Early systemic and local therapeutic options in COVID-19 disease

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INTRODUCTION

In the first months of the COVID pancemic, the expert panel of the NIH (US) was unable to recommend any therapy for COVID-19 outpatients (*see* NGO and RENDELL; end of May 2020). In their systematic review about registered trials for treatment of COVID-19, NGO and RENDELL mentioned only 44 trials with at least 100 participants (after excluding trials on TCM) which plan to finish enrollment until the end of the first half of 2020, and only 9 of these trials (20.5 %) refer to outpatients. NGO and RENDELL: *„We face a dilemma in having no currently approved prevention or treatment for outpatients with mild to moderate disease, the chief spreaders of SARS-Cov-2."*

About one year later (April 21st, 2021), the recommendations of the NIH for outpatients encompass only combinations of monoclonal antibodies (bamlanivimab 700 mg + etesevimab 1400 mg or casirivimab 1200 mg + imdevimab 1200 mg), restricted to outpatients with mild or moderate disease "at high risk of clinical progression". The NIH panel recommends against the use of chloroquine or hydroxychloroquine with or without Azithromycin, against dexamethasone or other systemic glucocorticoids in the absence of another indication, and against the use of antibacterial therapy (e.g., azithromycin, doxycline) in the absence of another indication.
https://www.covid19treatmentguidelines.nih.gov/outpatient-management/

In July 2021, the combination of bamlanivimab and etesevimab was no longer recommended due to potentially resistant variants; instead, casirivimab + imdevimab or sotrovimab (alone) were mentioned. There were no other new "positive" recommendations for outpatients not requiring hospitalization or supplemental oxygen (accessed July 22, 2021). Later, it became evident that Sotrovimab is ineffective against Omicron BA.2, and FDA stopped the use of Sotrovimab in regions were BA.2 dominates.

In April 2022, the NIH panel recommended for "patients who are at high risk of progressing to severe COVID-19" (among patients not requiring hospitalization or orxygen supplementation) the use of **Paxlovid (highest preference)** or **Remdesivir (second preference).**

Only when neither of these preferred therapies are "available, feasible to use, or clinically appropriate", the following alternative therapies are recommended: **Bebtelovimab or Molnupiravir (without preference for one of these two therapies).**

Dexamethasone and other corticosteroids are not recommended in the absence of another indication.

In an analysis of trial registry data from 2020, FORREST et al. found that only 6.0 % of 1970 registered clinical trials about candidate therapeutics for COVID treatment evaluate interventions to reduce hospitalization or transmission among ambulatory populations with an early diagnosis of COVID-19, but this portion of 6 % also includes prophylactic therapeutics for highly exposed populations. FORREST et al. conclude: *"The limited number of trials investigating therapeutics for early treatment of COVID-19 disease is disappointing since early treatment will likely yield the greatest treatment benefits to both patients and communities."*

In their systematic literature review on COVID-19 therapies (including altogether 42 clinical studies until cut-off October 14th, 2020), WELTE et al. reported about the "key finding" of a *"relationship between the disease phase of patients with COVID-19 and the efficacy of interventions. Several studies that investigated agents targeting processes early in the disease course of COVID-19, such as viral replication, showed improved efficacy in patients who received early treatment compared with late treatment …"*

In a JAMA article co-authored by Anthony Fauci, KIM et al. proclaim the need for early antiviral treatment for outpatients; they mention MK-4482 (EIDD-2801: Molnupiravir) (oral administration), SNG001 (nebulized formulation of interferon beta-1a) or camostat mesylate, beside the options of antibody therapies.

As of February 2021, only the following therapies received regulatory approval by EMA or FDA (according to WELTE et al.):

• Remdesivir (EMA: for treatment of adults and adolescents with pneumonia who require supplemental oxygen; FDA: for treatment of adults and adolescents who require hospitalization)

• Dexamethasone (only EMA: for adults and adolescents who require oxygen therapy)

• convalescent plasma (only FDA: for hospitalized patients)*

• Bamlanivimab or Casirivimab+Imdevimab (only FDA: in mild-to-moderate patients who are at high risk for progression to severe COVID-19 and/or hospitalization) (November 2021: EMA approved Casirivimab+Imdevimab for therapy, PREP and PEP and Regsanvimab for therapy)

• baricitinib in combination with remdesivir (only FDA: hospitalized patients who require supplemental oxygen, invasive mechanical ventilation or ECMO).

(*but see KOCAYIGIT et al.)

With regard to early therapy with the aim to avoid progression to severe disease and/or hospitalization, only one group of drugs (monoclonal antibodies) was approved, and this applied only to the FDA (as of February 2021).

No other treatment was approved about one full year after the start of the pandemic (!) that offers the chance for early treatment and the prevention of disease progression. Among the

approved drugs, convalescent plasma (only FDA) and remdesivir (EMA and FDA) *have the potential* to be helpful for that purpose (as will be discussed in this paper) if infused to early outpatients (what is as technically feasible as it is for monoclonal antibodies), but this early use was outside their current approval that needs, at least, hospitalization (as of February 2021).

As mentioned above, about one year later and now two years after the start of the pandemic, Remdesivir became meanwhile recommended for outpatients by the NIH, as did the new drugs Paxlovid (highest preference) and (with a lower degree of recommendation) Molnupiravir.

Until now, there was a lot of therapeutic nihilism for early COVID outpatients including those who have a substantial risk of progression to severe disease or hospitalization because of their age and/or comorbidities, and who are left alone in isolation with their risk and fate until the situation progresses to the stage of immediate hospitalization or need for emergency services. In many countries and settings, outpatients still have still problems to access early therapy, even if they belong to the group with increased risk for progression and hospitalization. Even if antivirals like Paxlovid are basically available to such outpatients, the high prices and a lot of bureaucracy with regard to their administration, and a lot of contraindications or interactions with other drugs often taken by older people, are serious limitations that prevent or delay early treatment – in a situation when every day and possibly every hour counts!

As a consequence, in many cases, any specific therapy against COVID-19 or its sequelae, like antiviral therapy, immunomodulation or therapy of COVID-induced complications like cytokine storms, coagulation disorders or severe pneumonia/ARDS can only start following hospitalization.

In an anonymyous and voluntary survey among PCR-positive individuals from California during **March 2022** in the era of Omicron, including 241 patients aged at least 65 years, 66.0 % of the elderly were aware of the possibility of treatment, 36.3 % sought treatment, but only 1.7 % got “antiviral” treatment like monoclonal antibodies, Molnupiravir or Paxlovid. Among those who got antiviral treatment, antibody therapies were prevailing, and neither Molnupiravir nor Paxlovid was mentioned by those aged 65 years or older. *(Of note, these rates are the results for patients >= 65 years, i.e. all of them have to be regarded as risk group simply because of age!).*

Among the younger respondents (18 – 64 years; n = 918), awareness of the treatment (~ 51 %) and treatment-searching behavior (~ 27 %) were a little lower, and about 3 % of the 918 patients got antiviral treatment (nearly exclusively monoclonal antibodies). Noone from the study reported receiving Paxlovid.

To be eligible for the survey, individuals had to have a positive RT-PCR test result within 7 days of enrollment (KOJIMA and KLAUSNER).

As PROCTER et al. pointed out in one of their papers about early ambulatory multidrug treatment, US had 877 deaths per million inhabitants (at the time of their writing) despite

technically advanced hospitals including sufficient hospital capacity, whereas India – *"a country with broad implementation of early COVID-19 treatment"* – had 102 deaths per million at the same time. *"The National Institutes of Health currently advise denial of early treatment and encourage late-stage hospitalization as the first window of treatment open to acutely ill patients with COVID-19"* (PROCTER et al.). *"In countries where therapeutic nihilism is prevalent, patients endure escalating symptoms and without early treatment can succumb to delayed in-hospital care and death"* (McCULLOUGH et al. 2; from the same study group).

The McCULLOUGH et al. (2) paper is highly recommended to read in full-text because it discusses in detail the devasting consequences of the "late treatment strategy" that was at followed at the time of their writing in US, Canada, UK, Western European Union, Australia and some South American Countries ("late hospitalization and delayed treatments [remdesivir, convalescent plasma, antiviral antibodies]") and offers a rationale for an early sequential multidrug ambulatory treatment for **every** patient with increased risks (i.e. 50 years or older; younger patients if at least one comorbidity or BMI > 30). If a patient belongs to one of these risk groups, the sequential multidrug regimen will start **immediately** after diagnosis, independent of the severity of his current symptoms.

Within the same concept and strategy, no specific treatment was advised in the absence of severe symptoms for healthy individuals with COVID-19 under 50 years, except for the need for the evaluation of oxygenation status and possibly chest imaging if lower respiratory symptoms develop (McCULLOUGH et al. [2]). However, one may ask meanwhile whether this therapeutic nihilism for people younger than 50 years can still be uphold at the time of the Delta variant, both with regard to the risk of serious outcomes also in middle-aged people and the risk of Long COVID.

Based on real data about the time course of viral load from real patients, several studies showed or calculated that antiviral therapy can only be successful if started before the peak of the viral load in each individual case. However, this peak already happens around the time of the first (often still very unspecific) symptoms, maybe a little earlier or later. Both higher cumulative viral load (cumulated over time) and higher maximal viral load are supposed to enhance the risk for a stronger (hyper-)reaction of the immune system; this may result in excessive immune reactions, hyperinflammation, cytokine storms and other deleterious sequelae which make COVID-19 much more dangerous than the virus itself. Therefore, it should be the aim of any antiviral treatment to reduce the maximum of the viral load, but this is only possible if antiviral therapy starts before this maximum is reached.

If antiviral therapy starts later (after the maximum), it was modeled that this therapy is unable to affect the course and amount of the virus load and the duration of viral shedding independent of the strength of the inhibitory effect of the antiviral (calculated with 99 % and 50 % inhibition by the authors to simulate the effects of a highly effective and a moderately effective antiviral) (IWANAMI et al.). Of course these calculations apply only to mere antivirals; the situation may be more complex for agents with an immunomodulatory effect in addition to their antiviral effect. For such agents, an influence on the course of the viral load may still be possible even when administered later (some time after the maximum). But agents with predominantly antiviral effects have to be applied (very) early to achieve a reduction of the maximum of the viral load during the course of the disease and to accelerate viral clearance (e.g. for umifenovir: ZHOU Y et al.). In their modellations based on

real patient data, IWANAMI et al. showed that antiviral treatment should start within the first 12 hours following exposure (and infection), but at least within the first 24 hours, in order to utilizise the full antiviral effects.

This is in full accordance with animal experiments with rhesus macaques: if Remdesivir treatment is starting exactly 12 hours after inoculation with a high dose of SARS-CoV-2, Remdesivir is unable to eradicate the inoculated virus immediately. However, treated animals develop only subclinical, asymptomatic or at worst case mild disease (WILLIAMSON et al.), though Remdesivir treatment did not reduce viral shedding from the upper respiratory tract.

In a mouse model with transgenic susceptible mice, starting Remdesivir administration exactly one day after COVID inoculation (and continued until study termination) significantly reduced lung damage, loss of pulmonary function and dramatically reduced lung viral load, though it could not prevent weight loss (compared to vehicle-treatet inoculated mice) (PRUIYSSERS et al.).

In contrast, the use of Remdesivir in hospitalized patients with pneumonia reduced mortality only by 30 % in a large multinational trial (Hazard Ratio 0.7) (BEIGEL at al.), and in the large WHO Solidarity trial, the reduction of mortality in hospitalized patients was negligible (9 %) and insignificant. However, the Solidarity Trial didn't consider "early" vs. "late" start of Remdesivir treatment in hospitalized patients.

A large trial (based on 346 patients) from MEHTA et al. found that Remdesivir reduces mortality with an OR of 0.44 (CI: 0.25 – 0.76) (fixed effect model) or 0.42 (CI: 0.25 – 0.75, random effect model) *if started within 9 days after onset of symptoms,* compared to start of Remdesivir after 10 days or more. This applied even to severe patients (OR 0.40, sign.) and (as a trend) to those who were mechanically ventilated (OR 0.51, n.s.).

Eventually, Remdesivir given to outpatients (3 doses; day 1, 2 and 3) reduced the risk of hospitalization by a HR of 0.134 (CI: 0.031 – 0.596); mortality was 0 vs. 0.34 % (RCT NCT04501942).

Moreover, first experiences with hydroxychloroquine (HCQ) for postexposure prophylaxis (PEP) hint to the enormous importance of the right time to start treatment. HCQ is not a mere antiviral (and its antiviral effect against SARS-CoV-2 in clinically tolerable doses is highly disputed), but has also immunomodulating (and, obviously, immunosuppressive) effects (see ROTHER et al.). It inhibits trained immunity at the functional and epigenetic level and reduces the expression of interferon-stimulated genes.

If HCQ PEP was started within the first four days following exposure (risk), its protective effect was small and insignificant (11.8 % got infected in the HCQ group and 14.3 % in the placebo group; risk reduction: 17.5 %) (BOULWARE et al.). These disappointing results were obtained in spite of high dose treatment: loading dose 800 mg, followed by 600 mg in the next 6 – 8 hours, and then 600 mg daily for the next four days. Higher doses than that cannot be recommended, particularly not for outpatients like in that trial.

However, a subgroup analysis taking into account the time interval between exposure and first HCQ dose (the loading dose) found that participants who took the loading dose within 24 hours after exposure did profit from a risk reduction of 49 %; that rate fell to 29 % if HCQ started on day 2, and to 16 % if it started on day 3. No protective effect (instead, an insignificantly increased risk of infection) was noted if HCQ started on day 4. The time-dependent effect became even more pronounced in the re-analysis of the BOULWARE dataset by WISEMAN et al. (for details, see the "chemoprophylaxis paper").

None of these associations based on a single day were statistically significant; the placebo-controlled trial was underpowered for that purpose to reach significant results on a daily base, and the trial was cancelled prematurely because of the disappointing overall results. Because of the assumed failure of the trial, the authors didn't analyze the statistical significance of that very obvious temporal trend between exposure and loading dose, and they also foregot multivariate regressions in spite of some other strong trends (e.g. with age: higher protective effects of HCQ in young people, increased infection risks with HCQ > 50 years; household contacts did profit much more than health care workers). All these associations were insignificant, maybe because of the early stop of the trial and underpowering. However, multivariate analyses might be helpful to better understand the results (but see the re-analysis of WISEMAN et al.). In spite of all of these limitations, the role of the time interval between exposure and start of HCQ PEP is in full accordance with theoretical expectations from modellations published by IWANAMI et al. and the results from WILLIAMSON et al. with early Remdesivir in rhesus macaques.

In their own mathematical modellations, SAVARINO and TAREK showed that HCQ is unable to accelerate viral clearance in a significant manner if it is not given early in the disease when the viral load is still in the range between 1 and 1000 virus copies per ml. This may explain the time trend found in the subgroup analysis of BOULWARE et al./WISEMAN et al.. In that sense, HCQ may help if it is started a very short time after inoculation with a high loading dose of HCQ, whereas effects of HCQ which are unfavorable in the early stage of the disease (like inhibition of trained immunity and reduced expression of interferon-stimulated genes) seem to overcompensate its antiviral effect when started a few days after inoculation when viral load has already increased. As noted above, it is doubtful whether any of these effects is based on *true* antiviral acitivity of HCQ, or its immunomodulatory properties.

Contrasting or heterogenous results from clinical trials with antivirals may be the results of (i) inclusion of patients with different time intervals and time frames between onset of symptoms and start of antiviral treatment, and (ii) inclusion of patients with fundamental endogenous differences in the natural history of their infection (quick clearance, intermediate clearance, slow clearance). To compare the effectiveness of different antivirals in trials (or different dosing schedules of the same antiviral), it might be helpful to include patients only within the first 24 hours after the onset of their symptoms. In this case, differences in endogenous natural clearance capabilities cannot influence the results as much (IWANAMI et al.).

Based on real patient data about viral load over time course too, GONCALVES et al. showed that in order to achieve a given reduction of the maximal viral load, the inhibitory strength of a given antiviral can be the smaller, the earlier it is applied in the course of the disease. Of course this can only work if the antiviral is started early enough to be administered before

the maximum of the viral load, thus, in fact and at best, before the start of the symptoms (in real life, this would mean PEP).

Further mathematical modellations showed that the administration even of highly potent antiviral therapeutics shortly after the peak of the viral load (i.e. at a time when infected people start to feel their first or more symptoms) may still reduce the time of viral shedding and the intensity of the immune response; however, they have little influence on the overall viral load (cumulated over time), which is dominated by early replication of the virus. The total (cumulated) viral load can only be reduced significantly if antiviral treatments start before the maximum of viral load, i.e. in a stage of infection which is still pre-symptomatic or pauci-symptomatic in many or most cases (GOYAL et al.). The authors recommend "early test and treat".

Based on longitudinal patient nasopharyngeal samples and airway epithelial organoids, CHEEMARLA et al. found that SARS-CoV-2 initially replicated exponentially with a doubling time of ~6 hours. Virus replication induced interferon stimulated genes (ISGs), but delayed relative to viral replication. The timing and degree of stimulation of ISGs then determines the extent of viral replication. *"Prior exposure to rhinovirus increased ISG levels at the start of SARS-CoV-2 infection and completely blocked SARS-CoV-2 replication. Conversely, inhibiting ISG induction abrogated interference by rhinovirus and increased SARS-CoV-2 replication rate."* (CHEEMARLA et al.).

In daily routine life and reality, any antiviral treatment will start too late, since the maximum of the viral load occurs around the time of the first (mostly still unspecific) symptoms; the symptoms may become more specific in the following days. First, it is not recommended to start COVID-specific antiviral therapy following the first experience of a little fever or nasal congestion or mild symptoms of an upper respiratory tract infection. There may be many other causes for such symptoms. Even at the maximum of the first wave of COVID epidemic in Germany, most of such infections were NOT caused by SARS-CoV-2, as shown in different surveillance systems of upper respiratory tract infections in Germany (e.g., ARE, SARI). In some cases, it may last a few days after their onset, until symptoms (e.g., loss of taste and smell, dry cough, undulating fever) may become more specific and more suggestive of COVID-19. Occurrence and frequency of specific early symptoms are also very dependent on SARS-CoV-2 variants, with a very different pattern e.g. for Omicron compared to the virus strain from the first phase of the pandemic. For example, disturbances or loss of smell and taste could be very early symptoms which may precede other symptoms by a few days in 2020, but the effect was less pronounced in Alpha and became nearly irrelevant for Omicron.

Therefore a COVID test, particularly a PoC test, may give earlier results than waiting for the course of the symptoms, and early testing strategies (with quick availability of results) are a precondition for any early treatment strategy.

It is problematic that in the VoCs like Delta, viral load rises earlier and more quickly than in the early SARS-CoV-2 variants what may reduce the chance for successful early antiviral prophylactic management (see "Warning" at page 1). The stronger rise of viral load is a consequence of immune evasion of the VoCs from the early innate immune response of the mucosal sites in the upper respiratory tract (e.g., interferon-mediated response).

Therefore, in real life, early antiviral treatment may be difficult to be accessed quickly enough; particularly if there is a demand to wait for the result of a PCR test (instead of trusting the result of a PoC test); if there is a demand to contact a doctor; if there is a need to get a prescription for the antiviral agent.

Taking into account that Remdesivir is a mere antiviral, the disappointing results for Remdesivir in hospitalized patients are not surprising. It may simply come too late there (*see below:* "Why wait another day?"). Unfortunately, the bad reputation of Remdesivir (after the recommendation of the WHO, not to use it any more) may hinder now its early use in the course of the disease, and the development of formulations with Remdesivir that may be suited for early treatment at home (and don't need to be infused). In fact, in an animal model with hamsters, it was already shown that Remdesivir dry powder inhaled twice daily achieves levels of Remdesivir and GS-441524 in the lungs and plasma that are high enough to provide antiviral activity (SAHAKIJPIJARN S et al.). Meanwhile it was demonstrated in an animal model (dog) that GS-441524 can be administered on the oral route; plasma concentrations were approximately 24-fold higher than the EC50 against SARS-CoV-2 and easily and safely sustained (YAN YC et al.). Moreover, the antiviral activity can be greatly enhanced by water soluble alpha-tocopherol derivatives.

But like the example of Remdesivir in hospitalized patients with pneumonia shows (see BEIGEL et al.), an antiviral treatment which starts several days after the onset of symptoms may not be absolutely useless and may still show some moderate success; however, one should consider this antiviral treatment only as an adjuvant since other therapeutics may be essential in that stage of the disease in case of hyperinflammation, cytokine storms or coagulation disorders. Considering viral kinetics, antiviral agents alone are now insufficient to treat progressed COVID-19 disease which meanwhile became complex and multifactorial. GARIBALDI et al. compared mortality among hospitalized patients in a retrospective multicenter cohort study and found a 28 day-mortality of 5.1 % for Remdesivir + dexamethasone, 9.2 % for Remdesivir without dexamethasone (aHR 0.14; CI: 0.02-1.03 for REM+DEX compared to REM alone), and 14.9 % for controls (no REM).

As long as there are no hints of hyperinflammation, cytokine storms, critical blood parameters or coagulation problems after one week or so after the onset of symptoms, the course of the disease seems to be benign, so there is no need to start antivirals at that point of time any more and the patient will probably be cured with or without antivirals. Late start of antivirals may possibly delay viral clearance (see ZHOU et al. for Arbidol).

However, if it's evident that the patient already suffers from dangerous sequelae of COVID-19 like hyperinflammation, need for oxygen, ARDS, cytokine storms, coagulation disorders and so on, or if blood parameters point to that in the future (from about the fourth day on after the onset of symptoms, see AGUILAR et al.; SRISKANDARAJAH et al.; see also HIPPCHEN et al. and PAYAN-PERNIA et al. for the predictive role of iron metabolism parameters like Fe↓ or ferritin↑ and others with high sensitivity and specifity for hospitalization and demand for oxygen support), antiviral treatment alone will not be enough, and antivirals will only be adjuvants to treatments that are directed against the dangerous complications mentioned above.

The evidence for the predictive value of different blood parameters (including imbalance of lymphocyte subpopulations) during the early course of the disease, which may be independent from the severity of symptoms at the time of blood draw, is very strong and addressed in a wealth of papers. It is outside the scope of this paper to discuss this enormous quantity of studies and informations. For example, see WEBER et al.. There are also indicators for mild or asymptomatic disease: patients with mild or asymptomatic disease develop significantly higher IL-12 and IL-2 levels during the acute phase of the infection (TJAN et al.).

The observation that there are as well blood indicators for progression as there are indicators for asymptomatic and mild disease makes it even more plausible to analyse blood parameters in the early course of the disease; a decision about a rigorous, aggressive therapy regimen or a "wait and see" strategy may then be based on the laboratory results.

Blood indicators from SIRSKANDARAJAH et al.

"Early risers" (< 7 days of disease onset): IL-6 > 7 pg/ml; ASAT > 40 U; creatine kinase: > 24 U
"Late bloomers" (> 7 days): D-dimer > 500 mg/l; cardiac troponin > 30 pg/ml; creatinine > 100 mmol/l
"General giants": neutrophil count > 6 x 10^9/l; lymphocyte count: < 1.1 x 10^9/l; serum ferritin: > 260 mg/l

Excurs:

(Though blood examinations starting about day 4 after the onset of symptoms would be very important to identify risk patients who will develop severe or critical disease, independent from the severity of their current symptoms, blood examinations are not established for outpatients. A nurse would have to visit the quarantined patients at home on day 3 or 4 and on following days to take blood from them which should be examined for critical markers of disease progression and prognosis; a lot of such early markers have been identified so far.

Of course, such a concept doesn't seem necessary for young or middle-aged patients without comorbidities and mild disease; however, it would be important to older infected people or those with relevant comorbidities independent of their age in order to detect early markers of progression and to initiate early treatment against hyperinflammation, cytokine storms, ARDS and other complications to avoid mechanical ventilation and other critical situations. Many trials have shown so far that even "top favorite agents" like Remdesivir or Tocilizumab come too late for patients under mechanical ventilation. However, no blood tests for outpatients with increased risks are established so far, though the rationale for such a concept is striking

Meanwhile, a simple quick blood test (< 1 min) which can be performed as point of care test with fingerstick blood (D2Dx immunity test, Nano Discovery Inc.) was described (DEB et al.) which allows to distinguish between type-1-biased immunity (favorable) and type-2-

immunity (unfavorable) against COVID-19. Type-2-biased immunity may result in type-3-hypersensitivity reaction with hyperinflammation and cytokine storms. Even patients with only moderate symptoms, but type-2-biased immunity may eventually develop critical disease and die. D2Dx immunity test is thus a prognostic test, and, most important, it works at best in the first days after onset of symptoms (see fig. 3 in DEB et al.). "Normal" scores in this test are around 0.6 or beyond; as shown in fig. 2, all patients who developed severe disease had scores below 0.3 in the first week after symptom onset. As shown in fig. 2 in DEB et al., no healthy, uninfected person had a score of less than 0.4.

Later, the scores may rise again in the direction of the normal range even in severe patients, and this explains why some "severe patients" have scores within in the normal range in figure 2. Thus it is important to perform this test in the first days after symptom onset. Only at that point of time sensitivity and specifity of this test are very high. If done later, sensitivity and specifity become lower.

Due to its cheapness (with regard to the price of each test kit) and simplicity with fingerstick blood, one can even consider to offer this test together with COVID PCR testing for symptomatic persons for whom it is well possible that they are infected, or immediately following a positive result of a rapid antigen test.

Such a test may become a gamechanger since it allows to decide very early, directly at the time of symptom onset/diagnosis, whether the patient will have a benign course which doesn't need any specific treatment, maybe except for antivirals to reduce his infectivity to others, or whether the patient will need both antiviral treatment (to reduce antigen load) and treatment against hyperinflammation / cytokine storms / overreaction of type-2-biased immunity).

An alternative method to distinguish early between a favorable and a less favorable prognosis might be the early analysis of other immune parameters. As CHAKRABORTY et al. pointed out, distinct features of the IgG Fab and Fc domain structures are present within three days of a positive test that predict the future outcome: early production of neutralizing antibodies leads to mild disease, whereas a rapid progression to more severe disease (after an initial period of mild symptoms!) was predicted by the absence of early nAbs with concomitant production of afucosylated IgGs, in addition to elevated frequencies of monocytes expressing the receptor for afucosylated IgGs (CD16a) (CHAKRABORTY et al.). However, the pattern may be different in vaccinated patients and such methods may only apply to those not yet vaccinated and without a history of COVID-19.

The need for earlymost antviral action doesn't mean that antivirals are unimportant at later stages of the disease. In the case of immunomodulation and the use of agents with some immunosuppressive effects, it may be very important to complement that with potent antiviral treatment in order to avoid a resurgence of the viral load. For example, Tocilizumab increases the risk for bacterial or fungal infections a lot (SOMERS et al., KIMMIG et al.), which may even contribute to mortality following tocilizumab treatment. So there is an urgent need for antiviral treatment in this situation to avoid rising or re-rising COVID viral loads. The same may apply to treatment with corticosteroids, which was controversary for a long time but is now well established in special clinical situations in hospitalized patients, e.g. if administered for a comparatively short time in subgroups of hospitalized patients

(GARIBALDI et al.). Rising CRP or increasing lung involvement may also indicate the start of steroids.

In summary, based on viral kinetics, exclusive antiviral treatment should start in an ideal (theoretical) setting within the first (half) day after exposure/infection. In real life, after the (i) onset of symptoms*, (ii) some observation time for the further development of symptoms*, (iii) COVID testing access*, (iv) waiting for the test results (if not an antigen test), (v) difficult and time-consuming access to a doctor and (vi) prescription for an antiviral agent, the first dose of the antiviral agent will probably be administered already after the maximum of the viral load has passed – and simply come too late.

*In the absence of a quick access to a COVID test (including rapid antigen tests), the combination of the following self-diagnostic tools may allow to distinguish whether early COVID-compatible symptoms are more or less likely due to COVID-19:

● **smell and taste tests.** Different smells should be tested (not only one). In COVID-19, it may happen that smell is not completely lost, but only with regard to some smells. For example, one can buy a series of small fragrance bottles with different smells, e.g. a set of different essential oils. It should include peppermint oil because it was found in a study from Asia that smell of peppermint is more often suppressed in COVID-19 compared to other smells. Smelling different smells (instead of only one or two) would increase sensitivity of that simple diagnostic tool.
(e.g. KHARE P et al., ISENMANN and ISENMANN, WEISS et al., PIERRON et al.).

Loss of smell is statistically correlated with a better outcome (less risk of severe disease or hospitalization) is a large meta-analysis (PIJRJA S et al.). However, it must be noted that early loss of smell and taste is less common in more recent VoCs like Alpha or Delta, limiting the efficiancy of this early and simple self-diagnostic tool. And loss of smell and taste lost its important role as a diagnostic tool in the context of Omicron.

● **pulse oximetry.** One can buy a simple pulse oximeter. It is of double diagnostic value. Reduction of the oxygen saturation starts only later in the disease, usually a few days after onset of symptoms, if it starts at all (it is a marker for a worse prognosis), so oxygen saturation is no tool for early diagnosis but a marker for worsening and need for more aggressive (or professional) treatment.

But pulse oximeters also show the heart rate, and the rise of the resting heart rate by about 10/min is an early indicator for infections, fever and COVID-19, and some surveillance systems (e.g. smart watches) are based on that observation (e.g. ISENMANN and ISENMANN). However, increase of resting heart rate may also occur in other infections and is not specific for COVID-19.

Of course, these methods cannot replace a COVID test, but in the absence of such a test (or in the meantime until such a test is available), it allows an estimation whether a diagnosis of COVID-19 is more or less probable. Based on that, early unspecific therapeutic interventions (e.g. local antiseptic interventions, inhalations) can be started before a positive COVID test

result is available. Moreover, antigen tests may yield false-negative results. A negative antigen test (e.g., as a self test) is no proof to be free of SARS-CoV-2.

Beside its possible role in diagnosis in some instances, oximetry is also of enormous importance for the **monitoring of outpatients.** As BONIFACE et al. showed, COVID patients who were monitored at home by oximetry, but had to be hospitalized because of worsening, had a much better prognosis than patients of a similar baseline state of health (i.e. after exclusion of progressed patients who had to be admitted immediately because of their acute situation) who were hospitalized directly instead of participation at the outpatient oximetry monitoring program:

Hospital stay 6.9 vs. 13.2 days
ICU admission: 3.6 % vs. 8.2 %
Mortality: OR 0.23 (CI: 0.11 – 0.49)

Of note, silent hypoxia (absence of dyspnea) is at least as dangerous as hypoxia with dyspnea (SIROHIYA et al.). In the study from SIROHIYA et al., the case fatality rate was even a little higher (but insignificantly) in patients with silent hypoxia compared to hypoxic patients with dyspnea.

Moreover, it is too late to buy “smell tests” (e.g., a series of fragrance bottles) and a pulse oximeter when one has already first symptoms. It is important to have them already at home as long as one can be sure to be healthy, in order to gather baseline data: what can I smell (and how strong) when I’m healthy? How is my oxygen saturation and my resting heart rate when I’m healthy? To know about these baseline data is mandatory to interpret the results when one has symptoms that are suspective of COVID-19.

● **Breathing rate:** whereas the normal respiratory rate at rest is 12 – 16/min, an increase to about 22 or more is an indicator for the development of a pneumonia, even when dyspnea is still absent. In that case, there is urgent need for professional help. However, an increase of the respiratory rate doesn’t occur as a very early symptom; it may occur a few days after symptom onset, if COVID-19 progresses to the pulmonary (inflammatory) stage. That said, an increased breathing rate cannot be regarded as a very early symptom; but it may be the first symptom that strongly hints to COVID-19 if prior symptoms had been interpreted as common cold, e.g. because of (false-)negative antigen tests.

Anyway, the breathing rate is a very important indicator in the course of the disease for outpatients, and a persistant increase is a warning signal for the need of professional help, independent of the presence or absence of dyspnea.

● **Body temperature:** even small increases of body temperature (+ 0.4 C relative to the usual temperature, measured at the same time of the day) or beyond 37.2 degrees Celsius may indicate early COVID-19, at least in old people like inhabitants of care facilities (ELHAMAMSY et al.). A change in temperature of > 1 C on its own has a sensitivity comparable to a rapid

SARS-CoV-2 antigen test, whereas the combination with other symptoms suggestive of COVID-19 has a sensitivity *"sufficiently high as to obviate the need to employ RTPCR or antigen testing to screen for and isolate coronavirus infected cases"* (KIM J et al.). KIM et al. concluded *„that home temperature monitoring could serve as an inexpensive convenient screen for the onset of COVID-19".*

These simple methods may still be helpful in the time of rapid antigen tests as self-tests, particular with respect of their risk of false-negative results.

● Moreover, fainting is also reported as an early (but rare) symptom of COVID-19. Unexplained and unusual fainting may be suggestive of COVID-19.

● In case of SARS-CoV-2 testing, it was found that viral loads in both saliva and nasal-swabs (taken by the participants themselves) were higher in the morning compared to evenings after symptom onset. Morning collection **immediately after waking up** results in significantly improved detection, and this advantage is most pronounced for tests with low to moderate sensitivity which likely would have missed infections in the evening (WINNETT et al.).

The results suggest also a higher risk of transmission in the morning.

There are several reasons that may explain this observation: (i) accumulation of material like cells, virions and RNA in the upper respiratory tract due to supine positioning (aiding mucociliary clearance) and decreased swallowing at night; (ii) reduced saliva production overnight that may result in a higher concentration of virus/RNA when saliva volumen is lower; (iii) a circadian rhythm of viral replication (WINNETT et al.).

In an *ideal world*, administration of highly effective antivirals like Paxlovid to elder people or those with comorbidities, i.e. to all of those who have the risk for a more severe disease, in the early stage of the disease might be the optimal treatment regimen. In case of contraindications to Paxlovid, Remdesivir infusions for 3 days or administration of monoclonal antibodies (if effective against the currently circulating variant) are alternatives; the latter may also work as PEP *(see the "chemoprophylaxis paper").* In the earliest studies, early administration of mAbs (like bamlanivimab) reduced the risk of hospitalization or need to visit an emergency department by 72 – 85 %, besides improvement of symptoms and good tolerability. This is very close to what one would expect from an optimal and highly effective early treatment, and it can be given ambulatory to outpatients (a single infusion). However, these favorable outcomes are meanwhile "historical", since the efficacy of mAbs will decrease when more variants of the virus are circulating (WIBMER et al., HU J et al., LIU H et al.). Even Sotrovimab, originally supposed to be a broad-sprectrum antibody against

SARS-CoV-2 and not very sensitive to mutations of the RBD, was meanwhile found to be ineffective against Omicron BA.2.

In the future, bispecific or multispecific antibodies will become necessary to be still effective against the mutating virus (see DE GASPARO et al). However, they will be more expensive, more difficult to produce and thus even more difficult to access for early treatment or PEP.

In the more distant future, multispecific **DARPIns** (=designed ankyrin repeat proteins; i.e. genetically engineered antibody mimetic proteins) seem to be better suited to cope with a large number of different critical mutants of SARS-CoV-2 (ROTHENBERGER et al.). Unfortunately, none of these antivirals is available so far.

As MARTINEZ et al. showed in a mouse model of severe COVID-19, early treatment with Remdesivir + mABs is highly effective. The combination was also part of the successful therapeutic regimen of the COVID infection of Donald Trump. This combination may also be important to avoid further selection of variants that escape from monotherapies (MARTINEZ et al.).

In reality, infected patients (with a new diagnosis of COVID-19) are usually sent in isolation at home and have to stay there until their situation becomes so bad that they have to call the emergency or hospital. It is absolutely unrealistic that, for example, a 60 year old man who just got his positive test result may go to a doctor, says “I’m 60 years old, I’m infected, I’m still well, but maybe because of my age I might get severe disease, so please give me paxlovid or an infusion of antibodies or remdesivir.” His desire may be risk-adapted and adequate, but it is unrealistic that something like that will ever become possible in a world of therapeutic nihilism for outpatients, as recently demonstrated in a survey from March 2022 among recently diagnosed patients from California (KOJIMA and KLAUSNER, *see above),* though many patients were aware of the possibility and therapy and even tried to get therapy. This is particularly critical for the subgroup analysis with patients at risk. Noone of the risk patients was offered Paxlovid!

This is clear evidence for therapeutic nihilism: Even if an early therapy regimen is approved and recommended by authorities, the access (and, most important, the *quick and early access*) to it will remain a critical problem even in highly developed countries – including the target group for such therapies like people with increased risk for progression to severe disease.

The relative risk for severe outcomes may be small in vaccinated people. However, even in times of the less aggressive Omicron variant, the risk of death of those diagnosed with symptomatic COVID-19 was about 0.6 % - 1.0 % in fully vaccinated patients (2 doses) aged 60 or more in Germany in March or April 2022; for boostered elderly (3+ doses of vaccine), it was still 0.3 – 0.4 %, and for unvaccinated elderly, it was 1.5 – 2.0 % (RKI, Berlin, weekly reports from March and April 2022). As RKI points out, these are provisional values that may still change (increase) if additional deaths occur within the underlying 4-week cohorts after censoring the data for the report. The given mortality rates apply to the full 4-week cohort of elderly (60+) with available informations on vaccination status, and are very probably higher in subgroups beyond the 60 years threshold, e.g. 70+ or 80+.

That said, it is not justified to exclude vaccinated or boostered patients with increased risk for disease progression, like elderly, from access to early antiviral treatment just because they are vaccinated. They are still in danger, though the probability of a severe outcome may be gradually smaller than in unvaccinated patients, but the risk still exists, and it is not so small that it is negligible, even if it is only 0.3 – 0.4 %. Moreover, the statistics mentioned above is only about death. The probability of a combined endpoint including death, ICU or serious consequences of long-term COVID-19 is probably much higher, but this is not subject of the RKI dataset on vaccine effectiveness.

At least as far as antiviral medications are concerned, the success rate of such a therapy may depend possibly on a few hours lag time (and this may apply even more to VoCs like Delta that are associated with very quick viral replication and a stronger rise of viral load within a short time):

WU J et al. found in their early study (on the Wuhan variant) that even a delay of a mean of 36 hours of the start of antiviral treatment results in a much worse prognosis. In their study, only three factors were associated significantly with the risk of progression: (i) age beyond 65 years, (ii) comorbidities, (iii) time (lag) between onset of symptoms and start of antiviral treatment.

HUANG G et al. showed in another early study (in a small group of 25 patients) that early treatment (until three days after onset of symptoms) was associated with milder CT results, and the CT pathologies resolved much more quickly (6 days vs. 13 days) compared to patients who started pharmacological treatment more than 3 days after onset of symptoms.

HUNG et al. reported that their recommended combination of lopinavir/ritonavir, ribavirin and interferon beta (1b) is superior to lopinavir/ritonavir alone only if treatment starts within 6 days after symptom onset, and CHAN et al. found in the case of MERS, that lopinavir/ritonavir reduces intubation and mortality rates only if administered early.

In the case of the combination of western medicine and TCM, early start of TCM (days 1-7) compared to days 8-14 or >15 after hospitalization (that occurred very early in China) was associated with shorter median conversion times of pharyngeal swabs and fecal nucleic acid, shorter hospital stay (13 vs. 16 vs. 21 days) and thus faster recovery (SHI MY et al.).

It would be an important progress if remdesivir would be made available for oral treatment of outpatients (see YAN YC et al.) or –probably still better or in addition to oral administration – for inhalation (see SAHAKIJPIJARN S et al. for the hamster model). A prodrug of remdesivir with high oral bioavailability and superior inhibitory effect on SARS-CoV-2 in Vero cells (9 to 24 times stronger than original Remdesivir) is described by SCHOOLEY et al.. Early remdesivir might become then a better alternative to Paxlovid for early outpatients, since the use of Paxlovid particularly in those who need it at most (elderly, patients with comorbidities) is limited by contraindications and possible interactions with other medications.

Plitidepsin (available as Aplidin; but not approved in the EU) seems to be a more potent alternative to Remdesivir. It proved to be highly efficient for early treatment (first dose was given 2 hours before virus inoculation) in two mouse models (WHITE KM et al.) and was already subject of a completed small clinical trial from Spain (NCT04382066; APLICOV-Pc; VARONA et al. According to informations on the homepage of PharmaMar (accessed January 2021, 29th), plitidepsin reduced viral load in hospitalized patients with median or high baseline viral load by a median of 50 % at day 7 and 70 % at day 15 (what doesn't sound very impressive in the absence of a comparator), but according to *in vitro* data, plitidepsin has 2400 – 2800-fold antiviral activity against SARS-CoV-2 in Vero cells and 80-fold activity in Calu Cells, compared to remdesivir. However, side effects were one of the reasons why Plitidepsin didn't get approval for multiple myeloma in the EU. The VARONA study was a dose-finding study (3 doses) with 45 patients (1 excluded after the first dose) without control group. 3 patients (6.7 %) died, all three patients were severe at baseline. Dose-dependent effects were found for discharge rates and improvement of inflammation markers. Like remdesivir, plitidepsin must be administered as infusion, and side effects seem to be a particular problem for this drug. And as of April 2022, there is no additional evidence from larger studies on Plitidepsin, and so far no experience with ambulatory patients. With the availability of Paxlovid as an oral drug for early antiviral treatment (as gold standard in early 2022), it is very improbable that plitidepsin may ever play a role in this setting.

While **favipiravir** is considered sometimes as an alternative to remdesivir, its role in mid and late stages of the disease is as controversary as it is for remdesivir. For example, a study with 150 hospitalized patients with moderate and severe disease showed no advantage for favipiravir compared to "no favipiravir" in patients of whom about 93 % (with and without favipiravir) were treated with others antivirals like CQ, HCQ, lopinavir/ritonavir or remdesivir (endpoints were mortality, disease progression, mechanical ventilation) (SZABO et al.). There was not even a small signal in that study that favipiravir might help a little bit. It probably came too late, and that reminds of the disappointing results for remdesivir in the WHO Solidarity trial and the recommendation from the WHO from November 2020 not to use it any more in hospitals. KIVRAK et al. reported that Favipiravir had the highest activity against SARS-CoV-2 only in the first 5 days.

However, more recent studies and meta-analysis eventually demonstrated that Favipiravir has no or only little beneficial effect in early outpatients or the treatment of mild to moderate outpatients (for details, see the "Favipiravir" chapter in the "Update section"), and it is evident that it cannot compete with antivirals like Paxlovid as the current gold standard (April 2022) for early antiviral therapy. In times of official recommendations for Paxlovid (first) or Remdesivir (second) for early therapy, Favipiravir is now out of the running.

ZHANG C et al. presented the most comprehensive **meta-analysis of all RCTs that were published (at least as a preprint) until December 19th 2020.** It included RCTs with outpatients (7) and inpatients (73), but studies about remdesivir or favipiravir were exclusively about inpatients. Whereas the combination of Remdesivir + baricitinib showed very favorable results (ACTT-2 trial), possibly due to the baricitinib component, both Remdesivir and Favipiravir alone were disappointing in hospitalized patients: very small

effect on mortality (~ - 10 %, n.s.) in REM and FAV, no reduction of mechanical ventilation by REM (FAV: unknown); but significant increase of hospital discharge for REM (FAV: small insignificant trend in favor of an increased discharge rate), and insignificant trends for faster viral clearance for both. Taken together, the advantages of REM and FAV for hospitalized patients are very limited. Since both drugs act as antivirals, earlier administration in the course of the disease (as early as possible) should be preferred, and thus there is an urgent demand to make REM available to outpatients as a tablet or inhalation. If so, it would have to be studied in direct comparison to Paxlovid. Even if not superior to Paxlovid, it is still important to have an alternative to Paxlovid for those who should avoid Paxlovid because of contraindications or interactions.

Most impressive, FANG et al. showed a strong association between the lag time between symptom onset and the start of a combined treatment of **Arbidol (umifenovir) and Lianhuaqingwen** in moderate patients and their outcomes like PCR conversion, CT improvement and duration of hospital stay. They performed regression analyses on a day by day base between 1 and 21 days (start of treatment relative to symptom onset). All results were significant ($p < 0.01$). The earlier the treatment started, the shorter the time to PCR conversion, CT improvement and the shorter hospital stay. In the regression analysis, each one day delay of therapy start resulted in 0.72 days delay of PCR conversion, 0.83 days delay of CT improvement and 0.66 days prolongation of hospital stay.

In another study from China, WONG CKH et al. used umifenovir in their Anhui cohort (hospitalized), in most cases together with TCM (33.5 % of the mostly mild-moderate 648 patients from the Anhui cohort got umifenovir and 87.2 % got TCM). Umifenovir was not associated with a composite outcome of ICU admission, mechanical ventilation or death (OR 0.84; CI: 0.42 – 1.69) in the Anhui cohort where such outcomes were rare. However, when Umifenovir was started within 7 days of symptom onset, there were no such events among 76 patients with early start of umifenovir compared to 5.2 % of a larger group of controls without any umifenovir (no OR calculated), whereas OR for the composite endpoint was 1.29 (CI: 0.64 – 2.56) when umifenovir started later than 7 days after symptom onset. TCM on its own had no effect (OR close to 1.0 for <= 7 days and for > 7 days).

ORs were calculated following propensity score matching and linear regression. Though insignificant probably because of too small power in that cohort with generally very good outcomes, this study sends another signal that early umifenovir may be helpful (at least if combined with TCM), whereas it seems to come too late when started more than 7 days after symptom onset.

ZHANG X et al. (2) demonstrated that early antiviral treatment, started in an asymptomatic stage directly following a positive PCR test, improved the outcome compared to those who got the same antivirals only after they had become symptomatic. They compared patients from different “generations” of an infection cluster in China. The fourth generation received PCR tests soon after their contact with confirmed patients, and once a test was positive, they got antiviral therapy though they were still asymptomatic. Antiviral treatment was Arbidol or Ribavirin or Lianhua Qingwen (herbal TCM), but most patients got two of the three medications at the same time. The antiviral treatment regimen was not different between both groups. In the early treatment group (the fourth “generation” of the cluster), there was less risk of becoming a severe case (4.35 % vs. 50 %), less CT anomalies like ground glass opacity (34.8 % vs. 100 %), less need for oxygen therapy (41.3 vs. 100 %), less need for

antibiotics (19.6 % vs. 100 %), better laboratory results (for many parameters), comparatively mild symptoms (less sore throat and dyspnea) and a shorter time to PCR-negativity (16 vs. 22 days). The authors attribute these differences to the early antiviral intervention, that already started within the incubation period.

FUJII et al. studied the effect of early Favipiravir on defervescence in hospitalized patients with early, non-severe disease in a retrospective cohort study. (Dose of favipiravir: 1800 mg twice daily on the first day, followed by 800 mg orally twice daily for up to 14 days; standard care included oxygen inhalation, oral or i.v. rehydration, electrolyte correction, antipyretics, analgetics, antiemetic drugs). The earlier favipiravir was initiated after the onset of fever, the quicker fever resolved. There was a linear relationship ($r = 0.548$, $p < 0.001$) between (i) the time interval from start of fever to start of favipiravir and (ii) the duration of fever. If taking 4 days (since onset of fever) as a cut-off between early and late treatment, the median days to defervescence were 7 vs. 13 days (early vs. late treatment). Unfortunately, that study reported only about defervescence and not about other outcomes (and was probably underpowered to do so; n=41).

Since fever is usually not very high in COVID-19 and not the main problem of patients, one might assume at the first glance that this aspect is quite unimportant. However, COVID-19 may develop to critical disease with ARDS, which typically begins approximately one week after the onset of symptoms; and particularly in patients who have a fever for >7 days, the condition may worsen suddenly (FUJII et al.). Thus FUJII et al. assume that *"the extension of the fever period may be one of the factors affecting the severity of COVID-19. Early initiation of favipiravir therapy (within four days of onset) is expected to lead to fever resolution within seven days in non-severe COVID-19 patients and thus, may prevent the development of severe forms of disease."* This conclusion doesn't necessarily mean that long duration of fever is the cause for severe disease. Long duration of fever is probably only an indicator for conditions that favor the development of severe disease, and early favipiravir may act against these underlying conditions. As mentioned above, Favipiravir can no longer be recommended for early therapy, but FUJII et al. demonstrate the importance of early start of antiviral treatment, and it is highly probably that this applies to other antivirals too, as is now well known from the RCTs of early antiviral therapy by Paxlovid or Molnupiravir.

All of the current difficulties to get access to early specific pharmacological treatments raise now the question what people either with a fresh positive COVID test result, or untested people with symptoms and a contact history which are compatible with a probable SARS-CoV-2 infection, can do to improve the outcome of their proven or suspected COVID disease in the absence of specific prescribed pharmacological treatment – independent of whether this situation occurs because such a treatment is not recommended to outpatients by authorities, or because it is not accessible due to all of the time-consuming obstacles or legal restrictions mentioned above?

Because of the important role of (i) viral kinetics, (ii) the maximum of the viral load and (iii) the cumulative viral load on the course of the disease and the risk of hyperinflammatory or hyperimmune or endothelial/coagulation complications, it is clear now that any antiviral actions (if not by pharmacological agents, then by other means) must start as early as possible. This means that people with suspected COVID-19 infection should also start antiviral actions, even if COVID-19 hasn't been confirmed so far. Even if antivirals may are

accessible to subgroups of outpatients (those with increased risk of progression to severe disease) following prescriptions by general practitioners, it is unlikely that people with only suspected (not yet proven) COVID-19 will get such prescriptions. But PoC self testing may be an important tool that offers the chance of early diagnosis.

As of April 29, 2022, https://c19early.com/ site analysed 40 different early treatments of COVID-19 (including drugs, antibodies, convalescent plasma, vitamins, nutritional supplements, oral/nasal antiseptics, exercise and others).

The metaregression, based on the most serious reported outcome of each included study, found a very strong association between the efficacy of the early treatment and the average treatment delay (defined as days since onset):

On average, efficacy was ~ 75 % if started within 2-3 days from onset, and then fell quickly to ~ 50 % at day 4, 25 % at day 5-6 and approaches 0 % between day 8 and 9.

These results are very well in accordance with the known kinetics of the viral infection and viral load in COVID-19.

There are several simple and accessible possibilities what early outpatients can do to reduce their viral load and – hopefully – the risk of an unfavorable course and outcome of their disease. Unfortunately, all of these methods are based upon either very small clinical trials or only upon theoretical considerations based on *in vitro* data. There is an urgent need for larger and randomized trials for the evaluation of the effectiveness of these methods. Moreover, as already mentioned in the “WARNING” section on page 1, it is not known whether agents that proved to be successful with the wildtype of SARS-CoV-2, still work (or work as well) in the case of infections with critical variants like Delta, Omicron and new VoCs in the future.

The advantage of at least some of these methods is that (i) they are low-threshold and can be practiced at home without expensive medicine or equipment and (ii) they may also help in other infections of the upper respiratory tract and influenza-like disease, so their (possible) effect and success is not restricted to people with COVID. They can be practiced directly after the onset of very early unspecific symptoms when it is still very unclear whether this may be COVID-19 disease or not. PoC tests often don’t show positive results in the very early disease because they need a higher viral load than PCR tests to give a positive result.

However, some of the local antiviral (antiseptic) methods may reduce the oropharyngeal or nasopharyngeal viral load, especially immediately (maybe 1 hour or so) after their administration, what may result in false-negative results in a subsequent COVID test. So they should not be practised within one hour or so of a planned COVID test (particularly PoC antigen test). In case of PCR, they may result in a higher Ct value.

Special note about hydroxychloroquine (HCQ) (HCQ is not subject of this paper)

It is important to note that a possible role of hydroxychloroquine in subgroups of early outpatients is still unclear. There are disappointing experiences (MITJA et al., SKIPPER CP et at.), but also favorable outcomes in controlled trials (e.g. IP et al., multicenter observational trial; OR for hospitalization: 0.53, sign.; SULAIMAN T et al., a large study from Saudi Arabia with favorable outcomes for HCQ; however, this was not a placebo-controlled RCT), and the timing of the start of HCQ treatment may also be important (the earlier, the better). But IP et al. found that HCQ reduced the risk of hospitalization in outpatients only when started within two days of symptom onset. DERWAND et al. found favorable outcomes in outpatients with a triple therapy for 5 consecutive days: zinc sulfate 220 mg capsule once daily (= 50 mg elemental zinc), HCQ (200 mg twice daily) without loading dose and azithromycin (500 mg once daily). Compared to 377 outpatients without triple therapy as controls, hospitalization rate for 141 patients with triple therapy was 2.8 % compared to 15.4 % (OR 0.16; CI: 0.06 – 0.50, $p < 0.001$) and mortality rate was 0.71 % vs. 3.5 % (OR 0.12; n.s.), and there was no intubation/ventilator in the treatment group. The fatal case in the treatment group was a patient with a history of cancer who took only one daily dose of the triple therapy before hospital admission. Therapy started in that study median 4 days after symptom onset.

Whereas the role of HCQ or HCQ+AZI in (early) outpatients is still controversial, a comprehensive systematic review and meta-analysis about the effects of HCQ with and without AZI in **hospitalized patients** (11932 participants HCQ, 8081 HCQ+AZI, 12930 controls, after exclusion of all studies with critical risk of bias) found an increased risk of mortality for HCQ+AZI (RR 1.27; CI: 1.04-1.64; based on 7 studies), but not for HCQ alone (RR 0.83; CI: 0.65-1.06; based on 17 studies; but RR was 1.09, CI: 0.97-1.24, if confined to the three RCTs among the 17 studies) (FIOLET et al.). The latter is well compatible with the RR of 1.09 (0.97 – 1.23) for hospitalized patients in the RECOVERY trial (HORBY et al., *see below*) and the meta-analysis of KUMAR J et al. (based on 8062 hospitalized patients) that HCQ was associated with a small increase in mortality compared to placebo or standard care (RR 1.10; CI: 1.00 – 1.20). In non-hospitalized cases, RR for mortality was 0.99 (0.14 – 6.98) in that study.

Furthermore, in a study from Switzerland, hospital stay was longer in patients who got HCQ (+3.75 days), lopinavir/ritonavir (+1.23 days) or both (+4.19 days) compared to standard care without any significant reduction of mortality (VERNAZ et al.).

The difference to the favorable results from DERWAND et al. is striking. Aside from methodological issues like the lack of a “true” control group in DERWAND et al., there may be real differences between the efficacy of HCQ+AZI in early outpatients vs. hospitalized patients (e.g. because of differences between symptom onset and start of HCQ+AZI), or the addition of high doses of zinc in DERWAND et al. is a critical favorable factor, as will be discussed below (in the “zinc” section). Meanwhile, it became evident that azithromycin is

ineffective for the antiviral therapy of COVID-19 (see below, "note on azithromyin"), increasing the probability that zinc and its combination with ionophores (like HCQ) may contribute to the favorable results in the DERWAND study.

Interestingly, the meta-analysis of KUMAR J et al. found a nearly significant trend that HCQ in outpatients is associated with a reduced risk of hospitalization (RR 0.57; CI: 0.31 – 1.02). However, it was found in the same study that HCQ has a higher risk of adverse events (RR 2.68; CI: 1.55 – 4.64). Whereas HCQ was associated with increased mortality in hospitalized patients in their meta-analysis (see above), KUMAR J et al. conclude: *"However, the positive effects of HCQ over the need for hospitalization without any increase in mortality in out-patients (mild disease) warrants further exploration."*

Results from the HCQMETA site (accessed April 29, 2022):

There were 183 (May 2, 2021: 126) studies that reported about the RR of mortality for **"late" (non-early) treatment** with HCQ. Based on 229,545 (May 2021: 172,422) patients (38450 deaths; May 2021: 29788 deaths), the RR for mortality was **0.81 (CI 0.76 – 0.86)** [May 2021: 0.79 (CI: 0.72-0.86)] according to HCQMETA. Of note, the dataset aggregates studies of HCQ alone, HCQ+AZI or HCQ+AZI+zinc, though there may be differences between these treatment regimens.

However, if one restricts the analysis to the 31 RCTs among the 183 studies, the RR for "improvement" in late therapy for HCQ was **0.87 (CI: 0.70 – 1.06),** based on 5287 patients on HCQ and 6728 controls. 21 of the 31 RCTs were analysed for the outcome "mortality". In 11 of these 21 studies, the RR for mortality ranged between 0.80 and 1.20; in 7 RCTs, it was < 0.80, and in 3 studies, RR was > 1.20. One of the RCTs with the most favorable results for HCQ (RR 0.34), REIS et al., 0/214 deaths in the HCQ group and 1/227 death in the control group) was misclassified because it was about outpatients, and hospitalization was one of the outcomes, thus it cannot be classified as a "late" treatment RCT.

For **"early" treatment,** HCQMETA stated a RR for mortality of **0.28 (CI: 0.19 – 0.43)** based on 15 studies with 52740 patients (compared to RR 0.81 for late treatment). About one year earlier, on May 2, 2021, RR was also 0.28 (CI: 0.18 – 0.43), based on 13 studies with 43926 patients. In April 2022, all but one of the "early treatment" studies with outcome "death" non-RCTs.

But the only RCT among these 15 studies reported a RR of 0.99 with 5 deaths in the HCQ group (n = 687) and 5 deaths in the control group (n = 682) (AVEZUM et al. RCT, NCT04466540).

The poor results for HCQ in the mortality analysis for "late treatment", both in "all studies" and studies confined to RCTs, and the null result for HCQ in the only (but large) RCT on "early treatment", warn that the favorable mortality signal for "early treatment" from the large number of non-RCTs with its RR of 0.28 may be missleading.

Based on the experience with "late" treatment studies, there have to be enormous doubts whether the favorable results of the favorable "early treatment trials" would persist in large RCTs. (This sentence was written here in May 2021, and the AVEZUM RCT is the first direct hint for that suggestion from 2021 in the meantime). Nevertheless, with a RR of 0.28 for non-RCTs (+1 RCT) in early treatment and a RR of 0.81 for non-RCTs + RCTs in late treatment, there is still signal that early treatment with HCQ may be more effective than late treatment. However, this difference may be confounded very seriously by the age signal that HCQ seems to be more helpful in younger patients

compared to older ones. “Late treatment” studies are biased to hospitalized and progressed patients, and these patients are typically older than a more randomly structured patient population that is amenable to early (outpatient) treatment regimens, particularly in countries with young populations where many HCQ trials come from.

However, due to the ongoing controversy about the effectiveness of HCQ in (early) outpatients, a lot of contraindications or the purported need for ECG monitoring, and difficult access (in a situation when every hour may count), **HCQ is not subject of this paper.** This doesn’t mean that it is regarded as completely useless for all subgroups of outpatients and that it may have possibly still a chance in combination with other agents (doxycycline? high dose zinc?, minocycline?), but it is outside the scope of a paper that will deal preferentially with early unspecific, easily and quickly accessible therapy options.

Readers who are interested in HCQ may look at PRODROMOS and RUMSCHLAG. In short, they performed a systematic review (until August 3rd, 2020). They included studies with HCQ alone or in combination with Azithromycin (AZI) and/or zinc. They identified 43 studies (11 with outpatients/day clinics, 32 with inpatients).

Among 11 studies with outpatients (7 of them peer-reviewed), 9 showed significant positive results and 2 (the only two RCTs among the 11 studies) showed a trend for positive results (decreased risk of hospitalization and improvement in symptom resolution), that didn’t reach statistical significance, maybe because they were underpowered. 4 of the 11 studies were about HCQ alone, 7 about HCQ+AZI. All 7 studies about HCQ+AZI reported positive results, but only 2 of the 4 studies about HCQ alone.

Among 32 studies with hospitalized patients, the results were less favorable. 14 studies reported positive results (43.8 %), 15 no improvement (46.9 %) and 3 worse results (9.4 %). With regard to the time line, among 9 studies, HCQ was administered within the first 48 hours after admission (6 reported improvement, 3 no improvement), whereas in 5 studies, HCQ was administered > 48 hours after admission or in ICU; only 2/5 showed improvements. Among the 32 studies with hospitalized patients, there were 5 RCTs; 1 showed positive results, 3 no effects and 1 negative results, but PRODROMOS and RUMSCHLAG discuss reasons why the latter might have been biased in favor of negative results.

Taken together, PRODROMOS and RUMSCHLAG conclude that *“there appears to be a relationship with time of initiation of treatment, with better results observed the earlier HCQ is provided.”*

However, though the results from PRODROMOS and RUMSCHLAG look favorable as far as “early” HCQ is concerned (in outpatients, but also early after hospital admission), there are two important limitations. First, they included only studies until August 3rd 2020, and some important and large trials were published later. Second, there is a need to dig deeper into the studies to look for subgroup analyses whether HCQ efficacy (or harm) is depending on age. As far as both PREP and PEP are concerned, different age groups respond differently to HCQ. Whereas younger adults profit from HCQ prophylaxis to a moderate extent, it is unfavorable for elder adults (higher risk of COVID-19 infection in case of HCQ prophylaxis,

see BOULWARE et al.), and the transition between a favorable and an unfavorable effect lies somewhere between 42 and 50 years (see http://freepdfhosting.com/863ed84c7f.pdf).

Since this applies to both HCQ PREP and PEP, one should consider the possibility that this may also apply to treatment, particularly early treatment? If it actually does, differences in the age structure of the patients may possibly explain the contradictory results for HCQ in the treatment of COVID-19 among different studies; for example, the patients in MILLION et al. (favorable results for HCQ) were on average about 25 years younger than those from MAGAGNOLI et al. (US veterans; unfavorable results).

Thus any HCQ study should perform subgroup analyses for different age groups and publish them even if the results fail to reach statistical significance (so that they are still available for meta-analyses). Based on the experience with HCQ PREP and PEP, a "null effect" for the whole group of participants may result from a "favorable" effect for younger participants and an "unfavorable effect (increased risk)" for older participants. As mentioned above, the cut-off may be quite young, less than 50 years, at least as far as prophylaxis is concerned.

That said, the discrepancies between the results for HCQ for "early" vs. "late treatment" in the meta-analyses from the HCQMETA site may simply reflect differences in the age structure: hospitalized patients ("late treatment") are commonly much older than ambulatory patients who may receive early HCQ for prevention of progression, and this applies particularly to developing countries with their young population structure where most of the HCQ studies for early (ambulatory) patients were conducted.

In fact, an age signal can be found in a re-analysis of the studies included in PRODROMOS and RUMSCHLAG. For 18 of 25 studies with "positive results" for HCQ or HCQ+AZI and all 3 studies with "negative" results, the median or mean age of the participants was given. Calculated *per study* (and not per participant), it was about 10 years younger in the studies with positive results compared to those with negative results (~ 57 years vs. ~ 67 years). AHMAD et al. was excluced from the analysis because it was about HCQ+doxycycline, not about HCQ+AZI as given by PRODROMOS and RUMSCHLAG. Taken that into account, the range of median or mean ages from the "negative studies" was 65.3 – 71 years (71 years in the "HCQ only" group from MAGAGNOLI et al.), whereas it was 43.6 (MILLION et al.) to 68 years (YU B et al.) in the positive group. But YU B et al. was confined to critically ill patients (who are, on average, usually older than non-critical patients). Excluding that study, the range is 43.6 – 64 years for "positive" studies, in obvious contrast to 65.3 – 71 years for the "negative studies".

Because of different ways of presentation of age data (median vs. mean; total group or separately for HCQ group and non-HCQ group), it is not possible to analyse the age data more precisely in a meta-analytic manner, but even (i) the difference in the crude data of about 10 years and (ii) in the age range of the positive vs. negative studies is so striking that it is evident that these differences can't be eliminated if a more precise age data analysis would have been possible. Thus there is an age signal that HCQ (or HCQ+AZI) seems to be more favorable (or less deleterious) in studies with (on average) younger patients compared to studies with older patients.

In another study that reported favorable results particularly for early administration of HCQ in hospitalized patients from China (SU Y et al.), the median age of the participants was only 39 years (IQR: 28 – 56). Because that study was published in December 2020, it was not included in PRODROMOS and RUMSCHLAG but adds additional evidence to the age signal described above.

Unfortunately, subgroup analyses of different age groups in the 28 studies were very scarce. Different age groups were often presented in the demographic data, and if so, they were used for adjustments, Cox regressions or matching, but there were only two subgroup analyses. The first was in a trial from the "positive study group", Fig. 3 in GUERIN et al., where individual patient data showed that HCQ+AZI was superior to both AZI alone and "neither HCQ nor AZI" in the age group 50 – 70 years. However, based on only 12 cases for HCQ+AZI, 12 for AZI and 10 for "no HCQ/no AZI" and a visual interpretation of the figure, this doesn't mean a lot. There were only 3 patients > 70 years, and none of them got HCQ. Moreover, only 58 % of the patients from the GUERIN trial had PCR confirmed COVID-19. The other patients were included due to symptoms that were compatible with COVID-19.

The second subanalysis was presented by the "negative study" from HORBY et al., a very large and highly rated RCT from the RECOVERY Collaborative Group (patients: 1561 HCQ, 3155 usual care). Median age for that study was 65.3 years (HCQ: 65.2 years, no HCQ: 65.4 years). Whereas the RR for mortality in the HCQ group vs. usual care was 1.09 (0.97 – 1.23) across all age groups, it was 1.03 (0.85 – 1.25) < 70 years, 1.17 (0.93 – 1.47) between 70 and 80 years and 1.14 (0.92 – 1.42) > 80 years, again hinting at an age signal. Unfortunately, the age group < 70 years was not divided in several subgroups, though 925 patients with HCQ and 1873 controls < 70 years would have allowed to do so. The original study design was restricted to these three pre-defined age groups.

Furthermore, 2 of the 17 studies from the "no improvement" (but not "worse results") group from PRODROMOS and RUMSCHLAG presented age-dependent subanalyses of HCQ efficacy.

SKIPPER et al. found that the reduction in the symptom severity score over 14 days was a little (but insignificantly) stronger in older patients who received HCQ compared to placebo, but the differences between the age groups were very small; in patients > 50 years: HCQ: -2.36 [reduction of symptom severity score], placebo: - 1.91, Δ – 0.45; 35-50 years: HCQ: -2.48, placebo: -2.20; Δ – 0.28; 18-35 years: HCQ: -2.89; placebo: -2.73; Δ – 0.16.

In their study with 1376 hospitalized patients from New York, GELERIS et al. found a strong age signal. The adjusted HR for the composite endpoint of death and/or intubation was 1.04 (CI: 0.82 – 1.32) for those who got HCQ compared to those who didn't. However, compared to <= 40 years taken as reference (1.0), the HR for 40 – 59 years was 1.52 (0.78 – 2.93), for 60 – 79 years it was 2.09 (1.05 – 4.13) and for > 80 years, it was 3.92 (1.88 – 8.20). There is a significant age signal that treatment with HCQ becomes the more deleterious the older the patients are. However, with 9.9 % of all patients who got HCQ < 40 years, and an aHR of 1.04 across all age groups, it becomes evident that HCQ must have had a favorable effect for those < 40 years (but probably statistically insignificant and thus not mentioned in the paper or table). Otherwise, HRs from 1.52 to 3.92 in the older age groups (compared to < 40 years) would have been mathematically impossible when the HR across all ages groups is 1.04.

Interestingly, in that study, HCQ starts to have a deleterious effect from 40 years or beyond, somewhere between 40 and 50 years, and this is well in accordance with prophylactic trials as discussed in the chemoprophylaxis paper (see above).

Among the RCTs with outcome "mortality" listed by HCQMETA (accessed Jaunary 16th, 2021), the study from DUBEE et al. also found an age signal. Though HCQ reduced death risk (28 day mortality) in that study with mild and moderate patients in both older and younger participants (RR 0.54 for the total group), RR was 0.77 for patients >= 75 years, thus RR for patients < 75 years must be much lower than 0.54. About half of the patients were >= 75 years. RR for 14-day mortality was 0.99 (all HCQ patients) and 1.55 (>= 75 years), thus much lower than 0.99 for patients < 75 years. RR for primary endpoint (mechanical ventilation or death) at day 14 was 0.63 for patients < 75 years and 1.44 for patients >= 75 years. All reported associations are only insignificant trends.

However, the SOLIDARITY results present an exemption from that age signal; raising the question whether the age signal applies also to later stages of treatment? Whereas the risk for in-hospital mortality was insignificantly higher in the total HCQ group compared to controls (RR 1.19; CI: 0.89 – 1.59), there was no age trend. For patients < 50 years, RR for mortality was 1.10 (0.47-2.57), for 50 – 69 years it was 1.66 (0.95-2.91), nearly reaching significance, whereas for patients >= 70 years, RR was 0.80 (CI: 0.42-1.53).

In summary, while the lack of subgroup analyses of different age groups in most of the HCQ studies excludes the possibility of a meta-analytic approach to study the effect of HCQ or HCQ+AZI in different age groups, the available (scarce) evidence suggests that the age signal that was found in PREP and PEP studies with HCQ can also be replicated in many *(but not all)* studies of HCQ treatment, and that HCQ treatment may have some profit in young patients (up to ~ 40 years), **but is deleterious in older patients,** and the threshold between a favorable and an unfavorable effect seems to be somewhere above 40, but probably below 50 years. As a consequence, those people who have higher risks of bad COVID outcomes because of age (or a higher probability of comorbidities that are correlated with increasing age) can't profit from HCQ, and instead, administration of HCQ to them has to be considered as an additional risk for them.

Eventually, the strongest support for these conclusions comes from a retrospective observational study with 4396 unselected hospitalized patients from Italy (February-May 2020) to clarify the role of HCQ in (hospitalized) COVID patients (DI CASTELNUOVO et al.). Individual characteristics of patients were analysed by hierarchical clustering (Gower distance) and then associated with mortality and the effect of HCQ on mortality. DI CATELNUOVO identified two clusters: one of 3913 younger patients with lower circulating inflammation levels and better renal function, and a cluster of 483 generally older and more comorbid subjects, dominated by men and with a higher proportion of smokers. HCQ was associated with lower mortality in the younger cluster (OR 0.46; CI: 0.39 – 0.54), but not in the older cluster (OR 0.89; CI: 0.65 – 1.22). Moreover, the effects were retained after further adjustments for additional medications and they were also concordant with associations of HCQ with disease severity: considering a combined endpoint of severe disease manifestations, ICU and death, the protective association of HCQ persisted in the low risk cluster (OR 0.67; CI: 0.57 – 0.79), whereas there was a null association in the high risk cluster

(OR 0.98; CI: 0.66 – 1.46). The authors suggest a particularly beneficial effect of HCQ within low risk patients, what correlates with younger patients and is an independent proof for the age signal described above. The difference in the median age between both clusters is about 12.5 years (calculated from their fig. 2), well in accordance with the difference of about ~ 10 years between studies with favorable vs. unfavorable outcomes based on the sorting of PRODROMOS and RUMSCHLAG (*see above*).

Interestingly, the age signal may not apply to nursing home residents. In their review, ALEXANDER PE et al. found and discussed several studies that showed that nursing home residents profited from HCQ-based early therapies. However, these therapies were usually multidrug therapies including also antibiotics, steroids, anticoagulants or supplements. It is unknown whether these treatments would have been effective to the same extent, or even more, in the absence of HCQ in that population. But maybe there is a true synergism. On the other hand, the situation for nursing home residents is very different from the general population because of frequent testing (as least in the case of an outbreak in the facility) that offers the chance for very early detection and initiation of treatment, possibly in an asymptomatic stage if COVID-19 was detected by a routine swab. This is a different situation compared to outpatients who have to find an opportunity for testing once they have symptoms that are suspective of COVID-19 and who will start treatment later, if at all (see ALEXANDER PE et al. for therapeutic nihilism in non-hospitalized patients).

In a separate systematic review, PRODROMOS et al. found no evidence that HCQ and AZI cause significant acute cardiac arrhythmic mortality, but that they decreased cardiac events (cardiac mortality, thrombosis, arrhythmia and cholesterol) in recent peer-reviewed studies and meeting presentations. It was found both *in vitro* (artificial heart model) and in clinical studies that the combination of HCQ + AZI attenuated the arrhythmic risk of HCQ or AZI alone (HEALY et al.). Thus the deleterious effect of HCQ in older patients doesn't seem to rely on adverse effects of HCQ or HCQ+AZI, but seems to be related to unwanted effects of HCQ on the immune system or mitochondria, and may be associated with age-dependent effects of HCQ on ageing mitochondria, the suppression of the age-sensitive innate immunity by HCQ or the suppression of interferon-stimulated genes (see ROTHER et al.) which may also be age-sensitive. Since innate immunity wanes with increasing age, the suppressive effects of HCQ on innate immunity may be more pronounced in older people.

However, LI W et al. used *"human pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) to systematically investigate the effects of HCQ and AZM individually and in combination."* They recapitulated the clinically observed QT prolongation by treatment with HCQ, and this effect was strongly enhanced by combined treatment with AZM (AZI), although AZM alone slightly shortened the interval. Furthermore, combined treatment with AZM and HCQ resulted in *"higher cardiotoxicity, more severe structural disarrangement, and more pronounced contractile and electrophysiological dysfunctions, compared to respective mono-treatments."* LI W et al. concluded: *"Taken together, our results highlight that combined treatment with HCQ and AZM strongly enhances the adverse effects on cardiomyocytes, providing mechanistic evidence for the high mortality in patients receiving HCQ/AZM combination treatment."*

That said, HCQ won't be subject of this paper here. In spite of studies like PRODROMOS and RUMSCHLAG that suggest some positive effects of HCQ in COVID-19, HCQ cannot be recommended for those who need effective treatment of COVID-19 at most, the elderly, when the cut-off between favorable and unfavorable effects may be between 40 and 50 years, probably between 40 and 45 years. Most patients who need early treatment because of risk of worse prognosis would be excluded by that cut-off age. Thus the controversy about favorable and unfavorable effects of HCQ may also be influenced by the age structure of different countries. In countries with a young population where most of the patients are younger than ~ 45 years, it may well be that HCQ shows favorable effects in the overall patient populations (since they are dominated by patients < 45 years), and authors who propose HCQ may have true experience that it works very well. In countries with aged populations and many patients > 50 or > 60 or > 70 years, the deleterious effects of HCQ on older age groups may become more visible, so that these countries restrain from giving or recommending HCQ. The question of treating COVID-19 with or without HCQ is thus not necessarily a question of "right" and "wrong", "good studies" or "bad studies" (though the question is treated usually that way), but it seems to be influenced by age or the age structure of the whole population or patient population of a given country, or a given cohort of patients.

Short note on thrombo-prophylaxis (not subject of this paper)

Eventually, **thrombo-prophylaxis** is another very important aspect of the management also for outpatients with increased risks (e.g. BELCARO et al.), and BELCARO et al. see the need for such prophylaxis in patients as young as 40 years (and older). Because of its complexity and unavailability **for isolated outpatients who have no access to medical care and are not reached by any outpatient visit system by professionals (e.g. nurses),** thrombo-prophylaxis is not considered in this paper. This doesn't mean that it is unimportant. The opposite is true (e.g. see RENTSCH et al. for early thromboprophylaxis in hospitalized patients). Whoever is infected with COVID 19 and belongs to any risk groups and has access to medical care, should ask for the need for thrombo-prophylaxis. Enoxparin or Fondaparinux should be preferred compared to unfractionated heparin (e.g., PAWLOWSKI et al.).

However, as TALASAZ et al. pointed out in their very detailed paper, **"the optimal thromboprophylactic regimens still remain unknown in patients with COVID19".**

That said, it seems even more important to fight against early viral replication and the progression of the disease as early as possible to avoid situations when decisions about "right or wrong" thrombo-prophylaxis regimens might become vital or lethal – another reason to criticize the "strategy" of therapeutic nihilism for (early) ambulatory outpatients (see McCULLOUGH et al. 2). In the light of so much uncertainty how to deal with progressed patients, the development of concepts for earlymost therapeutic regimens for elderly or people with relevant comorbidities should become mandatory.

Interestingly, BORGHI et al. showed in their case series that fondaprinux may also play an essential role for early treatment, starting immediately or a short time after symptom onset and not at stage II or later.

It is increasingly understood that COVID-19 is not only a respiratory infection, but also a **systemic inflammation of the endothelium.** This paradigm shift from the understanding of COVID-19 as a respiratory infection (that might in some cases progress to a systemic inflammation of the endothelium as a sort of complication) to COVID-19 as a systemic inflammation of the endothelium that was acquired as a respiratory infection, may strengthen the role of thromboprophylatic regimens also in the early phase of the disease. In the case series of BORGHI et al., fondaparinux was given in therapeutic doses.

Several studies indicate that a precise differential indication between prophylactic and therapeutic anticoagulation may matter with regard to serious outcomes.

In their review on RCTs of antithrombotic therapy of COVID-19 during the last 2 years, RIZK et al. (2) found that, in noncritically ill hospitalized patients, a therapeutic dose of anticoagulation with a heparin formulation might improve clinical outcomes, as does anticoagulation with a direct oral anticoagulant post hospital discharge. In contrast, *"nonhospitalized COVID-19 patients have an insufficient burden of events to be candidates for antithrombotic therapy."* (RIZK et al. 2).

Available evidence from RCTs with outpatients (until December 19th,2020)

The scarcity of trials with outpatients became very evident in a systematic review and network meta-analysis of all RCTs about COVID-19 treatment published until December 19th, 2020 by ZHANG C et al.. Only RCTs were considered by ZHANG et al., independent of their quality that was assessed separately (risk of bias).

After excluding herbal medicine and prophylaxis or outcomes incompatible with the design of the meta-analysis (endpoints: mortality, mechanical ventilation, hospital discharge, viral cure), 80 RCTs were included. But only 7 of them were about outpatients, all other studies included 100 % hospitalized patients (1 undetermined).

These are the 7 RCTs with outpatients included in ZHANG C et al.:

- NCT 04342663, LENZE et al., **fluvoxamine** *(discussed in detail below)*

+++ FAVORABLE RESULTS

- NCT 04304053, MITJA et al. (2), **HCQ + darunavir:**

Outpatients less than 7 days after symptom onset (median days since onset of symptoms: 3 days); mean age: 42 years. High risk of bias (classified by ZHANG C et al.).

O NO EFFECT AT ALL; no stronger reduction of viral load (only very small trend), no faster alleviation of symptoms.

- NCT 04308668, SKIPPER et al., **HCQ**

"Symptomatic, nonhospitalized adults with laboratory-confirmed COVID-19 or probable COVID-19 and high-risk exposure within 4 days of symptom onset." Only 58 % of participants received SARS-CoV-2 testing because of severe shortage of test material. 56 % enrolled within 1 day after symptom onset. Median age 41 vs. 39 (placebo). Low risk of bias for mortality.

Insignificant small trends in favor of HCQ (a minimally stronger reduction of symptom severity of 14 days; relative reduction: 12 %; ongoing symptoms after day 14: 24 % vs. 30 %. Adverse effects 43 vs. 22 %. COVID-associated hospitalisations: 4 vs. 8 (control); deaths: 1 vs. 1

(+) NO SIGNIFICANT EFFECTS; BUT WEAK FAVORABLE INSIGNIFICANT TRENDS

- NCT04349592, OMRANI AS et al., **HCQ or HCQ+AZI**

Median age 40-42 years. Mild or asymptomatic patients. Low risk of bias for mortality.

(+) NO SIGNIFICANT EFFECTS; SMALL TREND FOR ACCELERATED VIRAL CLEARANCE FOR HCQ+AZI, BUT NOT FOR HCQ ALONE

- NCT04331899, JAGANNATHAN P et al., **peginterferon-lambda** (180 microgram s.c. once).

Median age 36 years. No shortening of viral shedding, no faster improvement of symptoms. In subgroup analyses, lambda tended to delay shedding cessation in seronegatives (aHR 0.66, n.s.) and accelerated shedding cessation in seropositives (aHR 1.58; p for interaction:

0.03). Weak tendency on viral shedding on day 7 (HR 0.81) and symptom relief (8 vs. 9 days, HR 0.94, n.s.)

O NO SIGNIFICANT EFFECTS, ONLY VERY WEAK FAVORABLE TRENDS

- NCT04354259, FELD JJ et al., **peginterferon-lambda** (180 microgram s.c.once) within 7 days of sympom onset or first positive swab.

Median age 48 years. Accelerated viral clearance particularly in those with initial high viral load.

+ SIGNIFICANTLY ACCELERATED VIRAL CLEARANCE

- ISRCTN59048638, GONZALEZ-OCHOA et al., **Sulodexide** (500 LRU BID for 21 days).

243 patients (Mexico); patients who were at a high risk of severe clinical progression due to relevant comorbidities were included within three days of clinical onset

Need for hospitalization: 17.7 vs. 29.4 %; RR 0.6 (0.37-0.96; p = 0.03) (but no significant difference in hospital stay).

Oxygen support: 29.8 % vs. 42.9 %; RR: 0.71 (0.5-1; p = 0.05); duration of oxygen support: 9 vs. 11.5 days (p = 0.02)

mortality: 2.4 vs. 5.8 % (RR 0.41; 0.10 – 1.55, p = 0.19).

High risk of bias for mortality and ventilation.

++ FAVORABLE RESULTS

Added later (outside ZHANG et al.):

- NCT04425629, WEINREICH et al., **REGEN-COV 2400 mg and 1200 mg;** *discussed in detail below "Note on antibody treatment"*

+++++ VERY FAVORABLE RESULTS; > 70 % reduction of hospitalization or death, very large trial

Meanwhile, there are a few additional RCTs with outpatients available. They will be marked in green color, but only if they encompassed at least 200 participants (verum and controls together).

- O'BRIEN et al., REGEN-COV (Casirivimab + Imdevimab) in SARS-CoV-2 positive, still asymptomatic household contacts of index persons; 1200 mg subcutaneously
  (see: "Note on antibody treatment")

- GUPTA et al. (2), Sotrovimab (500 mg i.v.) (COMET-ICE-STUDY)
  (see: "Note on antibody treatment" and – for final results – "Updates")

- CHOUDHURY et al., 1 % povidone-iodine for mouthwash/gargle, nasal drops, eye drops in early outpatients (compared to lukewarm water)
  (see: "povidone-iodine")

- SEET et al., 0.45 % povidone-iodine throat spray 3 x a day in a prophylaxis setting (comparator: 500 mg vitamin C a day) (*note: no early treatment setting)*
  (see: "povidone-iodine")

- ROSSIGNOL et al.: nitazoxanide (2 x 300 mg daily)
  (see: "nitazoxanide")

- YU LM et al., budesonide inhalation; interim results of the PRINCIPLE trial
  (see: "early budesonide inhalation")

- GUTIERREZ-CASTRELLON et al., a special probiotic formulation from Spain

- HARAN et al., KB109 – a synthetic glycan

- TARDIF et al., COLCORONA trial, colchicine 0.5 mg twice daily for 3 days (then once daily)

- NCT04446429: proxalutamide in men (outpatients)

- CADEGIANI et al. (4): proxalutamide in men and women (outpatients)

- HINKS et al., Atomic2 trial, Azithromycin (500 mg daily for 14 days) in outpatients

- KORLEY et al., convalescent plasma with high titers in outpatients

- REIS G et al. (TOGETHER trial): fluvoxamine 100 mg twice daily

- MOVe-OUT (NCT04575597): Molnupiravir (outpatients at risk) (see "Updates")

- Paxlovid study from Pfizer (see "Updates")

- MILLAT-MARTINEZ et al.: early convalescent plasma for outpatients >= 50 years

- DUPUIS et al., Hesperidin (1000 mg daily) in outpatients

- DORWAND et al. (PRINCIPLE adaptive platform trial) about colchicine (0.4 mg) in outpatients

● TACKLE III trial, AZD7442 (Evusheld) (see “Updates”)

● BUTLER et al. (PRINCIPLE) for doxycycline for outpatients

● SULLIVAN et al. for convalescent plasma for early outpatients

● Remdesivir for outpatients (3 doses) (NCT04501952)

● https://clinicaltrials.gov/ct2/show/results/NCT04401202: Nigella sativa oil softgel capsules

● DELGADO-ENCISO et al.: Nebulized and/or intravenous neutral electrolyzed saline (outpatients)

Further limitations of this paper

This paper here will focus on *available results* from trials. A systematic analysis of trial registries for ongoing trials about early treatment is given by SCARABEL et al., and they analysed the trial registries up to December 4th 2020. Though a wealth of drugs, antibodies and supplements is investigated now in registered clinical trials, only some of them will be suited for outpatients or self-managed home treatments – though the latter seems most important for isolated people without immediate access to medical care. And as SCARABEL et al. point out: *“for most of the studies, the therapeutic setting (prevention, early treatment, treatment of moderate-to-severe cases) of the investigating drug was not always clearly defined”.* **This warns not to be too optimistic with regard to the availability of useful study results for outpatients, and particularly self-managing outpatients, in the future.**

SCARABEL et al. reported about 61 agents in *recruiting* trials of secondary prevention ranging from PEP to the treatment of non-severe cases. As mentioned above, this must not mean “early treatment” (after start of symptoms or positive diagnosis) in each of these studies.

They classified the 61 agents as follows:

● Entry inhibitors: HCQ/CQ; Pyronaridine-Artesunate; Niclosamide; Camostat (anti-TMPRSS2); Bromhexine; Apilimod Dimesylate; Umifenovir; DAS118
(entry inhibitors may be sensitive to mutations in the RBD of the spike protein, but see LEE J et al.; this doesn’t seem to apply to TMPRSS2 inhibitors)

● Protease inhibitors: Lopinavir+ritonavir; ASC09+ritonavir; Danoprevir+ritonavir; Lopinavir+rabeprazole; Ivermectin

● Polymerase inhibitors: Favipiravir; Remdesivir; Molnupiravir (EIDD-2801; see WAHL et al.; phase 2a results from FISCHER et al.); Triazavir; Ribavirin in association

● monoclonal antibodies

● plasma-derived Ig: convalescent plasma; Kamada; GS-5131; SAB-185

● immunomodulatory/antiinflammatory drugs: altogether 28 drugs or drug classes, including PUL-042 (anti-TLR), interferons; JAK-inhibitors (Ruxolinitib, Tofacitinib), Tocilizumab, Dexamethasone, Nitazoxanide, Ciclosonide, Colchicine, Methotrexate, Prazosil and many others

● anticoagulants/antiaggregants

● tranexamid acid

● ACIs and ARBs

● Dapagliflozin

● nitric oxid

● antibiotics: azithromycin, minocycline

● vitamins

● xylitol nasal spray

Of note, **early anakinra therapy** guided by elevated soluble urokinase plasminogen activator receptor (suPAR) prevented progression of COVID-19 pneumonia into respiratory failure in the SAVE-MORE multicenter trial with 594 hospitalized patients with moderate and severe COVID-19 pneumonia and plasma suPAR 6 ng/ml or more. HR for 28-day mortality was 0.45 ($p = 0.045$), and hospital stay was shorter (KYRIAZOPOULOS et al.). However, since anakinra is not available for early therapy of outpatients, anakinra is outside the scope of this paper.

Moreover, the antimalaria agent **mefloquine** was found to be a very promising candidate in several in vitro assays, in clear contrast to chloroquine/hydroxychloroquine. Unlike CQ, an in vitro study showed that mefloquine inhibits SARS-CoV-2 infection in physiologically relevant cells like pneumocytes and monocytes as an inhibitor of viral entry, prevents virus-induced enhancement of IL-6 and TNF-alpha, may accumulate in the lungs and synergizes with Remdesivir against viral entry (SACRAMENTO CQ et al.).

Unfortunately, there are so far no trial results available for mefloquine (as of July 2021). There is an ongoing prophylaxis trial (RCT: NCT 04847661) with mefloquine, but this trial won't be finished before August 31, 2021 (no results posted as of April 29, 2022, and clinical evidence in COVID-19 is still lacking).

Content

Prenote on steroids

There is no chapter on **steroids.** This does not mean that steroids are considered as unimportant; the opposite is true. However, the decision to take steroids must be made individually, based on results of examinations, e.g. increase of CRP, other inflammatory markers, lung involvement, oxygen saturation etc., and it seems to be contraindicated in the early, viral, prae-inflammatory phase of the disease. The right timing of the start (and end) of corticosteroids seems to be very critical, and if given at the wrong point of time, they may be harmful. This is different from many other agents mentioned here that may also have a time-dependent effect, but if they are taken too early or too late (like nutritional supplements or some mere antivirals), their effect is probably a zero effect, but not seriously deleterious as may be the case with steroids.

The right timing of steroids in COVID-19 outpatients (if given to outpatients at all) is a very difficult matter, and there is a need for a systematic review about this matter that goes far beyond the possibilities of this paper here. There is no doubt an urgent need for such a systematic review, but this would be a very large project. The best one can say here is to use simple und less contested early therapeutic options as early as possible in order to try to avoid to progress into a stage of the disease where steroids might be indicated or when the decision whether to give steroids or to avoid them might be life-saving of life-threatening: act early enough in order not to progress into a stage when the question of steroids may become critical.

A large study from US (based on 9058 patients) warns from early corticosteroids, including dexamethasone that was analyzed in a subanalysis (CROTHERS et al.; observational cohort study setting). In the stratified analysis, patients on „no oxygen“ experienced a 89% increased risk for 90-day mortality (HR 1.89; CI: 1.33 – 2.68) if they got corticosteroids compared to those who did not. For patients on low-flow nasal cannula oxygen, HR with corticosteroids was 1.21 (CI: 0.94 – 1.57). Corticosteroids were initiated within the first 48 hours of hospitalization.

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Sequential multidrug regimes **XXX024**

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