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Management of COVID-19 in the Hospitalized Patient

Prince Keside Amaechi MD*

Consultant Nephrologist, Spartanburg Nephrology Associates, 322 N Pine St., Spartanburg, South Carolina 29302, United States of America.

***Corresponding author:** Prince Keside Amaechi MD, Consultant Nephrologist, Spartanburg Nephrology Associates, 322 N Pine St., Spartanburg, South Carolina 29302, United States of America. Tel: 347-721-1920; Email: prince.md@outlook.com

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Abstract

As an illustrative example of the management of severe COVID-19 illness in a typical patient with co-morbidities, we present a 73-year-old male who presented with complaint of cough shortness of breath, headache and chills that began 2 days prior to presentation. The symptoms were considered typical of COVID-19 infection. A provisional diagnosis was made based on clinical data alone including hypoxia and typical radiographic appearance, he was started on dexamethasone in the emergency room. This was subsequently confirmed to a COVID-19 infection caused by the SARS-CoV-2 virus. We then added treatment with remdesivir to the corticosteroid and he was managed with supportive care including bronchodilators, non-invasive ventilation. However, he continued to deteriorate and expired on the fifth day of hospitalization.

Keyword and abbreviations: *COVID-19, SARS-CoV-2, severe COVID-19, ARDS, non-invasive ventilation, latest studies, management of COVID-19, WHO guidelines COVID-19, INH COVID-19, CDC COVID-19 guidelines, acute respiratory distress.*

Introduction

About December 2019 the Severe acute respiratory distress coronavirus 2 [SARS-CoV-2] syndrome emerged from the city of Hawaii in China. Since then, it has morphed into a global pandemic threatening populations, health systems and global economies resources. As of July 1, 2021, more than 205 million cases of COVID-19 have been reported globally, including more than 4.3 million deaths. This has put a lot of pressure on already scarce resources in most countries (Data available and constantly updated at: COVID-19 Map - Johns Hopkins Coronavirus Resource Center (jhu.edu) Accessed August 12, 2021). Persons of all ages and sex, are at risk for SARS-CoV-2 infection and severe disease. However, the likelihood of serious disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions [1]. Studies consistently show that the mortality rate has been highest in those aged >70 years, regardless of the presence of chronic medical conditions [2]. Conditions that may lead to a high risk for severe COVID-19 include cancer, ischemic heart disease, kidney disease, obesity, sickle cell disease, transplant status and patient with other immunocompromising conditions. The feared end result is usually acute respiratory distress syndrome (ARDS) [3]. The intention behind this is case study is to highlight the potential difficulties involved in taking care of patients infected with SARS-CoV-2 and to provide an update on the current and potential therapies of COVID-19 in a rapidly evolving pandemic. We went over the case from presentation, through hospital stay and unfortunately, eventual death.

Management

The illustrative case is a 73-year-old male who presented from home via emergency medical personnel with complaint of cough shortness of breath, headache and chills that began 2 days prior to presentation. He was somnolent so history was mostly given by his daughter-in-law. He used home oxygen at the rate of 2 liters per minute by nasal canula. He had been exposed to someone with diagnosis of COVID-19 one week before seeking medical care at the hospital. He expressed the desire not to be intubated as stated in a prior "Do not intubate or Resuscitate" directive. While in the emergency center, a chest radiograph (CXR) was obtained which showed cardiomegaly with mild pulmonary edema, an underlying infection not fully excluded (as read by the radiologist). Significant past medical histories include ischemic heart disease, chronic obstructive pulmonary disease, type 2 Diabetes Mellitus, and severe peripheral vascular disease. Due to his high-risk status and hypoxia (88%) while on 2 liters/minute oxygen, and high suspicion for COVID-19 infection [3] he was started on dexamethasone on admission. A real time qualitative detection of nucleic acid from SARS-CoV-2 by PCR showed that the virus was present in his nasopharynges, and this was diagnostic of COVID-19

infection. Over the 2nd day of hospitalization, he was transferred to the intensive care unit and placed on BiPAP, due to tachypnea (34/minute) and hypercapnia (pCO2 52). He was started on Combivent inhalers, and a planned 5-day course of remdesivir. Unfortunately, the patient continued to be near a constant state of distress and continued to deteriorate despite treatment. On the fifth hospital day (day 4 of remdesivir), he electively decided to discontinue aggressive treatment and choose comfort measures only. The patient died naturally on the fifth day of hospitalization.

Results

He had hypercapnia while on home oxygen of 2 liters nasal canula. As detected on an acid blood gas showing (ABG) pH 7.39, PCO2 52, PO2 82 on BiPAP FiO2 to 45%, showing hypercapnia. He had hypoxemia on pulse oximetry of 88% while on 2 liters nasal cannula. Examination of the right lung fields revealed rhonchi and rales. Examination of the left lung fields reveals rhonchi and rales. Decreased breath sounds, rhonchi and rales present bilaterally and he had 1 word dyspnea. CXR which was redone after the 2nd day showed progression from bilateral infiltrates, to diffused infiltrates throughout the chest consistent with ARDS. Unfortunately, patient continued to decompensate throughout days 3-5 of hospitalization and subsequently expired. The cause of death was confirmed as acute on chronic hypoxemic and hypercapnic respiratory failure due to ARDS secondary to Covid 19 pneumonia.

Discussion

The diagnosis of COVID-19 is usually established on the basis of detection of appropriate SARS-CoV-2 RNA in the respiratory system by PCR, and consistent radiological findings commonly showing bilateral ground-glass opacities [4].

The World Health Organization [WHO] severity index for COVID-19 defines severe COVID-19 any of oxygen saturation less than 90% on room air, respiratory rates greater than 30 breaths per minute in adults, or signs of severe respiratory distress such as use of accessory muscle, inability to complete full sentences or presence of any other general danger signs. Critical COVID-19 is defined by the criteria for acute respiratory distress syndrome [ARDS] [ratio of partial pressure of oxygen to the fraction of inspired oxygen (PaO2:FiO2) of less than 300 mmHg], sepsis, septic shock or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation or vasopressor therapy.

Patients with mild or moderate illnesses may not require admission to a hospital or clinic and can often be monitored as outpatient. Early identification of persons at risk for severe illness or who has severe illness should be identified quickly and admitted to a hospital or specialist center for treatment. Such patients should be monitored closely for deterioration and for control of potential nosocomial spread, clinicians must be protected with the appropriate Personal Protective Equipment. According to current guidelines, patients have a saturation of less than 90% on room air require oxygen and its usually administered by nasal cannula or mask. Clinicians should monitor closely for signs that indicate that patient need to be intubated, ultimately the decision to intubate is a judgment call and must be individualized. (see Hospitalized Adults: Therapeutic Management | COVID-19 Treatment Guidelines (nih.gov) Therapeutic Management of Hospitalized Adults With COVID-19. Last Updated: July 8, 2021). At the time of the management of our index patient, there was no availability of IL-6 inhibitors or Janus Kinase inhibitors, he also indicated that he did not want to be intubated even if clinically indicated.

Concern about bacterial or fungal superinfection

Studies show that few people experience secondary bacterial infections during a severe COVID-19 infection [5]. A recent systematic review of patients who were hospitalized reported that only 8% of the COVID-19 cases experienced a bacterial or fungal co-infection. There was no evidence that our index patient had any co-infection, although the hospital course was too short for this to be confirmed with certainty, it nevertheless seems unlikely.

Patients without oxygen requirement

For patients without oxygen requirement, it is reasonable to use remdesivir if it is anticipated that such patients might rapidly progress to worsening oxygen requirements or if tissue hypoxia is demonstrated in patients who may otherwise have a normal pulse oximetry reading. Patients who have no oxygen requirement should not be treated using dexamethasone (or tocilizumab or baricitinib), as in such patients, it has not been shown to be beneficial and may cause harm [6,10]. In accordance with guidelines from multiple bodies including the NIH and World Health Organization (WHO) our patient was treated with dexamethasone 6 mg daily. (see National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://covid19treatmentguidelines.nih.gov/ (Accessed on August 6, 2021)

Patients who require oxygen

In patients who become hypoxic, WHO suggests titrating peripheral oxygen saturation to the intended target, of greater than or equal to 94% during initial resuscitation and 90% or greater, for maintenance. Supplemental oxygen using a low flow system (up to 6 liters per minute) is appropriate (see Clinical management of COVID-19 patients: living guidance, 25 January 2021 (magicapp.org), from WHO. Accessed August 12, 2021). When higher oxygen flow rates are required, it is reasonable for the clinician to change the oxygen supply to a high flow system as higher percentages of oxygen fractions can be delivered more reliably and comfortably. The flow rate at which aerosolization increases is unknown.

Dexamethasone

For patients with low flow oxygen requirements, which were started due to hypoxia, dexamethasone alone or in combination with remdesivir may be used [6,7]. Dexamethasone remains the first medication to reduce mortality in COVID-19. In an open-label trial, a total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the

usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI) but not among those who were receiving no respiratory support at randomization [6].

Remdesivir

The use of remdesivir is justified based on a double-blind, randomized and possible control trial of remdesivir in 1062 adult patients (541 assigned to remdesivir and 521 to placebo), a study funded by the NIH (ACTT-1 trial), those who received remdesivir had at a median recovery time of 10 days (95% confidence interval), as compared with 15 days among those who received placebo (95% CI) (P:<0.001) [7]. Further studies have so far shown that remdesivir has limited benefit and the most beneficial effects may be only among patients who are already on corticosteroids [7,8]. In a randomized open controlled trial at 405 countries, 11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. In total, 1253 deaths were reported (median day of death day 8). In the remdesivir arm, death occurred in 301 of 2743 patients receiving remdesivir and in 303 of 2708 patients receiving its control (rate ratio, 0.95; 95% CI, P=0.50). These therapies of remdesivir, hydroxychloroquine, lopinavir and interferon regimens had little or no effect on hospitalized patients with COVId-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay [8].

A meta-analysis of remdesivir was published April 2021, the results showed that remdesivir administration was associated with a significant improvement in the 28-day recovery (RR = 1.09, 95%CI, 1.04–1.15), however the pooled median difference of the time to clinical improvement was 2.99 (95%CI = 2.71–3.28), did not remain significant during the sensitivity analysis. The authors wrote that they hoped that this would have provided an updated evaluation of scientific evidence on the use of remdesivir in COVID-19 patients. Based on these studies, for hypoxic patients needing supplemental oxygen, should be treated with dexamethasone, with the addition of remdesivir in patients who do not have any contraindications for its use [7,8].

Baricitinib

Janus kinase (JK) 1/2 inhibitors, such as baricitinib is one of the newer medications for the treatment of COVID-19 and attracted researchers due to its anti-inflammatory effects in inhibiting cytokine signaling, as well as its anti-viral effects which it does by disrupting endocyte signaling, by which the virus enters cells to infect them [10]. Baricitinib has been combined successfully with mortality benefit with remdesivir in the treatment of adults hospitalized with COVID-19 [11]. Out of 1033 patients, 515 received the combination treatment and 518 received placebo (control). The primary outcome was clinical status by day 15. Patients receiving the combination treatment had 30% higher odd of improvement, time of recovery of 6-8 days versus 7-9 days (95% CI, P=0.03), patients receiving high flow oxygen at enrollment had a time to recovery of 10 days compared with 18 days with the control group. Baricitinib is suggested to be given at 4 mg orally once daily for up to 14 days. It is indicated for patients who require oxygen, the dose is reduced in patients with renal insufficiency, and its use is not recommended if the estimated glomerular filtration rate (eGFR) is <15 mL/min per 1.73 m^2.

Tocilizumab

Tocilizumab did not improve survival in earlier trials [12,13] however in the RECOVERY trial where most of the participants (82%) were receiving steroids as part of usual care, the addition of tocilizumab improved survival [14]. The trial participants in this trial were hypoxic, and requiring oxygen therapy, and had evidence of inflammation (c-reactive protein >75 mg/L), they were randomized to usual care alone versus usual care plus tocilizumab at a dose of 400-800 mg depending on weight, given intravenously. A second dose could be given 12-24h later if the patient's condition had not improved. Consistent results were seen in all prespecified subgroups of patients, including those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% vs 50%; rate ratio 1·22; p<0·0001). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% vs 42%; risk ratio 0·84; 95% CI; p<0·0001). WHO and NIH guidelines now include the co-administration of IL-6 antagonists with steroids in patients hospitalized with severe or critical COVID-19 [14,15].

For treatment of COVID-19, it is not known whether an IL-6 inhibitor or a JK inhibitor is superior, although they benefit similar population. Studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19 are not available. However, there is a recommendation against the use of both medications together as these agents have not been studied together and the safety of coadministration is uncertain [15].

Pronation

For hypoxemic patients with respiratory failure on oxygen or non-invasive ventilation, ventilation in the prone position may improve lung mechanics and outcomes [16]. The optimal amount of time in the prone position has not been determined, however some clinical experts suggest 6-8 hours per day. In a review of 9 randomized controlled trials, the authors found no evidence of harm, however subgroups with hypoxemia at entry, early implementation of prone position and prolonged adoption, the results suggest that they may have a statistically significant survival advantage [17]. In a multicenter, prospective, randomized, controlled trial, where 466 patients with severe ARDS were assigned to undergo prone-positioning sessions of at least 16 hours or to be left in the supine

position. A total of 237 patients were assigned to the prone group, and 229 patients were assigned to the supine group. The 28-day mortality was 16.0% in the prone group and 32.8% in the supine group (P<0.001). The incidence of complications did not differ significantly between the groups, except for the incidence of cardiac arrests, which was higher in the supine group. In patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28-day and 90-day mortality [18].

Convalescent plasma

In the early days of the pandemic, in the United States, emergency use authorization was granted for high-titer convalescent plasma among hospitalized patients with COVID-19 who are early in the course of disease or have impaired humoral immunity. However, since then, clinical trials have not shown a clear role for patients, due to lack of evidence of benefit [19]. Retrospective data suggest that convalescent plasma may have a role for individuals with immunocompromising conditions, deficits in antibody production (e.g., those receiving anti-CD20 therapies, or those with hematologic malignancies). A retrospective cohort study using study was done (March 17,2020-January 21, 2021) using data from the COVID-19 and Cancer Consortium registry with propensity score matching evaluated patients with hematologic cancers who were hospitalized for COVID-19. A total of 966 individuals (mean [SD] age, 65 years were evaluated in this study. Among the subgroup of 338 patients admitted to the intensive care unit, mortality was significantly lower in convalescent plasma recipients compared with nonrecipients (HR for propensity score-matched comparison, 0.40; 95% CI, 0.20-0.80). Among the 227 patients who required mechanical ventilatory support, mortality was significantly lower in convalescent plasma recipients compared with nonrecipients [20].

Monoclonal antibodies

Monoclonal antibodies are currently only available for high-risk patients only through an emergency use authorization, or in general, part of a clinical trial. LY-CoV555, is an investigational neutralizing monoclonal antibody, which has been associated with a decrease in viral load and the frequency of hospitalizations or emergency department visits among outpatients with coronavirus disease 2019 (Covid-19). However, LY-CoV555, when co-administered with remdesivir, did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure. On October 26, 2020, in a study by ACTIV-3/TICO LY-CoV555 Study Group the data and safety monitoring board recommended stopping enrollment for futility after 314 patients had undergone randomization and infusion [21].

Conclusion

We used an illustrative case as our index patient for this manuscript. As the world continues to attempt grapple with the realities of the COVID-19 pandemic, we continue to learn many lessons. SARS-CoV-2 virus can result in asymptomatic infection, mild illness, or moderate to severe disease [22]. Some patients such as ours unfortunately have to contend with severe illness. We examined the course of illness in the hospitalized patient, and in the discussion that followed, we proposed how this disease may be managed. The limitation in a case study such as this include the fact that some patients may have atypical presentations, we did not discuss the complications that is commonly encountered in patients with severe disease, the preventive care or post hospital care involved as part of the management of such patients. These closely related topics are beyond the scope of this study. However, we hope that by presenting a typical case of severe COVID-19 that involves a common clinical scenario, we might also present a concise and updated review of the management of severe COVID-19 in the hospitalized patient. Hopefully, this would prove to be useful resource for patients and those who care for them in the hospital setting, in this gobal pandemic.

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