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Coronavirus Disease 2019 Interventions

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Abstract

Coronavirus disease 2019 has spread rapidly around the world, causing symptoms ranging from none to multi-system organ failure and death. Multiple promising interventions for reducing morbidity and mortality are being studied, with new findings released almost daily. Efficacy assessments have been limited by variability in natural history, number of participants in trials, timing of randomization with respect to symptom onset, trial duration, and controlling for risk factors. Expensive interventions such as remdesivir, monoclonal antibodies, and drugs like sitagliptin are less practical at onset of symptoms for the majority of patients, who would have mild disease even without any interventions. Steroids have been helpful when conditions have deteriorated, but earlier use may not be helpful, while inexpensive interventions like aspirin, zinc, vitamin D, and doxycycline may be helpful early in the disease. More trials with better controls and adequate numbers of participants are needed. Unconventional interventions might be considered for study, such as post-exposure hydrogen peroxide mouth rinses and induced controlled hyperthermia early in the illness.

Background

Twelve months after the emergence of the novel pandemic coronavirus in China, known as Severe Adult Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a number of potentially beneficial (but no magic bullet) interventions have been found. The disease caused by SARS-CoV-2, called coronavirus disease 2019 (COVID-19), causes a wide range of symptomatology varying from no symptoms to critical illness and death, as well as chronic debilitating symptoms.

Respiratory Interventions

Because the sickest patients with COVID-19 have shortness of breath and hypoxia, respiratory support ranging from supplemental oxygen to positive pressure ventilation is often required. In the early months of the pandemic, it became apparent that many of these respiratory-compromised patients did not require as much positive pressure in mechanical ventilation as is traditionally applied to adult respiratory distress syndrome patients, and other support measures like high-flow nasal cannula, non-invasive ventilation, and prone positioning might promote better outcomes.[1]

Pharmaceutical Interventions

Many COVID-19 patients had mild or moderate symptoms for the first few days to a week or more, only to get subsequent clinical deterioration. The patients with more severe illness have largely had risk factors such as obesity, diabetes, heart disease/hypertension, older age (mostly over 60), male sex, clotting disorders, and/or chronic lung disease. Type 2 diabetics have done significantly better in terms of clinical outcome, hospital discharge numbers, and mortality, if they were taking **sitagliptin** at the time of their admission.[2] It's potential benefits for COVID-19 may be due to its anti-inflammatory properties,[3] yet it remains to be seen if sitagliptin might benefit nondiabetics.

A meta-analysis of 7 randomized clinical trials found **systemic steroids** to significantly (odds ratio about 0.7) reduce mortality at 28 days after administration in 1703 critically ill COVID-19 patients.[4] Those steroids included dexamethasone, hydrocortisone, and methylprednisolone. The largest of those studies involved dexamethasone, and found benefit for patients requiring oxygen or ventilation, but not for those who did not require oxygen at the start of therapy.[5] Twenty-eight day mortality rates in those who received versus in those who did not receive dexamethasone, were 23% versus 26% in those requiring oxygen but not ventilation, and 29% versus 41% in those on ventilation at time of randomization. Other randomized controlled trials regarding steroids did not show significant reduction in mortality, but were stopped prematurely.[6-8] Other benefits, such as a greater number of ventilator-free days in the first 4 weeks,[7] and a greater number of "organ support-free" days in the first 3 weeks[8] of treatment were found with dexamethasone and hydrocortisone respectively. Inhaled steroids, in contrast to systemic steroids, have not been found to reduce mortality in asthmatics or individuals with chronic obstructive pulmonary disease.[9]

A smaller Italian study comparing use of anti-inflammatories, **tocilizumab** and/or methylprednisolone along with "standard of care," with just standard of care, found significantly less mortality at 30 days (14% versus 28% overall) in the anti-inflammatory group.[10] None were intubated at the time of randomization, which occurred within 3 days of hospitalization and at a mean of 8 days after onset of symptoms. Standard of care included hydroxychloroquine (400 mg bid) plus/minus darunavir/ritonavir. A large cohort tocilizumab

study found potential benefit if it was given within 2 days of ICU admission, but important confounders could not be ruled out.[11] In a randomized placebo-controlled trial (RPCT), tocilizumab without steroids, administered to severe patients, was *not* found to reduce intubation or death.[12]

Drugs that have been used against other pathogens have also shown promise against SARS-CoV-2. The most widely publicized one is **hydroxychloroquine** (HCQ).
This inexpensive drug has long been used for malaria prophylaxis as well as for rheumatologic conditions. In a recent study of U.S. veterans, taking HCQ did not affect the rate of COVID-19 infection, but was associated with reduced overall mortality (0.8% with and 1.2% without HCQ, odds ratio 0.7, p=0.003).[13] Of the 31 patients on HCQ who were infected with SARS-CoV-2, none died versus 7 of 78 not receiving HCQ dying with COVID-19 (p=0.19).

Large HCQ observational studies have had mixed results. A New York study of 1438 hospitalized COVID-19 patients found 25.7% mortality in patients given HCQ plus azithromycin (AZM), 19.9% with HCQ alone, 10% with AZM alone, and 12.7% with neither drug.[14] It was not randomized, and the groups that had the lowest mortality had the least risk factors (younger, less obesity, less diabetes, less chronic kidney disease, less congestive heart failure, and less hypoxia, tachypnea, and abnormal chest imaging within 24 hours of admission). The HCQ treatment was given fairly late in the disease course. In contrast, a Detroit area study of 2,541 COVID-19 patients found 20% mortality with HCQ+AZM, 13.5% with HCQ alone, 13.5% with AZM alone, and 22.4% with neither drug.[15] The HCQ alone group had 1202 patients and the neither drug group had 409 patients. Controlling for multiple variables, there was a 66% ($p<0.001$) reduction in mortality hazard ratio comparing HCQ to no drug, and a 71% ($p<<0.001$) decrease in mortality hazard ratio comparing the HCQ/AZM group to the neither drug group. The authors claimed that adjunct therapy (which included methylprednisolone and/or prednisone given to the majority of their patients) was not significantly associated with mortality, but around three fourths of HCQ and HCQ+AZM groups received steroids compared to 36% of no HCQ or AZM, and 39% of the AZM group receiving them. The steroids may have played a major role in their finding of possible HCQ protection.

Multiple randomized controlled trials (RCT) have also addressed HCQ efficacy, but unfortunately, they frequently also have important limitations, largely in their designs. An early one looking at nonhospitalized adults with COVID-19 only had 491 patients, 19% of whom were not even laboratory-confirmed cases.[16] Differences in symptom reduction and duration through 2 weeks, as well as hospitalizations, were not significantly different, although the study was underpowered and all of their outcome measures, except side-effects, were better in the HCQ group (10 hospitalizations in placebo group and 4 in HCQ group). Another one in Brazil was open labeled and randomized, with 667 suspected (504 confirmed) COVID-19 patients looking at clinical status at 15 days post treatment with HCQ, HCQ+AZM, or neither.[17] The groups were

well matched for age, but there were more males, hypertension, and diabetes in the HCQ group. Treatment (400 mg HCQ twice daily/500 mg AZM daily for 7 days) was begun up to 14 days after symptom onset in some patients (median time 7 days). No significant differences in outcomes were found between the three groups. Large doses of treatment drugs were given relatively late in the illness, in contrast to lower doses given earlier in the illness in the large Detroit study which found significant benefit associated with HCQ. Trials need to be standardized, enrolling higher risk patients who are more likely to have serious outcomes, and controlling time of HCQ versus placebo initiation with respect to onset of symptoms. **Zinc** and **vitamin D** should be provided for treatment and control groups alike. Zinc has some antiviral activity[18] and may act synergistically with HCQ.[19,20] Vitamin D, which supports the innate immune response, has been found to be deficient in a high percentage of serious COVID-19 patients and is associated with many high risk conditions.[21] The dose of HCQ should be 200 mg twice a day, since that is the dose that has been associated with favorable outcome studies.[13,15] Another large RCT found no benefit with HCQ, but a high dose was also used (1200 mg first day, then 400 mg twice a day for 9 days) and it is not clear how early in the illness it was started.[22] A most recently published randomized placebo-controlled trial (RPCT) with well-matched cohorts and dosing identical to the large Detroit study (400 mg twice on the first day followed by 200 mg twice a day for 4 days) found no real differences in outcomes between those who received HCQ and those who received placebo.[23] Unfortunately, they didn't assess zinc or vitamin D levels. It was otherwise a very well executed RPCT that provides good evidence against benefit of HCQ in the treatment of COVID-19.

Another drug used for rheumatologic conditions, **baricitinib**, has been found to have antiviral properties and immune-modulating properties that might be useful in counteracting COVID-19. It has shown some promise both clinically and in vitro in an Italian study.[24]

Remdesivir is an antiviral drug that has received a lot of press, and was given the status of emergency use authorization (EUA) after such status was revoked for HCQ. In a RPCT, hospitalized patients with lower respiratory disease who received up to 10 days of remdesivir had a significantly shorter average recovery time (10 vs 15 days), and almost significantly lower mortality rates as compared to the placebo group, at 15 and 29 days after randomization.[25] On the other hand, a large (450 hospitals in 30 countries) World Health Organization study did not find any significant benefit with remdesivir, nor with HCQ, interferon, or lopinavir.[26] Another RCT using the same dosing of remdesivir but with earlier (5-11 days vs 6-13 days) treatment after onset of symptoms, found no benefit in mortality with remdesivir over placebo. They did find better clinical status at 11 days after treatment in those who received 5 rather than 10 days of treatment.[27] Despite very little proven benefit, remdesivir was recently approved by the FDA for use in hospitalized patients with COVID-19.

At least a few other medications deserve mentioning. **Doxycycline** has anti-viral, anti-inflammation, cardiac protection, and immune modulation properties that may prove beneficial for severe COVID-19 patients. Its use in a New York study (although not case controlled or randomized) showed some promise,[28] but better evidence is needed. Another familiar drug, **ivermectin**, has shown antiviral activity against many viruses, in addition to impressive *in vitro* activity against SARS-CoV-2.[29] **Aspirin** has been associated with significant reduction for need of mechanical ventilation, ICU admission, and mortality when given within 24 hours or 7 days of hospital admission.[30] Yet another drug, normally used for anxiety, was found in a RCT to reduce clinical deterioration over 15 days after randomization in outpatients with symptomatic COVID-19. That drug, **fluvoxamine**, might be helpful by its affinity for an enzyme that is involved in regulation of inflammatory pathways.[31] All of the above drugs need to be studied in large RPCTs.

Other potentially beneficial interventions for COVID-19 are the use of **passive antibodies**, either with **convalescent plasma** from recently infected individuals, or monoclonal pharmaceutically-created antibodies. An early meta-analysis found some promise with plasma.[32] Plasma containing high anti-spike protein titers, administered within 3 days of hospital admission, compared to a control group, was associated with a significant decrease in mortality at 28 days post treatment.[33] A small study from China comparing 19 patients given convalescent plasma with 10 historical severity-matched controls found significantly better outcomes in the group receiving plasma.[34] On the other hand, a small, possibly underpowered RCT,[35] as well as a larger RPCT,[36] found no benefit from convalescent plasma when applied to severe COVID-19.

Monoclonal antibodies hold promise in the treatment of more severe COVID-19 patients.[37] Antibodies, whether from convalescent plasma or from monoclonal pharmaceutical sources, are more likely to be of benefit when given earlier in the course of illness to patients at higher risk for severe complications.

Considerations for Clinical Trials

Better trials are needed for each of the above interventions. Since symptomatic COVID-19 does not progress to severe illness in a high percentage of patients diagnosed in the early stages of illness, trials need to enroll very large numbers of participants and/or select participants based on high risk factors (including laboratory findings) if randomization (time when intervention versus placebo is begun) is done soon after symptom onset. Smaller numbers of participants may be feasible when randomization happens with onset of more severe symptoms such as hypoxia and shortness of breath, but the comparison groups need to be matched in severity, risk factors, and timing with respect to onset of symptoms. Most RCT trials so far have either

started the intervention too late or not had adequate numbers of participants at high enough risk to discern benefit from the intervention.

When drugs that work in conjunction with zinc, such as HCQ and ivermectin, are investigated, initial serum levels of zinc and vitamin D should be assessed, and all participants should receive supplementation of those two nutrients, with a dose range appropriate for levels found. Because steroids have better evidence of benefit when patient conditions are rapidly deteriorating, they should be given to all participants in those situations regardless of other trial interventions. Antibody interventions are most likely to be beneficial if given prior to critical illness, yet they, as well as remdesivir, are expensive, which limits feasibility for their universal use in milder stages of illness. Using them earlier in patients with the greatest risk factors may be a reasonable approach. More urgent attention to cheap interventions like aspirin, doxycycline, and ivermectin is needed. They could be more easily applied early in illness for more people.

Potential Alternative Interventions

Finally, other potentially beneficial post-exposure, or early disease interventions such as chemical (perhaps hydrogen peroxide like the dentists use on their patients) mouth rinses should be studied. Rinsing two or three times per day for the first five days after SARS-CoV-2 exposure might reduce viral replication during the incubation period. Another understudied aspect of COVID-19 is the effect of fever in the patient defense against SARS-CoV-2. One of the earlier studies from China found that only 2.2% of “severe cases” and 3.7% of “common cases” of 262 hospitalized COVID-19 patients experienced> 39°C (102.2°F) maximum temperatures.[38] That is not very high for such a deadly respiratory virus that is known to be inactivated at higher temperatures. That should be studied more. Perhaps actually inducing controlled hyperthermia for a relatively short period of time in the early stages of symptoms may enhance the ability of COVID-19 patients to clear the virus and avoid serious outcomes. Progress has been made in reducing morbidity and mortality of COVID-19, but we have a long way to go.

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