# CORONAVIRUS – COVID-19: Por que não usar a Cloroquina ou a Hidroxicloroquina?

Em meio a grave e letal pandemia produzida pelo Coronavirus SARS CoV-2 que vem atingindo praticamente todos os países do planeta e se propagando numa verdadeira progressão geométrica e em velocidade astronômica jamais vista antes, cujo número de pessoas infectadas já se aproxima de 2 milhões, com cerca de mais de 100 mil mortos, instalou-se uma lamentável e desnecessária crise política paralela, decorrente de uma inaceitável batalha tão letal e virulenta quanto o próprio Coronavirus, referente ao uso ou não de medicamentos com os princípios ativos conhecidos por Cloroquina (chloroquine) e a Hidroxicloroquina (hydroxychloroquine), já existentes para o combate de outras doenças, como a malária, a artrite e o lúpus, etc.

No mesmo sentido, grande parte da mídia traindo o seu direito/dever de informar a sociedade sobre o que há de verdade sobre o uso ou não dessas substâncias, passou deliberadamente a se posicionar de forma contrária ao seu uso, limitando-se, assim, a mostrar apenas as informações que abonam o seu posicionamento político, ao mesmo tempo em que omite praticamente todas as informações em sentido contrário, mesmo com consideráveis histórias de sucesso (notadamente em outros países) ou quando, raramente, se manifesta relativamente ao posicionamento contrário ao seu, o faz de forma demasiadamente critica, totalmente destrutiva, deixando, assim, de informar, com isenção, os dois lados da moeda, prejudicando sensivelmente a população, especialmente nesse momento de pânico generalizado, lockdown, medidas de isolamento social, pessoas sem trabalhar, comércio fechado, queda da economia, aumento de milhares de infectados, com mortes crescentes a cada dia, etc.

A maior crítica daqueles que se posicionam contra o uso da chloroquine e da hydroxychloroquine, é no sentido de que ainda não há estudos científicos definitivos, precisos e seguros quanto à eficácia com relação a COVID-19, bem como em razão das referidas substancias apresentam efeitos colaterais, que desautorizariam o uso daqueles princípios ativos, embora haja uma

unanimidade de opiniões no sentido de, até o momento, não existir nenhum remédio específico para enfrentar essa nova doença.

Importante destacar, que a referida doença surgiu na cidade de Wuhan, China, no final do ano passado (dezembro) e, obviamente, ainda não houve tempo hábil suficiente para a descoberta de remédios e/ou de vacinas para evitar a contaminação ou mesmo a cura da referida doença.

É bem verdade, que está havendo uma corrida mundial na busca da vacina e desses medicamentos, ainda que seja para diminuir a intensidade da doença, ou pelo menos para reduzir o prazo de recuperação dos enfermos, sendo certo, também, que em perspectivas mais otimistas se espera que se descubra uma vacina contra esse novo Coronavirus no próximo ano de 2021.

E até lá, o que deve ser feito? Cruzar os braços e deixar ir aumentando cada vez mais o número de infectados, com cada vez mais mortes? A resposta negativa me parece óbvia.

Sabidamente, nenhum serviço de saúde pública, nem mesmo dos países mais desenvolvidos do planeta, como Estados Unidos, Alemanha, França, Inglaterra, entre outros, estão preparados para socorrer um número cada vez maior de pessoas vítimas da COVID-19, por absoluta falta de infraestrutura de pessoal material e física, no que parte da mídia, nesse ponto, talvez por sensacionalismo ou para gerar o caos, tem mostrado à saciedade, as dificuldades que vem sendo enfrentadas pelos mais diversos países, como a falta de máscaras faciais, ventiladores pulmonares, oxigênio, espaço físico adequado nos hospitais (leitos, enfermarias e UTI's), etc., o que vem gerando uma incessante busca por equipamentos em outros países exportadores numa verdadeira corrida mortal contra o tempo, a fim de que cada um possa suprir as suas necessidades emergenciais o mais rápido possível.

Por outro lado e agora sim, uma luz no fim do túnel está surgindo como o uso off-label das substâncias chloroquine e da hydroxychloroquine, até destinada a outras doenças, mas que, ainda nesse curto espaço de tempo, tem apresentado resultados que surgem como uma verdadeira gota de esperança nesse sombrio momento de desespero e pavor de uma pandemia generalizada, com dimensões jamais imaginadas e com rápido e

crescente número de mortos, que a cada dia aumenta em verdadeira progressão geométrica.

O informativo alemão **Deutsche Welle (DW)**, trouxe importante comentário sobre o uso da cloroquina e da hirocloroquina, destacando, inclusive, uma pesquisa desenvolvida por cientistas franceses da cidade de Marselha, a qual ganhou espaço na comunidade médica-científica e vem acirrando e enriquecendo o debate, muito embora não se questione a validade do experimento ou a eficácia daquelas substancias, mas cautelosamente, afirmam ainda ser insuficiente para justificar a adoção daqueles princípios ativos em larga escala.

Ademais, a referida reportagem, em síntese, também salienta que há três grupos de medicamentos que estão sendo pensados para serem utilizados na Alemanha e, em um deles, estão os antivirais, onde se encontra a CLOROQUINA e a HIDROXICLOROQUINA, a quais são usadas profilaticamente contra malária No entanto, o referido princípio ativo, que inicialmente foi desenvolvido pela Bayer, no século passado e que atualmente vem sendo manufaturado, apenas em um único país do mundo, o Paquistão, enquanto que as empresas alemães agora, querem reativar a produção do medicamento, o mais rápido possível, enquanto que o Ministério da Saúde Alemão, já reservou grandes quantidades da droga.

> **“Could an existing drug help against the new coronavirus?**
> Medical researchers are working hard to find a vaccination against the novel coronavirus. But parallel to these efforts, the repurposing of existing drugs could shorten lengthy clinical trial phases and save lives.
>
> Perhaps no new drug against the novel coronavirus SARS CoV-2 needs to be found, as it is possible that existing active substances could help against the COVID-19 pathogen.
> The advantages of using drugs that are already on the market are obvious: Not only is it cheaper to repurpose drugs that have already been approved or developed, but, above all, it is much faster because the lengthy clinical test phases can be shortened.
> Although at least 68 vaccine projects have been started worldwide, the German pharmaceutical association VfA believes that even if a suitable vaccine is found in 2020, mass vaccinations are unlikely to be carried out even in Germany this year. So the only alternatives are either further isolation for

months or treatment with already existing or developed active substances.
Whichever active substance or drug is ultimately found to be the most effective against the new coronavirus, it is extremely important to wait until the drug authorities have carried out all the necessary tests and made scientifically sound decisions. All experts are warning urgently of possible side effects, especially if people self-medicate without consulting a doctor. So please wait and do not just swallow any medication for fear of the disease!
(...)

**Three different groups of drugs**

Currently, three groups of drugs are being tested for their efficacy against the new coronavirus SARS-CoV-2.
**Antiviral drugs** are designed to block the reproduction of viruses or prevent them from entering lung cells. Antiviral drugs have been developed, for example, for normal influenza, for hepatitis C, but also for HIV, Ebola and, importantly here, for the two diseases SARS or MERS, which are also caused by coronaviruses. Also being tested are well-known antimalarial drugs whose effectiveness against viruses was only recently discovered.

**Active ingredients against SARS, MERS, Ebola and influenza**

The obvious thing to do is, of course, to rededicate antiviral drugs that have already worked against other coronaviruses. After all, both Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) are caused by this type of virus. And the new pathogen SARS-CoV-2 is considered a variant of the SARS pathogen of 2002.
(....)
In 2014 it was successfully used against Ebola. In 2016, the Japanese government supplied favipiravir to Guinea as emergency aid to combat the Ebola epidemic. According to the Chinese government, promising clinical studies with Avigan are also expected to be available from Wuhan in China, the epicenter of the novel coronavirus.
(...)

**Active ingredients against malaria**

The well-known malaria drug Resochin has also caused a great stir in recent weeks. Its active ingredient, chloroquine, was formerly used as a malaria prophylaxis. In recent years, however, it has been prescribed only rarely. In tests conducted in Marseille, the active substance chloroquine is said to have shown in cell cultures that it inhibits the proliferation of the novel coronavirus, indicating that it could reduce the viral load of patients with more severe disease progressions. The active ingredient can therefore also be used antivirally, the physicians report.
So far, however, Resochin, which was developed in the 1930s at the Bayer laboratories in Germany, is manufactured at only one

> site in Pakistan. The German pharmaceutical and chemical company now wants to create production facilitiesnow wants to create production facilities for the active ingredient chloroquine in Europe as quickly as possible and donate the drug to governments free of charge. German Health Minister Jens Spahn has already reserved "larger quantities" of the drug.
> Other malaria drugs with the similar active ingredient hydroxychloroquine are also currently being tested. Novartis and Sanofi also plan to make millions of doses available to treat people around the world if the drug authorities give a positive decision.
> (...)
> Concerns were also expressed by the US Department of Health and Human Services after US President Donald Trump spoke out in favor of the use of chloroquine in the treatment of COVID-19 patients." (https://www.dw.com/en/could-an-existing-drug-help-against-the-new-coronavirus/a-53078043?maca=en-EMail-sharing – acessado em 12.04.2020)

Assim, facilmente se percebe que o governo alemão, já visualizando os potenciais benefícios das referidas substancias usadas atualmente no combate a malária e outras doenças, vem demonstrando a intensão de adotar aqueles princípios ativos para enfrentar o novo Coronavirus, tão logo quanto possível.

Necessário destacar, que a importante pesquisa científica desenvolvida pelos professores e cientistas, 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., na cidade de Marselha, em França, publicada no International Journal of Antimicrobial Agents e que está disponível US National Library of Medicine National Institutes of Health, traz valiosas e relevantes informações sobre o uso da hidroxicloroquina (hydroxychloroquine) no combate ao novo Coronavirus, em pacientes acometidos pela COVID-19.

O referido estudo que foi coordenado pelo **University Hospital Institute Méditerranée Infection** (Hospital Universitário de Infecção do Mediterrâneo), em Marselha, tendo sido recrutados pacientes internados em ambiente hospitalar, sofrendo com a CODIV-19. Para a pesquisa, foram excluídos aqueles que tinham alergia ao hydroxychloroquine ou chloroquine e os que apresentaram contraindicação ao uso dos referidos fármacos, incluindo retinopatia, irregularidade no espaço QT do

eletrocardiograma, além de pacientes que estavam gravidas ou amamentando.

O referido estudo apesar de ter se dirigido a um universo reduzido de amostras, os resultados são animadores, mostrando que a maioria dos pacientes superaram a COVID-19 de forma bastante célere, sem o registro de qualquer efeito colateral sério ou importante, que pudesse desaconselhar o uso daquelas substancias.

Destaca-se, a seguir, trechos do referido estudo cientifico, que mostra com clareza e precisão o êxito do uso da hidroxicloroquina (hydroxychloroquine) no tratamento dos pacientes com a COVID-19, salientando, ainda, que os efeitos da referida substancia foram potencializados, quando associados com a azitromicina (azithromycin).

> **"Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial**
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> The primary endpoint was virological clearance at day-6 post-inclusion. Secondary outcomes were virological clearance overtime during the study period, clinical follow-up (body temperature, respiratory rate, long of stay at hospital and mortality), and occurrence of side-effects.
>
> 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**.

## 1. Introduction

In late December 2019, an outbreak of an emerging disease (COVID-19) due to a novel coronavirus (named SARS-CoV-2 latter) started in Wuhan, China and rapidly spread in China and outside [1,2]. The WHO declared the epidemic of COVID-19 as a pandemic on March 12th 2020 [3]. According to a recent Chinese stud, about 80% of patients present with mild disease and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to 79 years and 14.8% in those aged ≥80 years [4]. However, there is probably an important number of asymptomatic carriers in the population, and thus the mortality rate is probably overestimated. France is now facing the COVID-19 wave with more than 4500 cases, as of March 14th 2020 [5]. Thus, there is an urgent need for an effective treatment to treat symptomatic patients but also to decrease the duration of virus carriage in order to limit the transmission in the community. Among candidate drugs to treat COVID-19, repositioning of old drugs for use as antiviral treatment is an interesting strategy because knowledge on safety profile, side effects, posology and drug interactions are well known [6,7].

A recent paper reported an inhibitor effect of remdesivir (a new antiviral drug) and chloroquine (an old antimalarial drug) on the growth of SARS-CoV-2 *in vitro,* [8] and an early clinical trial conducted in COVID-19 Chinese patients, showed that chloroquine had a significant effect, both in terms of clinical outcome and viral clearance, when comparing to controls groups [9,10]. Chinese experts recommend that patients diagnosed as mild, moderate and severe cases of COVID-19 pneumonia and without contraindications to chloroquine, be treated with 500 mg chloroquine twice a day for ten days [11].

Hydroxychloroquine (an analogue of chloroquine) has been demonstrated to have an anti-SARS-CoV activity *in vitro* [12]. Hydroxychloroquine clinical safety profile is better than that of chloroquine (during long-term use) and allows higher daily dose [13] and has fewer concerns about drug-drug interactions [14]. Our team has a very comprehensive experience in successfully treating patients with chronic diseases due to intracellular bacteria (Q fever due to *Coxiella burnetii* and Whipple's disease due to *Tropheryma whipplei*) with long-term hydroxychloroquine treatment (600 mg/day for 12 to 18 months) since more than 20 years. [15,16] We therefore started to conduct a clinical trial aiming at assessing the effect of hydroxychloroquine on SARS-CoV-2-infected patients after approval by the French Ministry of

Health. In this report we describe our early results, focusing on virological data in patients receiving hydroxychloroquine as All patients in Marseille center were proposed oral hydroxychloroquine sulfate 200 mg, three times per day during ten days (in this preliminary phase,we did not enrolled children in the treatment group based in data indicating that children develop mild symptoms of COVID-19 [4]). Patients who refused the treatment or had an exclusion criteria, served as controls in Marseille centre. Patients in other centers did not receive hydroxychloroquine and served as controls. Symptomatic treatment and antibiotics as a measure to prevent bacterial super-infection was provided by investigators based on clinical judgment. Hydroxychloroquine was provided by the National Pharmacy of France on nominative demand.

**2.5. Clinical classification**

Patients were grouped into three categories: asymptomatic, upper respiratory tract infection (URTI) when presenting with rhinitis, pharyngitis, or isolated low-grade fever and myalgia, and lower respiratory tract infections (LRTI) when presenting with symptoms of pneumonia or bronchitis.

**2.10. Statistics**

Assuming a 50% efficacy of hydroxychloroquine in reducing the viral load at day 7, a 85% power, a type I error rate of 5% and 10% loss to follow-up, we calculated that a total of 48 COVID-19 patients (ie, 24 cases in the hydroxychloroquine group and 24 in the control group) would be required for the analysis (Fleiss with CC). Statistical differences were evaluated by Pearson's chi-square or Fisher's exact tests as categorical variables, as appropriate. Means of quantitative data were compared using Student's t-test. Analyses were performed in Stata version 14.2.

**4. Discussion**

For ethical reasons and because our first results are so significant and evident we decide to share our findings with the medical community, given the urgent need for an effective drug against SARS-CoV-2 in the current pandemic context.

We show here that hydroxychloroquine is efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days, in most patients. A significant difference was observed between hydroxychloroquine-treated patients and controls starting even on day3 post-inclusion. These results are of great importance because a recent paper has shown that the mean duration of viral shedding in patients suffering from COVID-19 in China was 20 days (even 37 days for the longest duration) [19].

Very recently, a Chinese team published results of a study demonstrating that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 *in vitro* with hydroxychloroquine (EC50=0.72%µM) found to be more potent than chloroquine (EC50=5.47%µM) [14]. These *in vitro* results corroborate our

clinical results. The target values indicated in this paper [14] were reached in our experiments. The safer dose-dependent toxicity profile of hydroxychloroquine in humans, compared to that of chloroquine [13] allows using clinical doses of hydroxychloroquine that will be over its EC50 observed *in vitro* [14].

Our preliminary results also suggest a synergistic effect of the combination of hydroxychloroquine and azithromycin. Azithromycin has been shown to be active *in vitro* against Zika and Ebola viruses [20], [21], [22] and to prevent severe respiratory tract infections when administrated to patients suffering viral infection [23]. This finding should be further explored to know whether a combination is more effective especially in severe cases. Speculated potential risk of severe QT prolongation induced by the association of the two drugs has not been established yet but should be considered. As for each treatment, the cost benefits of the risk should be evaluated individually. Further studies on this combination are needed, since such combination may both act as an antiviral therapy against SARS-CoV-2 and prevent bacterial super-infections.

The cause of failure for hydroxychloroquine treatment should be investigated by testing the isolated SARS-CoV-2 strains of the non-respondents and analyzing their genome, and by analyzing the host factors that may be associated with the metabolism of hydroxychloroquine. The existence of hydroxychloroquine failure in two patients (mother and son) is more suggestive of the last mechanism of resistance.

Such results are promising and open the possibility of an international strategy to decision-makers to fight this emerging viral infection in real-time even if other strategies and research including vaccine development could be also effective, but only in the future. **We therefore recommend that COVID-19 patients be treated with hydroxychloroquine and azithromycin to cure their infection and to limit the transmission of the virus to other people in order to curb the spread of COVID-19 in the world. Further works are also warranted to determine if these compounds could be useful as chemoprophylaxis to prevent the transmission of the virus, especially for healthcare workers.** Our study has some limitations including a small sample size, limited long-term outcome follow-up, and dropout of six patients from the study, however in the current context, we believe that our results should be shared with the scientific community.

## 3. Results (detailed results are available in supplementary Table 1)

### 3.1. Demographics and clinical presentation

We enrolled 36 out of 42 patients meeting the inclusion criteria in this study that had at least six days of follow-up at the time of the present analysis. A total of 26 patients received hydroxychloroquine and 16 were control patients. Six

hydroxychloroquine-treated patients were lost in follow-up during the survey because of early cessation of treatment. Reasons are as follows: three patients were transferred to intensive care unit, including one transferred on day2 post-inclusion who was PCR-positive on day1, one transferred on day3 post-inclusion who was PCR-positive on days1-2 and one transferred on day4 post-inclusion who was PCR-positive on day1 and day3; one patient died on day3 post inclusion and was PCR-negative on day2; one patient decided to leave the hospital on day3 post-inclusion and was PCR-negative on days1-2; finally, one patient stopped the treatment on day3 post-inclusion because of nausea and was PCR-positive on days1-2-3. The results presented here are therefore those of 36 patients (20 hydroxychloroquine-treated patients and 16 control patients). None of the control patients was lost in follow-up. Basic demographics and clinical status are presented in Table 1 . Overall, 15 patients were male (41.7%), with a mean age of 45.1 years. The proportion of asymptomatic patients was 16.7%, that of patients with URTI symptoms was 61.1% and that of patients with LRTI symptoms was 22.2%). All patients with LRTI symptoms, had confirmed pneumonia by CTScan. Hydroxychloroquine-treated patients were older than control patients (51.2 years vs. 37.3 years). No significant difference was observed between hydroxychloroquine-treated patients and control patients with regard to gender, clinical status and duration of symptoms prior to inclusion (Table 1). Among hydroxychloroquine-treated patients six patients received azithromycin (500mg on day1 followed by 250mg per day, the next four days) to prevent bacterial super-infection under daily electrocardiogram control. Clinical follow-up and occurrence of side-effects will be described in a further paper at the end of the trial.

**3.3. Effect of hydroxychloroquine on viral load**

The proportion of patients that had negative PCR results in nasopharyngeal samples significantly differed between treated patients and controls at days 3-4-5 and 6 post-inclusion (Table 2 ). At day6 post-inclusion, 70% of hydroxychloroquine-treated patients were virologicaly cured comparing with 12.5% in the control group (p= 0.001)

We could isolate SARS-CoV-2 in 19 out of 25 clinical samples from patients." (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102549/ - acessado em 12,04.2020) – os grifos não são do original.

Destarte, muito embora o respeitado estudo científico não tenha se detido a análise de um universo grande de pacientes, as conclusões relativas aos casos tratados, são bastante animadoras, que na ausência de qualquer outro medicamento, atualmente disponível para enfrentar o Coronavirus e a COVID-19,

já se mostra um forte aliado ao uso da cloroquina e, principalmente da hidroxicloroquina, cujas substancias já são conhecidas para o tratamento de outras doenças, inclusive de seus possíveis efeito colaterais, que o experimento não trouxe nenhuma situação grave digna de registro.

No mesmo sentido os cientistas Jianjun Gao, Zhenxue Tian e Xu Yang, da **República da China**, se reportando as experiencias chinesas no enfrentamento a nova doença provocada pelo novo Coronavirus, divulgaram online uma carta aberta, publicada pela BioScience Trends. 2020 14(1):72-73. (www.biosciencetrends.com), onde esclarecem que em estudos clínicos o fosfato de cloroquina tem mostrado aparente eficácia no tratamento da COVID-19 associada a pneumonia (Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumoniain clinical studies).

Esclarecem, ainda, que foram realizados testes em mais de 100 pessoas, e que a referida substância mostrou-se eficaz no tratamento da COVID-19 associada a pneumonia, em diversas cidades chinesas e que foi recomendada a sua inclusão no *Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19* (Guia de prevenção diagnóstico e Tratamento da pneumonia causada pela COVID-19 e que não foi notado qualquer efeito colateral no uso da referida substancia.

> **“SUMARY**
> The coronavirus disease 2019 (COVID-19) virus is spreading rapidly, and scientists are endeavoring to discover drugs for its efficacious treatment in China. Chloroquine phosphate, an old drug for treatment of malaria, is shown to have apparent efficacy and acceptable safety against COVID-19 associated pneumonia in multicenter clinical trials conducted in China. The drug is recommended to be included in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future.
> The coronavirus disease 2019 (COVID-19) virus, emerged in December 2019, has spread rapidly, with cases now confirmed in multiple countries.
> As of February 16, 2020, the virus has caused 70,548 infections and 1,770 deaths in mainland China and 413 infections in Japan (1). A great deal of effort has been made to find effective drugs against the virus in China (2).

On February 17, 2020, the State Council of China held a news briefing indicating that chloroquine phosphate, an old drug for treatment of malaria, had demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China (3).

In the early in vitro studies, chloroquine was found to block COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) greater than 100 μM (4).

A number of subsequent clinical trials (ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029837, ChiCTR2000029826, ChiCTR2000029803, ChiCTR2000029762, ChiCTR2000029761, ChiCTR2000029760, ChiCTR2000029740, ChiCTR2000029609, ChiCTR2000029559, and ChiCTR2000029542) have been quickly conducted in China to test the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of COVID-19 associated pneumonia in more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo (5).

Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course according to the news briefing. **Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients**.

Given these findings, a conference was held on February 15, 2020; participants including experts from government and regulatory authorities and organizers of clinical trials reached an agreement that chloroquine phosphate has potent activity against COVID-19. The drug is recommended for inclusion in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China. Chloroquine is used to prevent and treat malaria and is efficacious as an anti-inflammatory agent for the treatment of rheumatoid arthritis and lupus erythematosus. Studies revealed that it also has potential broad-spectrum antiviral activities by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV (6,7). The anti-viral and anti-inflammatory activities of chloroquine may account for its potent efficacy in treating patients with COVID-19 pneumonia.

The coronavirus disease 2019 (COVID-19) virus is spreading rapidly, and scientists are endeavoring to discover drugs for its efficacious treatment in China. Chloroquine phosphate, an old drug for treatment of malaria, is shown to have apparent

> efficacy and acceptable safety against COVID-19 associated pneumonia in multicenter clinical trials conducted in China. The drug is recommended to be included in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future.
> Chloroquine is a cheap and safe drug that has been used for more than 70 years. In light of the urgent clinical demand, chloroquine phosphate is recommended to treat COVID-19 associated pneumonia in larger populations in the future." (DOI: 10.5582/bst.2020.01047Letter-file:///C:/Users/User/AppData/Local/Packages/microsoft.windowscommunicationsapps_8wekyb3d8bbwe/LocalState/Files/S0/8/Attachments/14_2020.01047[5188].pdf – acesso em 12.04.2020) – os grifos não são do original.

Sem divergir, a **Índia** também está se antecipando na vanguarda do combate ao Coronavirus e para isso, não apenas liberou o uso da hidroxicloroquina para pacientes clínicos diagnosticado com COVID-19, mediante prescrição médica, mas também voltou a permitir as exportações para diversos e importantes países.

Assim, o governo da Índia, por sua vez, decidiu relaxar a proibição de exportar hidroxicloroquina (Hydroxychloroquine) uma vez que esse medicamento despertou o interesse mundial, no que se refere ao tratamento e prevenção da COVID-19, tendo em vista que diversos laboratórios produzem a referida substância em larga escala e também a exportam referida substância, conforme artigo divulgado na página eletrônica do site DhyeyaIAS (www.dhyeyaias.com).

> **"Hydroxychloroquine - Daily Current Affair Article for UPSC, IAS, Civil Services and State PCS Examinations**
> The government has decided to ease its ban on the export of hydroxychloroquine, a drug that has garnered global interest in the treatment and prevention of COVID-19.
> About Hydroxychloroquine
> - Hydroxychloroquine (HCQ), sold under the brand name Plaquenil among others, is a medication used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. Other uses include treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda
> - Hydroxychloroquine was approved for medical use in the United States in 1955. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.

- Common side effects include vomiting, headache, changes in vision, and muscle weakness. Severe side effects may include allergic reactions.

Hydroxychloroquine Issue

- In a study last month in the International Journal of Antimicrobial Agents (IJAA), French scientists reported: “Twenty cases were treated… and showed a significant reduction of the viral carriage compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin (an antibiotic) added to hydroxychloroquine was significantly more efficient for virus elimination.”
- The study was flagged as being too small to draw a definitive conclusion. On April 3, the International Society of Antimicrobial Chemotherapy, which owns the IJAA, said the study did “not meet the society’s expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety”.
- However, by March 21, Trump had begun to call the drug a “game changer” and has since been pushing it.
- At the end of last month, the Indian Council of Medical Research (ICMR) issued an advisory recommending the use of hydroxychloroquine in asymptomatic healthcare workers treating COVID-19 patients, and also allowed doctors to prescribe it for household contacts of confirmed COVID-19 patients.
- However, the government has stressed that the drug can only be used in COVID-19 treatment on prescription, and that it should not instill a sense of “false security”.
- The US has been looking to procure the drug for emergency use. On March 21, Ipca told stock exchanges here that the US Food and Drug Administration had “made exception” to its import alert against the company so that it could get stocks.
- India decided to ban exports of the drug on April 4. On Tuesday, the government decided to ease the ban.
- On April 7, US President Donald Trump tweeted about “retaliation” if India did not heed his request for the drug.
- Later, India said it would supply to countries that needed it the most, and to neighbours who were “dependent on India’s capabilities”.

Hydroxychloroquine Market in India:

-Hydroxychloroquine had a market size of only around Rs 152.80 crore in the 12 months ended February 2020, according to pharmaceutical market research firm AIOCD Awacs PharmaTrac.
- However, several countries source the drug from India.
- Mumbai-headquartered Ipca Laboratories had nearly 82% of the market, with its brands HCQS and HYQ. Around 80% of the volumes produced by Ipca are exported. Ahmedabad-

headquartered Cadila Healthcare (Zydus Cadila) prepares the brand Zy Q, with 8% of the market.
- Wallace Pharmaceuticals (OXCQ), Torrent Pharmaceuticals (HQTOR) and Overseas Healthcare Pvt Ltd (CARTIQUIN) have smaller shares
- Two of India's top drug makers — Ipca Laboratories and Zydus Cadila — have received orders to produce anti-malarial drug chloroquine for the American market, amid the outbreak of the COVID-19 pandemic.
- US President Donald Trump has called chloroquine a potential "game changer" for treating the disease caused by the novel coronavirus SARS-COV-2, and the US Food and Drug Administration (FDA) has partially lifted a three-year-old 'import alert' on Ipca's two plants to import the medicine. Zydus Cadila has also received a "sizeable" order from the US for the decades-old drug.
Is hydroxychloroquine actually effective
- Two large trials are under way on the effectiveness of hydroxychloroquine, and even chloroquine, in COVID-19 treatment. In the World Health Organization (WHO) solidarity trial, of which India is a part, clinicians worldwide are to follow a common protocol to treat patients with hydroxychloroquine.
- The second is the chloroquine accelerator trial, largely funded by the Wellcome Trust and the Bill and Melinda Gates Foundation.
- As of now, the jury is still out on how effective these drugs can be against the virus,
- "Both of these are testing very large numbers of patients according to the random testing protocol used to test medicines. The results of those trials are not available yet . "If people in high exposure situations such as health workers are taking hydroxychloroquine/chloroquine as a preventive measure in limited ways, it may be fine. But, it is not all right for the general public to go around popping these drugs hoping that they will be protected. They may not be protected, but they will definitely cause themselves some harm." (https://www.printfriendly.com/p/g/PpT9w2 - acesso em 12.04.2020) – os grifos não são do original.

No que se refere a **Austrália**, também se pode observar, que o sistema de saúde daquele país vem ulizando a cloroquina no tratamento da COVID-19.

O periódico inglês, THE GUARDIAN, divulgou com destaque, que os famosos atores de Hollywood, Tom Hanks e sua mulher Rita Wilson, contraíram Coronavirus e ainda a bordo do avião que os levava para a Austrália, Rita começou a apresentar sintomas da COVID-19 e acabou por ser foi hospitalizada e tratada

com cloroquina, que embora tenha sentido desagradáveis efeitos colaterais, hoje o casal está totalmente recuperado e retornam para Los Angeles, onde moram.
Desse fato, podemos concluir que a Austrália também está usando a cloroquina para o tratamento da COVID-19 e que os sintomas que Rita Wilson experimentou, apesar de desagradáveis (severos como ela afirma), a febre logo baixou e hoje ela está totalmente recuperada, não tendo a referida medicação trazido maiores consequências e nem deixado qualquer sequela, sendo certo que Rita, é daquelas pessoas consideradas dentro do grupo de risco, eis que já teve câncer há cerca de 5 anos e foi submetida a uma mastectomia dupla (https://www.theguardian.com/film/2020/apr/17/rita-wilson-tom-hanks-coronavirus-choloroquine-covid?CMP=Share_iOSApp_Other) – acesso em 16.04.2020

A **Turquia,** também, experimentou o uso da hidroxicloroquina em pacientes sofrendo pela COVID-19, cuja pneumonia decorrente infecção da doença provocada pelo Coronavirus reduziu dramaticamente.

De acordo com matéria divulgada pelo informativo **Middle East Eye**, fonte oficial turca informou que os pacientes no estágio inicial da doença e que foram tratados com controversa droga para malária, tiveram significante progresso no tratamento da doença produzida pelo Coronavirus e que a hidroxicloroquina vem sendo vendida com o nome de “Plaquenil”.

Acrescenta, ainda, que muitos países estando ministrando essa substância, apenas em pacientes entubados, entretanto o conselho de ciência turco sugeriu que a droga é realmente benéfica nos estágios iniciais da doença , para evitar que o vírus se espalhe pelo corpo e, que, assim, acrescenta que, iniciando mais cedo o tratamento com a hidroxicloroquina, ocorre uma redução da infecção pulmonar entre os pacientes.

Aduz, também, que inobstante a controversa pesquisa francesa, desenvolvida em Marselha, pelo Dr. Didier Raoulit, no início do mês (março), médicos da China relataram que a hidroxicloroquina tinha ajudado na rápida recuperação de alguns pacientes com sintomas suaves.

**“Coronavirus: Turkey says hydroxychloroquine dramatically reduces pneumonia cases**

Most coronavirus patients taken to intensive care or put on ventilators are there because they have developed pneumonia

Turkey has made significant progress in treating coronavirus patients in the early stages of the disease with the controversial malaria drug hydroxychloroquine, Turkish officials have said.

“Turkey had stockpiled one million units of them before the first case appeared in the country,” Turkish Health Minister Fahrettin Koca said on Tuesday evening in a live broadcast, without specifying the name of the drug.

A senior Turkish official with knowledge of the stockpile told Middle East Eye that the drug was hydroxychloroquine and that it was being sold under the brand name Plaquenil.

“Many countries prescribe this drug to intubated patients,” Koca said. “However, our science board suggested that the drug is really beneficial in the early stages to prevent the spread of the virus in the body.”

The health minister reminded viewers that one of the fundamental features of the disease was lung infection.

“We believe beginning early treatment [with this drug] played a big role in reducing the rate of lung infection among the patients,” he said.

Ever since US President Donald Trump promoted the drug as a “game-changer” for treating patients, medical professionals around the world have expressed mixed views on its use.

Trump’s comments followed clinical research by French doctor Didier Raoult, who claimed that he saw promising results on a small sample of patients in February.

However, Raoult’s research has come under fire over its methodology.

Many doctors argue that the drug has not been tested enough yet to be used to treat coronavirus patients.

However, earlier this month, doctors in China reported that hydroxychloroquine had helped to speed up the recovery of some patients who had mild symptoms.

**Dramatic fall in pneumonia rates**

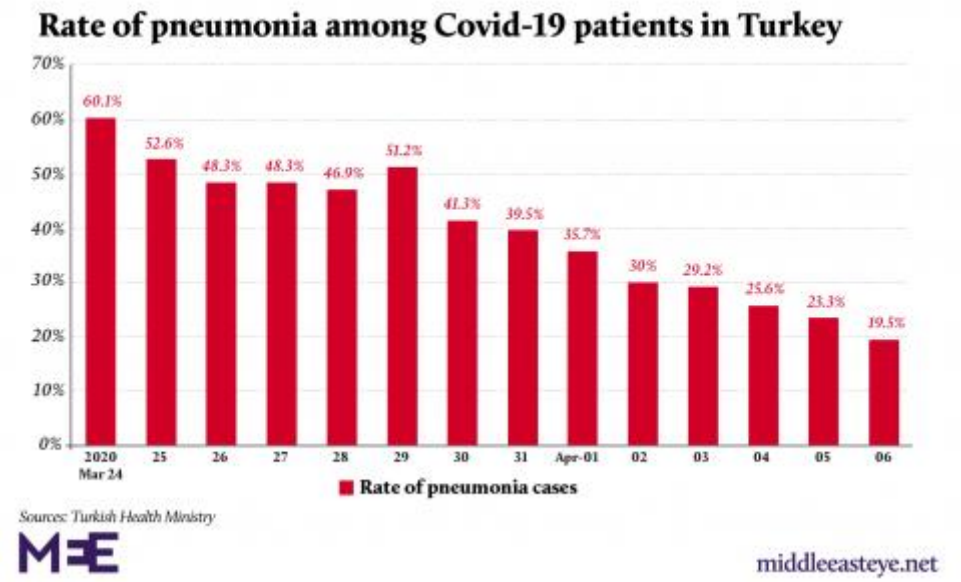
The Turkish official told MEE that the drug was effective against pneumonia, which is seen as among the leading causes of death for coronavirus patients.

Most of the patients taken to intensive care or who are put on ventilators are there because they have developed pneumonia.

“The minister, instead of underlying the importance of the drug itself, has pointed out the benefit of using the drug in the early stages, before the patient becomes severely ill,” the official said.

Statistics released by the Turkish health ministry on Tuesday showed that since beginning the treatment, new cases of lung disease among coronavirus patients have greatly decreased.

On 24 March, 60 percent of coronavirus cases registered were patients with pneumonia, while on 6 April that had fallen to 19.5 percent.




The Turkish Clinical Microbiology and Infection Diseases Association (KLIMIK) said last month that data on the use of the drug was still limited, and warned that it should not be used as a prophylaxis (a treatment given to prevent a disease).

“It should be appropriate to use it in the early stages for some of the coronavirus patients with symptoms,” the statement said.

The association warned that it would not be appropriate to use the drug for medical workers to protect themselves before engaging with the virus.

**Mandatory confinement extended**

Koca said hospitals in Turkey had enough stocks of the drug and that the country was in a better state than many Western nations.

“Our intensive care units capacity is only at 62 percent use. Even the use of bed capacity hasn't reached 50 percent,” he said.

Turkey announced on Tuesday that 76 more people died from the disease in the last 24 hours, bringing the total to 725.

The health ministry said that 3,892 more patients had tested positive, the highest in a single day so far, with the surge in numbers taking the total to 34,109 cases.

However, health officials said given the increase in the numbers of daily tests, which reached 20,023 on Tuesday, the new number of infections was not a matter of concern because the numbers were stalling.

The country has conducted 222,868 tests so far.

Since the virus reached Turkey, the government has unleashed an array of measures aimed at curbing its spread, including closing down schools, universities and cafes, banning congregational prayers, indefinitely postponing sporting events and suspending flights to many countries.

> Last week, Turkish President Recep Tayyip Erdogan extended a mandatory confinement order for everyone under the age of 20, but stopped short of declaring a complete lockdown.
>
> The government earlier imposed a curfew on senior citizens above the age of 65.(https://www.middleeasteye.net/news/coronavirus-turkey-hydroxychloroquine-malaria-treatment-progress - acesso em 15-04-2020)

Na **Itália,** de acordo com matéria divulgada pela conceituada mundialmente editora **TIME**, onde a pandemia provocada pelo Coronavirus atingiu dramáticas proporções com milhares de pessoas infectadas e mortas, especialmente na Lombardia, o médico Luigi Cavanna, faz a diferença, não apenas indo à casa dos pacientes e tratando-os na própria residência, mas também utilizando a hidroxicloroquina, associada a um outro medicamento para HIV.

> **The Italian Doctor Flattening the Curve by Treating COVID-19 Patients in Their Homes**
> Luigi Cavanna is the head of the oncology ward in the nearby Piacenza hospital. From the second week of March, when the lockdown in Italy began, he realized that too many seriously ill COVID-19 patients were arriving in the emergency room — while most of them could have been treated at home earlier, before their symptoms became too grave.
> That's why he now travels throughout the areas around Piacenza every day, along with several colleagues. Together, his three teams have visited more than 300 people with COVID-19 symptoms. They bring patients medicine and a device that monitors the levels of oxygen in the blood, which they return after they've recovered. In more critical cases Cavanna leaves tanks of oxygen and, as with Sartori's mother, bags of fluid with nutrients for non-oral feeding. "My mother is already better," says Sartori. "Being in her own bed rather than in a crowded hospital is what made the difference."
> "When I realized that the emergency room was overcrowded with people already in serious condition, I knew something was wrong," Cavanna explains. "This is not a stroke or a heart attack, but a virus that can hit in different ways and that follows its course. We have to try to stop it before it damages the lungs in a way

that is sometimes irreversible." According to the data he collected during the first month, fewer than 10% of the patients he treated at home worsened to the point where they had to be hospitalized.

**Until last week, Cavanna was giving most of his patients both hydroxychloroquine (commonly used for malaria and certain inflammatory disorders like rheumatoid arthritis) and an antiviral that is usually prescribed for HIV**. Then AIFA, Italy's equivalent to the U.S.'s Food and Drug Administration, issued a note advising to be very careful in prescribing them together. So now, except in rare cases, he uses hydroxychloroquine on its own. Although the drug hasn't been tested for the coronavirus, he says it is the "most effective treatment for now."

The White House has also been enthusiastically recommending the drug as treatment for coronavirus, with President Donald Trump describing it as a "miracle cure" — an endorsement that is risking shortages. Cavanna stresses the importance of having a doctor prescribe and monitor the medication vigilantly. "Every day I receive dozens of phone calls and answer all of them. I prefer answering the phone at 2 a.m. rather than hearing that a patient is getting worse," Cavanna says.

Now that Italy's rate of coronavirus cases has plateaued, medical officials are looking at what worked and what didn't — and increasingly they are turning to new initiatives such as the one pioneered by Cavanna. Local administrations in other regions and nonprofits like Doctors Without Borders are organizing groups of doctors to provide services at home and in facilities most at risk, such as nursing homes.

"We made a mistake, especially in Lombardy" explains Ivan Cavicchi, professor of sociology of health at the University of Tor Vergata in Rome. "We were totally focused on increasing the number of beds in intensive care units, without having enough anesthesiologists," he says. "But in situations like this, strengthening the entire system is essential. Only then can hospitals function properly."

He says that instead general practitioners and other primary care providers were "abandoned" and "left without protection." So far nearly 100 doctors have died in Italy, about half of them general practitioners.

Cavanna and his team are able to enter the patients' homes because they have the necessary protective gear, provided both by the hospital where they work and by private donors. During their expeditions they wear a protective suit that Cavanna jokingly describes as similar to ones worn by "aviators in the movies," and on top of it, at each visit, they wear an additional disposable gown. They also wear googles, two masks, two gloves, two caps and shoe covers.

Officials are also trying to prepare facilities for a possible resurgence of the coronavirus. "In addition to reorganizing the hospitals, we need to reorganize the doctors' studios throughout the region", explains Pier Luigi Bartoletti, deputy secretary of FIMMG, the Italian federation of family doctors. Bartoletti and his collaborators are already thinking about next winter, when—in the worst case scenario—the virus could strike again with force.

"As early as October, the waiting rooms of doctors' offices must be redesigned, with separate routes for those with flu symptoms," he says. "In addition, we need to offer doctors protective gear and training to use it properly, along with the appropriate diagnostic tools." Bartoletti is working with doctors at the Spallanzani Hospital in Rome to test a device that would allow for rapid COVID-19 testing using just a drop of blood taken from the finger.

Today, coronavirus tests may require 4 or even 5 days to get a result. That's too long, if you are following the preventative strategy. Instead of waiting for the tests, Cavanna takes along a device the size of a mobile phone to perform ultrasound chest scans. "We know that in such an affected area people with signs of bronchitis or pneumonia are almost certainly positive," he explains. "I keep the swab in case of doubt or for post treatment, to make sure they're no longer contagious once cured."

Doctors and experts agree that the pandemic has been an eye opener — not only for Italians but also for the rest of the world — with regard to the strengths and weaknesses of the various healthcare systems. But no system has yet proven equipped to deal with an extreme situation such as the current pandemic. "We were taken by surprise at a time when we felt immortal, but now it is clear to everyone that this is not the case", says Pier Luigi Bartoletti. "If we repeat the same

mistakes, it will be our fault too." (https://time.com/5816874/italy-coronavirus-patients-treating-home/ - acesso em 15.04.2020) – os grifos não são do original,

No estado da **Virginia** nos Estados Unidos, a **EVMS-Eastern Virginia Medical School** (Escola de Medicina da Virginia Oriental), apresentou relevante estudo onde recomentada o uso da cloroquina e da Hidroxicloroquina, no tratamento da COVID-19, baseado em estudos de caos e da experiência de ouros países, formulando um protocolo a ser largamente divulgado, onde recomenda o uso daquelas substâncias, inclusive, associada a outros fármacos e monitorização dos Pacientes, para observar a eventual ocorrência de efeitos colaterais, entre outras o espaçamento QT no eletrocardiograma.

**EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL Developed and updated by Paul Marik, MD Chief of Pulmonary and Critical Care Medicine Eastern Virginia Medical School, Norfolk, VA April 6th 2020**

URGENT! Please circulate as widely as possible. It is crucial that every pulmonologist, every critical care doctor and nurse, every hospital administrator, every public health official receive this information immediately. This is our recommended approach to COVID-19 based on the best (and most recent) available literature including the Shanghai Management Guideline for COVID. **We should not re-invent the wheel but learn from the experience of others around the world**. It is important to recognize that COVID-19 does not cause your "typical ARDS"… this disease must be treated differently and it is likely we are exacerbating this situation by causing ventilator induced lung injury. This is a very fluid situation; therefore, we will be updating the guideline as new information emerges. Please check on the EVMS website for updated versions of this protocol. EVMS COVID website: https://www.evms.edu/covid-19/medical_information_resources/ Short url: evms.edu/covidcare

"If what you are doing ain't working, change what you are doing"

Dr AB (NYC). "We have zero success for patients who were intubated. Our thinking is changing to postpone intubation to as long as possible, to prevent mechanical injury from the ventilator. These patients tolerate arterial hypoxia surprisingly well. Natural course seems to be the best." This is not your "typical ARDS". Mechanical Ventilation may be doing harm. We need to think of alternative treatment strategies.

Suggested approach to prophylaxis and treatment of COVID-19 Prophylaxis While there is very limited data (and none specific for COVID-19), the following "cocktail" may have a role in the prevention/mitigation of COVID-19 disease, especially amongst the most vulnerable citizens in our community; i.e. those over the age of 60 years and those with medical comorbidities. While there is no high level evidence that this cocktail is effective; it is cheap, safe and should be readily available. So what is there to lose? • Vitamin C 500 mg BID and Quercetin 250-500 mg BID • Zinc 75-100 mg/day (acetate, gluconate or picolinate). Zinc lozenges are preferred. After 1-2 months, reduce the dose to 30-50 mg/day. • Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 1-2 mg at night • Vitamin D3 1000-4000 u/day (optimal dose unknown). Likely that those with baseline low 25OH vitamin D levels and those > living at 40o latitude will benefit the most. Mildly Symptomatic patients (on floor): • Vitamin C 500mg BID and Quercetin 250-500 mg BID (if available) • Zinc 75-100 mg/day • Melatonin 6-12 mg at night (the optimal dose is unknown) • Vitamin D3 1000-4000 u/day • Enoxaparin 40-60mg day (if not contraindicated; dose adjust with CrCl < 30ml/min) • Optional (and if available): **Chloroquine 500 mg PO BID for 5 days or hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days** • Observe closely. • N/C 2L /min if required (max 4 L/min; consider early t/f to ICU for escalation of care). • Avoid Nebulization and Respiratory treatments. Use "Spinhaler" or MDI and spacer if required. • Avoid non-

invasive ventilation • T/f EARLY to the ICU for increasing respiratory signs/symptoms.

Respiratory symptoms (SOB; hypoxia- requiring N/C ≥ 4 L min: admit to ICU): Essential Treatment 1. Chloroquine 500 mg PO BID for 5 days or hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days. 2. Ascorbic acid (Vitamin C) 3g IV q 6 hourly until extubated or for at least 7 days. Early termination may result in a rebound effect (see Figure below): Also see dosage adjustment and caution with POC glucose testing (below). 3. Anticoagulation. Unless contraindicated we suggest FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e 1 mg kg s/c q 12 hourly (dose adjust with Cr Cl < 30mls/min). Heparin is suggested with CrCl < 15 ml/min. Alternative approach: Half-dose rTPA: 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation. On transfer to floor, consider reducing enoxaparin to 40-60 mg /day. 4. Corticosteroids: Hydrocortisone 50 mg q 6 for 7 days or methylprednisolone 60mg IV daily for 7 days.

Optional Treatment Components (the Full Monty) 5. Thiamine 200mg q 12 (PO or IV). 6. Azithromycin 500 mg day 1 then 250 mg for 4 days (has immunomodulating properties including downregulating IL-6; in addition Rx of concomitant bacterial pneumonia). 7. Melatonin 6-12 mg at night (the optimal dose is unknown). 8. Zinc 75-100 mg daily. 9. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.4 mmol/l. Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). 10. Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture (no bronchoscopy). Co-infection with other viruses appears to be uncommon, however a full respiratory viral panel is still recommended. Superadded bacterial infection is reported to be uncommon (however, this may not be correct). 11. Maintain EUVOLEMIA (this is not non-cardiogenic pulmonary edema). Due to the prolonged “replicative phase” with flu-like symptoms (6-8 days) patients may

be volume depleted. Cautious rehydration with 500 ml boluses of Lactate Ringers may be warranted, ideally guided by non-invasive hemodynamic monitoring. Diuretics should be avoided unless the patient has obvious intravascular volume overload. 12. Early norepinephrine for hypotension. While the angiotenin II agonist Giapreza ™ has a limited role in septic shock, this drug may uniquely be beneficial in patients with COVID-19 (downregulates ACE-2). 13. Optional: Atorvastatin 40-80 mg/day. Of theoretical but unproven benefit. Statins have been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial and antiviral effects. In addition, statins decrease expression of PAI-1. 14. Optional: Tocilizumab (if available) may have a role in cytokine storm (specific IL-6 inhibitor). 15. Corticosteroids: a. The only study on the use of corticosteroids and COVID-19 (from Wuhan) demonstrates a marked mortality reduction with methylprednisolone (60mg daily for 7 days). It appears that BOTH corticosteroids AND vitamin C are required to down-regulate the cytokine storm. b. During the early viral replicative stage, corticosteroids should be avoided. c. During the hyperimmune/hypercoagulable phase (day 6-8 onward) in patients with hypoxia: Hydrocortisone 50mg IV q 6 or methylprednisolone for 7 days is suggested. d. Patients may evolve into an HLH/cytokine vortex phase, marked by increasing ferrin, CRP, IL-6 and worsening oxygenation. These patients may benefit from high dose methylprednisolone. (dose?? 200-500 mg q 12). 16. Consider plasma exchange for cytokine storm/HLH picture. The use of CVVH filters that remove cytokines should also be considered.

17. Escalation of respiratory support (steps); Try to avoid intubation if at all possible • Accept “permissive hypoxemia” (keep O2 Saturation > 86%) • N/C 1-6 L/min • High Flow Nasal canula (HFNC) up to 60-80 L/min • Trial of inhaled Flolan (epoprostenol) • Attempt proning (cooperative proning; see Figure) • Intubation … by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be

avoided. • Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cmH2O. • Moderate sedation to prevent self-extubation • Trial of inhaled Flolan (epoprostenol) • Prone positioning • ?? ECMO < 60 yrs. and no severe commodities/organ failure.

There is widespread concern that using HFNC could increase the risk of viral transmission. There is however, no evidence to support this fear. HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

A group of patients with COVID-19 deteriorates very rapidly (see graphic below). Intubation and mechanical ventilation may be required in these patients.

18. Monitoring • Daily: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer, Mg, CRP and Ferritin are good biomarkers and track disease severity. Thromboelastogram (TEG) on admission and repeated as indicated. • In patients receiving IV vitamin C, the Accu-Chek™ POC glucose monitor will result in spuriously high blood glucose values. Therefore, a laboratory glucose is recommended to confirm the blood glucose levels. • Monitor QTc interval if using chloroquine/hydrochloroquine and azithromycin and monitor Mg++ (torsades is uncommon in monitored ICU patients) • No routine CT scans, follow CXR and chest ultrasound. • Follow ECHO closely; Pts develop a severe cardiomyopathy.

**A few General thoughts:**

1. We are facing a Global Health Crisis of unimaginable magnitude. We are all in this together. We need to break down the barriers to solving this crisis. We need to act decisively and immediately; there is no time to lose. Patients are dying needlessly.

2. **The attack rate of COVID-19 is calculated using mathematical models; estimates of the basic reproduction number (R0) of 2–3, suggests that 50–60% of the entire world population will eventually be infected because most humans are naive to the new virus;** this is a sobering and

frightening statistic. 3. COVID-19 results in a dysregulated and exuberant immune response. Patients requiring intensive care have significantly higher levels of IL-6, IL-10 and TNFα and fewer CD4+ and CD8+ T cells. Downregulating the cytokine storm is an essential component of the treatment of severe COVID-19 disease. 4. COVID-19 patients developed a severe hypercoagulable state (see Figures). This likely results in pulmonary micro- and macrovascular disease which may lead to hypoxia/pulmonary shunting. These patients also have an increased risk of pulmonary and cerebral emboli (see Figure). 5. The course of the disease is quite predictable. Acute respiratory failure occurs on day 6-8 concomitant with the cytokine storm and hypercoagulable state. In those patients requiring supplemental oxygen, we need to be very aggressive to prevent disease progression and mechanical ventilation. Once intubated, the mortality is high. 6. This is not your "typical" ARDS… but something else (weird). Chest CT shows bilateral, discreet, irregular, multilobar "ground-glass" infiltrates and not the typical dependent air-space consolidation ("sponge lung/baby lung") characteristic of "typical" ARDS. Physiologically "COVID-19 ARDS" is different; our preliminary data suggests that lung water (EVLWI) is normal or only marginally increased (therefore by definition this is NOT ARDS). Furthermore, lung compliance is quite good yet there is severe hypoxia (due to shunting). This suggest microvascular and/or macrovascular disease… or some other alternative explanation. In addition, pulmonary embolism appears to be very common in these patients and may be the cause of sudden death (see Figure). The typical ARDS that develops over time (see Figures) is due mechanical ventilator induced lung injury and/or superadded bacterial pneumonia. 7. 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. It will likely take many months before this study is completed and the results are available; many tens of

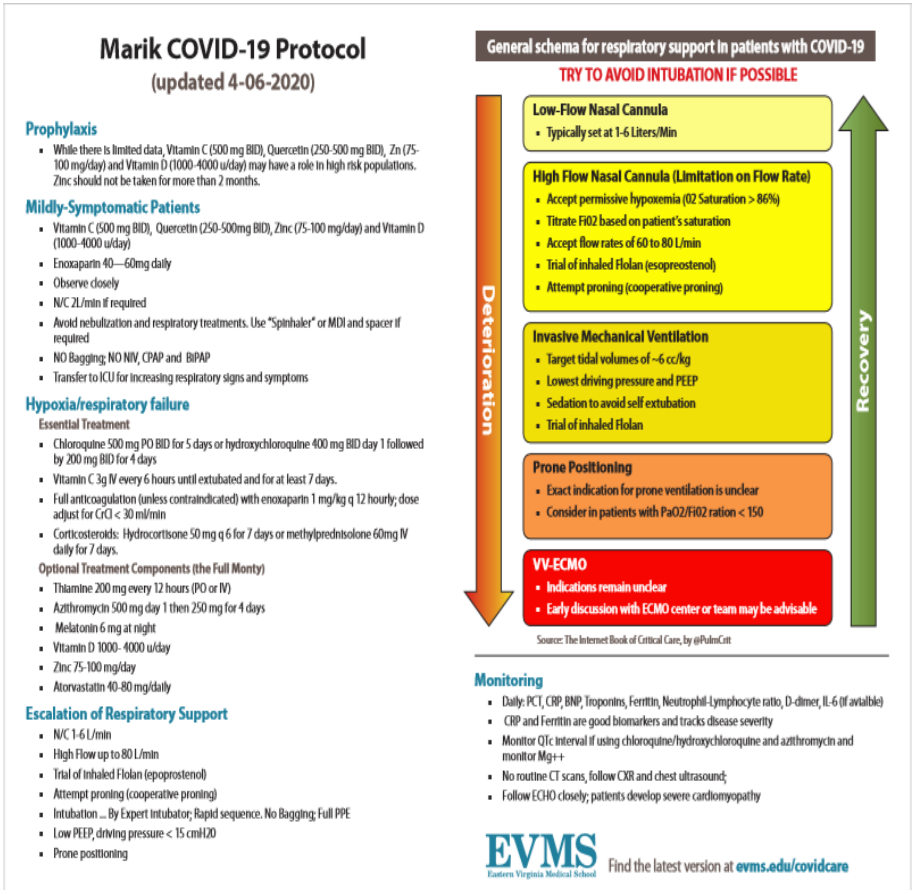
thousands of patients will die from COVID-19 related complications in the intervening time. 8. Good medical practice and the best interests of the patient require that physicians use legally available drugs according to their best knowledge and judgement. If physicians use a product for an indication not currently approved, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. 9. It is important to stress that there is no known drug/treatment that has been proven unequivocally to improve the outcome of COVID-19. This, however, does not mean we should adopt a nihilist approach and limit treatment to “supportive care”. Furthermore, it is likely that there will not be a single “magic bullet” to cure COVID-19. Rather, we should be using multiple drugs/interventions that have synergistic and overlapping biological effects that are safe, cheap and “readily” available. The impact of COVID-19 on middle- and low-income countries will be enormous; these countries will not be able to afford expensive designer molecules.

10. Preliminary data suggests that chloroquine and hydroxychloroquine decrease the duration of viral shedding. In addition, chloroquine has favorable immunomodulating properties including inhibition of PAI-1 expression. **These agents are now FDA approved for the treatment of COVID19. These agents (if available) could be used to mitigate/curtail the spread of this virus and could be used in elderly patients with comorbidities at risk of progression and death**. 11. Zinc (Zn++) inhibits viral RNA dependent RNA polymerase (replicase). Chloroquine and hydroxychloroquine are potent Zn ionophores that increase intracellular Zn concentrations. 12. Ascorbic acid has numerous proven biological properties (anti-inflammatory, anti-oxidant, immune enhancing, antiviral) that are likely to be of benefit in patients with COVID-19 disease. Furthermore, it is important to stress that ascorbic acid has proven synergistic effects when combined with corticosteroids. Therefore, steroids are recommended

in patients with COVID-19 and respiratory failure. The benefit of ascorbic acid (without corticosteroids) in patients with severe respiratory failure appears to be limited. While the optimal dose of ascorbic acid is unknown, we suggest 3 g IV q 6 hourly. It should be noted that in the presence of free iron (released from ferritin) ascorbic acid may potentially have pro-oxidant effects. Therefore, the trends in CRP and ferritin need to be closely monitored; in those patients who ferritin AND CRP are increasing, reducing the dose to 1.5g q 6 hourly should be considered. 13. Very recent data suggests that in addition to being a potent anti-oxidant, melatonin may have direct antiviral effects against COVID-19. In healthy people, melatonin levels plummet after the age of 40 years. This may partly explain the increased risk of death in patients with COVID-19 who are over the age of 40. Melatonin may therefore have a role in both the prevention and treatment of COVID-19. 14. Vitamin D has important immune-enhancing effects. Much of the population, especially the elderly have sub-optimal vitamin D levels, particularly during the winter months. Low vitamin D levels have been shown to increase the risk of developing viral upper respiratory tract infections. Therefore, prophylactic vitamin D should be considered especially in the elderly. 15. Quercetin is a plant phytochemical. Experimental and early clinical data suggests that this compound has broad antiviral properties (including against coronavirus) and acting at various steps in the viral life cycle. Quercetin is a potent inhibitor of heat shock proteins (HSP 40 and 70) which are required for viral assembly. This readily available and cheap plant-derived compound may play a role in the prophylaxis of COVID-19 in high-risk populations.

Premature discontinuation of Corticosteroids and Vitamin C (after 4 days), and the effect of reinitiation of this Vital Combination on CRP. Clinical course followed CRP profile. (evms.edu/covidcare – acesso em 15.04.2020)

Assim, a EVMS elaborou um Protocolo resumido para profilaxia e tratamento da COVID-19, onde aparece tanto a **cloroquina** quanto a **hidroxicloroquina**.



## Marik COVID-19 Protocol
(updated 4-06-2020)

### Prophylaxis
- While there is limited data, Vitamin C (500 mg BID), Quercetin (250-500 mg BID), Zn (75-100 mg/day) and Vitamin D (1000-4000 u/day) may have a role in high risk populations. Zinc should not be taken for more than 2 months.

### Mildly-Symptomatic Patients
- Vitamin C (500 mg BID), Quercetin (250-500mg BID), Zinc (75-100 mg/day) and Vitamin D (1000-4000 u/day)
- Enoxaparin 40—60mg daily
- Observe closely
- N/C 2L/min if required
- Avoid nebulization and respiratory treatments. Use "Spinhaler" or MDI and spacer if required
- NO Bagging; NO NIV, CPAP and BIPAP
- Transfer to ICU for increasing respiratory signs and symptoms

### Hypoxia/respiratory failure
Essential Treatment
- Chloroquine 500 mg PO BID for 5 days or hydroxychloroquine 400 mg BID day 1 followed by 200 mg BID for 4 days
- Vitamin C 3g IV every 6 hours until extubated and for at least 7 days.
- Full anticoagulation (unless contraindicated) with enoxaparin 1 mg/kg q 12 hourly; dose adjust for CrCl < 30 ml/min
- Corticosteroids: Hydrocortisone 50 mg q 6 for 7 days or methylprednisolone 60mg IV daily for 7 days.

Optional Treatment Components (the Full Monty)
- Thiamine 200 mg every 12 hours (PO or IV)
- Azithromycin 500 mg day 1 then 250 mg for 4 days
- Melatonin 6 mg at night
- Vitamin D 1000- 4000 u/day
- Zinc 75-100 mg/day
- Atorvastatin 40-80 mg/daily

### Escalation of Respiratory Support
- N/C 1-6 L/min
- High Flow up to 80 L/min
- Trial of inhaled Flolan (epoprostenol)
- Attempt proning (cooperative proning)
- Intubation ... By Expert Intubator; Rapid sequence. No Bagging; Full PPE
- Low PEEP, driving pressure < 15 cmH20
- Prone positioning

## General schema for respiratory support in patients with COVID-19
TRY TO AVOID INTUBATION IF POSSIBLE

Deterioration

**Low-Flow Nasal Cannula**
- Typically set at 1-6 Liters/Min

**High Flow Nasal Cannula (Limitation on Flow Rate)**
- Accept permissive hypoxemia (02 Saturation > 86%)
- Titrate Fi02 based on patient's saturation
- Accept flow rates of 60 to 80 L/min
- Trial of inhaled Flolan (esopreostenol)
- Attempt proning (cooperative proning)

**Invasive Mechanical Ventilation**
- Target tidal volumes of ~6 cc/kg
- Lowest driving pressure and PEEP
- Sedation to avoid self extubation
- Trial of inhaled Flolan

**Prone Positioning**
- Exact indication for prone ventilation is unclear
- Consider in patients with PaO2/Fi02 ration < 150

**VV-ECMO**
- Indications remain unclear
- Early discussion with ECMO center or team may be advisable

Recovery

Source: The Internet Book of Critical Care, by @PulmCrit

### Monitoring
- Daily: PCT, CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer, IL-6 (if avialble)
- CRP and Ferritin are good biomarkers and tracks disease severity
- Monitor QTc interval if using chloroquine/hydroxychloroquine and azithromycin and monitor Mg++
- No routine CT scans, follow CXR and chest ultrasound;
- Follow ECHO closely; patients develop severe cardiomyopathy

EVMS Eastern Virginia Medical School — Find the latest version at evms.edu/covidcare

No mesmo sentido, consta na página eletrônica da reconhecida **Associação Paulista de Medicina** o destaque para um estudo sobre o uso da cloroquina e da hidroxicloroquina, que ao final, recomenda o uso das referidas substâncias, aduzindo que esses fármacos, até o momento, são a melhor forma de tratamento – *"Despite our small number of cases, the potential of HCQ in the treatment of COVID-19 has been partially confirmed. Considering that there is no better option at present, it is a promising practice to apply HCQ to COVID-19 under reasonable management. However, Large-scale clinical and basic research is still needed to clarify its specific mechanism and to continuously optimize the treatment plan."*

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**COVID-19**

**08/04/2020 - Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial**

**Abstract Aims:** Studies have indicated that chloroquine (CQ) shows antagonism against COVID-19 in vitro. However, evidence regarding its effects in patients is limited. This study aims to evaluate the efficacy of hydroxychloroquine (HCQ) in the treatment of patients with COVID-19.

**Main methods:** From February 4 to February 28, 2020, 62 patients suffering from COVID-19 were diagnosed and admitted to Renmin Hospital of Wuhan University. All participants were randomized in a parallel-group trial, 31 patients were assigned to receive an additional 5-day HCQ (400 mg/d) treatment, Time to clinical recovery (TTCR), clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment to evaluate the effect of HCQ.

**Key findings:** For the 62 COVID-19 patients, 46.8% (29 of 62) were male and 53.2% (33 of 62) were female, the mean age was 44.7 (15.3) years. No difference in the age and sex distribution between the control group and the HCQ group. But for TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group. Besides, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31). Notably, all 4 patients progressed to severe illness that occurred in the control group. However, there were 2 patients with mild adverse reactions in the HCQ treatment group.

**Introduction**

Coronaviruses are enveloped positive-sense single-stranded RNA viruses belonging to the family Coronaviridae and are broadly distributed in humans and other vertebrates, eventually causing damage in digestive, respiratory and even multiple systems. In December 2019, a series of pneumonia cases of unknown etiology appeared in Wuhan, Hubei, China [1]. Sequencing analysis of throat swabs samples and electron

microscope observations indicated a novel coronavirus, which was named SARS-CoV-2 (formerly known as 2019-nCoV) [2]. Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has been confirmed to have obvious human-to-human characteristics [3,4]. As of March 20, 2020, more than two hundred thousand confirmed cases have been identified globally, for a total of 8778 deaths[5]. As the epidemic is spreading to many countries, COVID-19 poses a severe threat to global health [6]. Therefore, it is urgent to develop effective drugs against COVID-19.

The recent publication of results showing the activity of chloroquine (CQ) against SARS-CoV-2 in vitro [7], some experts and researchers also have been recommended the efficacy of this antimalarial drug in patients with COVID-19 [8,9]. For this, the U.S. Food and Drug Administration (FDA) has been working to investigate the use of CQ in COVID-19 [10]. As a derivative of CQ, hydroxychloroquine (HCQ) has similar therapeutic effects and fewer adverse effects. Based on its characteristics of immunity regulation, antithrombotic activity, and inflammation improvement, HCQ has been routinely used in the clinical treatment of systemic lupus erythematosus (SLE) [11]. However, the efficacy of HCQ in COVID-19 remains unknown.

Interestingly, through a follow-up survey, we found that none of our 80 SLE patients who took long-term oral HCQ had been confirmed to have SARS-CoV-2 infection or appeared to have related symptoms. In addition, among the 178 patients diagnosed with COVID-19 pneumonia in our hospital, none were receiving HCQ treatment before admission. All predicting the use of HCQ in SARS-CoV-2 infections. As one of the clinical research registration units in China, we aimed to investigate the efficiency of HCQ in patients with COVID-19 in this study.

(….)

**Results**

62 patients were identified as having COVID-19 and enrolled in this study, none quit (Figure 1). As shown in Table 1, For all patients, the age was 44.7 (15.3) years old, 46.8% (29 of 62) were male and 53.2% (33 of 62) were female. Patients were randomly assigned into two groups. There was no significant difference in the age and sex distribution between the two groups of patients, but there are significant differences in TTCR between the two groups. For fever, 17 patients in the control group and 22 patients in the HCQ treatment group had a fever in day 0. Compared with the control group [3.2 (1.3) days], the body temperature recovery time was significantly shortened in the HCQ treatment group [2.2 (0.4) days]. For cough, 15 patients in the control group and 22 patients in the HCQ treatment group had a cough in day 0, The cough remission time was significantly reduced in the HCQ treatment group.

Notably, a total of 4 of the 62 patients progressed to severe illness, all of which occurred in the control group not receiving HCQ treatment. For adverse effects, it should be noted that there were two patients with mild adverse reactions in the HCQ treatment group, one patient developed a rash, and one patient experienced a headache, none severe side effects appeared among them.

To further explore the effect of HCQ on pneumonia, we compared and analyzed the chest CT of patients on day 0 and day 6. **In our study, pneumonia was improved** in 67.7% (42/62) of patients, with 29.0% moderately absorbed and 38.7% significantly improved. Surprisingly, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31). Besides, 61.3% of patients in the HCQ treatment group had a significant pneumonia absorption.

**Discussion**

CQ and its derivatives have been broadly used as immunomodulators in the treatment of systemic lupus erythematosus (SLE) and other rheumatism [12]. As the pharmacological mechanism of CQ is further elucidated, its additional clinical applications, especially the antiviral activity, are also increasingly valued [13]. **The efficiency of CQ has been proven in a variety of viruses, including human coronavirus** [[14], [15], [16]]. Researchers have even reported both prophylactic and therapeutic advantages of CQ for SARS-CoV infection [17]. The severe acute respiratory syndrome caused by SARS-CoV-2 in several patients is quite similar to SARS-CoV in 2002 and is currently seriously threatening global health by triggering COVID-19. However, none specific drugs are available for the prevention or treatment of COVID-19.

Recently, Wang et al. identified that CQ could effectively inhibit the replication and spread of SARS-CoV-2 in vitro [7]. **Experts and guides for COVID-19 in China have also recommended chloroquine phosphate superior to the treatment of SARS-CoV-2 infection** [8,9]. To assess the safety and effects of CQ in patients with COVID-19, we registered this trial in ChiCTR and chose HCQ (the sulfate and phosphate salts of CQ) as the intervention agent. **The data in this study revealed that after 5 days of HCQ treatment, the symptoms of patients with COVID-19 were significantly relieved, manifesting as shorten in the recovery time for cough and fever. At the same time, a larger proportion of patients with pulmonary inflammatory has been partially absorbed in the HCQ treatment group, indicating the immune modulation and anti-inflammatory properties of HCQ in non-malarial diseases** [17]. At present, the multiple actions of HCQ such as regulation in pro-inflammatory cytokines [e.g. Tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-1 (IL-6)], antioxidant activities, also promote it widely performed in

rheumatic diseases such as SLE [11,17]. According to current research, a higher pro-inflammatory cytokine storm existed in COVID-19 patients with a severe or critical illness, eventually affected the prognosis [18]. For this, IL-6 antibody blocker, transfusion of convalescent plasma, and other therapies have been applied to counteract the cytokine storm [19,20]. **Therefore, with antiviral and autoimmune regulation effects, HCQ should be a protector in SARS-CoV-2 infection. In the present study, the reduced risk of progression to severe illness in patients with HCQ treatment also explained the intervention effect of HCQ on the pathological process of the COVID-19**.

Although HCQ has proven to be effective, with advantages of inexpensive and easily accessible, its potential detrimental effects in viral diseases must also be taken seriously. Retinopathy is one of the major adverse reactions of long-term therapy with HCQ [21]. Besides, patients with rheumatoid diseases treated with HCQ occasionally experience arrhythmias [22]. Other rare adverse reactions caused by HCQ include gastrointestinal reactions, cramps, liver dysfunction, itching, headache, dizziness, insomnia, peripheral neuropathy [13]. Fortunately, deciding on individual treatment plans scientifically, monitoring adverse reactions timely, to avoid overdose, short-term application of HCQ is relatively safe.

**Conclusion**

**Despite our small number of cases, the potential of HCQ in the treatment of COVID-19 has been partially confirmed. Considering that there is no better option at present, it is a promising practice to apply HCQ to COVID-19 under reasonable management**. However, Large-scale clinical and basic research is still needed to clarify its specific mechanism and to continuously optimize the treatment plan.

(http://associacaopaulistamedicina.org.br/especiais/efficacy-of-hydroxychloroquine-in-patients-with-covid-19-results-of-a-randomized-clinical-trial - acesso em 15.04.2020)- os grifos não são do original

Recentemente, o **Ministério da Saúde**, em boa hora apesar de um pouco tarde, adotando uma posição de vanguarda, embora cauteloso, na esteira das pesquisas já realizadas e da experiencia de sucesso, que já vem ocorrendo em vários outros, editou uma nota informativa, não apenas autorizando o uso da cloroquina e da hidroxicloroquina, mas também se referido a distribuição dos citados fármacos para todos os Estados da federação e o Distrito Federal.

**NOTA INFORMATIVA Nº 5/2020-DAF/SCTIE/MS**

1. ASSUNTO 1.1. Uso da Cloroquina como terapia adjuvante no tratamento de formas graves do COVID-19.
2. JUSTIFICATIVA
2.1. Considerando a pandemia ocasionada pelo novo coronavírus humano (COVID-2019) declarada pela OMS e a situação epidemiológica brasileira (WHO,2020a); 2.2. Considerando a inexistência de terapias farmacológicas e imunobiológicos específicos para COVID-19 e a taxa de letalidade da doença em indivíduos de idade avançada em razão da insuficiência de alterna!vas terapêu!cas para essa população em específico (BRASIL, 2020a);
2.3. Considerando as publicações recentes com dados preliminares sobre o uso da cloroquina e hidroxicloroquina em pacientes com COVID-19 (Chatre, 2020, Touret, 2020; Gautret, 2020; Riera, 2020);
2.4. Considerando que o uso de cloroquina é um tratamento de baixo custo, de fácil acesso e também facilmente administrada;
2.5. Considerando a capacidade nacional de produção de cloroquina pelos laboratórios públicos brasileiros em larga escala e da capacidade de abastecimento desse medicamento a nível estadual e municipal, este Ministério informa que:
2.6. A cloroquina e o seu análogo hidroxicloroquina são fármacos derivados da 4-aminoquinolonas, que clinicamente são indicados para o tratamento das doenças artrite reumatoide e artrite reumatoide juvenil (inflamação crônica das ar!culações), lúpus eritematoso sistêmico e discoide, condições dermatológicas provocadas ou agravadas pela luz solar e malária. A apresentação farmacêu!ca da cloroquina varia entre 50mg a 150mg, enquanto a da hidroxicloroquina é de 400mg. Ambos são fármacos administrados pela via oral ou injetável, no caso da cloroquina, podendo se distribuir extensamente pelos tecidos. São metabolizados pelo complexo de isoenzimas CYP do Lgado e possuem meia-vida de eliminação por volta de 60 dias (cloroquina) e 50 dias (hidroxicloroquina) com depuração predominantemente renal. Os resíduos desses fármacos podem perdurar semanas ou meses no organismo (Micromedex e FTN, 2010).
2.7. Algumas publicações cienNficas internacionais têm sugerido que esses fármacos podem inibir a replicação de SARS COV, por meio da glicosilação terminal da Enzima Conversora de Angiotensina 2, produzida pelos vasos pulmonares, que pode afetar nega!vamente a ligação vírus receptor (Al Bari, 2017 e Savarino 2006). **Com relação ao SARS COV 2, Gautret e colaboradores demonstraram que após 6 dias de tratamento com hidroxicloroquina (e hidroxicloroquina em associação com azitromicina), 70% dos pacientes estava sem detecção viral em relação ao grupo controle, o que em caráter preliminar, pode sugerir um potencial efeito an!viral no coronavírus humano**. Em uma recente revisão sistemá!ca rápida foi observado o efeito

da cloroquina na inibição da infecção viral por meio do aumento do pH endossômico, permi!ndo assim a fusão viral/celular. Ademais, também foi observado que esse medicamento contribuiu para a prevenção da disseminação do vírus em culturas celulares. Os modelos animais incluídos nesta revisão mostraram que a cloroquina e hidroxicloroquina podem interromper a infecção viral. (Paho, 2020).

2.8. **Os eventos adversos relatados a longo prazo devido ao uso da cloroquina incluem retinopatia e distúrbios cardiovasculares. Considera-se que o uso de cloroquina ou de hidroxicloroquina pode ser seguro, embora, a janela terapêutica (margem entre a dose terapêutica e dose tóxica) seja estreita (Touret, 2020, UptoDate). O seu uso deve, portanto, estar sujeito a regras estritas**, e automedicação é contra-indicada.

2.9. Neste sen!do, com base na Lei n. 13.979 de 06 de fevereiro de 2020, na Medida Provisória n. 926 e Decreto n. 10.282, ambos datados, a posteriori, 20 de março de 2020, que alteram a Lei já publicada, **o Ministério da Saúde do Brasil disponibilizará para uso, a critério médico, o medicamento cloroquina como terapia adjuvante no tratamento de formas graves, em pacientes hospitalizados, sem que outras medidas de suporte sejam preteridas em seu favor**. A presente medida considera que não existe outro tratamento específico eficaz disponível até o momento. Importante ressaltar que há dezenas de estudos clínicos nacionais e internacionais em andamento, avaliando a eficácia e segurança de cloroquina/hidroxicloroquina para infecção por COVID-19, bem como outros medicamentos, e, portanto, essa medida poderá ser modificada a qualquer momento, a depender de novas evidências cienNficas.

3. INDICAÇÕES NA TERAPIA ADJUVANTE NAS FORMAS GRAVES

OBS: A escolha da antibioticoterapia ficará a critério da equipe médica do hospital, de acordo com as recomendações da comissão de infecção hospitalar local.

4. OBSERVAÇÕES IMPORTANTES

4.1. Realizar ECG antes do início da droga e acompanhar durante toda a internação o intervalo QT, pois a cloroquina pode aumentar esse intervalo, especialmente se utilizada com outras drogas que prolongam o QT. A suspensão se dará por avaliação clínica individualizada.

4.2. Na presença de insuficiência renal ou insuficiência hepá!ca graves, reduzir a dose de cloroquina para 50%.

5. CRITÉRIOS PARA A PRIMEIRA DISTRIBUIÇÃO DA CLOROQUINA NA REDE SUS:

5.1. Com o aumento dos casos da COVID-19 e a velocidade de transmissão do coronavírus no Brasil, projeta-se para a primeira distribuição um quantitativo calculado com base no número de casos notificados no últi!mo boletim oficial do MS

(25/03/2020) e um estoque de reserva. Portanto, o quantitativo enviado a cada estado e Distrito Federal, será suficiente para atender de imediato os pacientes hospitalizados e para o pronto atendimento de novos casos.
5.2. Fator embalagem do difosfato de cloroquina - caixa com 500 comprimidos. Cada paciente receberá 2 blister c/ 10 comprimidos, para evitar fracionamento. Nenhuma UF receberá menos de 4 caixas (2.000 comprimidos).
5.3. O medicamento será distribuído pelo Ministério da Saúde às Secretarias Estaduais de Saúde, que realizarão o envio aos hospitais de referência de sua região. 5.4. A primeira distribuição será iniciada em 27 de março de 2020. (file:///C:/Users/User/AppData/Local/Packages/microsoft.windowscommunicationsapps_8wekyb3d8bbwe/LocalState/Files/S0/8/Attachments/MS---0014167392---Nota-Informativa.pdf[5186].pdf - os grifos não são do original) - acesso em 15.04.2020.

No mesmo sentido, o jornal **Correio Brasiliense**, traz uma noticia bastante importante, no sentido de que toda a rede municipal de saúde da cidade de São Paulo, a maior e mais populosa cidade do país, **vai incluir a cloroquina como uma das formas de tratamento para o Coronavirus nos hospitais municipais**.

> “O prefeito de São Paulo, Bruno Covas, anunciou, hoje (9), que a Secretaria Municipal da Saúde vai incluir a cloroquina como uma das formas de tratamento para o Coronavirus nos hospitais municipais. No entanto, lembrou que o uso da substância só é autorizado para pacientes internados e sob duas condições, quando houver prescrição do médico e desde que seu uso seja autorizado formalmente pelo paciente ou por sua família.
>
> “Já determinei à Secretaria de Saúde para que ela possa adquirir mais desse material. Temos hoje 6 mil cápsulas à disposição. Como cada paciente precisa de seis, já temos medicamentos para tratar mil pessoas que estejam internadas”, disse o prefeito.
>
> “Ainda não é possível ser uma política pública porque não temos ainda pesquisas concluídas [sobre a eficiência do medicamento]. Mas havendo prescrição do médico e a concordância do paciente, a secretaria passou a integrar esse medicamento no protocolo de atendimento da covid-19”, disse Covas.
> Infectologista
> Continua depois da publicidade

> Ontem (8), em entrevista coletiva, o infectologista David Uip, coordenador do Centro de Contingência do Coronavirus em São Paulo, disse que o uso da cloroquina deve ser feito com muito cuidado, já que se trata de um medicamento com efeitos colaterais. “A cloroquina está indicada para pacientes internados, desde que prescrita pelos médicos com aceite formal assinado pelo paciente. Temos enorme experiência com a cloroquina. Ela é usada há muitos anos no tratamento da malária. É uma droga importante, mas com efeitos colaterais, não desprezíveis. Ela deve ser utilizada sob prescrição e observação médica”, disse Uip, ressaltando que sua eficiência ainda foi comprovada cientificamente.
>
> Também ontem (8), o secretário estadual da Saúde, José Henrique Germann, disse que São Paulo já recebeu 200 mil comprimidos de cloroquina, que está sendo distribuído para uso nos hospitais públicos.” (https://www.correiobraziliense.com.br/app/noticia/brasil/2020/04/09/interna-brasil,843491/bruno-covas-anuncia-uso-da-cloroquina-no-tratamento-da-covid-19.shtml - acesso em 15.04.2020)

Por outro lado e na contramão da tendência mundial, o **Hospital do Sírio-Libanês** elaborou o Parecer Técnico n° 123, no sentido de não recomendar o uso da cloroquina e da hidroxicloroquina no tratamento da doença provocada pelo novo Coronavirus, *“Com base nos achados nesta revisão sistemática rápida, a eficácia e a segurança da hidroxicloroquina e da cloroquina em pacientes com COVID-19 é INCERTA e seu uso de rotina para esta situação NÃO pode recomendado até que os resultados dos estudos em andamento* do original.” – os grifos são do original.
(https://www.cnj.jus.br/e-natjus/arquivo-download.php?hash=3662fc98904c4e52296b31c6d21c5ebabfef6cb9)

Necessário salientar que, enquanto médicos e cientistas de todo o mundo, buscam desesperadamente, numa corrida de vida ou morte contra o tempo, uma melhor forma de tratamento da COVID-19, que vem infectando milhões de pessoas e já levando a óbito mais de 100 mil pessoas ao redor do mundo e não existindo, pelo menos até o momento, qualquer medicamento especifico para a remissão da doença desencadeada pelo novo Coronavirus, o referido Parecer Técnico, parecendo alheio a dramática crise mundial de saúde pública, recomenda o não uso dos referidos fármacos que vem mostrando resultados otimistas não apenas nas reduzidas pesquisas até então desenvolvidas, mas

também na utilização dessas substancias de forma exitosa por diversos outros países, em razão da pesquisa do conceituado médico da Cidade de Marselha, em França, não ter seguido os padrões protocolares para a realização de pesquisas dessa natureza.

É importante frisar, que o que vem justificando a realização de diversas pesquisas emergenciais, é a ausência de medicamento específico para combater essa nova doença, a velocidade de transmissão e, principalmente o grande número de mortos que aumenta a cada dia. Tais Circunstâncias são demasiadamente preocupantes e graves e é exatamente por isso, que têm justificado a comunidade médica-científica, em todo o planeta, tentar alternativas de tratamento, ainda que com medicamentos off-label, baseando-se em estudos experimentais e na experiência de sucesso de diversos outros países.

Oportuno destacar, que a referido Parecer Técnico, que teve como base a pesquisa francesa elaborada em Marselha, conforme anteriormente mencionado, se limitou a chegar as suas conclusões, numa rápida revisão, esquecendo de mostrar os diversos casos de sucesso em diversos países, que também é um dado bastante importante para que possa se chegar a qualquer conclusão. Mas essa nota técnica, parece que se preocupou exclusivamente em criticar a desautorizar pesquisa positiva desenvolvida em Marselha e fechou os olhos para o que vem acontecendo em outros lugares do planeta, como o uso da cloroquina e da hidroxicloroquina e de forma tão rápida quanto a sua avaliação, apressou-se em não aconselhar o uso daquelas substancias, muito embora haja inúmeros outras experiencias concretas, que noticiam o absoluto sucesso no uso daquelas substancias para a COVID-19.

Importante grifar, que ainda não há qualquer outro medicamento específico para o tratamento dessa nova doença, a qual surgiu na China em dezembro do ano passado e, se já existem estudos, mesmos que fora dos padrões, além do uso daquelas substancias em diversos países e que se mostrou, pelo menos, com alguma eficácia, por que não utilizá-la?

Quantos aos efeitos colaterais, além da experiencia recente não ter mostrado nenhum sintoma mais grave, os referidos princípios ativos, já são conhecidos e, inclusive, aprovados pela

ANVISA, para profilaxia da malária e tratamento do lúpus e da artrite reumatoide, além de serem vendidas nas farmácias do país, sem qualquer restrição ou controle, o que vem demonstrar que as citadas substâncias, não oferecem maiores riscos ao seu uso, especialmente, como no caso do tratamento da COVID-19, que o tempo de utilização dos medicamentos, via de regra, é inferior a 14 dias. Obviamente, que se o paciente apresentar alguma condição pessoal que aumente demasiadamente o risco no uso desses fármacos ou mesmo alergia a eles, essas substancias não devem ser ministradas. E, em qualquer caso, o Paciente tratado com a cloroquina ou a hidroxicloroquina, diante da possibilidade, embora não frequente, devem ser monitorados, apara avaliar eventuais efeitos colaterais importantes e, se for o caso descontinuado imediatamente o tratamento.

O que não se pode é deixar o paciente morrer, sem que se tenha tentado o uso de substancias, que vem sendo empregadas, com alguma eficácia em outros lugares, e sem a frequente ocorrência de efeitos colaterais importantes, simplesmente por que ainda não foi comprovada, em padrões científicos, a sua eficácia para essa nova doença que vem assolando o mundo.

Ocorre, entretanto, que a mídia deu uma exacerbada e extraordinária importância a referida nota técnica do hospital paulista, deixando de mostrar inúmeros outros estudos semelhantes, mas em sentido diametralmente contrário, bem como a experiencia de sucesso em diversos outros países, o que acabou por gerar um quase generalizado descrédito às referidas substâncias, que passaram a ser não recomendada por diversos Órgãos.

Com efeito, feitas essas simples constatações em breves e apressadas linhas, pode-se concluir que não há nenhuma razão extraordinariamente importante, que pudesse não recomendar/aconselhar o uso, em caráter emergencial e temporário, da cloroquina e da hidroxicloroquina, as quais já estão no mercado há cerca de 70 anos e vem sendo usadas de forma frequente e regular para prevenir e tratar diversas doenças, as quais tem aprovação pela ANVISA e cujos efeitos colaterais já são exaustivamente conhecidos e permitem o gerenciamento através de exames de sangue, imagem, monitorização do intervalo QT, entre outros. Aliás, as informações técnicas (bulas) dos referidos

medicamentos, que via de regra são usados por longo tempo, tem mostrado que com a redução ou diminuição da dosagem os efeitos colaterais ou desaparecem ou se mostram com pouca intensidade, enquanto que o utilização desses produtos para o combate a COVID-19, tem sido utilizado durante um curtíssimo tempo (cerca de 14 dias no máximo), o que também afasta qualquer outro feito que pudesse ocorrer com o uso por longo prazo.

Necessário aduzir que, se essas substâncias, normalmente apresentassem frequentes efeitos colaterais importantes, com certeza não seriam ministradas com regularidade ou seriam substituídas por outras. Aliás, os efeitos colaterais mais severos, embora incomuns, quando surgem, além de poderem facilmente serem monitorizados por médicos, rapidamente cessam com a descontinuidade do uso da substância, havendo, portanto, recuperação total do paciente.

O fato de não haver, ainda, estudos definitivos com essas substâncias para a COVID-19, até pela recentissidade do surgimento da doença, não afasta a possibilidade de seu uso off-label, mesmo porque o máximo que pode acontecer é não fazer efeito, muito embora a experiência da China, Turquia, Coreia, entre outros, bem como os estudos em Marselha, EUA (Estado da Virgínia), China, etc. mostram que as citadas substâncias tem funcionado no tratamento dessa nova doença.

Assim, os efeitos colaterais que as substâncias apresentam, não afastam a possibilidade do seu uso, mesmo porque esses efeitos, são os mesmos para quem usa essas substâncias para outras doenças, inclusive de uso contínuo. Importante lembrar, que os efeitos mais graves são tão raros e eventuais (embora cessem com a descontinuidade do uso) que se utiliza a cloroquina em larga escala, até mesmo em caráter profilático, para se evitar o acometimento pela Malária.
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