Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER

25

COVID-19 pandemic: Case studies and perspectives

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INTRODUCTION

Initially reported in China in December 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19, result in significant global morbidity and mortality, with the World Health Organization declaring the outbreak as a global pandemic on March 11th, 2020 [1r,2c]. The mortality rate reported is approximately 10-fold higher than the seasonal influenza at 2.3%, and symptoms ranges from asymptomatic to mild upper respiratory tract symptoms such as cough and fever, to pneumonia, and multiple organ failure [3M]. There is no specific antiviral therapy recommended for coronavirus infections, and treatments are based on in-vitro or limited case reported cases against prior coronavirus outbreaks, such as the SARS-coronavirus in 2002, and the Middle Eastern respiratory syndrome coronavirus since 2012.

The risk for direct transmission without any personal protective equipment is up to 15% in public, and ranges from 3% to 10% through household contacts [4H]. The risk for indirection transmission is not established, although infectivity of the viral on a plastic surface at room temperature may last between 6–9 days [5E]. As a result, the Food and Drug Administration (FDA) recommends adhere to social distancing of at least 6 ft from suspected or known COVID-19 patients, and practice good hand hygiene with soap and water for at least 20 s, especially after direct or indirect transmission exposure [6S]. If soap and water are not readily available, then the FDA recommends applying hand sanitizer containing at least 60% alcohol.

For health care personnel caring for patients with known or suspected COVID-19, the Infectious Diseases Society of America recommends appropriate personal protective equipment necessary for contact and droplet precautions [7M]. Either surgical mask or N95 mask may be utilized in conventional or crisis settings, with the exception of aerosol-generating procedures for the former where N95 mask is recommended.

Diagnosis of COVID-19 is based on the presence of signs and symptoms, and/or diagnosis by reverse transcription polymerase chain reaction (RT-PCR) and/or serology testing for COVID-19 antibodies with either rapid test or enzyme-linked immunosorbent assay (ELISA) [8R,9S]. The specificity of RT-PCR tests approved for Emergency Use Authorized (EUA) by the FDA for the detection of COVID-19 RNA ranges from 99% to 100% based on 95% confidence interval (CI), while the sensitivity ranges from 35% to 100%, depending on the physical collection site with the highest sensitivity if collected through the nasopharyngeal (95% CI 92%–100%) compared to the lowest sensitivity through oral collection (95% CI 35%–77%). The variation in sensitivity is due to the differences in risks for contamination from the external environment, and the concentration of the COVID-19 RNA within each bodily cavity [10S]. All of the serology tests approved by the FDA's EUA have high sensivity (95% CI 98.3%–100%). The specificity, however, varies significantly from as low as 27.3% to 100%, since they are based on the presence of detectable serum threshold of immunoglobulins M and immunoglobulins G.

There were concerns for vertical transmission of COVID-19 in pregnant women, however, of the 9 COVID-19 pregnant patients that gave nine livebirths, no neonatal asphyxia or presence of the virus were reported [11c]. Cancer patients on chemotherapy may also be at risk for worsening outcomes in COVID-19 patients than non-cancer COVID-19 patients, as the case fatality reported in cancer patients were 5.6% compare to 2.3% in the

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general population [12r]. However, an observation study of 29 COVID-19 infected cancer patients had a mortality rate of 28.6% [13c], much higher than the 5.6% previously mentioned. The higher mortality rate reported may be attributed to timing of the antitumor medication in relationship to the diagnosis of COVID-19: antitumor treatment received within the past 14 days since COVID-19 diagnosis (hazard ratio [HR] of 4.079, 95% CI 1.086–15.322, $P = 0.037$), and patchy consolidation on computed topography (CT) on admission (HR of 5.438, 95% CI 1.498–19.748, $P = 0.010$) were associated with a higher risk of severe events, defined as requiring intensive care admission, mechanical ventilation, or death. Fingolimod, an immunomodulatory medication that inhibits lymphocyte release from lymph nodes and typically use for multiple sclerosis, may predispose COVID-19 patients for the development of pneumonia and ICU admission, as reported in a case report of a multiple sclerosis patient [14c]. The patient's oxygenation improved 2 days after the medication was discontinued, and the patient was subsequently transferred out of the ICU to the internal medicine floor and was discharged.

The Centers for Disease Control and Prevention has determined among 74439 patients, the most common chronic conditions at greatest risk for both hospitalization and intensive care unit (ICU) admissions are type-II diabetes mellitus, chronic lung disease including chronic obstructive pulmonary disease, cardiovascular disease, and immunocompromised patients [15MC]. There is also a strong association for ICU admissions (HR 3.6, 95% CI 2.5–5.3, $P < 0.001$) in patients <60 years with body mass index (BMI) equal or greater than 35 kg/m^2 [16MC].

Based on the pathophysiologic endocytosis of COVID-19 into the host cell in the alveolus via angiotensin converting enzyme (ACE)-2, there was initial concern that patients who are on ACE inhibitors or angiotensin receptor blockers (ARBs) may have increased morbidity and mortality from COVID-19 as a result of upregulation ACE-2 [17r]. However, this is based on conceptual preclinical models that have not been evaluated or reported in any human clinical trials, and discontinuation or not prescribing ACE inhibitors or ARBs in certain patient population where these drugs have demonstrated significant morbidity and mortality benefits, such as in heart failure and myocardial infarction patients, may cause significant harm. As a result, the Heart Failure Society of America, American College of Cardiology, and American Heart Associated recommend a joint statement, essentially advising not basing the decision of whether to add, change, or remove these medications on the presence of COVID-19 beyond standard clinical practice [18r].

ANTI-VIRAL THERAPIES

Chloroquine and hydroxychloroquine (SEDA-42, 294) with or without azithromycin (SEDA-40, 318; SEDA-42, 555)

Both chloroquine (CQ) and hydroxychloroquine (HCQ) have demonstrated in-vitro activity against COVID-19 through blockade of its endosomal transport, and pH elevation of intracellular organelles [1r]. A parallel, double-blinded, randomized phase IIb clinical trial evaluated two different dosages of CQ for patients with established COVID-19: high dose (600 mg oral twice daily for 10 days; cumulative dose of 12 g) and low dose regimen (450 mg oral twice daily for 5 days; cumulative dose of 2.7 g) [2c]. The high dose group had a greater incidence of QTc prolongation >500 milliseconds compare to the low dose regimen (7/37 [18.9%] vs 4/36 [11.1%], $P = 0.51$), as well as ventricular tachycardia (2/37 [5.4%] vs 1/36 [2.8%], $P = 0.51$), although there was no statistical significant difference. The United States FDA's Center for Veterinary Medicine has issued a letter as a result of a single mortality of an adult in the United States who died from an intentional, self-administration of chloroquine intended for aquarium fish [19S].

Compare to CQ, HCQ is ~40% less toxic, and also possessed anti-inflammatory effects against COVID-19 [1r]. A randomized clinical trial found 2 out of 31 COVID-19 patients who received HCQ 400 mg oral daily for 5 days developed mild adverse reactions from HCQ, with one patient developed a headache, and the other patient developed a rash [20c]. No cardiac or QTc prolongation was reported. The likely primary mechanism of QTc prolongation associated with HCQ and CQ is sodium and potassium channel blockade, due to the structural similarity of HCQ and CQ to quinine (SEDA 16, 193), a sodium channel blocking antiarrhythmic agent with QTc prolongation effects [21A].

A meta-analysis evaluated the effectiveness of HCQ or CQ from 4 randomized controlled trials, 10 observational cohort studies, and 9 case series [22M]. Overall, the meta-analysis found conflicting findings on the effectiveness of either agents, with only 2 small randomized controlled trials finding improvement in pulmonary computed topography. For adverse events, majority of the studies did not evaluate such events. Of the studies that have evaluated adverse events in their analysis, diarrhea was reported in two randomized controlled trials (absolute risk differences ranged from 10% to 13.3%), and 1 cohort reported a QTc interval prolongation of more than 60 milliseconds from baseline with HCQ (absolute risk difference of 7.8%), as well as greater prevalence of ventricular tachycardia with CQ (absolute risk difference of

5.4%). Since not all adverse events were reported or monitored, due to the high risk of bias for majority of the studies included in the analysis based on the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool by two investigators, as well as the lack of placebo-controlled in majority of these studies, it is difficult to definitively conclude the incidence of both the efficacy and safety profiles of HCQ and CQ in COVID-19 patients.

A case report documented a male patient was diagnosed with COVID-19 despite being prescribed HCQ 200 mg by mouth twice a day for 1 year for sarcoidosis [23r]. However, a blood serum trough concentration of HCQ resulted in <200 ng/mL (target serum trough for sarcoidosis is >950ng/mL), therefore the patient was non-adherent on the prescribed HCQ.

A randomized, double-blind, placebo-controlled trial evaluated the effectiveness of HCQ 800 mg by mouth once, followed by 600 mg in 6–8 h, then 600 mg daily for four additional days, in asymptomatic adults across the United States and Canada that have been exposed to a confirmed COVID-19 patients for >10 min within 6 ft distance, and either not wearing either a face mask or eye shield, or wearing a face mask only [24C]. In addition, this exposure must have occurred within 4 days from the initial enrollment into the trial, and follow-up via e-mail and/or telephone calls on days 1, 5, 10, and 14 days, and 6 weeks were sent in regard to follow-up testing, illness, or hospitalizations. Of the 821 participants, there was no difference in any of these follow ups between the HCQ group compare to the placebo group (49 out of 414 [11.8%] vs 58 of 407 [14.3%] for the HCQ and placebo groups, respectively. 95% CI, −7.0 to 2.2; $P = 0.35$). Side effects were more common with the HCQ compare with the placebo group (40.1% vs 16.8%), with majority of the effects were gastrointestinal in-nature, including nausea, diarrhea, or vomiting. No serious adverse events or mortality such as arrhythmia-like symptoms occurred.

The effectiveness of azithromycin 500 mg oral on day 1 followed by 250 mg daily for the next 4 days, in combination with HCQ 200 mg oral three times per day for 10 days is based on the statistical significant proportion of COVID-19 patients that had negative nasopharyngeal PCR by day 6 post-inclusion, compare to HCQ 200 mg oral three times per day for 10 days and control patients in an open-label, non-randomized clinical trial (6/6 [100%] vs 8/14 [57.1%] vs 2/16 [12.5%], respectively, $P < 0.001$) [25c]. A case report detailed the development of QTc prolongation of 620 milliseconds after a single dose of HCQ, and 3 days of intravenous azithromycin in a 66-year-old female COVID-19 patient [26A]. The patient's serum potassium and magnesium levels were within normal limits, and since the patient required HCQ for COVID-19 treatment, the patient was administered intravenous lidocaine 100 mg. A follow-up 12 lead electrocardiogram revealed the shortening of the QTc to 550 milliseconds, which enabled the patient on completing the 5-day course of HCQ without any sequelae from the drug combination of HCQ and azithromycin.

A retrospective analysis in hospitalized Veteran Affairs patient found increased mortality in the HCQ, and HCQ with azithromycin groups compare to a group that did not received either HCQ or azithromycin (27/97 [27.8%] vs 25/113 [22.1%] vs 18/158 [11.4%], respectively, $P < 0.001$) [27c]. However, the study did not report whether the increased mortality is attributed to QTc prolongation or cardiac dysrhythmias, and the greater mortality in the HCQ group over the HCQ with azithromycin group may be attributed to imbalance baseline characteristics, with the HCQ group having statistical significant worst parameters of pulse oxygenation ≤94%, lymphopenia <0.8 cells/mm^3, C-reactive protein >28mg/dL, and cerebrovascular disease.

A large, multi-center retrospective study evaluated 25 hospitals on the adverse events of HCQ with azithromycin ($n = 735$), HCQ monotherapy ($n = 271$), azithromycin monotherapy ($n = 211$), and neither agents ($n = 221$) [28MC]. The most commonly prescribed dosing regimen of HCQ was 400 mg oral twice a day (90.3% of patients), while for azithromycin was 500 mg oral once a day (92% of patients). Compared to the azithromycin monotherapy group and patients receiving neither agents, both the HCQ with azithromycin and HCQ monotherapy groups had statistical significant higher incidences of diarrhea (11.6% and 17% for the HCQ with azithromycin, and HCQ monotherapy, respectively, compare to 8.5% for the azithromycin monotherapy group, and 7.2% for neither treatments; $P = 0.003$), cardiac arrest (15.5%, 13.7%, 6.2%, and 6.8% for the HCQ with azithromycin, HCQ only, azithromycin only, and neither agents, respectively; $P < 0.001$), and both arrhythmia and QT prolongation (27.1%, 27.3%, 16.1%, and 14% for the HCQ with azithromycin, HCQ only, azithromycin only, and neither agents, respectively; $P < 0.001$). Despite the higher incidence of cardiac arrest, and arrhythmia and QT prolongation with the HCQ with azithromycin group and patients receiving only HCQ, no differences in mortality were found in either groups (HR of 1.35 [95% CI, 0.76–2.40] and HR of 1.08 [95% CI 0.63–1.85] for the HCQ with azithromycin, and HCQ only groups, respectively) when compare to the azithromycin only group (HR of 0.56 [95% CI, 0.26–1.21]).

Based on the lack of efficacy of HCQ or CQ to treat or mitigate COVID-19 in these trials, the FDA has revoked the EUA of HCQ and CQ for this indication as of June 2020 [29S].

Remdesivir

Remdesivir is a prodrug that inhibits viral ribonucleic acid (RNA) polymerases and have been shown to have in-vitro activity against COVID-19 [30r]. An observation study evaluating the compassionate use of remdesivir 200 mg intravenously on day 1 follow by 100 mg intravenously daily for the following 9 days reported multiple adverse events, including increased hepatic enzymes, renal impairment, rash, diarrhea, and hypotension in 32/53 (60%) of patients who received the medication, with 2 patients necessitating discontinuation of the drug secondary to elevated hepatic enzymes [31c]. Of the 53 patients, 12 patients (23%) developed multiple organ dysfunction syndrome, acute kidney injury, and septic shock. Since this observation study did not evaluate the incidence of the adverse events compare to placebo, it remains inconclusive whether the events were attributed to the underlying disease of COVID-19 or the medication. Clinical improvement, defined as live discharge from the hospital or a decrease in 2 points from baseline from a severity ordinal scale by the World Health Organization, was observed in 36 out of 53 patients (68%).

A randomized, open-label, phase 3 trial evaluated the effectiveness of remdesivir 200 mg once then 100 mg once daily for either 5 days ($n = 200$ patients) or 10 days ($n = 197$) in hospitalized, COVID-19 patients [32C]. The primary outcome was clinical improvement on a 7-point ordinal scale, defined as follows: 1, death; 2, hospitalized and either receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 3, hospitalized and either receiving non-invasive mechanical ventilation or high-flow oxygen; 4, hospitalized and received low-flow supplemental oxygen; 5, hospitalized and does not require oxygenation of any kind yet require medical care; 6, hospitalized and does not require oxygenation or medical care besides remdesivir administration; and 7, no hospitalization required. By day 14 of enrollment, there was a 2-point clinical improvement in 64% of patients on the 5-day group compare to 54% in the 10-day group ($P = 0.14$). The most commonly reported adverse events for both groups were nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%). However, due to the lack of placebo-controlled, it remains inconclusive whether the events were attributed to the underlying disease of COVID-19 or the medication.

Favipiravir and arbidol

Favipiravir and arbidol are inhibitors of viral RNA polymerases, with favipiravir having a half maximal inhibitory concentration (IC50) between 0.013 and 0.48 microgram/mL compare to the half maximal effective concentration (EC50) between 2.7 and 13.8 microgram/mL of arbidol against influenza A [33r]. A randomized clinical trial evaluated the efficacy and safety of favipiravir and arbidol against COVID-19 reported greater incidences of increased serum uric acid level in patients treated with favipiravir compare to the arbidol group (16/120 [13.8%] vs 3/120 [2.5%], $P = 0.0014$) [34c]. No significant improvement in clinical recovery were found with either inhibitors.

Lopinavir-ritonavir (SEDA-39, 278; SEDA-41, 311)

Lopinavir-Ritonavir, a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, demonstrated in-vitro inhibitory activity against COVID-19 [35C]. A historical cohort during the 2004 SARS outbreak demonstrated lopinavir-ritonavir 400 mg and 100 mg in addition to ribavirin reduced both the severity of acute respiratory distress syndrome or death and viral load compare to ribavirin monotherapy [36C]. However, the study had several critical limitations, including the lack of control group, randomization, and concomitant use of glucocorticoids and ribavirin. Cao B, et al. conducted a randomized, controlled, open-label trial of COVID-19 hospitalized patients to either lopinavir-ritonavir 400–100 mg twice a day for 14 days in addition to standard care, compare to standard care alone. The primary endpoint was clinical improvement of two points on a seven-category ordinal scale or discharge from the hospital. The scale is similar to the scale utilized by Goldman et al. [32C] except the severity is inversely related: death was 1 in the trial by Goldman JD, compare to 7 in this trial by Cao et al. A total of 99 patients were assigned to the lopinavir-ritonavir group compare to 100 patients in the standard-care group. There was no statistical significant difference in time to clinical improvement for the lopinavir-ritonavir group compare to the standard-care group (HR for clinical improvement, 1.31; 95% CI, 0.95–1.80). In addition, there was no difference in mortality at 28 days for the lopinavir-ritonavir group, with the incidence at 19.2% compare to 25% in the standard-care group (95% CI, −17.3 to 5.7). For adverse drug events, gastrointestinal events such as vomiting and diarrhea were more common in the lopinavir-ritonavir group, although serious adverse events such as respiratory failure and acute kidney injury were greater in the standard-care group. The investigators reported that 13.8% of patients in the lopinavir-ritonavir group discontinued the treatment early because of adverse events, although further details are not provided on what these events were.

SUPPORTIVE MEDICATIONS

Dexamethasone (SEDA-39, 407; SEDA-40, 507; SEDA-41, 461)

Corticosteroids such as dexamethasone may be beneficial in modulating immune-mediated lung injury and cytokine storm associated with COVID-19 [37MC]. The RECOVERY Trial, which is a randomized, controlled, open-label, multi-center trial involving 6425 patients was conducted on evaluating the effects of dexamethasone 6 mg once daily for up to 10 days vs usual care on 28-day mortality. In the study, 2104 were allocated to the dexamethasone group while the remaining 4321 patients received standard care. The risk for mortality at 28 days is lower with dexamethasone than usual care (age-adjusted rate ratio [RR] 0.83, 95% CI 0.74–0.92; $P < 0.001$), with the greatest lowering of mortality observed in patients on invasive mechanical ventilation (RR 0.65, 95% CI 0.51–0.82; $P < 0.001$). Patients who are receiving oxygen yet not on mechanical ventilation also experience lower 28-day mortality, although not as significant as those on invasive mechanical ventilation (RR 0.80, 95% CI 0.70–0.92; $P = 0.002$). Lastly, there was no significant difference in 28-day mortality for those not receiving any respiratory support between the dexamethasone group or the usual care (RR 1.22, 95% CI 0.93–1.61; $P = 0.14$). Adverse events were not evaluated in the study.

FAMOTIDINE (SEDA-26, 294)

In-vitro famotidine has been demonstrated to inhibit HIV replication, while computational methods predicts the drug is likely to inhibit the 3-chymotrypsin-like protease, which is a protein encoded by COVID-19 essential for viral replication [38C]. A retrospective single-center cohort of 1620 patients included all COVID-19 patients that have received any form or dose of famotidine within 24 h of hospital admission compare to those that did not. Patients in the famotidine group received a median duration of therapy of 5.8 days in the hospital, with median daily dose of 136 mg (63–233 mg); 28% of the cohort were given intravenously. Compare to the no famotidine group, the famotidine group was associated with lower composite outcome of either death or intubation (8/84 [10%] vs 332/1536 [22%]; adjusted HR 0.42 [0.21–0.85]). Although there was no statistical significant difference on baseline characteristics between both groups, there was a clinical significant greater number of patients in the no famotidine group with chronic pulmonary disorders (8% vs 2%; $P = 0.07$). In addition, the composite outcome of death and intubation are not equivocal and are not reported separately by the investigators. Adverse events were not evaluated in the study.

Tocilizumab

Tocilizumab is an interleukin-6 receptor antagonist that may mitigate the inflammatory cytokine syndrome associated with moderate and severe COVID-19 [39C]. A single-center, prospective observational study evaluated its effectiveness in 239 COVID-19 patients. Patients received a single intravenous dose of 8 mg/kg, not to exceed 800 mg per dose. A second dose may be administered if the BMI is elevated, although this was not elaborated further. The primary outcomes are survival and mechanical ventilation between severe and non-severe COVID-19 patients. Patients treated with tocilizumab experienced no difference in survival between severe and non-severe patients (83% vs 91%; $P = 0.11$). Nevertheless, severe patients on mechanical ventilation treated with tocilizumab had a survival of 75% (95% CI 64%–89%), or a mortality of 25%. Although there was no controlled group, the mortality rate is less than those reported in China in mechanical ventilated COVID-19 patients, with a mortality rate of 66%, although still less than what was reported with remdesivir at 8% [32C].

Unfractionated heparin (SEDA-41, 403) and enoxaparin (SEDA-41, 403)

Heparin has been described as potentially beneficial in COVID-19 patients, due to its potential effects on attenuating the disseminated intravascular coagulation associated with COVID-19 [40c]. In a single-center case series reported in Brazil, a total of 27 consecutive COVID-19 patients received either enoxaparin 0.5 mg/kg subcutaneously every 24 h, or unfractionated heparin (UFH) 5000 units every 6–8 h, with every 6 h given to patients with a body mass index of 35 or higher. However, the dosing of enoxaparin may increase in the event of decrease oxygenation, increase D Dimer, or the presence of an acute thrombotic event. For UFH, the route may be change to intravenous targeting an activated partial thromboplastin time (aPTT) 1.5–2 times the normal ranges in patients experiencing shock, or an aPTT 2–2.5 times in the presence of an acute thrombotic events. Within 72 h of initiating anticoagulation, oxygenation as measured by the fraction of partial pressure of arterial oxygen over forced inspiratory oxygen, improved significantly from 254 (±90) to 325 (±80), $P = 0.013$, with 81% of patients discharged within a mean time of 11.4 (±7.9) days. No adverse events were reported. Limitations of this case series is the lack of placebo-controlled in order to determine the significance of these findings, and

methylprednisolone 40 mg daily may be initiated based on worsening of radiological pattern. As shown in the RECOVERY trial [37MC], corticosteroids may improve survival in mechanically ventilated COVID-19 patients, and in this case series 67% were mechanically ventilated.

In a single-center, retrospective study of 449 severe COVID-19 consecutive patients, 94 patients received enoxaparin 40–60 mg subcutaneous per day, while 5 received UFH 10 000–15 000 units subcutaneous per day [41c]. There was no difference in 28-day mortality between patients that received either enoxaparin or UFH compare to non-users. However, patients in the former group had lower 28-day mortality in those with a d-dimer >6 times the upper limit of normal (32.8% vs 52.4%; $P = 0.017$).

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