COVID-19 STRATEGIC COMMENTARY

FINDING THE SILVER BULLET – 18 MAY 2020

By Professor Frank Gannon

Many of us would have been at or seen a protest march, where the anthem was, "What do we want? XXX. When do we want it? NOW". In the context of COVID-19, XXX worldwide is more than a single word. It is a list that includes rapid accurate tests, a pill that would kill the virus, and a vaccine that would mean we could all go about our business as usual. In parallel, as the numbers reduce in some regions, there is a growth in the impatience to abandon any caution and get things going again. Simultaneously, some countries still do not have enough PPE, reagents for assays, or Intensive Care Units to ensure that cruel triaging does not have to take place. On a global scale, there are a lot of things that we want.

All statistics point to Australia being in a very good place and ahead of most countries. Still, there is the continuous concern that the virus could strike again if you turn your back, like in a horror movie. As I am confined to the sunny West Coast of Ireland, I compare the daily figures in different countries. This country feels it is doing well, as the daily deaths reduce to approximately 20 and the daily new cases hover around 120. So, XXX in the chant "What do we want?" is different here than in Australia. Yet in the global world (pardon the tautology), Australia needs to have healthy tourists, customers and supply chain deliverers, so the problems elsewhere impinge on normality and the economy and health locally.

Is a cure nearly there?

Recently, I posted a commentary soon after the media excitement about Remdesivir. There are daily updates and positive rumours that are hard for all to miss…they are on TV every night. I still await the clinical trial data and the follow-up analysis by the professionals. That will come, and I will not talk about R here. In the interim, it is worth noting that the language has shifted from *cure* to *treatment*. Any improvement in treatment is very welcome, of course, as it frees up facilities quicker and is very positive for the individual. However, if success is defined by getting out of a hospital bed, it means that COVID-19 remains intrusive to life in a way that, for example, a head cold is not.

When all of this started, I thought that a small molecule drug would be found and *cure* COVID-19 in a relatively short time. XXX in the protest chant equaled cure. After all, although this is a new Coronavirus, the earlier challenges of SARS, MERS and others meant that researchers had been actively looking for such a drug for closely related targets. The pharmaceutical companies have a stock of compounds and Med Chem driven variations that could be tested. In addition, they have a major financial motivation to get to the market. When I checked the published literature in March, using *Coronavirus Treatment* as keywords, there were 700 papers on PubMed. Today, when I search using the more specific *COVID-19 Treatment*, there are 2,896 publications. (I note that PubMed reassign some publications, and that number can change as a result). People have been actively writing up their results. At the time of that search, there are only 49 publications when the word cure is used instead of treatment. Many of these publications have the word *potential* before the word *cure*. So, we are looking at the likelihood of a new treatment and have to forget the word cure for the moment. In this commentary, I will look at different aspects of the state of play for a COVID-19 treatment.

The HIV precedent

My optimistic view was that the treatment would come before the vaccine. That may be the case given the uncertainty of the delivery of a vaccine. Some known diseases have to wait a long time, and some are still waiting; think TB, Malaria or HIV. In all cases, treatments came first or remain the only option. The timeline of HIV treatment is a guide here.

The first cases of AIDS were reported in 1981 with the viral causative agent described in 1984. A commercial diagnostic test for HIV was licensed in 1985. The first drug that helped in the treatment of HIV was AZT (repurposed from a cancer drug), and it was approved in 1987. It was 1996 before the more effective combination called HAART (Highly Active Antiretroviral Therapy consisting of up to five different drugs) was developed and approved. That is a long time to wait, and in the COVID-19 context would place a robust treatment some 10 years away. But the advantages of the very rapid identification and availability of the sequence of COVID-19, together with the insights from the other Coronaviruses will help. Researchers all over the world have galvanised their efforts to provide a treatment that would blunt the impact of COVID-19.

Certainly, those who have published think that they have the answer. Look at the references 1-16 below. These are some of the multiple proposals that I selected from the PubMed *COVID 19 Treatment* list of possibilities. There many more and I am not prioritising these publications. As I know that it takes a second effort by the reader to move to the publication and read it, I have included key comments from the papers to help you get to the heart of the message. All have good reason to set out their stall and try to attract attention. As it is unclear why the virus is so pugnacious (17), there is room for many diverse suggestions. Some target the virus, some the interaction of the virus and a cell, some the intercellular interactions of the virus, some the immune response, others the cytokine storm. But which one will have an impact? Which will be safe? Which one is a good partner for another compound even if it has a weak effect on its own? Some other more general papers are included (18-20). Others are listed in my commentary on Remdesivir.

Moving from compassionate use to trials

One inescapable consequence of the outbreak is that clinicians have to try whatever treatment they have access to and believe in. This means that almost all of the initial publications are, at best, preliminary reports. Some that have been positive at the time of publication are over-turned by a more comprehensive trial. One of the early favorites was Lopinavir/Ritonavir (15), but then a more comprehensive clinical trial showed that, as used, it was not effective (21). There is significant hope for (hydroxyl) Chloroquinone as the silver bullet. Again, there are positive and then negative results and commentary (22-26). The most complete trial suggests that it is not the answer, at least not on its own, and at least not at the doses and timing used. Ivermectin had its moment, and then there is a publication that says the dose required is toxic (27). Some of these trials get attention even when they are under construction, (28,29 for example) others do not. There may not be an objective basis for the differentiation; it may be geographic with a result from the United States trumping (pun intended) one from, for example, Italy. Economics and politics are not necessarily the best guide to treatment. The focus on treatments and combinations that involve drugs that are propriety with good financial return potential (as opposed to products that are out of patent) also deserves some attention. More sites are now available to follow the progress of the trials (30 for example).

A constant claim in the commentaries and editorials (23, 31-33 for example) is the need for correct case controlled adequately powered trials. Hopefully, they will appear in the literature soon. Until then, the success of re-purposing drugs remains on hold. I feel that progress could be accelerated if

the WHO (for example) defined the criteria for enrolling patients and the required endpoint. I noticed, for example, that one study was carried out on patients where the average age was less than sixty. The question for those interested in avoiding deaths is the impact on those that are over seventy. So, any good news needs to be relevant to the major problem. If the studies were performed in an internationally standardised manner, it would be clearer which treatment had the most promise comparatively. Then, the subsequent studies on the dose, the timing, the frequency and the combinations with other drugs could be launched to get improvements to reach a HAART equivalent.

Beyond re-purposing

The advantages of repurposing drugs that have a known safety profile are that they can be introduced to the clinic rapidly. As the months pass, it seems that the right compound has not yet turned up for COVID-19. Some new options are needed. Researchers in universities, research institutes and companies must have better COVID-19 specific assays now in place. These could be for specific viral proteins or for cell systems where COVID-19 can develop. Screening of libraries of compounds for their efficacy must be well advanced. We look forward to the fruits of that work.

An alternative is to use modelling as a guide for computer-aided design of compounds that should interact with a target. One early report (34) generated a large number of prospective drugs. They are available to the scientific community. It could take a very long time to synthesise and test this library, and I do not know the rules attached related to IP on any successful molecule. This may be a case of "a little more than a little is by much too much", to quote Shakespeare.

Another approach is underway, spearheaded by the not-for-profit Structural Genomics Consortium. They include in their membership several pharmaceutical companies that provide access to researchers to their chemical libraries. Generally, the next step is to see if a compound can be found for a particular target. In a variation of this, they have supported a project where structural information on the key viral protease (big crystal fragment screen), generated in the Diamond X-ray synchrotron in the UK is available, and researchers are asked to define a molecule that they anticipate will bind and inhibit this key enzyme (Moonshot). In a very short period, I am told that they had over 4,000 submissions from 300 researchers worldwide. The first reports from this project are now appearing.

What we need now

A cure for COVID-19 is needed. A treatment that over time might grow into a cure through incremental changes and combinations would be a very welcome first step. That is "what we need NOW." There are dozens of proposed solutions. Some are moving forward to trials. Remdesivir is one of them, (or has that been stopped according to the latest press commentary?), and I refer to others above. Standardisation of the trials globally would add value to each trial and allow potential synergies to be identified and poor responders to be eliminated from consideration. Inevitably, the first wave of candidates has come from the repurposing of drugs. Hopefully, they will get us to first base, which may allow time for some new targeted drugs to be identified. That will probably require some years before the victory flag can be waved. In the meantime, perhaps an effective vaccine or some other silver bullet will be loaded.

1. Putative Inhibitors of SARS-CoV-2 Main Protease from A Library of Marine Natural Products: A Virtual Screening and Molecular Modeling Study.
Gentile D, Patamia V, Scala A, Sciortino MT, Piperno A, Rescifina A.Gentile D, et al. Mar Drugs. 2020 Apr 23;18(4): E225. doi: 10.3390/md18040225. Mar Drugs. 2020. PMID: 32340389

Seventeen potential SARS-CoV-2 M^{pr} inhibitors have been identified among the natural substances of marine origin. As these compounds were extensively validated by a consensus approach and by molecular dynamics, the likelihood that at least one of these compounds could be bioactive is excellent.

2. Teicoplanin: an alternative drug for the treatment of COVID-19?
Baron SA, Devaux C, Colson P, Raoult D, Rolain JM. Baron SA, et al. Int J Antimicrob Agents. 2020 Apr;55(4):105944. doi: 10.1016/j.ijantimicag.2020.105944. Epub 2020 Mar 13.Int J Antimicrob Agents. 2020. PMID: 32179150

Teicoplanin, an antibiotic used to treat staphylococcal infections, previously showed efficacy to inhibit the first stage of the Middle East respiratory syndrome coronavirus (MERS-CoV) viral life cycle in human cells. This activity is conserved against SARS-Cov-2, thus placing teicoplanin as a potential treatment for patients with this virus.

3. Why tocilizumab could be an effective treatment for severe COVID-19?
Fu B, Xu X, Wei H.Fu B, et al. J Transl Med. 2020 Apr 14;18(1):164. doi: 10.1186/s12967-020-02339-3. J Transl Med. 2020. PMID: 32290839

Our research has identified that pathogenic T cells and inflammatory monocytes incite inflammatory storm with large amount of interleukin 6, therefore monoclonal antibody that targets the IL-6 pathways may potentially curb inflammatory storm. Moreover, Tocilizumab treatment that blocking IL-6 receptors showed inspiring clinical results including temperature returned to normal quickly and respiratory function improved.

4. COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection?
Sargiacomo C, Sotgia F, Lisanti MP. Sargiacomo C, et al. Aging (Albany NY). 2020 Mar 30;12(8):6511-6517. doi: 10.18632/aging.103001. Epub 2020 Mar 30. Aging (Albany NY). 2020. PMID: 32229706

Two host receptors have been proposed for COVID-19. One is CD26 and the other is ACE-2 (angiotensin-converting enzyme 2). Interestingly, both CD26 and the angiotensin system show associations with senescence. Similarly, two proposed therapeutics for the treatment of COVID-19 infection are Azithromycin and Quercetin, both drugs with significant senolytic activity. Also, Chloroquine-related compounds inhibit the induction of the well-known senescence marker, Beta-galactosidase. Other anti-aging drugs should also be considered, such as Rapamycin and Doxycycline, as they behave as inhibitors of protein synthesis, blocking both SASP and viral replication.

5. Metronidazole; a Potential Novel Addition to the **COVID-19 Treatment** Regimen.
Gharebaghi R, Heidary F, Moradi M, Parvizi M. Gharebaghi R, et al. Arch Acad Emerg Med. 2020 Mar 30;8(1): e40. eCollection 2020.Arch Acad Emerg Med. 2020. PMID: 32259129

…metronidazole could decrease the levels of several cytokines, which are known to increase during the COVID-19 infection, including interleukin (IL)8, IL6, IL1B, tumor necrosis factor (TNF)α, IL12, IL1α, and interferon (IFN)γ, as well as the levels of C-reactive protein (CRP) and neutrophil count. Furthermore, the drug could decrease neutrophil-generated reactive oxygen species during inflammation.

6. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension.
Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, Yang R, Di W, Wang Z, Li Z, Gao H, Liu L, Zhang G.Meng J, et al. Emerg Microbes Infect. 2020 Dec;9(1):757-760. doi: 10.1080/22221751.2020.1746200.Emerg Microbes Infect. 2020. PMID: 32228222

We observed that patients receiving ACEI or ARB therapy had a lower rate of severe diseases and a trend toward a lower level of IL-6 in peripheral blood. In addition, ACEI or ARB therapy increased CD3 and CD8 T cell counts in peripheral blood and decreased the peak viral load compared to other antihypertensive drugs.

7. Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19.
Yang N, Shen HM. Yang N, et al. Int J Biol Sci. 2020 Mar 15;16(10):1724-1731. doi: 10.7150/ijbs.45498. eCollection 2020.Int J Biol Sci. 2020. PMID: 32226290

"…we will focus on the importance of the endocytic pathway as well as the autophagy process in viral infection of several pathogenic CoVs inclusive of SARS-CoV, MERS-CoV and the new CoV named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and discuss the development of therapeutic agents by targeting these processes."

8. CD147 as a Target for **COVID-19 Treatment**: Suggested Effects of Azithromycin and Stem Cell Engagement.
Ulrich H, Pillat MM.Ulrich H, et al. Stem Cell Rev Rep. 2020 Apr 20:1-7. doi: 10.1007/s12015-020-09976-7. Online ahead of print. Stem Cell Rev Rep. 2020. PMID: 32307653

"*…Studies suggest beneficial effects of azithromycin in reducing viral load of hospitalized patients, possibly interfering with ligand/CD147 receptor interactions.*"

9. Tilorone: a Broad-Spectrum Antiviral Invented in the USA and Commercialized in Russia and beyond.
Ekins S, Lane TR, Madrid PB. Ekins S, et al. Pharm Res. 2020 Mar 25;37(4):71. doi: 10.1007/s11095-020-02799-8.Pharm Res. 2020. PMID: 32215760
"*…a broad-spectrum agent tilorone dihydrochloride (Tilorone). Tilorone, 2,7-Bis[2-(diethylamino)ethoxy]-9H-fluoren-9-one) which is a small-molecule (410.549 Da) that is orally bioavailable that was originally discovered in the USA and is currently used clinically as an antiviral in Russia and the Ukraine*
…we have identified additional promising antiviral activities against Middle East Respiratory Syndrome, Chikungunya, Ebola and Marburg which highlights that this old drug may have other uses against new viruses."

10. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed.
Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, Richards D, Hussell T. Feldmann M, et al. Lancet. 2020 May 2;395(10234):1407-1409. doi: 10.1016/S0140-6736(20)30858-8. Epub 2020 Apr 9.Lancet. 2020. PMID: 32278362

11. Effectiveness of glucocorticoid therapy in patients with severe coronavirus disease 2019: protocol of a randomized controlled trial.
Qin YY, Zhou YH, Lu YQ, Sun F, Yang S, Harypursat V, Chen YK.Qin YY, et al. Chin Med J (Engl). 2020 May 5;133(9):1080-1086. doi: 10.1097/CM9.0000000000000791.Chin Med J (Engl). 2020. PMID: 32149773
Glucocorticoid therapy was used in the treatment of severe SARS because early anecdotal experience supported it, and radiologic findings and histologic features of critically ill patients with SARS were similar to those of patients with acute respiratory distress syndrome (ARDS).

12. Type 1 interferons as a potential treatment against COVID-19.
Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Sallard E, et al. Antiviral Res. 2020 Apr 7;178:104791. doi: 10.1016/j.antiviral.2020.104791. Online ahead of print. Antiviral Res. 2020. PMID: 32275914

13. COVID-19: Melatonin as a potential adjuvant treatment.
Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, Liu C, Reiter RJ. Zhang R, et al. Life Sci. 2020 Jun 1;250:117583. doi: 10.1016/j.lfs.2020.117583. Epub 2020 Mar 23.Life Sci. 2020. PMID: 32217117
"…evidence suggests that excessive inflammation, oxidation, and an exaggerated immune response very likely contribute to COVID-19 pathology. This leads to a cytokine storm and subsequent progression to acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and often death. Melatonin, a well-known anti-inflammatory and anti-oxidative molecule, is protective against ALI/ARDS caused by viral and other pathogens."

14. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China.
Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S.Zhang W, et al. Clin Immunol. 2020 May; 214:108393. doi: 10.1016/j.clim.2020.108393. Epub 2020 Mar 25.Clin Immunol. 2020. PMID: 32222466
"…we will discuss the clinical and immunological characteristics of severe patients, and summarize the current evidence and share our experience in anti-inflammation treatment, including glucocorticoids, IL-6 antagonist, JAK inhibitors and choloroquine/hydrocholoroquine, of patients with severe COVID-19 that may have an impaired immune system."

15. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR.
Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, Choe KW, Kang YM, Lee B, Park SJ.Lim J, et al. J Korean Med Sci. 2020 Feb 17;35(6):e79. doi: 10.3346/jkms.2020. 35. e79. J Korean Med Sci. 2020. PMID: 32056407

Interestingly, after lopinavir/ritonavir (Kaletra, AbbVie) was administered, β-coronavirus viral loads significantly decreased and no or little coronavirus titers were observed.

16. Traditional Chinese medicine for **COVID-19 treatment**.
Ren JL, Zhang AH, Wang XJ.Ren JL, et al. Pharmacol Res. 2020 May;155:104743. doi: 10.1016/j.phrs.2020.104743. Epub 2020 Mar 4.Pharmacol Res. 2020. PMID: 32145402

Among the 701 confirmed cases treated by QPD (qingfei paidu decoction, 130 cases were cured and discharged, clinical symptoms of 51 cases disappeared, 268 cases of symptoms improved, and 212 cases of stable symptoms without aggravation [3]. The effective cure rate of QPD against COVID-19 is over 90 %.

17. How does **COVID-19** kill? Uncertainty is hampering doctors' ability to choose treatments.
Ledford H. Ledford H. Nature. 2020 Apr;580(7803):311-312. doi: 10.1038/d41586-020-01056-7.Nature. 2020. PMID: 32273618
Clinical data suggest that the immune system plays a part in the decline and death of people infected with the new coronavirus, and this has spurred a push for treatments such as steroids that rein in that immune response. But some of these treatments act broadly to suppress the immune system, stoking fears that they could actually hamper the body's ability to keep the viral infection in check.

18. Antiviral Treatment of COVID-19

Serap Şimşek Yavuz [1], Serhat Ünal [2]
Turk J Med Sci. 2020 Apr 21;50(SI-1):611-619. doi: 10.3906/sag-2004-145.
There have been more than 300 clinical trials going on, various antiviral and immunomodulating agents are in various stages of evaluation for COVID-19
…chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir and remdesivir will be reviewed here. Nitazoxanide and ivermectin were also included in this review as they have recently been reported to have an activity against SARS-CoV-2 in vitro.

19. Update on treatment of COVID-19: ongoing studies between promising and disappointing results.
Esposito S, Noviello S, Pagliano P. Esposito S, et al. Infez Med. 2020 Ahead of print Jun 1;28(2):198-211.Infez Med. 2020. PMID: 32335561

"…Through PubMed, we explored the relevant articles published on treatment of COVID-19 and on trials ongoing up to April 15, 2020."

20. COVID-19 treatment by repurposing drugs until the vaccine is in sight.
Phadke M, Saunik S. Phadke M, et al. Drug Dev Res. 2020 Mar 29. doi: 10.1002/ddr.21666. Online ahead of print. Drug Dev Res. 2020. PMID: 32227357

"*…one can repurpose known therapeutic drug molecules such as angiotensin receptor 2 blocker, a commonly used antihypertensive drug, to control COVID-19 virus from gaining entry into the host cell by blocking the angiotensin receptor. Clinical trials should also be undertaken to use statins, which are lipid-lowering drugs but have anti-inflammatory and immunomodulatory properties to prevent acute lung injury in COVID-19 infection*".

21. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe **Covid**-**19**. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C.Cao B, et al. N Engl J Med. 2020 May 7;382(19):1787-1799. doi: 10.1056/NEJMoa2001282. Epub 2020 Mar 18.N Engl J Med. 2020. PMID: 32187464
"*…In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care."*

22. Hydroxychloroquine and azithromycin as a treatment of **COVID**-**19**: results of an open-label non-randomized **clinical trial**. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D.Gautret P, et al. Int J Antimicrob Agents. 2020 Mar 20:105949. doi: 10.1016/j.ijantimicag.2020.105949. Online ahead of print. Int J Antimicrob Agents. 2020. PMID: 32205204
"*…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."*

23. Chloroquine and hydroxychloroquine in covid-19. ; Use of these drugs is premature and potentially harmful. Ferner RE, Aronson JK. Ferner RE, et al. BMJ. 2020 Apr 8;369:m1432. doi: 10.1136/bmj.m1432.BMJ. 2020. PMID: 32269046 (Editorial)
Currently, at least 80 trials of chloroquine, hydroxychloroquine, or both, sometimes in combination with other drugs, are registered worldwide.

"…chloroquine inhibited dengue virus in some cell cultures 14 but failed to shorten the illness in a randomised study of 37 patients.

…We need better, properly powered, randomised controlled trials of chloroquine or hydroxychloroquine."

24. Hydroxychloroquine in patients with COVID-19: an open-label, randomised, controlled trial. Tang W et al. *medRxiv.* 2020; (published online April 14.) (preprint).
https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1.full.pdf.
"*…The administration of HCQ did not result in a higher negative conversion rate but more alleviation of clinical symptoms than SOC alone in patients hospitalized with COVID-19 without receiving antiviral treatment, possibly through anti-inflammatory effects. Adverse events were significantly increased in HCQ recipients but no apparently increase of serious adverse events*."

25. COVID-19 **coronavirus** research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine.
Alexander PE, Debono VB, Mammen MJ, Iorio A, Aryal K, Deng D, Brocard E, Alhazzani W. Alexander PE, et al. J Clin Epidemiol. 2020 Apr 21: S0895-4356(20)30371-1. doi: 10.1016/j.jclinepi.2020.04.016.
"*…We found that the COVID-19 research methodology is very poor in the area of chloroquine/hydroxychloroquine research. In screening the literature, we observed the same across COVID-19 research in relation to potential treatments. The reporting is very poor and sparse, and patient-important outcomes needed to discern decision-making priorities are not reported."*

26. 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: A Randomized **Clinical Trial**.
Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, Mourão MPG, Brito-Sousa JD, Baía-da-Silva D, Guerra MVF, Hajjar LA, Pinto RC, Balieiro AAS, Pacheco AGF, Santos JDO Jr, Naveca FG, Xavier MS, Siqueira

AM, Schwarzbold A, Croda J, Nogueira ML, Romero GAS, Bassat Q, Fontes CJ, Albuquerque BC, Daniel-Ribeiro CT, Monteiro WM, Lacerda MVG; CloroCovid-19 Team.Borba MGS, et al. JAMA Netw Open. 2020 Apr 1;3(4): e208857. doi: 10.1001/jamanetworkopen.2020.8857.JAMA Netw Open. 2020. PMID: 32339248
"*…Primary outcome was reduction in lethality by at least 50% in the high-dosage group compared with the low-dosage group*
…The preliminary findings of this study suggest that the higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. These findings cannot be extrapolated to patients with nonsevere COVID-19."

27. The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19.
Schmith VD, Zhou JJ, Lohmer LR.Schmith VD, et al. Clin Pharmacol Ther. 2020 May 7. doi: 10.1002/cpt.1889
"…Plasma ivermectin concentrations of total (bound and unbound) and unbound concentrations do not reach the IC_{50} , even for a dose level 10x higher than the approved dose."

28. **COVID-19**: A Brief Overview of the Discovery **Clinical Trial**.
Vanden Eynde JJ.Vanden Eynde JJ. Pharmaceuticals (Basel). 2020 Apr 10;13(4): E65. doi: 10.3390/ph13040065.Pharmaceuticals (Basel). 2020. PMID: 32290348
"*…This short communication focuses on four treatments recommended by WHO and included in the first clinical trial of the European Discovery project."*

29. A new **clinical trial** to test high-dose vitamin C in patients with **COVID-19**.
Carr AC. Carr AC. Crit Care. 2020 Apr 7;24(1):133. doi: 10.1186/s13054-020-02851-4.Crit Care. 2020. PMID: 32264963
"...In this trial, the investigators will treat 140 patients with a placebo control or intravenous vitamin C at a dose of 24 g/day for 7 days. They will assess requirements for mechanical ventilation and vasopressor drugs, organ failure scores, ICU length of stay and 28-day mortality."

30. A living systematic review protocol for COVID-19 clinical trial registrations.
Maguire BJ, Guérin PJ.Maguire BJ, et al. Wellcome Open Res. 2020 Apr 2;5:60. doi: 10.12688/wellcomeopenres.15821.1. eCollection 2020.Wellcome Open Res. 2020. PMID: 32292826
*"…This living systematic review aims to provide an open, accessible and frequently updated resource summarising the characteristics of **COVID-19 clinical trial** registrations. ...This living systematic review will provide a useful resource of **COVID-19 clinical trial** registrations for researchers in a rapidly evolving context."*

31. Non-steroidal anti-inflammatory drugs and covid-19.
Little P. Little P. BMJ. 2020 Mar 27;368:m1185. doi: 10.1136/bmj.m1185.BMJ. 2020. PMID: 32220865

32. Drugs and the renin-angiotensin system in covid-19. Aronson JK, Ferner RE
"*…Some suggestions for drug treatment seem problematic.1 They include various antiviral drugs, some of which have primary targets that are DNA viruses not RNA; immunomodulatory drugs, which may suppress potentially protective acute inflammatory responses and do not specifically target the virus; the antimalarial drugs chloroquine and hydroxychloroquine, which have some antiviral activity in vitro but no evidence of clinical benefit in human viral infections and also have many adverse effects; and corticosteroids, which may be harmful when used to treat infection with the related virus SARS-CoV-1.2*

…Theoretically, ACE-1 inhibitors and ARBs could be harmful in covid-19 since increased ACE-2 activity might increase viral entry into cells. Alternatively, increased ACE-2 activity could increase conversion of angiotensin II to angiotensin-(1-7), a peptide with potentially protective anti-inflammatory properties.9 However, that effect would probably be small, and it is unclear whether increasing anti-inflammatory activity is harmful or beneficial in covid-19.10
Although understanding underlying mechanisms can inform drug treatment in many ways, it is unwise to base any treatment on an untested mechanistic hypothesis.11 ACE inhibitors and ARBs should not be used to treat covid-19 without convincing evidence of clinical efficacy from randomized clinical trials or data mining studies.

33. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. Tu YF, Chien CS, Yarmishyn AA, Lin YY, Luo YH, Lin YT, Lai WY, Yang DM, Chou SJ, Yang YP, Wang ML, Chiou SH. Tu YF, et al. Int J Mol Sci. 2020 Apr 10;21(7):2657. doi: 10.3390/ijms21072657.Int J Mol Sci. 2020. PMID: 32290293
"…The initial clinical studies revealed the promising therapeutic potential of sever4l of such drugs, including favipiravir, a broad-spectrum antiviral drug that interferes with the viral replication, and hydroxychloroquine, the repurposed antimalarial drug that interferes with the virus endosomal entry pathway. We speculate that the current pandemic emergency will be a trigger for more systematic drug repurposing design approaches based on big data analysis".

34. Rapid Identification of Potential Inhibitors of SARS-CoV-2 Main Protease by Deep Docking of 1.3 Billion Compounds. Anh-Tien Ton et al. Mol Inform. 2020 Mar 11[Online ahead of print] [1] PMID: **32162456** DOI: 10.1002/minf.202000028

> *"…we applied Deep Docking to all 1.3 billion compounds from ZINC15 library to identify top 1,000 potential ligands for SARS-CoV-2 Mpro protein. The compounds are made publicly available for further characterization and development by scientific community".*