COVID-19: Prospective therapies – evidence / guidance

- Mahase, E. **NEWS: Covid-19: what treatments are being investigated?** *BMJ* (2020): 368, doi: https://doi.org/10.1136/bmj.m1252

  With no current specific treatment for covid-19, the race is on to develop or repurpose drugs to help end the epidemic. The World Health Organization has now launched the SOLIDARITY trial to investigate four potential treatments: remdesivir, chloroquine/hydroxychloroquine; lopinavir and ritonavir; and lopinavir and ritonavir plus interferon-β.1 The trial will not be double blind, as WHO said it needed to find a balance between gold standard research practice and speed, but it will include thousands of patients from several countries. These are not, however, the only treatments being considered for covid-19. Here is a breakdown of the drugs that have been suggested so far:-
    - *Chloroquine*
    - *Lopinavir and ritonavir (Kaletra)*
    - *Interferon β 1a (SNG001)*
    - *Remdesivir*
    - *Tocilizumab (Actemra)*
    - *Favipiravir (Avigan)*

Convalescent Plasma

- Roback, JD & Guarner, J. **Editorial: Convalescent Plasma to Treat COVID-19: Possibilities and Challenges**. *JAMA* (2020): Published online March 27, 2020. doi:10.1001/jama.2020.4940. https://jamanetwork.com/journals/jama/fullarticle/2763982

- Shen, C. et al. **Preliminary communication: Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma**. JAMA (2020): Published online March 27, 2020. doi:10.1001/jama.2020.4783. https://jamanetwork.com/journals/jama/fullarticle/2763983

  Case series

  Importance: *Coronavirus disease 2019 (COVID-19) is a pandemic with no specific therapeutic agents and substantial mortality. It is critical to find new treatments.*

  Objective: *To determine whether convalescent plasma transfusion may be beneficial in the treatment of critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.*

  Design, Setting, and Participants: *Case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; Pao2/Fio2 <300; and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.*

  Exposures: *Patients received transfusion with convalescent plasma with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA]) and a neutralization titer greater than 40 (end point dilution titer) that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission.*

  Main Outcomes and Measures: *Changes of body temperature, Sequential Organ Failure Assessment (SOFA) score (range 0-24, with higher scores indicating more severe illness), Pao2/Fio2, viral load, serum antibody titer, routine blood biochemical index, ARDS, and ventilatory and extracorporeal membrane oxygenation (ECMO) supports before and after convalescent plasma transfusion.*

  Results: *All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and Pao2/Fio2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.*

  Conclusions and Relevance: *In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.*

- Casadevall, A. & Pirofski, L. **Viewpoint: The convalescent sera option for containing COVID-19.** *The Journal of Clinical Investigation* (2020): https://doi.org/10.1172/JCI138003
  Review
  As of early 2020, humanity is confronting a pandemic in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 causes coronavirus disease, abbreviated as COVID-19. At the time of this writing, SARS-CoV-2 is spreading in multiple countries, threatening a pandemic that will affect billions of people. This virus appears to be a new human pathogen. Currently there are no vaccines, monoclonal antibodies (mAbs), or drugs available for SARS-CoV-2, although many are in rapid development and some may be available in a short time. This Viewpoint argues that human convalescent serum is an option for prevention and treatment of COVID-19 disease that could be rapidly available when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing serum

Chloroquine and Hydroxychloroquine

- **Chloroquine and Hydroxychloroquine not licensed for coronavirus (COVID-19) treatment**
  Medicines and Healthcare products Regulatory Agency (25/03/2020)
  https://www.gov.uk/government/news/chloroquine-and-hydroxychloroquine-not-licensed-for-coronavirus-covid-19-treatment

    - *Chloroquine and hydroxychloroquine are not licensed to treat COVID-19 related symptoms or prevent infection.*
    - *Clinical trials are ongoing to test chloroquine and hydroxychloroquine as an agent in the treatment of COVID-19 or to prevent COVID-19 infection. These clinical trials are still not completed, so no conclusions have been reached on the safety and effectiveness of this medicine to treat or prevent COVID-19.*
    - *Until we have clear, definitive evidence these treatments are safe and effective for the treatment of COVID-19, they should only be used for this purpose within a clinical trial*

- Touret, F. & de Lamballerie, X. **Commentary: Of chloroquine and COVID-19.** *Antiviral Research* (2020): 177. https://doi.org/10.1016/j.antiviral.2020.104762
  Review/Commentary
  Recent publications have brought attention to the possible benefit of chloroquine, a broadly used antimalarial drug, in the treatment of patients infected by the novel emerged coronavirus (SARS-CoV-2). The scientific community should consider this information in light of previous experiments with chloroquine in the field of antiviral research.

- Cortegiani, A. et al. **A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19**. *Journal of Critical Care* (2020): In Press, Corrected Proof.
  https://doi.org/10.1016/j.jcrc.2020.03.005
  Systematic Review
  Purpose: *COVID-19 (coronavirus disease 2019) is a public health emergency of international concern. As of this time, there is no known effective pharmaceutical treatment, although it is much needed for patient contracting the severe form of the disease. The aim of this systematic review was to summarize the evidence regarding chloroquine for the treatment of COVID-19.*
  Methods: *PubMed, EMBASE, and three trial Registries were searched for studies on the use of chloroquine in patients with COVID-19.*
  Results: *We included six articles (one narrative letter, one in-vitro study, one editorial, expert consensus paper, two national guideline documents) and 23 ongoing clinical trials in China. Chloroquine seems to be effective in limiting the replication of SARS-CoV-2 (virus causing COVID-19) in vitro.*
  Conclusions: *There is rationale, pre-clinical evidence of effectiveness and evidence of safety from long-time clinical use for other indications to justify clinical research on chloroquine in patients with COVID-19. However, clinical use should either adhere to the Monitored Emergency Use of Unregistered Interventions (MEURI) framework or be ethically approved as a trial as stated by the World Health Organization. Safety data and data from high-quality clinical trials are urgently needed.*

- Colson, P. et al. **Hot Topic: Chloroquine and hydroxychloroquine as available weapons to fight COVID-19.** *International Journal of Antimicrobial Agents (2020): In Press, Corrected Proof.*
  https://doi.org/10.1016/j.ijantimicag.2020.105932
  Review
  Repositioning of drugs for use as antiviral treatments is a critical need [1]. It is commonly very badly perceived by virologists, as we experienced when reporting the effectiveness of azithromycin for Zika virus [2]. A response has come from China to the respiratory disease caused by the new coronavirus (SARS-CoV-2) that emerged in December 2019 in this country. Indeed, following the very recent publication of results showing the in vitro activity of chloroquine against SARS-CoV-2 [3], data have been reported on the efficacy of this drug in patients with SARS-CoV-2-related pneumonia (named COVID-19) at different

levels of severity [4,5]. Thus, following the in vitro results, 20 clinical studies were launched in several Chinese hospitals. The first results obtained from more than 100 patients showed the superiority of chloroquine compared with treatment of the control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects [4,5]. This has led in China to include chloroquine in the recommendations regarding the prevention and treatment of COVID-19 pneumonia [4,6].

- Guatret, P. et al. **Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.** *International Journal of Antimicrobial Agents* (2020): In Press, Journal Pre-proof. https://doi.org/10.1016/j.ijantimicag.2020.105949
  Open label, non randomised trial
  Background: *Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2, and reported to be efficient in Chinese COV-19 patients. We evaluate the role of hydroxychloroquine on respiratory viral loads.*
  Patients and methods: *French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day6-post inclusion was considered the end point.*
  Results: *Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms.*
  Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.
  Conclusion: *Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.*

Kaletra, (Lopinavir-Ritonavir)

- Cao, B. et al. **A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19**. *New England Journal of Medicine* (2020). DOI: 10.1056/NEJMoa2001282 : https://www.nejm.org/doi/full/10.1056/NEJMoa2001282
  Open Label, randomized controlled trial

  Background: *No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-*
  Methods: *We conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.*
  Results: *A total of 199 patients with laboratory-confirmed SARS-CoV-2 infection underwent randomization; 99 were assigned to the lopinavir–ritonavir group, and 100 to the standard-care group. Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. In a modified intention-to-treat analysis, lopinavir–ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). Gastrointestinal adverse events were more common in the lopinavir–ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.*
  Conclusions: *In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit. (Funded by Major Projects of National Science and Technology on New Drug Creation and Development and others; Chinese Clinical Trial Register number, ChiCTR2000029308. opens in new tab.)*

Remdesivir

- Al-Tawfiq, JA, et al. **Remdesivir as a possible therapeutic option for the COVID-19.** *Travel Medicine and Infectious Disease* (2020): In press, corrected proof. https://doi.org/10.1016/j.tmaid.2020.101615
  Letter to the editor
  …Remdesivir (with a development code GS-5734) is a broad-spectrum antiviral agent. This medication is an experimental drug and had not been licensed or approved at the time of writing this article. It was synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection. It is a monophosphoramidate prodrug and is an adenosine analog. Remdesivir is metabolized into its active form, GS-441524, that obscures viral RNA polymerase and evades proofreading by viral exonuclease, causing a decrease in viral RNA production. The antiviral mechanism of remdesivir is a delayed chain cessation of nascent viral RNA…

- Wang, M.et al. **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro**. *Cell Research* (2020): 30, pp–271. https://www.nature.com/articles/s41422-020-0282-0
  Letter to the editor
  An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating related viral infections. The 2019-nCoV belongs to Betacoronavirus which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial.3 In this study, we evaluated the antiviral efficiency of five FAD-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV in vitro.

Favipiravir (Avigan)

- Chen, C. **Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial**. *Medrxiv* (2020): preprint, https://doi.org/10.1101/2020.03.17.20037432
  Randomised controlled trial
  Importance: WHO has made the assessment that coronavirus disease 2019 (COVID-19) can be characterized as a pandemic. So far, there is no clinically proven effective antiviral drug for COVID-19.
  ***Objective:** To compare the efficacy and safety of favipiravir and arbidol to treat COVID-19 patients on clinical recovery rate of day 7.*
  ***Design:** Prospective, multicenter, open-label, randomized superiority trial in February, 2020.*
  ***Setting:** Multicenter study.*
  ***Participants:** Patients with confirmed COVID-19 admitted to 3 hospitals from Feb. 20, 2020 to Mar. 12, 2020.*
  ***Interventions:** Conventional therapy + favipiravir or arbidol.*
  ***Main Outcomes and Measures:** The primary outcome was clinical recovery rate of day 7. Duration of fever, cough relief time and auxiliary oxygen therapy or noninvasive mechanical ventilation rate were the secondary outcomes. The patients with chest CT imaging and laboratory-confirmed COVID-19 infection, aged 18 years or older were randomly assigned to receive favipiravir or arbidol. Safety data were collected for further follow-up for a week.*
  ***Results:** 120 patients were assigned to favipiravir group (116 assessed) and 120 to arbidol group (120 assessed). In full analysis set (FAS) cohort, for moderate patients with COVID-19, clinical recovery rate of day 7 was 55.86% in the arbidol group and 71.43% in the favipiravir group (P=0.0199). For moderate COVID-19 patients and COVID-19 patients with hypertension and/or diabetes, the latency to fever reduction and cough relief in favipiravir group was significantly shorter than that in arbidol group (both P<0.001), but there was no statistical difference was observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both P>0.05). The most frequently observed treatment-associated adverse events were abnormal LFT, psychiatric symptom reactions, digestive tract reactions and raised serum uric acid (3 [2.50%] in arbidol group vs 16 [13.79%] in favipiravir group, P<0.0001).*
  ***Conclusions and Relevance:** In moderate COVID-19 patients untreated with antiviral previously, favipiravir can be considered as a preferred treatment compared to arbidol because of superior clinical recovery rate of day 7 and more effectively reduced incidence of fever, cough besides some manageable antiviral-associated adverse effects.*

TB Vaccine – BCG

- Miller, A. et al. **Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study**. *Medrxiv* (2020): preprint, https://doi.org/10.1101/2020.03.24.20042937
  COVID-19 has spread to most countries in the world. Puzzlingly, the impact of the disease is different in different countries. These differences are attributed to differences in cultural norms, mitigation efforts, and health infrastructure. Here we propose that national differences in COVID-19 impact could be partially explained by the different national policies respect to Bacillus Calmette-Guerin (BCG) childhood vaccination. BCG vaccination has been reported to offer broad protection to respiratory infections. We compared large number of countries BCG vaccination policies with the morbidity and mortality for COVID-19. We found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies. Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population. We also found that BCG vaccination also reduced the number of reported COVID-19 cases in a country. The combination of reduced morbidity and mortality makes BCG vaccination a potential new tool in the fight against COVID-19

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