NOVEL UNORTHODOX STRATEGIES TO REDUCE THE CASE FATALITY RATE OF COVID-19 IN HIGH RISK GROUPS INCLUDING PATIENTS USING ACE INHIBITORS.

Prof. Tibor Hlavaty, MD, PhD[1,2], Anna Krajcovicova, MD, PhD[2]
1 Department of Internal Medicine V., Comenius University Faculty of Medicine, University Hospital Bratislava
2 Gastroenterology center Ruzinov, Bratislava

Corresponding author:
Prof. MUDr. Tibor Hlavatý, PhD.
Dept. of Internal Medicine V., Comenius University Faculty of Medicine
University hospital Bratislava
Ruzinovska 6
82606 Bratislava
Slovak Republic

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Letter to the editor

Dear editors,

We propose novel strategies to combat the COVID-19 outbreak, that are aimed at high-risk groups and might reduce the progression to severe forms of COVID and thus decrease the very high case fatality rate.

Following the first reports of the outbreak of several cases of acute respiratory distress syndrome in the Chinese city of Wuhan at the end of December 2019, a novel beta coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV) as the main causative agent was identified while the disease associated with was named by WHO as COVID-19 (1, 2).

Early on, it has been confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV (2) (3). ACE2 usage was found to be a key determinant of SARS-CoV as well as SARS-CoV-2 transmissibility.

The outbreak has rapidly spread globally with more than 150.000 cases detected in over 100 countries as of March 13 2020. The overall case-fatality rate (CFR) of COVID-19 in China was 2.3%, but globally it seems to be higher in the range of 3-5% (4). At present, no specific antivirals or approved vaccines are available to combat COVID-19. Many patients however receive off-label antivirals such as lopinavir/ritonavir, ribavirin and/or chloroquine and /or interferons. Several new antivirals such as remdesivir are studied in ongoing clinical trials.

Exponential spread with high CFR has resulted in unprecedented epidemiological measures from health authorities in all affected countries and regions such as lockdowns and states of emergency. These measures are draconian and severely disruptive to economic and social life in affected countries.

Given the alarming global situation and rapidly evolving large scale pandemics, there is an urgent need for effective strategies to prevent the spread of the disease and decrease its high CFR. The gravity of the situation requires to consider even novel unorthodox strategies to control the outbreak and high lethality of COVID-19.

Risk factors of severe pneumonia in COVID-19

According to a large epidemiological study of COVID-19 from Chinese Center for Disease Control and Prevention, the overall case-fatality rate (CFR) was 2.3% (1023/44 672 confirmed cases) (4) . The most important risk factors for severe morbidity and mortality are older age and comorbidities.

In patients with no pre-existing conditions the CFR was however only 0.9%. Those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. CFR was elevated among those with pre-existing comorbid conditions 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer. Among the 44 672 cases, a total of 1716 were health care professionals (3.8%). In this group 5 (0,3%) deaths were observed

A recent retrospective analysis of 191 severe inpatients with COVID-19 from Wuhan revealed that comorbidities were present in nearly half of the patients, with hypertension being the most common, followed by diabetes and coronary heart disease. (5). The median age of the analysed 191 patients was 56.0 years (IQR 46·0–67·0) and most patients were male. Comorbidities were a significant predictor of mortality, including hypertension with OR 3·05 (1·57–5·92) (48% of non-survivors vs 23% in survivors, p=0.0008), diabetes with OR 2·85 (1·35–6·05) (31% vs 14%, p=0.005), coronary heart disease with OR 21·40 (4·64–98·76) (24% vs 1%, p<0.0001, chronic kidney disease (CKD), (4% vs 0%, p=0.02).

From another perspective the overall CFR in hospitalized patients with hypertension was 26/58 (45%) in those with diabetes 17/36 (47%), coronary heart disease 13/15 (87%) and both hospitalized CKD patients died. On the other hand, CFR in patients with severe COVID-19 and no comorbidities was 18/100 (18%).

In a study conducted by Guan et al, which included 1099 patients with confirmed COVID-19, 173 had severe disease with comorbidities of hypertension (23.7%), diabetes mellitus (16.2%), coronary heart diseases (5.8%), and cerebrovascular disease (2.3%). (6).

Although the concomitant medication was not analysed in these reports, it is obvious that these risk factors share in common the widespread use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin – receptor blockers (ARB) in these patients. Furthermore, the mortality seems to correlate with the proportion of patients using ACE inhibitors in these diseases. It thus seems plausible to speculate that the mortality in hospitalized patients using ACE inhibitors might be extremely high >50%.

Recently it has been hypothesised that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2- upregulating drugs such as ACEi or ARB are at higher risk of severe COVID-19 infection (7).

It has been shown that the concentration of angiotensin-converting enzyme increases during chronic treatment with ACE inhibitors (8). For example, enalapril, an ACE inhibitor, in the range of 0.3 to 10 mg/kg/day in rats induced dose- and time-dependant increases in plasma ACE up to two to three times control values. There was significant increase in the steady state ACE mRNA in the lung (32%), duodenum (64%) and aorta (324%) and 40% to 140% increase in membrane-bound enzyme concentration in these tissues and in the heart and kidney (9).

Jewell at al. (10) showed the effects of the medications on the expression of ACE2 and ACE mRNAs in the left ventricle and kidney in rats. 12-day administration of either lisinopril or losartan was associated with 54% and 33% increases in cardiac ACE2 mRNA and 54% and 43% increases in cardiac ACE mRNA, respectively. Lisinopril induced a 3.1-fold (P 0.05) increase in renal cortical expression of ACE2, whereas losartan increased ACE2 mRNA 3.5-fold (p=0.05). Removal of ANG II activity either by reducing its synthesis or preventing the ligand from binding to the AT1 receptor stimulated increased ACE and ACE2 gene expression in both cardiac and renal cortical tissue.

Aldosterone antagonists (eg, spironolactone and eplerenone) have been shown to increase ACE2 enzymatic activity and ACE2 gene expression in human macrophages (11). ACE2 activity and mRNA expression increased by 300% and 654%, respectively.

In the study of Cao et al. (12) propofol treatment dose-dependently increased the ACE2 protein level and the cell membrane of human pulmonary artery endothelial cells ACE2 activity. Propofol in the concentration range of 10–40 μmol/l increased the ACE2 mRNA

level in a statistically significant dose- and time-dependent manner within 24 h of treatment. Although treatment for 6 hours with propofol at 1–50 μmol/l showed no significant effect on the ACE2 mRNA level.

Angiotensin-converting enzyme inhibitors are one of the most frequently prescribed classes of medication that are commonly used to treat hypertension, diabetes, heart failure (HF), myocardial infarction (MI) and renal disease (RD). For instance, in 2013, ramipril was the first antihypertensive medication with more than 24 million prescriptions dispensed in community pharmacies in the UK (13). In a small recent study from Italy 9% of patients over 75 years used ACEi as confirmed by their general practitioners (14).

Given the published data we might speculate the following pathophysiology of severe COVID-19. Coronavirus spreads easily in the community with an estimated R0 of 2.2 - 4.0. In vast majority of cases it causes only mild and transient respiratory and/or digestive symptoms such as sore throat, cough, diarrhoea or nausea. The virus`s progression to severe pneumonia is facilitated in a subgroup of patients who are immunosuppressed to some degree due to the advanced age, severe chronic diseases, use of immunosuppresants or use of chronic ACE upregulating medications such as ACEi, ARB or spironolactone. In patients using ACEi, the increased expression of ACE facilitates penetration of virus into the lungs and results in severe respiratory failure, that is resistant to treatment.

Implications for prevention and treatment of severe COVID-19 in high-risk groups

The above presented hypothesis leads to some very important implications, that should be considered, given the severity of the rapidly evolving COVID-19 pandemics. First, there are large groups of population that are at high-risk of developing severe forms of COVID-19. These include patients with hypertension, diabetes and coronary heart disease and it is plausible to assume that the USE of ACE upregulating medications such as ACE or ARB is a significant contributing factors. Second the high risk groups include also seniors (>65 years), immunosuppressed patients and/or patients with severe comorbidities even if they do not take ACE upregulating medications.

Implications for patients taking ACEi and other ACE upregulating drugs

Patients with chronic use of medications that upregulate ACE2 such as ACEi or ARB or spironolactone represents a significant proportion of general population (~5-8%).

In this large group several measures should be considered.

First, patients using ACE2 upregulating drugs should be thoroughly evaluated and possible alternative therapies considered, such as calcium channel blockers for the treatment of hypertension or beta-blockers for the treatment of coronary heart disease.

Second, once a patient taking ACE2 upregulating drugs is suspected to contract the SARS-CoV-2 virus or was in a close contact with a confirmed case of COVID-19, the use of ACEi or ARB or spironolactone should be very thoroughly re-evaluated. Unless there is a vital indication, these medications should be stopped until the resolution of the infection. Although there is limited data on the velocity of ACE downregulation, it is prudent to assume it is in the range of a few days. Given the mean dealy of development of severe respiratory complications in COVID-19 of approximately 8-10 days, it could have clinical significance.

Third, if taking ACE2 upregulating drugs is vital for the patient, then he/she should be considered to belong to high-risk group. In this case prophylactic use of coronavirus-proteases

blocking drugs should be considered as outlined below. The use should be indicated in the early stage of suspected or confirmed COVID-19 or even prophylactically during the outbreaks of COVID-19 in a community.

Chemoprophylaxis in high risk groups.

There are two widely available medications that were shown to inhibit the SARS-CoV proteases, hydroxychloroquine (HCQ, Plaquenil) or chloroquine (CQ, various generic brands) and lopinavir/ritonavir (LPV/r, Kaletra or Alluvia, AbbVie). Others such as remdesivir are late stages of clinical development.

Chloroquine/Hydroxychloroquine

Chloroquine (CQ) has been used worldwide for more than 70 years for the treatment and prophylaxis of malaria. It is widely available, cheap and has an established clinical safety profile. In some countries its base, hydroxychloroquine (HCQ, various brands e.g. Plaquenil…), is used instead. Other uses include treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda. Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*. Chloroquine is widely distributed in the whole body, including lung, after oral administration. Chloroquine is extensively distributed with an enormous total apparent volume of distribution (Vd) more than 100 L/kg, and a terminal elimination half-life of 1 to 2 months (15). As a consequence, distribution rather than elimination processes determine the blood concentration profile of chloroquine. Caution has to be exercised for the development of leukopenia, anaemia, thrombocytopenia, retinopathy and QT prolongation on ECG.

Very recently CQ has been shown to be highly effective in reducing viral replication of coronavirus SARS-CoV-2. Effective concentration (EC)90 of 6.90 μM can be easily achieved with standard dosing, due to its favourable penetration in tissues, including the lung (16). Vincent et al observed that the inhibitory effects of chloroquine on SARS-CoV infectivity and cell spread occurred in the presence of 1–10 μM chloroquine , which are plasma concentrations achievable during the prophylaxis and treatment of malaria (varying from 1.6–12.5 μM) and hence are well tolerated by patients (17, 18). Concentrations of 10 μM completely abolished SARS-CoV infection. Pre-treatment with 1 and 10 μM chloroquine reduced infectivity by 53%, and 100%, respectively. When chloroquine was added after the initiation of infection, there was a dramatic dose-dependent decrease in the number of virus antigen-positive cells. As little as 0.1–1 μM chloroquine reduced the infection by 50% and up to 90–94% inhibition was observed with 33–100 μM concentrations (17).

Meanwhile there are 23 ongoing clinical trials in China, that evaluate the use of CQ for COVID-19, although the results are pending (19). Severe expert opinion based guidelines recommend to include CQ or HCQ in the treatment protocols of severe cases of COVID-19. The Dutch Center of Disease control (CDC), in a public document on its website, suggested to consider a HCQ regimen in adults in a dose of 600 mg of HCQ at baseline followed by 300 mg after 12 hours on day 1, then 300 mg BID orally on days 2–5 days (Dutch, Accessed on 14th March 2020) (20). The Italian group of intensive care experts GiViTI recommends CQ 500 mg BID or HCQ 200 mg BID for 5 days according to clinical severity (Teleconference in Italian, Accessed on 14th March 2020) (21). Belgian group experts recommend HCQ 400mg at suspicion or diagnosis, 400mg 12 hours later followed by 200mg BID up to Day 5 (22).

The dose of chloroquine administered should target plasma concentration in a range of 1-3 μM, that is both safe and effective according to in-vitro studies discussed above. According to Mackenzie a cumulative dose of 5 grams of chloroquine over a period of approximately 3

weeks is necessary to reach a plasma concentration of 1μM and 10 grams to reach plasma concentration of 10 μM (23). In this report, the safe dosage zone was calculated to be less than 4.0 mg/kg per day for chloroquine and less than 6.5 mg/kg per day for hydroxychloroquine, while the toxic threshold is 5.1 and 7.8 mg/kg per day, respectively.

Lopinavir/ritonavir

Many *in vitro* studies have shown that SARS-CoV could be inhibited by LPV/r in given in commonly prescribed dosing (24). In a clinical trial by Chu et al., 41 patients with SARS, followed for 3 weeks, were treated with a combination of lopinavir/ritonavir and ribavirin (25). Patients were administered lopinavir (400 mg)/ritonavir (100 mg) orally every 12 hours for 14 days. The clinical progress and virological outcomes were monitored and compared to 111 patients treated with ribavirin only, who served as historical control. The adverse clinical outcome (ARDS or death) was significantly lower in the treatment group than in the historical control (2.4% v 28.8%, $p<0.001$) on day 21 after the onset of symptoms. Patients had a decreasing viral load and rising peripheral lymphocyte count.

Another study by Park et al. assessed the efficacy of ribavirin and LPV/r as post-exposure prophylaxis for healthcare workers (HCWs) exposed to patients with severe MERS-CoV pre-isolation pneumonia (26). Lopinavir/ritonavir was administered orally at a dose of 400 mg/100 mg every 12 h for 11-13 days. Ribavirin was administered orally at a loading dose of 2000 mg followed by 1200 mg every 8 h for 4 days and then 600 mg every 8 h for 68 days. Post-exposure prophylaxis was associated with 40% decrease in the risk of infection among HCW. There were no severe adverse events during PEP therapy.

This data reveal that LPV/r has a potential to prevent and mitigate the course of a coronavirus infection, especially in the early stage (24). However, this data is from the trials with SARS or MERS coronaviruses and the results of recent LPV/r trials in COVID-19 are still pending.

Proposed medical prophylactic measures in high risk groups.

The proposed prophylactic regimes of hydroxychloroquine, chloroquine and lopinavir/ritonavir is presented in Table 1. The dosing of HCQ and CQ was calculated to reach and maintain a plasma steady state concentration of 1-3 umol/L that is both safe and effective to decrease viral replication as discussed above. Given the narrow therapeutic window, body weight dosing is preferred to fixed dose regime. Contraindications for chloroquine has to be thoroughly considered especially the risk of hypoglycaemia in diabetic patients. LOP/r should be used instead in patients where HCQ or CQ use is risky.

Table 1.

Proposed prophylactic regimes of chloroquine, hydroxychloroquine and lopinavir/ritonavir for prevention of COVID

Drug	**Prophylactic regime induction**	***Duration of prophylaxis***
Hydroxychloroquine	5 mg/kg/day for 5 days, then 2,5mg/kg/day divided into two daily doses	14 days or until risk persists
Chloroquine	8mg/kg/day for 5 days, then 4mg/kg/day divided into two daily doses	

Lopinavir/ritonavir	400/100mg twice a day	

Note: The dosing of HCQ and CQ was calculated to reach and maintain a plasma steady state concentration of 1-3 μmol/L that is both effective to decrease viral replication of coronavirus SARS-CoV-19 and safe (16, 23).

The prophylactic measures for high-risk groups for severe COVID-19 are summarized in the Table 2. We suggest that patients with high risk of severe COVD-19 take a short prophylactic course of available drugs shown to inhibit the SARS-CoV proteases, i.e. hydroxychloroquine and/or lopinavir/ritonavir. If hydroxychloroquine is not available chloroquine should be used instead. Second, we suggest that patients taking ACE upregulating drugs such as ACEi, ARB or spironolactone should be switched under medical supervision to alternative medications if these are readily available.

Table 2. Proposed prophylactic measures for patients in high-risk groups for COVID-19 severe pneumonia.

High-risk group	**Scenario**	**Proposed measures ****
Seniors > 65 years Immunosuppressed patients	Community outbreak, no close contact with a confirmed case	Prophylactic use of HCQ or CQ until outbreak control
	Close contact with a confirmed case	Prophylactic use of HCQ or CQ days and/or LOP/r until outbreak control
	Confirmed positive test for SARS-CoV-2	Early treatment with CQ or HCQ and/or antivirals according to local protocols
Patients treated with ACE upregulating drugs *	Community outbreak, no close contact with a confirmed case	If possible switch to alternative therapy under medical guidance,
		If switch is not feasible, prophylactic use of HCQ or CQ or LPV/r until outbreak control
	Close contact with a confirmed case	If possible Switch to alternative therapy under medical guidance
		AND prophylactic use of HCQ or CQ and/or LOP/r
	Confirmed positive test for SARS-CoV-2	Switch to alternative therapy under medical guidance, unless there is a vital indication for ACEi or ARB
		Early treatment with HCQ or CQ and/or antivirals according to local protocols

CQ= chloroquine, HCQ=hydroxychloroquine, LPV/r= lopinavir/ritonavir, ACEi= angiotensin-converting enzyme inhibitors, ARB= angiotensin – receptor blockers
* Include i.a. ACEi, ARB, spironolactone and eplerenon
** prophylaxis should be given under strict medical supervision and respecting the contraindications and risk factors. HCQ is preferred to CQ due to more favourable safety profile.

Model of the impact of proposed prophylactic measures on the case fatality rate

Case fatality rate of COVID-19 is considerably higher than that of other viral disease such as flu. It contributes to the psychological stress and strain on the health care systems. We thus chose to analyse the hypothetical impact of proposed measures

In the modelling of the impact of the above outlined prophylactic measure in high-risk groups following assumptions we considered:

- patients with ACEi or ARB represent 5% of the population
- patients >65 years represent 15% of the population of most developed countries
- patients with immunosuppression and other severe diseases represent 5% of the population
- the progression of high-risk groups to severe COVID-19 is 25% and mortality in high risk groups is 40%
- the progression of low risk groups to severe COVID-19 is 10% and mortality is 1%
- the progression of COVID to severe forms in high risk groups users could be decreased by 50% by prophylactic measures
- the mortality of severe cases in high risk groups could deceased to the level of comorbidities-free subgroup, i.e. by 50%
- Furthermore, based on the experience with LPV/r in SARS at least 40% prevention of COVID could be achieved in all high-risk groups.

Table 3. Model of the prophylactic measures in high-risk groups

HIgh risk group	% of population	**No prophylactic measure**				**With prophylactic measures**			
		Progression to severe forms of COVID	Mortality in the severe form COVID group	CFR	Contribution to population CFR	Reduction of progression	Reduction of mortality	CFR	Contribution to population CFR
Patients using ACE upregulating medications (eg ACEi, ARB)	5%	25%	40%	10,0 %	0,5%	50%	50%	2,5 %	0,1%
Patients >65 years (no ACEi)	15%	25%	40%	10,0 %	1,5%	50%	50%	2,5 %	0,4%
Immunosuppressed and other high risk groups	5%	25%	40%	10,0 %	0,5%	50%	50%	2,5 %	0,1%
Low risk groups	75%	10%	2,0%	0,20 %	0,2%	0%	0%	0,2 %	0,2%

Total CFR	**2,65%**				**2,65%**				**0,78%**
Total CFR after prophylactic measures	**0,78%**								
CFR reduction rate	**-70,8%**								

Under these assumptions the CFR of COVID-19 could be reduced by 70,8%. Depending on the region and the number of confirmed cases as the denominator of CFR, the CFR ~ 0.7-6.0% could be decreased to ~ 0,19 – 1,6%

This CFR is not much higher than that of the confirmed influenza cases. This might have very important positive psychological, social and economic consequences.

Conclusions

There is a striking difference in the case fatality rate among various risk groups. The high-risk groups comprise patients with advanced age, comorbidities and immunosuppressed patients. There are several lines of evidence showing that the use of ACE upregulating medications might be a significant risk factor as well.

Current strategies to control the outbreak of COVID-19 have been non-discriminatory and have implied draconian epidemiological measures such as lockdowns of entire countries for a long period of time. Their long-term effectiveness remains to be proven. We propose another unorthodox approach. More consideration should be given to high risk groups, as they carry the highest risk of complicated course of the disease as well as the highest burden for the limited health care resources of affected countries.

First, we suggest short-term prophylactic use of approved medications with established SARS-CoV-19 anti-viral activity in high-risk groups We propose short course of hydroxychloroquine or chloroquine and/or lopinavir/ritonavir. These drugs are generally safe and well tolerated. The risk of use in high risk groups is acceptable. especially when confronted with the 40% mortality of severe COVID-19.

Second, as angiotensin converting enzyme 2 is the gate of entry for SARS-CoV-2, a number of medications upregulates ACE2 and patients with diseases treated with these medications have high case fatality rate, we propose a medically supervised switch of ACE upregulating drugs such as ACE, ARB or spironolactone to alternative therapies if these are readily available. That is the case in most patients with mild hypertension, diabetes or coronary heart disease.

Analysis of the impact of these measures reveals potential to reduce the case fatality rate in these large high-risk groups significantly. Reduction of CFR seems to be vital to mitigate the medical, psychological, social and economic impact of the COVID-19 pandemics.

Given the rapid spread of the pandemics, high mortality and resulting paralysis of societal functioning, we believe the proposed measures have a favourable risk/benefit ratio and should be considered in scientifically controlled setting.

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