusion.
Clinical Implications	One dose of CP with high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes with minimal adverse reactions.
Limitations	First, patients received additional treatment beyond CP, which may have contributed to clinical outcomes. Additionally, this study had a small sample size and was unblinded, increasing risk of bias. Finally, some patients received glucocorticoid therapy, which could interfere with the immune response and delay virus clearance, altering study findings.

Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection

Bin Zhang et al.

Chest
March 31, 2020
DOI: 10.1016/j.chest.2020.03.039

Purpose	Document the clinical course in four critically ill COVID-19 patients treated with convalescent plasma and supportive care.
Study design	Case series (n=4)
Level of evidence	Level 3
Methods	Four patients with positive SARS-CoV-2 infection with ages ranging from 31-73 years were given different combinations of arbidol, lopinavir-ritonavir, interferon alpha-2b, oseltamivir, and ribavirin as initial treatment.. Their conditions progressed from moderate to severe. Transfusion convalescent plasma was given as a last resort and the course of disease was monitored.
Findings	- Case 1: The patient's viral loads significantly dropped. CT scans showed absorption of consolidation and a negative RT-PCR test for SARS-CoV-2. Patient was discharged. - Case 2: The patient's PO2/OI increased from 50/135mmHg to 97/198mmHg, one day following plasma transfusion. CT scans indicated absorption of pneumonia and RT-PCR test results were negative. Patient was discharged. - Case 3: The patient tested positive for anti-SARS-CoV-2 IgG and had decreased serum IgM. CT scans showed absorbed infiltrative lesions and RT-PCR tests of sputum in deep lungs were negative. Patient was transferred to the unfenced ICU for further treatment of underlying diseases and multiple organ failure. - Case 4: The patient's anti-SARS-CoV-2 IgM tested negative while IgG levels were positive. CT scan showed absorption of opacities and RT-PCR tests were negative. Patient was discharged.
Clinical Implications	Convalescent plasma therapy may prove to be beneficial as a last resort treatment for severely ill patients infected with SARS-CoV-2. No serious adverse reactions were observed in these 4 patients associated with the transfusion of convalescent plasma.
Limitations	The relative benefits of supportive care, medications, and the patient's immune response could not be determined. Whether convalescent plasma can provide any clinical benefit must still be tested by randomized control trial.

Convalescent plasma transfusion for the treatment of COVID-19: Systematic review

Karthick Rajendran et al.

Journal of Medical Virology
May 1, 2020
DOI: https://doi.org/10.1002/jmv.25961

Purpose	To determine the efficacy of convalescent plasma transfusion (CPT) therapy on COVID-19 patients.
Study design	Systematic Review
Level of evidence	Level 3
Methods	A systematic search was conducted using electronic databases such as PubMed, EMBASE and Medline to identify case studies and clincial trials regarding treatment of COVID-19 patients using CPT therapy. Studies were published literature between December 1, 2019 to April 19, 2020. "Convalescent plasma AND COVID-19" was used as the search term and there were no restrictions placed on the comparator in each study. The primary endpoints were clinical effects, survival benefits, viral load & antibody titer status and adverse events. Two authors independently assessed the studies to reduce the risk of bias.
Findings	Amongst all 8 of the studies reviewed, 5 were selected for further evaluation. These 5 studies had a total of 27 patients enrolled that received the CPT therapy. All the patients received CPT between Day 6 and Day 50, however, it varied between the studies the dosage administered and the length of treatment. **All 5 studies found zero mortality rate for patients that had CPT administrated**, albeit it being in varying doses. Every study also found that CPT, in conjunction with other antiviral treatments, reduced the viral load and increased the level of neutralizing antibody titer. Every single patient had also received more than one antiviral drug in addition to the CPT. Almost all patients also showed improvement of their symptoms such as their body temperature. Furthermore, **CPT treatment was well tolerated by all the patients and no adverse reactions were noted.**
Clinical Implications	Although there is limited scientific data, it appears that COVID-19 patients treated with CPT treatment have positive outcomes. Further randomized controlled trials are urgently needed to determine the ideal dosage and treatment time for CPT therapy for optimal outcomes.
Limitations	The included studies were predominantly case reports or case series and lacked proper control groups. It is also difficult to determine that CPT alone reduced the viral load and increased antibody titers because all patients were given multiple therapies. Additionally, the authors did not compare different doses of CPT with outcomes, making it difficult to understand what dose might be most effective.

Life-saving effect of convalescent plasma treatment in covid-19 disease: Clinical trial from eastern Anatolia

Mehmet Ali Erkurt et al.

Elsevier Public Health Emergency Collection
June 27, 2020
DOI: https://doi.org/10.1016/j.transci.2020.102867

Purpose	To describe the results of convalescent plasma (CP) treatment in patients with SARS-CoV-2.
Study design	Cohort Study
Level of evidence	Level 3
Methods	Plasma was collected from qualifying patients who had contracted SARS-CoV-2 with mild or moderate infection at least 14 days after complete recovery. Laboratory values were collected in 26 patients (mean age= 67.4 years) admitted to the intensive care unit (ICU) and were identified to be positive for SARS-CoV-2 using quantitative reverse transcriptase-polymerase chain reaction. These patients were given one session of CP. Patients had laboratory values including leukocyte, neutrophil, lymphocytes, hemoglobin, platelet, ferritin, LDH, sO2, ALT, AST, total bilirubin, and CRP values compared just before and one week after CP administration. These patients were also administered hydroxychloroquine and azithromycin, then favipravir along with supportive treatment.
Findings	**No significance was determined between leukocyte, neutrophil, lymphocytes, platelet, ferritin, LDH, sO2, ALT, AST, total bilirubin, and CRP values.** However, significance was determined for hemoglobin levels just before and one week after CP treatment, however, the authors suggest that this results from dilutional anemia due to due to the hydration applied to patients in the ICU. Of the 26 patients included in the study, 17 (65.4%) required mechanical ventilation support in the ICU. Of these 17 patients requiring mechanical ventilation, 6 (35.3%) died. The 20 patients that survived infection with SARS-CoV-2 had an average age of 61.85 years, while the 6 deceased patients had an average age of 74.6 years. **This difference in age was determined to be statistically significant (p=0.018). Additionally, lymphocyte counts between the survivor cohort, 1.18 x 103/µL, and deceased cohort, 0.47 x 103/uL, were determined to be significant (p = 0.001).**
Clinical Implications	CP has been used to provide passive immunity with satisfactory efficacy in the treatment of SARS-CoV-1, MERS-CoV, and H1N1 viruses and is therefore has been approved by the FDA for experimental use for treatment in individuals with SARS-CoV-2. **CP therapy has the potential to provide treatment options before effective vaccines or treatments are identified. For early stage COVID-19 patients who do not need mechanical ventilation, CP therapy may be a curative treatment option contributing to virus shedding and longer survival. However, it cannot reduce mortality in critically ill patients.**
Limitations	The study only included 26 individuals who were already admitted to the ICU which may not represent the greater population of patients who present to the hospital with SARS-CoV-2 infection and influence the generalizability of the study. Additionally, only 8 of the 26 patients (30.8%) were female which may introduce gender bias in the study.

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, Multicenter trial

Yeming Wang, et al.

The Lancet
April 29, 2020
DOI: https://doi.org/10.1016/S0140-6736(20)31022-9

Purpose	To determine the effect of Remdesivir on time to clinical improvement in patients with severe coronavirus disease 2019 (COVID-19).
Study design	Randomized, double-blind, placebo-controlled, multicenter trial at ten hospitals in Hubei, China
Level of evidence	2
Methods	Patients admitted with severe cases of confirmed COVID-10 were randomly assigned in a 2:1 ratio of IV Remdesivir (200mg on day 1 followed by 100mg on days 2-10 with a single daily infection) or the same volume of placebo infusions for 10 days. Patients received concomitant use of lopinavir-ritonavir, interferons and corticosteroids. The primary endpoint of this study was time to clinical improvement within 28 days after randomization. This was defined as the time in days from randomization to a decline of two levels on a six-point ordinal scale (1= discharged, 6=death), or discharge alive from the hospital, whichever came first.
Findings	- **Remdesivir use was not associated with a statistically significant difference in time to clinical improvement compared to the control population.** - Although not statistically significant, **patients receiving Remdesivir had a numerically faster time to clinical improvement compared to those receiving placebo among patients with symptom duration of <10 days.** - Adverse events were reported in (66%) Remdesivir patients and (64%) of patients who received the placebo. More patients in the group discontinued the study due to severe adverse events (12% in Remdesivir group vs 5% in placebo group)
Clinical Implications	- In Adult patients hospitalized for severe COVID-19, **Remdesivir was not associated with statically significant clinical benefits** beyond those receiving the standard of care. - The higher rate of adverse events observed in the Remdesivir group increases concern that a lengthened course of treatment or a higher dose regimen to improve outcomes might not be feasible
Limitations	The study did not reach its target enrollment, leading to insufficient power to detect difference in clinical outcomes. Additionally, restrictions on hospital bed availability resulted in most patients being enrolled later in the course of disease, so research could not adequately assess whether earlier Remdesivir treatment might have provided additional clinical benefit. Finally, concurrent treatment with lopinavir-ritonavir, interferons and corticosteroids may have influenced clinical outcomes.

Compassionate Use of Remdesivir for Patients with Severe COVID-19

Jonathan Grein et al.

New England Journal of Medicine
April 10, 2020
DOI: 10.1056/NEJMoa2007016

Purpose	To determine the clinical outcome of compassionate use Remdesivir (inhibits viral RNA polymerases) in the treatment of Covid-19 infection, caused by the SARS-CoV-2.
Study design	Open-label clinical trial (n = 53)
Level of evidence	3
Methods	It is a multicenter study conducted at sites in United States, Japan, Italy, Austria, France, Germany, Netherlands, Spain, and Canada. PCR-confirmed SARS-CoV-2 infection defined as oxygen saturation of 94% or less while on ambient air or oxygen support. Participants needed a creatinine clearance greater than 30 ml/min and liver enzymes (alanine transaminase, ALT and aspartate transaminase, AST) 5 times below the upper limit of normal. The duration of Remdesivir therapy is 10 days, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. The main outcomes were discharge or death.
Findings	**During a median follow-up of 18 days, 36 (68%) of the patients improved clinically. Seven (13%) died after at the end of Remdesivir treatment.** A total of 32 patients reported adverse events mostly elevated liver function tests (LFTs), rash, diarrhea, hypotension, and renal impairment, worse with those on invasive ventilation.
Clinical Implications	68% of patients diagnosed with severe Covid-19 improved with the use of Remdesivir. Therefore, compassionate use of the medication is clinically valuable in the management of severe Covid-19 infection.
Limitations	Most of the study participants (75%) were men ranging between 23 to 82 years, which may introduce gender bias. The small sample size and non-randomization of participants, missing data were limitations in the data interpretation and results. There were no clearly stated inclusion and exclusion criteria. Even though compassionate use of the medication should be investigated for efficacy, it is difficult to draw useful conclusions from uncontrolled studies like this.

Case reports study of the first five patients COVID-19 treated with Remdesivir in France

Marie Dubert et al.

International Journal of Infectious Diseases
June 30, 2020
DOI: https://doi.org/10.1016/j.ijid.2020.06.093

Purpose	To evaluate the efficacy of Remdesivir against SARS-CoV-2 in patients in France.
Study design	Case Series (n=5)
Level of evidence	Level 4
Methods	Data was collected from five COVID-19 patients (all male, ages 31, 39, 70, 76 and 80) admitted to the ICU for severe pneumonia, all of whom were treated with Remdesivir, at the University Hospital of Bichat in Paris, France. Patients received IV Remdesivir with a loading dose of 200mg, followed by a maintenance daily dose of 100mg for 14 days. SARS-CoV-2 RT-qPCR was monitored in nasopharyngeal and bronchoalveolar samples collected from patients.
Findings	Four out of five patients (80%) had a significant decrease in SARS-CoV-2 in nasopharyngeal viral load after treatment. However, two patients (40%) died with active SARS-CoV-2 infection in the lower respiratory tract. Remdesivir had to be interrupted in 4 out of 5 patients due to side effects, such as alamine aminotransferase (ALT) elevation (2/5; 40%) and kidney failure (2/5; 40%).
Clinical Implications	Results suggest that Remdesivir may lower viral load in the upper respiratory tract. For treating acutely ill patients who may have co-morbidities of renal and hepatic function, clinicians should be mindful of hepatic and kidney function monitoring when administrating this treatment.
Limitations	The small sample size of this study limits the generalizability of the findings. This study was a case series rather than a controlled trial, making it difficult to determine the efficacy of Remdesivir and also whether it was Remdesivir or the SARS-CoV-2 virus that was responsible for kidney failure and ALT elevation in patients. Further studies are necessary to assess the efficacy of Remdesivir against SARS-CoV-2. In the meantime, alternative novel therapies will be needed to control disease progression in severely ill patients.

Tocilizumab treatment in COVID-19: A single center experience.

Pan Luo et al.

Journal of Medical Virology
April 6, 2020
DOI: https://doi.org/10.1002/jmv.25801

Purpose	To analyze the treatment responses of Tocilizumab (TCZ), a monoclonal antibody against interleukin-6 (IL-6) in COVID-19 infected patients and provide guidance for future use.
Study design	Retrospective Observational (n=15)
Level of evidence	Level 4
Methods	The demographic, treatment, laboratory parameters of C-reactive protein (CRP) and IL-6 before and after TCZ therapy and clinical outcomes within 1 week of treatment in 15 COVID-19 patients were obtained from medical records and analyzed. CRP was defined as elevated when higher than 5.0 mg/L and IL-6 was if higher than 7.0 pg/mL.
Findings	**CRP levels were all far above normal before treatment and improved rapidly in all patients (126.9 to 11.2 mg/L; P<0.01**). Although of the four critically ill patients who received a single dose of TCZ, three died and the other patient's CRP level failed to return to the normal range. **Serum IL-6 levels initially spiked but decreased after TCZ therapy in 10 patients. There was a persistent and dramatic increase of IL-6 in the four patients that failed treatment.** One patient also had a clinical outcome of aggravation.
Clinical Implications	Overall, TCZ appears to be a possible effective treatment option in relieving inflammatory activity in COVID-19 patients with a risk of cytokine storms. In most patients, acute phase reactant levels were decreased after TCZ administration. It is reacommended that critically ill patients with elevated IL-6 levels receive a repeated dose of TCZ since a single dose of TCZ failed to improve disease activity in critically ill patients although used in combination with glucocorticoid.
Limitations	The study was limited by its small sample size and not being compared to control subjects. It is also difficult to know which lab parameters are optimal in defining disease activity of COVID-19. It is unclear if outside factors such as comorbidities and age may have played a role in the study outcomes.

Effective Treatment of Severe COVID-19 Patients with Tocilizumab

Xiaoling Xu et al.

ChinaXiv

April 14, 2020

DOI: 10.12074/202003.00026

Purpose	To assess the efficacy of Tocilizumab in severe patients with COVID-19.
Study design	Case Series (n=21)
Level of evidence	Level 4
Methods	Patients diagnosed as severe or critical COVID-19 were given tocilizumab (400 mg once through IV Drip) in addition to routine therapy between February 5, 2020 -February 14, 2020. Changes in clinical manifestations (Body temp., Oxygen saturations etc), CT scan images (performed on admission and 1 week after receiving therapy), and laboratory examinations were retrospectively analyzed.
Findings	**Within a few days, the fever returned to normal and all other symptoms improved remarkably**. 75% of patients had lowered their oxygen intake and one patient no longer needed Oxygen therapy. **CT scan manifested that the lung lesion opacity absorbed in 90.5% of patients.** The percentage of lymphocytes in peripheral blood decreased in 85% of patients before treatment, returned to normal in 52.5% of patients on Day 5 of treatment. Abnormally elevated C-reactive protein decreased significantly in 84.2% of patients. **No obvious adverse reactions were observed during the duration of treatment.** 90.5% of patients were discharged an average of 13.5 days after treatment with tocilizumab and the rest were recovering well at the end of the trial period.
Clinical Implications	Clinical data showed that symptoms, hypoxemia and CT opacity changes were improved immediately after treatment with tocilizumab in most patients. - Tocilizumab is hypothesized to be an effective treatment in severe patients of COVID-19, which may provide a new therapeutic strategy for severe patients, but larger randomized trials must be performed.
Limitations	The number of patients were rather limited and no control group was included. This was a single observation study and significant bias could possibly exist. The patients received standard of care treatment (lopinavir, methylprednisolone, other symptom relivers and oxygen therapy) in addition to Tocilizumab. As a result, the possibility that these agents could have contributed to positive clinical outcomes cannot be ruled out.

Off-label use of Tocilizumab in patients with SARS-CoV-2 infection

Simona Di Giambenedetto et al.

J Med Virol 2020
April 16, 2020
DOI: https://doi.org/10.1002/jmv.25897

Purpose	The purpose of this study is to look at the efficacy of (humanized anti-human interleukine-6 receptor antibody) tocilizumab in patients with Covid-19.
Study design	Case Series (n=3)
Level of evidence	Level 4
Methods	The study followed Chinese and Italian guidelines, which support the use of tocilizumab (at the dosage of 8 mg/kg, with a second dose 12 hours after the first and a possible third dose after further 24-36 hours, according to clinical response), in case of rapid clinical and/or radiological worsening and exclude contraindications to the use of this medication (transaminases levels> 5 times the upper limit of normal, neutrophils count<500 cells/µL, platelets count< 50,000 cells/µL, presence of documented sepsis, complicated diverticulitis/intestinal perforation, cutaneous infection, immunosuppressive anti-rejection therapy).
Findings	The article describes the outcomes of 3 patients aged 71, 45 and 53 years old who were hospitalized in a Level III Italian Hospital following the diagnosis of COVID-19 and developing rapidly worsening respiratory insufficiency. They were all prescribed tocilizumab when their respiratory symptoms worsened despite standard therapy. Rapid relief of respiratory symptoms, resolution of fever and reduction in CRP were the first effects noted following tocilizumab administration in all three patients within 48-72 hours. Of note, no adverse events were registered during the follow-up of the three patients.
Clinical Implications	These observations highlight the efficacy of tocilizumab in the treatment of COVID-19 even after a short time. **Tocilizumab may represent an effective option in the treatment of SARS-CoV-2- infected patients with severe pneumonia, and randomized trials should be started soon.**
Limitations	There was a small number of subjects, a lack of controlled randomized trial, and no controlling of pre-existing conditions for patients. The route of administration for Tocilizumab was not specified.

Acute hypertriglyceridemia in patients with COVID-19 receiving tocilizumab

Austin R. Morrison et al.

Journal of Medical Virology
April 21, 2020
DOI: https://doi.org/10.1002/jmv.25907

Purpose	To report on two cases of acute hypertriglyceridemia in patients with COVID-19 treated with tocilizumab leading to the recommendation of future monitoring.
Study design	Letter to Editor
Level of evidence	N/A
Methods	This article was written in response to the Luo et al. study of Tocilizumab (TCZ) for COVID-19 in a single center in China and due to no reports of acute adverse events with TCZ treatment in COVID-19 thus far. The authors discuss two cases of acute hypertriglyceridemia in patients with COVID-19 treated with TCZ with one developing acute pancreatitis.
Findings	- Cases 1 and 2, a 65-year old-male and 43-year-old male respectively, were both in the ICU with respiratory failure and ARDS who received lopinavir/ritonavir, ribavirin, and hydroxychloroquine for COVID-19 treatment. Both patients received TCZ due to persistent fevers, severe ARDS, and elevated inflammatory markers. Following TCZ, both cases had a significant increase in TG levels, with case 1 developing acute pancreatitis as defined by elevated amylase and lipase levels. - Both patients received propofol prior to treatment, but the effect of propofol on increased TGs is typically seen 2.25-7 days after starting therapy, with normalization occurring within 72 hours. Therefore, patients receiving TCZ and propofol may require more frequent monitoring. - Membrane-bound soluble IL-6 receptor inhibition with TCZ administration may result in increased triglyceride levels by interfering with the metabolic pathways of IL-6, but exact mechanisms are unknown
Clinical Implications	**Clinicians should consider monitoring for hypertriglyceridemia and acute pancreatitis for those receiving TCZ treatment for severe COVID-19** as well as to remain vigilant for other acute adverse effects that are difficult to detect in small sample clinical trials.
Limitations	The article only discusses two cases of hypertriglyceridemia, and both patients received other treatments for COVID-19 prior to TCZ. Further data collection is needed to determine the true relationship between increased TG levels and TCZ treatment in COVID-19. As a letter to the editor, it is unclear if this article has been peer-reviewed.

Tocilizumab for the Treatment of Severe COVID-19

Rand Alattar et al.

Journal of Medical Virology
May 5 2020
DOI: https://doi.org/10.1002/jmv.25964

Purpose	To report on the clinical outcomes and laboratory findings of patients with severe COVID-19 that were treated with Tocilizumab (TCZ), an interleukin 6-inhibitor.
Study design	Retrospective Review (n=25)
Level of evidence	Level 4
Methods	The study completed a retrospective chart review of patients in Qatar with laboratory confirmed severe COVID-19 that received TCZ for 14 days and followed from day 1 through 14. The primary outcome was discharge from the ICU by day 14. Twenty-five patients were eligible; these patients had a median age of 58 years old, median BMI of 29 kg/m2, and the majority were male (92%).
Findings	- The decline in temperature and serum CRP levels are likely a reflection of TCZ's immune modulating effect. Median oral temperatures on day 1, day 3 and day 7 were 38.0°C, 37.3°C (P 0.043) and 37.0°C (P 0.064), respectively, while corresponding median CRP was 193 mg/L, 7.9 mg/L (P <0.0001) and <6 mg/L (P 0.0001). - At the time of TCZ administration, 84% of patients were on invasive ventilation, which declined to 60% on day 7 (P 0.031) and 28% on day 14 (p 0.001). There was radiological improvement on patient's chest x-rays for 44% of patients by day 7 and 68% by day 14. - Nine patients (36%) were discharged alive from the ICU and three (12%) died. Since the median age of the patients was 58, it is possible this played a role in the low mortality, since older age has been found to be associated with poorer COVID-19 outcomes. - The majority (92%) of patients experienced at least one adverse event. However, patients were critically ill and received other investigational antiviral therapies, so it is difficult to conclude if any were specifically due to TCZ.
Clinical Implications	**Patients with severe COVID-19 that were treated with TCZ had a dramatic decline in inflammatory markers, radiological improvement, and reduced ventilatory support requirements.**
Limitations	Limitations in this study include it being retrospective, lack of a control comparison, and potential confounding effects from concomitant investigational antivirals. Further randomized controlled trials are necessary to conclude effectiveness of TCZ treatment.

Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE)

Marta Colaneri et al.

Microorganisms
May 9, 2020
DOI: https://doi.org/10.3390/microorganisms8050695

Purpose	To assess the effect of tocilizumab (TCZ) on ICU admission and mortality rates in COVID-19 infected patients.
Study design	Retrospective analysis of matched cases (n=21 matched pairs)
Level of evidence	Level 4
Methods	Patient data from the SMAtteo COvid19 REgistry (SMACORE) database was collected on 112 patients hospitalized between March 14-27, 2020 with confirmed SARS-CoV-2 pneumonia. Retrospective analysis via linear regression and generalized linear mixed models were performed on 21 matched pairs of patients receiving either standard of care (SOC) (hydroxychloroquine (HCQ): 200 mg BID, azithromycin: 500 mg once, low weight heparin, methylprednisolone: tapered dose of 1 mg/kg up to a maximum of 80 mg for 10 days) or SOC + TCZ (8 mg/kg IV, capped at 800, repeated 12 hours later). Patients in the SOC + TCZ treatment group were required to meet certain laboratory criteria (C-reactive protein [CRP] >5 mg/dL, procalcitonin <0.5 ng/mL, arterial partial pressure of oxygen/fractional inspired oxygen [PF ratio] <300, and alanine aminotransferase [ALT] <500 U/L). Pairs were matched based on propensity scores calculated from demographic and clinical variables. Primary outcomes included 7 day mortality and ICU admission. Secondary outcomes included CRP, international normalized ratio (INR), lymphocyte and neutrophil counts, platelets, lactate dehydrogenase (LDH), and ALT.
Findings	Treatment with TCZ did not significantly affect likelihood of ICU admission (odds ratio, OR: 0.11) or 7 day mortality (OR: 0.78) when compared to patients receiving SOC. TCZ treatment was correlated with a significant down trend in CRP and INR, an uptrend in ALT, and stable platelet counts. TCZ was not associated with significant hepatotoxicity or secondary infection.
Clinical Implications	Preliminary data suggest that TCZ does not have a profound impact on COVID-19 patient mortality or ICU admission when compared to SOC (combination of HCQ, heparin, azithromycin, and methylprednisolone). TCZ is associated with up trending ALT levels and should be used with caution in those with increased potential for severe liver injury. Further data is required to determine utility of TCZ in this clinical context.
Limitations	This study was observational, involved a short follow up period, and included a relatively small sample size. As an observational study, analysis is subject to bias, although attempts were made to limit this through propensity score matching. In addition, both treatment groups received methylprednisolone, which could potentially confound anti-inflammatory effects of TCZ.

Use of Tocilizumab for COVID-19-Induced Cytokine Release Syndrome: A Cautionary Case Report

Jared Radbel et al.

Chest Journal
April 25th, 2020
DOI: 10.1016/j.chest.2020.04.024

Purpose	To determine the effectiveness of tocilizumab in treating cytokine release syndrome (CRS) in COVID-19 patients.
Study design	Case Report
Level of evidence	Level 4
Methods	The authors analyzed data from two patients with COVID-19, a 40-year-old male with no medical conditions and a 69-year-old female with underlying conditions, who developed cytokine release syndrome and its more severe form, secondary hemophagocytic lymphohistiocytosis (sHLH). These syndromes are distinguished by their excessive inflammatory cytokine production and it is theorized that tocilizumab – an anticytokine therapy – may treat the underlying CRS.
Findings	- **Despite treatment with various doses of tocilizumab, both patients' conditions worsened from CRS to sHLH, resulting in both patients' deaths**. Prior to treatment, the 40-year-old male slowly developed acute respiratory distress syndrome, septic shock, and elevated interleukin-6 (IL-6) levels. Although C-reactive protein levels decreased after 400 mg IV tocilizumab treatment on day 4 of admission, this patient presented with decompensation and increasing inflammatory markers. Laboratory results indicated the development of sHLH and viral myocarditis as well. - The 69-year-old female was initially treated for rapidly developing hypoxemic respiratory failure, septic shock, and basic symptoms before being given a 560 mg IV dose of tocilizumab. Despite treatment, this patient's inflammatory markers increased and prompted a second dose (700 mg IV). Similarly, this patient displayed decompensation and a decrease in C-reactive protein levels. The patient's condition deteriorated as she developed sHLH and passed away.
Clinical Implications	This case report highlights the outcomes of two COVID-19 patients who, despite treatment with tocilizumab, progressed from CRS to sHLH before passing away. These results are similar to studies from Wuhan, China, and suggest that tocilizumab may not be useful in treatment or may even exacerbate immunosuppression in these patients.
Limitations	Further research is required to elucidate any treatment effects on COVID-19 patients due to the second patient already having underlying conditions. Both patients received a differing quantity and number of doses of tocilizumab, which complicates conclusions.

Tocilizumab Challenge: A Series of Cytokine Storm Therapy Experiences in Hospitalized COVID-19 Pneumonia Patients

Betul Borku Uysal et al.

Journal of Medical Virology
May 29, 2020
DOI: https://doi.org/10.1002/jmv.26111

Purpose	To recognize the period of exaggerated cytokine response in patients with COVID-19 pneumonia and to describe the clinical outcomes of using tocilizumab as a treatment option.
Study design	Retrospective Case Series
Level of evidence	Level 2
Methods	Retrospective analysis of 12 COVID-19 pneumonia patients followed inpatient clinics of Biruni University Medical Faculty Hospital (Istanbul, Turkey) from March 18th, 2020 to April 8th, 2020. All patients were initially treated with hydroxychloroquine and oseltamivir, while 7 patients also received moxifloxacin and the remaining 5 received azithromycin. Despite this standard treatment regimen, all patients were deemed to have progressed to the cytokine storm period and thus received tocilizumab. Diagnostic tests, laboratory examinations, clinical findings, and computed tomography of the thorax results were all evaluated on the day of diagnosis, pre-tocilizumab (defined as the day prior to treatment), and post-tocilizumab (defined as 48 hours following treatment).
Findings	The most common comorbidities were diabetes mellitus and hypertension (n=7 for both) among the 12 COVID-19 patients (average age=65.83 years, 50% male). Of the cohort, 2 patients required short-term ventilator support. All patients were discharged home with good health. **Eosinophil values (cells/μL) significantly increased (155.33 ± 192.69) following tocilizumab treatment** as compared to day of COVID diagnosis (10 ± 17.06) and pre-tocilizumab treatment (39.17 ± 31.75) . **CRP values (mg/L) significantly decreased following tocilizumab treatment (13.08 ± 12.89)** as compared to day of COVID diagnosis (54.25 ± 44.82) and pre-tocilizumab treatment (109.83 ± 55.78). **All the 12 patients had a fever pre-tocilizumab, while nonne of the patients had a fever following treatment .Patient arterial oxygen (O2) saturation levels (%) returned to normal levels (94.42 ± 1) post-tocilizumab treatment** from lowered pre-tocilizumab levels (87.58 ± 3.12). Ground-glass appearance was seen in all 12 patients' CT images upon diagnosis; one patient hospitalized long enough to observe radiological improvement saw **visible improvement in CT imaging.**
Clinical Implications	**Utilization of tocilizumab could potentially decrease the overall number of COVID-19 patients in the ICU and shorten the length of stay of those patients.** Tocilizumab is most effective when applied as the cytokine storm has initially begun. It can help fight the overall inflammatory state promoted by COVID-19.
Limitations	A small retrospective cohort study does not solely provide the statistical power necessary to verify the conclusions from this project. Tocilizumab'smethod of action is via IL-6 inhibition; however, IL-6 levels were not examined in this study.

Tocilizumab among patients with COVID-19 in the intensive care unit: a multicenter observational study

Noa Biran et al.

The Lancet Rheumatology
August 14, 2020
DOI: https://doi.org/10.1016/S2665-9913(20)30277-0

Purpose	To investigate differences in hospital-related mortality between COVID-19 ICU patients who received tocilizumab therapy and those who did not receive tocilizuma.
Study design	Multicenter Retrospective Observational Study
Level of evidence	Level 2a
Methods	This study consisted of a retrospective analysis of 764 COVID-19 patients hospitalized in the ICU from March 1, 2020 to April 22, 2020 at the 13 hospitals within the Hackensack Meridian Health network. ICU support was defined as all patients receiving mechanical ventilator support, patients hospitalized within a dedicated ICU, and patients with assignment to ICU staff regardless of geographical placement. Off-label use of tocilizumab was recommended as treatment in patients with evidence of ARDS on mechanical ventilation or worsening oxygenation with high oxygen requirements (80-100%) on high-flow nasal cannula or 15 L non-rebreather mask. Primary outcome was defined as hospital-related mortality and secondary outcomes were defined as changes in inflammatory markers, changes in oxygenation requirements, infections, and use of vasopressors. Researchers performed propensity score matching to reduce the confounding effects inherent to a retrospective cohort study (n=630).
Findings	**The overall mortality rate was 57% (358/630) including 102 patients who received tocilizumab treatment (49%) and 256 patients who did not receive tocilizumab treatment (61%). Causes of death among the patients who received tocilizumab were respiratory (n=57), cardiac (n=21), infectious (n=3), and other causes (n=10). In patients who did not receive tocilizumab, the primary causes of death were respiratory (n=127), cardiac (n=57), infectious (n=15), and other causes (n=20).** In the 61% in patients who did not receive tocilizumab (n=256) the Primary cause of death was Respiratory (n=127), cardiac (n=57), infectious (n=15), other (n=20). **In the subgroup of 587 patients who required mechanical ventilation, patients who received tocilizumab less than 65 years old (n=307) had reduced hospital-related mortality (p=0.023). Finally, Tocilizumab exposure was associated with decreased hospital-related mortality in 286 patients with C-reactive protein level ≥ 15 mg/dL (p=0.0025)**
Clinical Implications	**Treatment with tocilizumab in COVID-19 ICU patients was associated with a reduction in hospital-related mortality, especially for patients who required mechanical ventilator support and those younger than 65 years.** Analysis suggests that tocilizumab may exert its effects among patients whose COVID-19 illness is progressing to an inflammatory state, as a significant decrease in morality was seen in patients receiving tocilizumab with a CRP level ≥ 15 mg/dL.

Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19).

Lei Zha et al.

Medical Journal of Australia
April 8, 2020
DOI: https://doi.org/10.5694/mja2.50577

Purpose	To determine the efficacy of early corticosteroid treatment in patients with COVID-19 not presenting with acute respiratory distress.
Study design	Observational comparison study
Level of evidence	Level 3
Methods	31 patients with COVID-19 were drawn from two designated hospitals in Wuhu, China. Records were reviewed of patients admitted between January 24th and February 24th, 2020 with confirmed SARS-CoV-2 infection by local health agencies using RT-PCR. Patients who received at least one dose of corticosteroids within 24 hours of admittance were compared against those who did not receive any. The primary outcome was time to clearance of the virus, whereas secondary outcomes were duration of clinical recovery, and length of hospital stay. Patients were followed until February 29th, 2020. Those patients who received corticosteroids within 24 hours of arrival were compared against patients not-receiving corticosteroids. All patients received standard therapies.
Findings	Eleven patients received corticosteroids (40 mg methylprednisolone) once or twice per day for a median of 5 days. The patients receiving steroids had a higher maximum temperature on admission (38.8°C vs 37.8°C, P=0.002), symptoms including myalgia or fatigue (100% vs 40%, P=0.004) and cough (91% vs 40%, P=0.018), higher median CRP level (84.0 vs 18.7 mg/L, P=0.026), and lower median lymphocyte count (0.99 vs 1.54×1e9/L, P=0.012). However, no significant difference in virologic and clinical outcomes was seen between the corticosteroid and control groups. This suggests there is no additional benefit to use of corticosteroids in COVID-19 patients who are not in acute respiratory distress syndrome (ARDS). There was an unplanned association found between prolonged viral clearance and hepatitis B virus (HBV) infection (mean difference: 10.6 days, P<0.001). However, this study is underpowered to detect a true association.
Clinical Implications	Early dosing of corticosteroids may not be indicated in patients presenting with mild COVID-19 and may not improve health outcomes or hospital length-of-stay. **Therefore, corticosteroids should be avoided unless indicated for other reasons.**
Limitations	The sample size was only 31 patients. It is not apparent what the inclusion and exclusion criteria were. Overall, the study population is younger (average age of 39) and all had a mild disease at presentation. The study is observational; trial and control groups were not randomized. The patients who received steroids did not all receive same daily dose or the same duration of treatment.

Creating a framework for conducting randomized clinical trials during disease outbreaks

Natalie E. Dean et al.

New England Journal of Medicine
April 2, 2020
DOI: 10.1056/NEJMsb1905390

Purpose	To address some of the challenges faced when conducting clinical trials during pandemics and proffer important recommendations.
Study design	Review
Level of evidence	N/A
Methods	This article closely observed the trends of two major randomized trials during the Ebola epidemic: The Partnership for Research on Ebola Virus in Liberia (PREVAIL) and Investigational Therapeutics for the Treatment of People with Ebola Virus Disease (PALM) conducted in Liberia and Congo (DRC).
Findings	Authors call for the implementation of a generalized protocol, which would serve as a reliable model across multiple infectious disease outbreaks. The details are as below: All clinical trials should be published regardless of the results or clinical outcomes as clearly stated in the Declaration of Helsinki. This serves to eliminate publication bias. Inconclusive results are useful to support the evidence of the safety and efficacy of the agent under investigation. The PREVAIL study using ZMapp did not show a clear efficacy, but ZMapp was the control used in the PALM trials. A Core or Master Protocol is being proposed to regulate the conduct of clinical trials during pandemics. Specifically, this proposal focuses on diseases that occur irregularly, yet still relatively frequently, like Ebola. Efficacy data should not be released from trials that have not been completed due to insufficient enrollment. In these cases, an independent monitoring team can use interim results to make recommendations on whether or not the trial should continue, but the investigators would not be made aware of the results of these analyses.
Clinical Implications	Common challenges of conducting clinical trials during an outbreak include unpredictable sample size, duration of outbreaks and geographic location. Regardless of the outcome of these clinical trials, they all provide important information to determine treatment and evaluate potential vaccines for emerging diseases only if they are designed under a "core protocol", which meets the conventional standards for licensure and is applicable to various infectious disease outbreaks.
Limitations	The conclusions of this review were drawn mostly from smaller scale disease outbreaks and failed to compare the conduction of clinical trials during pandemics.

COVID-19 infection and rheumatoid arthritis: Faraway, so close!

Ennio Giulio Favalli et al.

Autoimmunity Reviews
March 20, 2020
DOI: https://doi.org/10.1016/j.autrev.2020.102523

Purpose	To analyze the viral infectious risk in rheumatoid arthritis (RA) patients and the negative or positive effects of anti-rheumatic drugs used to treat SARS-CoV-2.
Study design	Systematic review
Level of evidence	Level 4
Methods	117 studies on the pathophysiology of COVID-19, the risk of viral infections in RA patients, and the impact of anti-rheumatic drugs on viral infections were reviewed.
Findings	Studies have shown that patients with RA have a significantly higher risk of serious (risk ratio, RR: 1.53) and hospitalized (RR: 1.88) infections. **An analysis showed that each 0.6 unit increase in Disease Activity Score 28 (DAS28) correlates to a 25% increased rate of infections requiring hospitalization (incident rate ratio, IRR: 1.25, P=0.03)** and 4% increased rate of outpatient infections (IRR:1.04, P=0.01). Risk of serious infections increased progressively in patients with low (adjusted IRR: 1.69) to moderate (adjusted IRR: 1.30) disease activity, showing that maintaining good disease control reduces infectious complications. Anti-rheumatic drugs such as Corticosteroids/nonsteroidal anti-inflammatory drugs (CS/NSAIDs), csDMARDs, bDMARDs, and tDMARDs were studied, showing that CS has negative effects on infections like MERS-CoV and SARS-CoV. There are no clear benefits from CS in patients with COVID-19. The use of csDMARDs without CS showed a small decrease mild infection risk (adjusted RR: 0.90) and was not associated with increased serious infection risk (adjusted RR: 0.92). Literature shows no increased risk of infection in patients receiving methotrexate (MTX) (RR: 1.14). RA patients taking bDMARDs have a slightly higher risk of infection (from 1.5- up to 2-fold) compared with csDMARDs. The risk of serious infection in RA patients taking tDMARDs/JAK inhibitors is roughly the same as bDMARDs.
Clinical Implications	The use of biologic disease-modifying drugs can be associated with potential increase of serious infections. Furthermore, poor control of RA disease activity in patients has an even greater infectious risk factor. RA patients are encouraged to continue treatment during the COVID-19 outbreak to prevent bridging therapy like corticosteroids, which may increase the risk of viral infection.
Limitations	Further research is needed on the effects of RA on respiratory viral infections like SARS-CoV-2.

Traditional Chinese and Western medicines jointly beat COVID-19 pandemic

Guang-chao Qing et al.

Chinese Journal of Integrative Medicine
May 2, 2020
DOI: 10.1007/s11655-020-3095-6

Purpose	To review the efficacy and propose the use of Chinese medicine (CM) combined with and Western medicine (WM) in in the treatment of COVID-19.
Study design	Retrospective observational review
Level of evidence	N/A
Methods	Authors reviewed four studies that implemented a combination of CM and WM in the treatment of patients with COVID-19. The studies investigated the combination of WM drugs arbidol and tocilizumab with CM drugs Toujie Quwen granules and Xuebijing injections. Integrated CM and WM treatment has been approved for clinical use according to the Handbook of Prevention and Treatment of the Pneumonia Caused by the Novel Coronavirus, which was issued by the Chinese authorities.
Findings	- Indexes such as serum amyloid A, lymphocyte percentage, creatine kinase isoenzyme MB, alanine transaminase, aspartate transaminase, and blood urea nitrogen in patients treated with combination medicine therapy recovered faster than those receiving WM alone. - Combination administration of Toujie Quwen and arbidol up-regulated the expression of peripheral blood CD4+/CD8+ and lymphocyte levels in 37 cases of mild COVID-19 while treatment with arbidol alone did not. - In a comparative study on 710 cases, patients treated with Xuebijing and WM reduced the mortality rate of severe pneumonic patients by 8.8% (p=0.006). It was also found that Xuebijing injection has certain antiviral and anti-inflammatory factors in vitro.
Clinical Implications	**The outbreak of COVID-19 in China has, for the most part, been contained. The combined therapy of CM and WM may prove to be more effective and economical in combating COVD-19 than administration of either medicine alone, according to the four studies reviewed in this paper.**
Limitations	The mechanisms and pathways through which CM and WM function together are not well-defined and require further investigation. Side effects, dosage, and drug-drug interactions should also be evaluated. There is a lack of randomized clinical trials for the proposed CMs.

Association of Renin-Angiotensin System Inhibitors with Severity or Risk of Death in Patients with Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China

Juyi Li et al.

JAMA Cardiology
April 23, 2020
DOI: 10.1001/jamacardio.2020.1624

Purpose	To determine whether patients with hypertension who are taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) have increased severity or risk of mortality during hospitalization for COVID-19.
Study design	Retrospective, single-center case series (n=1178; 362 with hypertension; 115 taking ACEI/ARBs)
Level of evidence	Level 4
Methods	Patients with COVID-19 (confirmed by real-time reverse transcription polymerase chain reaction) admitted to Central Hospital of Wuhan (Hubei Province, China) from January 15, 2020 to March 15, 2020, were stratified based on the severity of COVID-19 pneumonia symptoms. Hypertension was defined as a history of blood pressure of 140/90 mmHg or greater or a history of antihypertensive medication use. Statistical analysis was preformed on all 1178 patients hospitalized with COVID-19 to determine if there was a statistically significant difference in clinical severity or outcome for patients taking ACEIs/ARBs for their hypertension.
Findings	The frequency of severity of illness, acute respiratory distress syndrome, and mortality did not differ with respect to ACEI/ARB therapy. Similarly, the percentage of patients with hypertension taking any drug or drug combination did not differ between those with severe and nonsevere infections and nonsurvivors and survivors. The findings, however, confirm data that patients with hypertension have more severe illness and higher mortality rates than those without hypertension.
Clinical Implications	This study shows data to support the continuation of hypertensive medication during hospitalization for COVID-19.
Limitations	The study was limited by a small sample size of patients with hypertension on ACEI/ARB therapy who were hospitalized with COVID-19. In addition, the current findings may not be generalizable to all patient with hypertension and it is still possible that ACEIs/ARBs could affect the chance of hospitalization. It was also not certain whether ACEI/ARB treatment at baseline was maintained throughout the hospitalization for all patients.

Searching therapeutic strategy of new coronavirus pneumonia from angiotensin-converting enzyme 2: the target of COVID-19 and SARS-CoV

Shu-ren Li et al.

European Journal of Clinical Microbiology and Infectious Diseases
April 13, 2020
DOI: 10.1007/s10096-020-03883-y

Purpose	To summarize the role of angiotensin-converting enzyme 2 (ACE2) in multiple organ damage caused by COVID-19 and SARS-CoV, targeted blocking drugs against ACE2, and drugs that inhibit inflammation to provide a basis for further research, diagnosis and treatment, and drug development.
Study design	Review article
Level of evidence	N/A
Methods	This article is a summary of pre-existing literature.
Findings	ACE2 is responsible for the degradation of angiotensin II (AngII) and it is down-regulated after viral infections. This is thought to contribute to the inflammatory response. **An imbalance of the AngII signaling system is thought to play an important role in end organ damage.** ACE2 is widely distributed and appears to be involved with the damage seen in various tissues (specifically cardiac, kidney, testicular, liver, and intestines). As such, cardiac damage is a concern in high-risk groups with COVID-19. Due to the potential pathophysiology in the gastrointestinal (GI) tract, there is the possibility for fecal-oral transmission of COVID-19. **The use of ACE inhibitor in COVID-19 patients is still controversial and there are conflicting theories surrounding whether ACEIs are beneficial or harmful in these patients**. There are some small molecules on the market that target ACE2 and they have been shown to be effective at blocking SARS-CoV infection. However, the key amino acids in the SARS S protein that interact with ACE2 don't seem to be conserved in COVID-19 and there is no data to show whether these molecules are effective for COVID-19. In a study done in spontaneously hypertensive rats, a decrease in thrombotic ACE2 activity was associated with an increase in thrombosis.
Clinical Implications	Be aware of the potential for fecal-oral transmission, cardiac damage in high risk groups, testicular and renal involvement and abnormal coagulation in COVID-19 patients
Limitations	It is reasonable to believe that ACE2 plays a role in the pathophysiology of COVID-19, but the clinical significance remains to be determined.

Prevention and Therapy of COVID-19 via Exogenous Estrogen Treatment for Both Male and Female Patients; An Opinion Paper

Zsuzanna Suba

Journal of Pharmacological Sciences
April 22, 2020
DOI: 10.18433/jpps31069

Purpose	To discuss the proposed efficacy of Exogenous estrogen therapy in COIVD-19.
Study design	Opinion paper
Level of evidence	N/A
Methods	Authors review the epidemiology of COVID-19 disease (caused by SARS-CoV-2) in humans and animal models of SARS-CoV that studied the effects of estrogen on pathogenesis and outcome of SARS-CoV disease.
Findings	**Patient demographics for COVID-19 disease (caused by SARS-Cov-2) at the time of this publication show that males more often experience disease and have higher mortality than women. Literature exists for SARS-CoV murine experiments that demonstrate an estrogen protective effect.**
Clinical Implications	The authors speculate that exogenous estrogen treatment may be beneficial for men experiencing COVID-19 disease.
Limitations	The authors provide a somewhat unorthodox approach for treatment for COVID-19 disease in males. Nevertheless, prospective clinical studies might be warranted, i.e., determine the efficacy of exogenous estrogen treatment for COVID-19 disease in men.

Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment.

Zhenwei Wang et al.

BioScience Trends
March 16, 2020
DOI: https://doi.org/10.5582/bst.2020.01030

Purpose	To determine the efficacy of antiviral treatment, alongside traditional Chinese medicine such as Shufeng Jiedu Capsule (SFJDC) on subjects with COVID-19 associated pneumonia.
Study design	Retrospective case series (n = 4)
Level of evidence	Level 4
Methods	Baseline data were collected using medical records of 4 patients that were admitted to Shanghai Public Health Clinical Center in Shanghai, China. Throat swabs were obtained from the upper respiratory tract and RT-PCR was performed for COVID-19 diagnosis. All patients were also given CT or chest radiograph. Patients were diagnosed as having COVID-19 associated pneumonia on admission and they were followed from January 21st-24th, 2020 to February 4th, 2020. All patients were treated with combined Lopinavir 400 mg/Ritonavir 100 mg, q12h, po (HIV medication), Arbidol 0.2 g, tid, po, (an antiviral treatment for influenza infection used in China and Russia) and Shufeng Jiedu Capsule 2.08 g, TID, PO (Chinese medicine used to treat influenza), for 6-15 days.
Findings	All patients exhibited common symptomatology and exhibited ground-glass opacities and consolidation were the most common radiological findings. Using the combination medication, 3 of the 4 patients showed improvement. Two of those patients tested negative for COVID-19 following treatment and were discharged. The patient with severe pneumonia was given an intubated ventilator-assisted breathing therapy, as well as human seroalbumin and y-immunoglobulin.
Clinical Implications	The study indicates a favorable outcome for the combined treatment; however, further verification of this method is warranted.
Limitations	This study was limited by its small sample size, as well as a very short clinical follow up period. The efficacy of antiviral treatment using these agents warrants further investigation. The MOA of Arbidol and SFJDC is unknown, so cannot determine drug interactions or pharmacologic implications.

Flooded by the Torrent: The COVID-19 drug pipeline

Asher Mullard

Lancet
April 18, 2020
DOI: https://doi.org/10.1016/S0140-6736(20)30894-1

Purpose	To discuss the current state of clinical trials for COVID-19 treatments.
Study design	Opinion
Level of evidence	N/A
Methods	This is an opinion piece written after interviews with researchers and medical executives. It looks at the current state of clinical trials for COVID-19 treatments and focuses on the new umbrella trial called Solidarity developed by the WHO. It also mentions other large-scale trials such as the RECOVERY trial in the UK. The key defining feature of these trials is their large scale, and multi-arm design allowing them to study multiple drugs at once across a wide population. The author posits that trials such as these or those that align their criteria and outcomes will be most beneficial in determining efficacy of new treatments.
Findings	Participation in large multicenter, international umbrella clinical trials, such as the WHO's Solidarity trial, should be the priority for testing treatments for COVID-19. Small case-reports and multiple individual studies with different criteria make it difficult to draw large scale conclusions about efficacy. Enrolling as many and as diverse of a population as possible with improve data collection. Organizations creating their own trials should attempt to align their criteria and clinical determinants with other studies to improve generalizability and make merging of databases possible in the future. For the drug pipeline to work effectively there will also need to be coordination at the levels of manufacturing, regulation, supply and access.
Clinical Implications	· **Researchers considering starting their own trials should first determine if they can fit within currently active large-scale trials rather than on their own.** · **Researchers conducting their own trials should review other articles and attempt to align their criteria to other studies underway.** · Small-scale studies and case reports may not be generalizable and may not help determine efficacy of new treatments.
Limitations	This is an opinion piece written by one author. While it includes quotes from other sources their opinions may not be representative of the field. Author interviewed researchers directly involved in the studies the article supports, they are not un-biased opinions.

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

Qingxian Cai et al.

Engineering
March 18, 2020
DOI: 10.1016/j.eng.2020.03.007

Purpose	Evaluate the effects of Favipiravir (FPV) compared to Lopinavir (LPV)/Ritonavir (RTV) for treatment of COVID-19 pneumonia.
Study design	Open-label non-randomized control study (n= 80)
Level of evidence	3
Methods	In the experimental arm of the study, 35 patients with laboratory-confirmed COVID-19 received oral FPV (Day 1: 1600 mg 2x/day; Days 2-14 600 mg 2x/day). In the control group, 45 patients with laboratory-confirmed COVID-19 were treated with LPV/RTV (Days 1-14: 400 mg/100mg 2x/day). Both groups were also treated with IFN-alpha by aerosol inhalation. Patients with severe clinical condition were excluded from the study. Treatment was continued with anti-viral therapy until viral clearance was attained or until 14 days had passed. The primary endpoints were time to viral clearance and the improvement rate of chest computed tomography (CT) scans on Day 14 after treatment.
Findings	The median time of viral clearance (Kaplan-Meier survival curves) for patients treated with FPV was 4 days compared to patients treated with LPV/RTV, which was 11 days. After controlling for confounding factors, antiviral therapy when comparing FPV to LPV/RTV had a Hazard Ratio = 3.434 and 95% Confidence Interval = 1.162-10.148 demonstrating that FPV had a greater effect on viral clearance. Patients treated with FPV had a greater improvement rate in CT on day 14 after treatment compared to the control arm of the study (91.4% compared to 62.2%, P=.004) In the FPV treated group, 4 patients (11.43%) experienced adverse reactions (diarrhea, liver injury and poor diet). In the group treated with LPV/RTV, 25 patients (55.56%) experienced adverse reactions (diarrhea, vomiting, nausea, rash, liver injury, chest tightness and palpitations).
Clinical Implications	-**Both CT imaging and time to viral clearance showed greater improvement in patients treated with RPV compared to LPV/RTV, demonstrating better treatment outcomes in the FPV group.** -These clinical results should be confirmed with a Randomized Control Trial (RCT), to better understand both the adverse effects of each medication as well as their clinical efficacy.
Limitations	The study was limited by a small sample size, inherent selection bias in patient recruitment and a lack of randomization. Because patients with severe clinical condition were excluded from the study, the results may be less applicable to any patients with a more severe clinical course.

A SARS-CoV2 Protein Interaction Map reveals targets for drug repurposing

David E. Gordon et al.

Nature
April 30, 2020
DOI: https://doi.org/10.1038/s41586-020-2286-9

Purpose	To identify potential human proteins or host factors associated with CoV-2 that can be targeted by drug therapy.
Study design	Laboratory study
Level of evidence	Level 5
Methods	Researchers aimed to identify potential COVID-19 therapeutic targets by systematically exploring the host dependencies of the SARS-CoV2 virus to identify other host proteins already targeted by existing drugs. This was done by systemically mapping the interaction landscape between SARS-CoV-2 proteins and human proteins by identifying PPI's (SARS-COV-2 Human Protein-Protein Interactions). Two in vitro viral assays were used to test antiviral activity of the selected drugs.
Findings	-Identified 332 high confidence SARS-Cov-2 human PPIs connected to **multiple biologic processes, including protein tracking, translation, transcription and ubiquitination.** -Against the 332 targets they **identified 69 drugs (ranging from FDA approved drugs, drugs in clinical trails, and investigational drugs not yet currently in clinical trials)** that can target SARS-COV2 PPI's (Please see article for full proposed drug list) - Antiviral tests revealed two broad sets of active drugs and compounds that are proposed to have a high therapeutic benefit: **those impairing translation and those modulating Sigma1 and Sigma2 receptors.** - Approved drugs like Clemastine and Cloperastine, currently used as antihistamines and antitussives, do not have clear roles sustainable for antiviral therapy. Based on their side effect profile, the authors caution against their use in treatment outside of control studies. - **Dextromethorphan has been shown to harbor proviral activity and increase viral titers** possibly worsening disease course, thus, it's use in treatment should merit caution.
Clinical Implications	- Dozens of approved drugs are active against Sigma receptors; this has great promise for repurposing and the optimization of these new agents in the fight against COVID-19. - Host-directed intervention as an antiviral strategy overcomes problems associated with drug resistance and also can provide pan-viral therapies as we prepare for the next pandemic.
Limitations	While the cells used in the study have been proved to be permissive to SARS-CoV2 infections, it does not represent the physiological site of infection - the lung tissue. As a result, there is a risk that some of the findings in the study may not apply as successfully clinically. Additionally, this study is limited simply in this mechanistic based reasoning. All hypotheses require further study to identify the clinical effectiveness of these proposed therapies.

Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

Muthiah Vaduganathan et al.

The New England Journal of Medicine
April 23, 2020
DOI: 10.1056/NEJMsr2005760

Purpose	To highlight the current data on the use of renin-angiotensin-aldosterone system (RAAS) inhibitors in patients with Covid-19 and to discuss the possible harm of withdrawal of these agents during treatment for Covid-19.
Study design	Special Report
Level of evidence	Level 5
Methods	This special report reviewed the limited studies available describing the relationship between RAAS via angiotensin-converting enzyme 2 (ACE2) and severe acute respiratory syndrome coronaviruses. It then posits a possible benefit for continued use of RAAS inhibitors in patients with Covid-19, as well as describing the harms of withdrawal of these agents.
Findings	The principle cellular receptor for SARS-CoV-2 in lung alveolar epithelial cells is ACE2, an enzyme that counters RAAS activation. Preclinical studies suggest that RAAS inhibitors increase ACE2 expression, thereby increasing risk of SARS-CoV-2 infection. This is further supported by the high proportion of patients with hypertension admitted with Covid-19 in China. Experimental animal models and small human studies have also suggested a possible benefit in disruption of the RAAS system in patients with Covid-19 by interrupting acute lung damage mediated by the ACE2 receptor and providing cardioprotection with promotion of myocardial recovery after viral infection.
Clinical Implications	No guidance currently exists for use of RAAS inhibitors in patients with Covid-19. Due to the possibility of adverse health outcomes, abrupt withdrawal of RAAS inhibitors in patients with high-risk conditions (including those who have heart failure or have had myocardial infarction) is not preferable. This report recommends maintaining stable patients on their previously prescribed RAAS inhibitors while being treated or evaluated for Covid-19 since these medications likely do not alter Covid-19 risk.
Limitations	Authors note that the data available in humans is too limited to currently support or refute either the use or discontinuation of RAAS inhibitors in patients with Covid-19 to maintain cardiovascular health.

Interleukin-1 Blockade with High-dose Anakinra in Patients with COVID-19, Acute Respiratory Distress Syndrome, and Hyperinflammation: A Retrospective Cohort Study

Giulio Cavalli et al.

The Lancet Rheumatology
May 7, 2020
DOI: https://doi.org/10.1016/S2665-9913(20)30127-2

Purpose	To determine the efficacy of treatment with Anakinra (recombinant Interluekin-1 receptor antagonist) in patients with moderate to severe COVID-19.
Study design	Retrospective cohort study
Level of evidence	Level 3
Methods	This study was conducted in patients with COVID-19 complicated by moderate-to-severe acute respiratory distress syndrome and hyperinflammation (defined as a serum C-reactive protein >100mg/L, Ferritin >900ng/mL, or both) managed with non-invasive ventilation outside of the ICU. Patients received 200mg hydroxychloroquine twice a day orally and 400mg lopinavir with 100mg ritonavir twice a day orally (standard treatment group). These patients were compared to a cohort who received additional treatment with anakinra (either 5mg/kg twice a day IV [high dose] or 100mg twice a day subcutaneously [low dose]). 29 patients received high dose anakinra with standard treatment, 7 received low dose anakinra with standard treatment, and 16 received stranded treatment alone. The primary endpoint was to compare survival, mechanical ventilation free survival, changes in CRP, respiratory function, and clinical status of each subgroup as assessed at 21 days.
Findings	At 21 days, 72% of patients receiving high dose anakinra demonstrated a decrease in serum C-reactive protein and progressive improvement in respiratory function, survival rate was 90%, and mechanical ventilation-free survival rate was 72%. 50% of patients receiving standard therapy showed respiratory improvement and reduction in serum C-reactive protein at 21 days, with a survival rate of 56% and mechanical ventilation-free survival rate of 50%. Discontinuation of anakinra was not followed by inflammatory relapse.
Clinical Implications	In patients with COVID-19 and ARDS managed with non-invasive ventilation outside of the ICU, **treatment with high-dose anakinra in addition to standard therapy was safe and associated with superior clinical improvement when compared to standard therapy alone**.
Limitations	The retrospective nature and relatively small sample size of cohorts limited the interpretation of the results and precluded the ability to make definitive conclusions. Additionally, this study lacked a control group which requires caution before considering high-dose intravenous anakinra as an anti-inflammatory treatment for COVID-19.

Myth Busters: Dietary Supplements and COVID-19

Kathleen K. Adams et al.

Annals of Pharmacotherapy
May 12, 2020
DOI: https://doi.org/10.1177/1060028020928052

Purpose	To review the theoretical mechanisms and current evidence of the efficacy and safety of select supplements in treatment and prevention of COVID-19 infection.
Study design	Review article
Level of evidence	Level 5
Methods	Authors reviewed recent evidence-based literature on supplements and COVID-19 infection. The study focused specifically on vitamin C, vitamin D, zinc, elderberry, and silver supplements, which were those most frequently mentioned in the news and social media. Studies were not reviewed systematically.
Findings	**Vitamin C (Vit C):** Evidence does not support its use for prevention of viral infections and shows only limited benefits of intravenous (IV) administration for acute respiratory distress syndrome and shock. Chinese studies have reported shorter hospital stays for COVID-19 patients treated with high-dose IV Vit C, but these investigations are under powered and use much higher doses than that available over the counter (OTC). **Vitamin D (Vit D):** COVID-19 patient data has shown a high prevalence of hypovitaminosis D. Studies have demonstrated that oral Vit D3 supplementation can reduce the risk of acute respiratory tract infection, particularly in those with low 25-hydroxyvitamin D levels (<25ng/mL). Patients should follow the recommended daily allowance of Vit D (800-4000IU). **Zinc:** Studies on supplementation are mixed with only moderate evidence supporting reduction in common cold symptoms. Although reports on zinc consumption for the management of COVID-19 are beginning to emerge, no literature is currently available on its supplementation in the context of COVID-19. **Elderberry:** Some studies support its use to reduce viral respiratory symptom duration, but they are underpowered and of poor quality. Elderberry may cause several serious adverse effects by interacting with other drugs and its unripe berries are toxic. There is no evidence to support its use in COVID-19. **Silver:** Colloidal silver has been claimed to be antibacterial and antiviral, however the safety and efficacy are poor. OTC products containing silver are not recognized as safe or effective due to the potential for harmful adverse effects, including neurotoxicity.
Clinical Implications	Physicians and pharmacists should be aware that news and social media may influence a patient's supplement use in the context of COVID-19 infection. None of the above-mentioned supplements are currently recommended for COVID-19 prophylaxis or treatment and some may cause serious adverse effects. Healthcare workers should inquire if a patient is using supplements to prevent or treat COVID-19 and be prepared to educate about risks.

SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19?

Gabriela Kuster et al.

European Heart Journal
March 20, 2020
DOI: https://doi.org/10.1093/eurheartj/ehaa235

Purpose	To discern whether the administration and/or initiation of renin-angiotensin system (RAAS) inhibiting therapies would be contraindicated in patients diagnosed with or at high risk for contracting SARS-CoV2.
Study design	Systematic review
Level of evidence	Level 3
Methods	Review of 23 studies relevant to the interaction between RAAS and SARS-CoV2 was completed, integrating mechanistic data from human and animal studies to reach a recommendation concerning the maintenance and initiation of RAAS-inhibiting therapy in COVID-19 patients.
Findings	Initial data suggests that patients with diabetes, hypertension and cardiovascular disease (populations treated with RAAS inhibitors) are 3-4x more likely to reach the primary endpoints of ICU admission, mechanical ventilation or death secondary to SARS-CoV2 infection, suggesting a possible relationship between RAAS inhibitors and COVID-19 mortality. Animal studies and human trials suggest ACE2 upregulation following ACE-Inhibitor (ACE-I) or Angiotensin II receptor blockers (ARB) therapy. Though ACE2 has been established as a receptor for viral cell entry, there is not an established causal relationship between ACE2 expression and COVID-19 severity or mortality. Additionally, SARS-CoV2 has been found in cell types not expressing ACE2, suggesting that the presence of ACE2 alone may not be sufficient for infection. Conversely, a mouse model demonstrated down-regulation of ACE2 with SARS-CoV spike protein exposure; this study also established that ARB administration provided protection from COVID-19 associated lung injury. This gave rise to the theory that RAAS activation may be a greater risk factor for SARS-CoV2 associated mortality than RAAS inhibition. **Due to the lack of data and inability to establish a causal relationship between RAAS inhibiting therapies and COVID-19 mortality, the risk-benefit ratio would favor maintenance of ACE-I and ARB therapies in patients with cardiovascular disease**. It has been well established that discontinuation of RAAS inhibition progresses to deterioration of cardiac function within days-weeks with significant increase in mortality.
Clinical Implications	Due to the lack of relationship between RAAS inhibitors and COVID-19 mortality, maintenance and/or initiation of ACE-Is, ARBs and MRAs in patients with heart failure, hypertension or myocardial infarction is recommended regardless of SARS-CoV2 status.
Limitations	It is not yet possible to establish a causal relationship between ACE-I or ARB therapies and COVID-19 mortality due to confounding comorbidities. Further research is indicated. Additionally, more research is needed to characterize the relationship between SARS-CoV2 viral load, disease severity, ACE2, the RAAS system and therapies that alter the RAAS.

Early Outcomes with Utilization of Tissue Plasminogen Activator in COVID-19 Associated Respiratory Distress: A Series of Five Cases

Benjamin Christie III et al

Journal of Trauma and Acute Care Surgery
May 21, 2020
DOI: https://doi.org/10.1097/ta.0000000000002787

Purpose	To assess the efficacy of a thrombolytic agent, Tissue Plasminogen Activator (tPA), in treating respiratory distress and hypoxemia in patients with COVID-19.
Study design	Retrospective case series (n=5)
Level of evidence	Level 5
Methods	This retrospective case series examines the effects of tPA administration of five patients meeting certain criteria including: positive COVID-19 test, decline in respiratory function, PaO2 < 80 indicating severe hypoxemia despite standard supportive actions, increasing requirements for supplemental oxygen, and a D-dimer result > 1.5ug/mL. An initial 25 mg IV bolus of tPA was administered over two hours with a subsequent 25 mg continuous infusion of tPA over 22 hours, after which a heparin infusion was administered in a weight-based manner. Several outcomes are assessed post-tPA, with an emphasis on PaO2, supplemental oxygen requirements, and d-dimer.
Findings	All patients showed an improvement in their respiratory function following tPA administration and suffered no deleterious effects secondary to tPA use. Each patient's PaO2 levels showed a higher post-tPA than pre-tPA and increased over time. Supplemental oxygen requirements tended to decrease after treatment and three out of the five patients were able to avoid intubation. Patients' d-dimer levels increased during a 24-hour post-tPA period as expected and returned to normal or near-normal levels after administration of a heparin drip.
Clinical Implications	This study suggests that tPA may be a promising treatment option for hypoxemia in COVID-19 patients seeing as administration of tPA was associated with a rise in PaO2 levels and decreasing supplemental oxygen requirements. However, further studies and clinical trials will be necessary to verify these findings.
Limitations	Limitations noted by the authors include a lack of controls, unknown significance of various non-thrombolytic medications patients received during their hospital stay, and administration of tPA at varying points of disease progression in patients. Additionally, the limited number of participations (n=5) makes it difficult to determine the generalizability of the findings.

Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19)

Neil Mehta et al.

JAMA Cardiology
May 5, 2020
DOI: 10.1001/jamacardio.2020.1855

Purpose	To determine the association of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) use with testing positive for coronavirus disease 2019 (COVID-19) and to study the severity of clinical outcomes of those taking ACEIs/ARBs who tested positive for COVID-19.
Study design	Retrospective Cohort Study (n=18,472)
Level of evidence	Level 3
Methods	A retrospective cohort analysis was performed on all patients tested for COVID-19 between March 8 and April 12, 2020 within the Cleveland Clinic Health System in Ohio and Florida using data from electronic health records (EHRs). Primary analysis examined the association of SARS-CoV-2 test positivity and use of ACEI and/or ARB using overlap propensity score weighting. Secondary analysis included clinical outcomes of patients with positive test results.
Findings	The mean age of the patients was 49 years, 7384 (40%) were male, and 12 725 (69%) were white. Of the patients tested for COVID-19, 2285 (12.4%) were taking ACEIs or ARBs at the time of testing. Among all patients with positive test results (1735, 9.4%), 116 (6.7%) were taking ACEIs, and 98 (5.6%) were taking ARBs. Comparing test positivity rate of those taking ACEIs or ARBs and those who did not, the **investigators found that taking either an ACEI or ARB was not associated with an increased likelihood of testing positive for SARS-CoV-2 infection.** Additionally, overlap propensity score-weighted analysis showed higher likelihood of hospital admission in those who tested positive and were taking either ACEIs or ARBs, and higher likelihood of ICU admissions for those taking ACEIs.
Clinical Implications	ACEIs and ARBs are important medications in the management of cardiovascular disease and diabetes, and may impose serious health risks if withdrawn. This study suggests there is no association between ACEI/ARB use and increased likelihood of testing positive for COVID-19. Therefore, ACEIs and ARBS should continue to be used during the COVID-19 pandemic, as recommended by several professional societies.
Limitations	This analysis was performed early in the course of the pandemic with a small sample of ACEI and ARB users; therefore, it needs to be repeated with larger data sets and later in the course of the pandemic. Additionally, data did not include information on the duration of ACEI or ARB use, thus the effect of duration could not be considered. Furthermore, medication lists in EHRs are sometimes inaccurate due to patient noncompliance and accidental omittance of medications. Finally, the majority of patients in the study were white, limiting the generalizability of the results.

Famotidine Use and Quantitative Symptom Tracking for COVID-19 in Non-Hospitalised Patients: A Case Series

Tobias Janowitz et al.

Gut

June 4, 2020

DOI: http://dx.doi.org/10.1136/gutjnl-2020-321852

Purpose	To examine the effects of famotidine use on several different symptoms in non-hospitalized COVID-19 patients.
Study design	Case series
Level of evidence	Level 4
Methods	Numerous data points were collected longitudinally from ten non-hospitalized COVID-19 patients taking high-dose famotidine orally . The most notable data points being severity scores for various symptoms including anosmia, headaches, fatigue, shortness of breath, and cough. Symptom severity scores were collected on a 4-point scale with 1 being "not affected," 2 being "little affected," 3 being "affected," and 4 being "severely affected." These scores were recorded one day prior to starting famotidine and ending 14 days after of famotidine use. Patients also provided a baseline score. Statistical analysis was run on combined symptom severity scores. Famotidine dosage was between 20 mg three times per day and 80 mg three times per day for 5-21 days, with the 80 mg regimen being the most common (n=6).
Findings	All ten patients experienced a self-reported improvement in symptoms after taking famotidine. **There was a significant improvement in the combined symptom severity score in the first 24 hours of famotidine use and this improvement continued until nearly baseline symptom scores were reached after 14 days of famotidine use.** Furthermore, all patients tolerated the famotidine well and only three reported mild side effects due to famotidine.
Clinical Implications	This case series is unique in terms of its use of patient-reported symptom tracking method for Covid-19. This quantitative method offers various advantages such as symptoms can be documented in a quantifiable way, experiences from many patients become comparable and can be pooled for analysis Results suggests that high-dose famotidine taken orally can be useful in improving COVID-19 related symptoms such as anosmia, headaches, fatigue, shortness of breath, and cough in an outpatient setting. Given these results, further evaluation of famotidine as a treatment for COVID-19 in non-hospitalized patients may be warranted.
Limitations	The authors note that recall bias, enrollment bias, and placebo effect may have affected this study seeing as it was not controlled or blinded. Furthermore, this study could not rule out an improvement of symptoms due to natural convalescence rather than famotidine use. Finally, the generalizability of these findings is unknown given the small sample size (n=10) and the fact that only non-critical patients not requiring hospitalization were studied.

Combination of thrombolytic and immunosuppressive therapy for coronavirus disease 2019: A case report

Panagiotis Papamichalis et al.

International Journal of Infectious Diseases
June 1st, 2020
DOI: 10.1016/j.ijid.2020.05.118

Purpose	To propose a treatment plan for SARS-CoV-2 patients through a combination of thrombolytic and immunosuppressive therapies.
Study design	Case Report
Level of evidence	Level 4
Methods	A 68-year old man positive for SARS-CoV-2 with a high-grade fever for over 10 days was presented to physicians. The patient had been taking antibiotics as well as an antiviral drug before admission, with no improvement, and required intubation due to respiratory failure and P/F ratio of 115 mmHg. This confirmed the criteria for moderate acute respiratory distress syndrome and labs were consistent with cytokine release syndrome. The patient was treated with anakinra from day 3 to day 10 of hospitalization. TThree days after anakinra was discontinued, his respiratory response significantly deteriorated (P/F ratio of 158 mmHg), capillary refill time increased, and dark hypoperfused regions appeared. His D-dimer levels increased from 4.9 µg/ml to 9.8 µg/ml , his ferritin increased from 2820 ng/ml to 3850 ng/ml and his CRP increased to 179 mg/l from 164 mg/l. He was treated with a 25 mg infusion of recombinant tissue plasminogen activator (rt-PA) over 2 hours and another 25 mg continuous infusion over 22 hours. Enoxaparin was administered for its potential anti-inflammatory effects. Eight hours after beginning rt-PA, the patient was administered 400 mg of tocilizumab over 2 hours.
Findings	The patient showed a positive response to combination treatment twelve hours after beginning rt-PA infusion. His capillary refill time normalized, extremities became warm, and his P/F ratio as well as his areas of ischemia improved. However, this improvement lasted 48 hours, after which the P/F ratio fell below 150 mmHg. The patient was eventually diagnosed with acute myeloid leukaemia (AML) and died of candidemia and Pseudomonas bacteremia 45 days later.
Clinical Implications	COVID-19 patients typically present with multiple syndromes due to immunothrombosis. Treating such patients with a combination of thrombolysis and immunosuppressive treatments may present a treatment option. Daily monitoring of D-dimer, CRP, and ferritin should be done to monitor the need for this intervention.
Limitations	This improvement was demonstrated in one patient, but further research and trials on additional patients are needed to observe its generalizability.

COVID-19: Melatonin as a potential adjuvant treatment

Rui Zhang et al. et al.

Life Sciences
June 01, 2020
DOI: 10.1016/j.lfs.2020.117583

Purpose	To gain insight into the use of melatonin as a potential add-on therapy in COVID-19.
Study design	Retrospective literature review
Level of evidence	Level 5
Methods	The authors discussed the pathogenesis of COVID-19 and where melatonin can exert its effects in the related pathways. They then cited evidence supporting the potential use of melatonin in similar clinical manifestations found in COVID-19.
Findings	- Although melatonin is not a direct anti-viral agent, **its effects of reducing oxidative stress**, inflammatory molecules (IL-1B, IL-2, IL-6, IL-8, IL-10, IFN-γ, TNF-α, VEGF) andand improving the proliferation and maturation of neutrophils, lymphocytes, CD8+ T cells **help mitigate the severity of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) found in COVID-19.** - Inflammation: Melatonin down-regulates NF-kB and induces regulation of NF-E2-related factor (Nrf2), which is an agent that helps reduce lung injury; **Melatonin reduces pro-inflammatory cytokines and up-regulates the production of IL-10 (an anti-inflammatory molecule)**. - Oxidative stress: Melatonin up-regulates anti-oxidative enzymes and down-regulates pro-oxidative enzymes; it also directly interacts with reactive oxygen species (ROS) thus preventing their effects. In multiple conditions that cause ALI (radiation, sepsis, brain ischemia, gastritis), **melatonin has been shown to produce anti-inflammatory actions via interactions with Toll-like receptor 4 (TLR4)**. - Immunomodulation: Melatonin promotes the proliferation and maturation of T cells, B cells, granulocytes, and monocytes in multiple tissue types. - Cytokine levels: Varying doses of melatonin reduce pro-inflammatory cytokines, such as TNF-α and IL-6, so it may reduce these in COVID-19 patients. - Supportive adjuvant effects: Experimental evidence demonstrates that **melatonin promotes the integrity of the vascular endothelial layer by suppressing VEGF in vascular endothelial cells.** Evidence also suggests that it protects against sepsis, myocardial infarction (MI), and other cardiovascular pathologies.
Clinical Implications	Melatonin has been shown to enhance the immune response by attenuating/reducing levels of pro-inflammatory/oxidative molecules, and by promoting anti-inflammatory/anti-oxidative molecules. Furthermore, melatonin promotes overall well-being by improving sleeping patterns.
Limitations	**There is no data on how melatonin affects COVID-19** since this was based on evidence in the context of infection-induced respiratory pathologies.

Effect of combination antiviral therapy on hematological profiles in 151 adults hospitalized with severe coronavirus disease 2019

Xin Li et al. 2020

Pharmacological Research, Elsevier Public Health Emergency Collection
June 18, 2020
DOI: https://doi.org/10.1016/j.phrs.2020.105036

Purpose	To find a new antiviral combination regimen by reviewing the frequency of clinically relevant and clearly identified comorbidities in patients hospitalized with severe COVID-19 by clustering clinical syndromes and varying results of treatment based on various antiviral drugs used to treat patients.
Study design	Retrospective Chart Review
Level of evidence	Level 3
Methods	A retrospective chart reviewed was performed on 151 patients diagnosed with severe COVID-19 infections that illustrated the clinical potential during a 25-day medication period. Potential differences in disease severity, clinical outcomes, hematological profile, comorbidity clusters and various pharmacologic treatments were analyzed.
Findings	Of the patients in cluster 1 (n = 96) with hematological indicators within normal limits and elevated D-dimer levels, 70.8% showed marked improvement in response to > Umifenovir (group 1), Umifenovir and Lianhua Qingwen (group 2), Umifenovir, ribavirin, and Lopinavir/Ritonavir (LPV/r) (group 3), and Umifenovir, Ribavirin, LV/r, Peramivir, Sodium Chloride, Oseltamivir, Penciclovir, and Ganciclovir (group 5). All patients in cluster 2 (n = 33) had severe cases and showed the greatest improvement ratio, 28/33 (84.9%) with combinatorial treatment with Umifenovir, Ribavirin, LPV/r, and Lianhua Qingwen. Patients in cluster 3 (n = 22) had the most severe cases, with 20/22 (90.9%) of patients classified as presenting with critical illness. These patients showed the least improvement in response to treatment with Umifenovir, Umifenovir and Lianhua Qingwen, Umifenovir, Ribavirin, and Lopinavir/ritonavir (LPV/r), and Umifenovir, Ribavirin, LPV/r, and Lianhua Qingwen. All improvement rates were found to be significant to P<1.001. However, no significance was determined across the treatment regimens within patient clusters 1 and 3.
Clinical Implications	T**he effects of the combination of Umifenovir, Rivavirin, LPV/r, and Lianhua Qingwen resulted in the greatest improvement rates for patients with severe COVID-19 conditions**. The effects of combinatorial treatment may be superior due to the different mechanisms of actions of the drugs targeting different components of viral infection and replication.
Limitations	Although patient improvement ratios were significant, within patient clusters the effects of combinatorial antiviral treatment versus a single drug must be studied in greater detail. Of the patients presenting with critical illness, 16/22 (72.7%) of the cohort were male. Understanding treatment outcomes in female populations with critical COVID-19 illness must be studied in greater depth. Umifenovir is not approved by the FDA in the United States and is used as an antiviral treatment for influenza infection in Russia and China. Lianhua Qingwen is a traditional Chinese medicine that is not approved for use in the United States by the FDA.

Integrated Survival Estimates for Cancer Treatment Delay Among Adults with Cancer During the COVID-19 Pandemic

Holly E Hartman et al.

Journal of American Medical Association Oncology
October 29, 2020
DOI: 10.1001/jamaoncol.2020.5403

Purpose	To develop an integrated web-based survival model to serve as a decision aid by providing personalized quantitative estimates of overall mortality for immediate or delayed cancer treatment conditions
Study design	Multicenter Retrospective Cohort Study
Level of evidence	Level 2B
Methods	Data werre extracted from the Surveillance, Epidemiology, and End Results database of the National Cancer Institute for age-specific and cancer-specific estimates of overall survival pre-COVID-19. 25 total cancer types were extracted from the data set from March17-May 21, 2020. For each cancer type, Cox proportional hazards and Fine and Gray regression models were used to estimate all-cause mortality and cancer-specific mortality as function of patient age and cancer stage. Data from 5,436,896 individuals were used to estimate the independent impact of treatment delay. Data from 275 patients in a nested case-control study were used to estimate the COVID-19 mortality rate. A daily risk of infection was calculated by intergrating probability of COVID-19 exposure, COVID-19 mortality and delay of cancer treatment. A web application (OncCOVID) calculated the estimates of the cumulative overall survival and restricted mean survival time of patients who received immediate vs. delayed cancer treatment.
Findings	OncCOVID model allows for selection of 47 inputs, 18 covariates (ex: age and comorbidities) and 29 parameter estimates (ex: HR for delay of treatment). **Substantial mortality variability existed between cancer type and stage of disease .** For example, this ranged from < 1% for Type I Thyroid Cancer to >80% for Glioblastoma Multiform**e. The model also has significant variability in estimated impact of delayed treatment between cancer types and stages.** For example, Harm of treatment delay outweighs COVID-19 specific mortality (ex: Pancreatic Cancer). A tiered system categorized patients who should receive immediate treatment, delayed treatment for brief interval, and potentially delayed treatment. OncCOVID was unable to distinguish between patients who benefitted most from the receipt of immediate vs. delayed cancer treatment.
Clinical Implications	OncCOVID application was created in hopes of improving current recommendations and providing quantitative estimates to optimize the outcomes of patients with cancer during the global pandemic. OncCOVID can be utilized by clinicans to optimize hospital resource allocation in a COVID-19 pandemic world where resource scarcity can exist.
Limitations	One of the major sources of information is the currently available COVID-19 Johns Hopkins data, which may be an under-representation of the total COVID-19 cases. Availability of chemotherapy regimens was treated as a binary variable in the model, not accounting for the variability in treatment regimens. Long-term health consequences from COVID-19 are currently unknown and the constantly evolving changes in COVID-19 policy can alter different variables within the model.

Monoclonal Antibodies for Prevention and Treatment of COVID-19

Mary Marovich et al.

JAMA

June 15, 2020

DOI: 10.1001/jama.2020.10245

Purpose	To discuss the clinical utility of monoclonal antibodies for prophylactic and therapeutic use against COVID-19.
Study design	Opinion/Literature Review
Level of evidence	Level 4
Methods	N/a
Findings	-SARS-CoV-2 monoclonal antibodies have the potential to be used for both prevention and treatment of COVID-19. -The target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells via the ACE-2 receptor. -Trials using convalescent plasma have reported a low number of adverse effects. -Even as a vaccine(s) becomes available, the weeks of time necessary to generate an effective immune response emphasizes the immediate benefit of preventative passive immunity, especially for our most vulnerable and at-risk populations. -Most challenges regarding the use of neutralizing monoclonal antibodies exist around the logistics of clinical research to prove efficacy in both prevention and treatment of COVID-19, especially in those who are asymptomatic or present with severe disease.
Clinical Implications	Although mRNA vaccine candidates are currently under expedited FDA review, it may still be months before vaccines are readily available to the general public, and even longer before widespread heard immunity is seen. In the meantime, neutralizing monoclonal antibodies provide an alternative avenue for the prevention and recovery of COVID-19. As several monoclonal antibody products enter clinical trial, a drug that reliably prevents the progression of disease, as well as provides a therapeutic tool, could help to reduce the uncertainty associated with SARS-CoV-2 infection.
Limitations	Prophylactic use of SARS-CoV-2 neutralizing monoclonal antibodies is not a long-term solution for prevention of the COVID-19 disease. Other limitations in the use of monoclonal antibody therapy include: the variability of binding and neutralizing titers, risk of transfusion reactions, the unknown bioavailability of passively infused IgG in tissues like the lungs, as well as the effect of viral diversity.

Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial

Renato D. Lopes MD, PhD

JAMA

January 19, 2021

DOI: https://www.doi.org/10.1001/jama.2020.25864

Purpose	To investigate whether discontinuation compared with continuation of ACEIs or ARBs changed the number of days alive and out of the hospital through 30 days in patients hospitalized with mild to moderate COVID-19
Study design	Randomized Clinical Trial
Level of evidence	Level 1
Methods	Patients with diagnosis of COVID-19 hospitalized at 29 different centers in Brazil who were taking either an ACEI or ARB prior to hospital admission were eligible for the study. Randomization was a 1:1 allocation ratio to continue or discontinue ACEI or ARB therapy for 30 days. The primary outcome for this study was the number of days alive and out of the hospital from randomization through 30 days. Secondary outcomes included length of hospital stay, cardiovascular mortality, COVID-19 progression, and incidence of other various systemic issues.
Findings	The total study population was 659 with 334 randomized to discontinue use of ACEI or ARB and 325 randomized to continue use of ACEI or ARB. The baseline characteristics were well-matched between the 2 groups with a median age = median age of 55.1 years (14.7% older than 70), 40.4% women. In participants, 16.7% were taking an ACEI and 83.3% taking an ARB for median of 5 years prior to randomization. T**he mean number of days alive and out of the hospital for patients randomized to discontinue was 21.9 days vs. 22.9 days for those who continued use of ACEI or ARB. The mortality rate at 30 days for patients randomized to discontinue was 2.7% vs. 2.8% for those that continued use of ACEI or ARB.**
Clinical Implications	**Discontinuing use of ACEI or ARB therapy for 30 days did not affect the number of days alive and out of the hospital for patients hospitalized with COVID-19.** There was no significantdifferences between groups in death, cardiovascular outcomes, or COVID-19 progression.
Limitations	The in-hopsital nature of this study may limit the generalizability of these results to patients with COVID-19 in other settings. There was a rather small population within the study of patients that took ACEI so it may not be plausible to make the results applicable to patients currently taking ACEI.

Covid-19: Pfizer's Paxlovid is 89% Effective in Patients at Risk of Serious Illness, Company Reports

Elizabeth Mahase

British Medical Journal
November 8, 2021
DOI: 10.1136/bmj.n2713

Purpose	To assess the efficacy of Pfizer's randomized control trial for paxlovid
Study design	Randomized Control Trial, Double-Blind
Level of evidence	1
Methods	Interim analysis was performed on 1219 participants who had enrolled in the Evaluation of Protease Inhibition for COVID-19 (EPIC – SR) by 29 September 2021. Patients who had laboratory-confirmed diagnosis of SARS-CoV-2 infection within a five-day period with mild-moderate symptoms and had at least one underlying medical condition associated with increased risk of illness from COVID-19. The study was performed in North & South America, Europe, Africa & Asia, with 45% of participants in the U.S. Patients were randomized 1:1 and received paxlovid or placebo q12hr for five days.
Findings	Individuals who received paxlovid treatment within 3 days of confirmed SARS-CoV-2 infection, the risk of hospitalization or death within 28 days after randomization from any cause was 89% lower than the respective risks associated with the placebo group. Of the individuals treated with paxlovid, 0.8% (3/389) were admitted to the hospital, whereas 7% (27/385) of the individuals in the placebo group were admitted, along with 7 deaths ($p<.0001$). Of individuals treated with paxlovid within 5 days of symptom onset, 1% (6/607) were admitted to the hospital compared to 6.7% (41/612) with 10 deaths in the control group.
Clinical Implications	The data presented suggests that paxlovid is significantly effective at reducing hospitalizations in individuals treated within 3- and 5-days of symptom onset of COVID-19. Therefore, this medication may help reduce the hospital-patient burden by preventing moderate-to-severe symptoms and death..
Limitations	The data regarding the efficacy of paxlovid is specific to the cohort of individuals with mild to moderate disease, and therefore may not be effective in individuals with severe disease.

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

Angélica Jayke Bernal et al.

The New England Journal of Medicine
December 26, 2021
DOI: https://doi.org/10.1056/NEJMoa2116044

Purpose	To evaluate the safety and efficacy of molnupiravir in non-hospitalized unvaccinated adults with mild-to-moderate laboratory confirmed COVID-19 and at least one risk factor for severe illness.
Study design	Double-blind, randomized, placebo-controlled trial (n= 1433)
Level of evidence	Level 2
Methods	Within 5 days of symptom onset, participants were randomized to receive either 800 mg PO molnupiravir or a placebo twice daily for 5 days. The primary endpoint was the incidence of hospitalization for any cause or death at day 29. The secondary endpoint was improvement or progression of signs and symptoms of COVID-19
Findings	At interim analysis (n= 775) the rate of hospitalization or death in the molnupiravir group was 7.3% (28 of 385 participants) compared to the placebo 14.1% (53 of 377) (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; P=0.001). In the analysis of the entire study group, risk of hospitalization or death for the molnupiravir group was 6.8% (48 of 709) and for the control group it was 9.7% (68 of 699) [difference, −3.0 percentage points; 95% confidence interval, −5.9 to −0.1]. There was one death in the molnupiravir group and 9 in the control. Adverse effects were reported in 30.4% (216 of 710) in the molnupiravir group and 33% (231 of 701) in the control group. The most common adverse effects were COVID pneumonia, bacterial pneumonia, worsening COVID-19, and diarrhea. The molnupiravir group showed a greater improvement in COVID symptoms compared to the control group.
Clinical Implications	Molnupiravir was found to decrease rates of hospitalization and death associated with COVID-19 in unvaccinated adults with risk factors for severe COVID infection. There were no safety concenres associated with molnupiriavir.
Limitations	This study was limited by its sample size. Both groups had fairly low rates (6.8% vs 9.7%) of hospitalization or death limiting the analysis of the difference between the two groups. There were more women in the placebo group who have a lower risk for severe disease; however, post hoc analysis adjusted for sex was consistent with the primary analysis.

Early Remdesivir to Prevent Progression to Severe COVID in Outpatients

Robert Gottlieb et al.

The New England Journal of Medicine
December 22, 2021
DOI: 10.1056/NEJMoa2116846

Purpose	To determine if remdesivir is effective at preventing the progression of COVID-19 in non-hospitalized symptomatic patients with a high risk of disease progression.
Study design	Randomized controlled trial (n=562)
Level of evidence	Level 2
Methods	Patients were recruited from medical sites in the US, UK, Spain, and Denmark between September 2020 and and April 2021. All patients were ≥ 12 years old, had a confirmed COVID-19 infection with symptoms, were not hospitalized, had not received a COVID-19 vaccine, and had ≥ 1 risk factor making them susceptible to progression to severe disease. Risk factors for progression to severe disease included age ≥ 60, particular medical conditions, and obesity. Patients were separated into a treatment group (n=279) and placebo group (n=283). The treatment group received 200 mg IV remdesivir on the first day of the study and 100 mg IV remdesivir the following 2 days. Primary endpoints included hospitalization due to COVID-19 or death by day 28 and adverse events. The secondary endpoint was a medical visit due to COVID-19 or death by day 28.
Findings	Two patients (0.7%) in the treatment group experienced hospitalization due to COVID-19 compared to 15 patients (5.3%) in the placebo group (hazard ratio = 0.13, 95% CI 0.03-0.59). Four patients (1.6%) in the treatment group had a medical visit related to COVID-19 compared to 21 patients (8.3%) in the placebo group (hazard ratio = 0.19, 95% CI 0.07-0.56). Zero patients died by the 28th day. Within the treatment group, 42.3% of patients experienced an adverse event compared to 46.3% in the placebo group. Overall, 3 days of remdesivir lowered the risk of hospitalization or death by 87% and lowered the risk of a medical visit related to COVID-19 by 81% compared to placebo.
Clinical Implications	This study suggests that remdesivir is a safe and effective way to prevent progression to severe COVID-19 in non-hospitalized high-risk patients with symptomatic COVID-19.
Limitations	This study underrepresented Black and Asian patients, patients with chronic liver or kidney disease, patients with cancer, and immunocompromised patients. Additionally, a majority of patients were from the US, possibly limiting the generalizability of these findings. Furthermore, this study took place before the delta or omicron variants emerged and thus cannot speak to the effects of remdesivir against these variants. Finally, the study did not include patients vaccinated against COVID-19.