CME

Managing hospitalized patients with COVID-19

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ABSTRACT

Treatment for COVID-19 has significantly changed since the beginning of the pandemic and continues to change as new evidence is published. This article describes which COVID-19 patients require hospitalization and how to manage hospitalized patients based on current evidence from randomized clinical trials.

Keywords: COVID-19, hospitalization, respiratory failure, dexamethasone, remdesivir, tocilizumab

Learning objectives

- Describe when a patient with COVID-19 needs to be hospitalized.
- Discuss treatments for hospitalized patients with COVID-19.
- Outline clinical trial results for treatments used for hospitalized patients with COVID-19.

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According to the World Health Organization Coronavirus (COVID-19) Dashboard, more than 769 million cases of COVID-19 and more than 6.9 million deaths have been reported worldwide.[1] In the United States, more than 103 million cases and more than 1.1 million deaths have been reported.[1] As the virus evolves, variants emerge with different transmissibility rates and severity of illness. The CDC classifies variants based on transmissibility, treatment efficacy, and vaccine efficacy. The classifications from least to most significant are variant of interest, variant of concern, and variant of high consequence.[2] Vaccines, which have been available since early 2021 and offers varying degrees of protection against variants, have resulted in a lower incidence of infection, hospitalization, and mortality.[3-5] The CDC estimated that as of December 2022, vaccinated patients who had received a bivalent booster were 14 times less likely to die from COVID-19 than unvaccinated patients, and three times less likely to die compared with patients who had only received the original monovalent vaccines.[6]

For patients with a known COVID-19 infection, the CDC recommends vaccination beginning after the resolution of symptoms or at the end of the isolation period in asymptomatic patients; this can be delayed by 3 months because the patient will have innate protection from their body's immune response to the virus.[7] Despite the availability of the vaccine, COVID-19 continues to result in hospitalization. This article describes identification and treatment for these patients.

THE CLINICAL SPECTRUM OF INFECTION

Patients infected with SARS-CoV-2 present with a range of clinical features, from asymptomatic to critically ill. According to the National Institutes of Health COVID-19 Treatment Guidelines, adults with SARS-CoV-2 infection generally can be grouped into one of five severity of illness categories, although criteria may overlap and clinical status may evolve during the course of the illness:

- **Asymptomatic or presymptomatic infection:** Patients without symptoms
- **Mild illness:** Patients with flu-like symptoms but without shortness of breath or radiologic findings in the chest
- **Moderate illness:** Patients with lower respiratory disease without hypoxia
- **Severe illness:** Patients with hypoxia or significant infiltrates identified on imaging
- **Critical illness:** Patients with respiratory failure with septic shock or multiple organ dysfunction.[8]

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Key points

- Vaccination for COVID-19 has resulted in a lower incidence of infection, hospitalization, and mortality, but some patients still require hospital care.
- Patients who present with acute hypoxic respiratory failure requiring supplemental oxygen should be admitted to the hospital.
- Dexamethasone is the mainstay of treatment for patients with COVID-19 and respiratory failure; remdesivir often is used in conjunction with dexamethasone for patients with severe or critical illness.
- Patients with rapidly worsening respiratory status may be candidates for tocilizumab or baricitinib in addition to dexamethasone and remdesivir.

WHO NEEDS HOSPITALIZATION?

Patients with COVID-19 may present to their primary care provider, urgent care center, or ED with lymphopenia, respiratory alkalosis, and viral pneumonia on imaging, findings that are consistently seen in patients with the virus.[9,10] Patients with oxygen saturations in the mid-90s and above (NIH classification of moderate or below) generally are able to go home with supportive care or may be prescribed medications by their healthcare provider. Patients who present with acute hypoxic respiratory failure requiring supplemental oxygen (NIH classification of severe or critical) should be admitted to the hospital. COVID-19-specific therapies have the greatest benefit for hospitalized patients who have acute hypoxic respiratory failure. Prophylactic treatments exist for patients considered high-risk. Categories that have been linked to increased risk for severe disease include age (older than 65 years), medical comorbidities (including cancer; chronic kidney, liver, heart, or lung disease; diabetes; and immunocompromise), and socioeconomic factors.[11] These patients may be treated as outpatients if they are not hypoxic.

TREATMENT

Patients with COVID-19 often present with exacerbations of other chronic medical conditions that need to be treated simultaneously. The following sections on treatment for COVID-19 focus on common treatments requested and used for patients requiring hospital admission, but also briefly discuss medications that may have been used in the outpatient setting.

The NIH guidelines provide evidence-based guidance for the therapeutic management of adults hospitalized for COVID-19, with recommendations organized by disease severity (**Table 1**).[8]

Dexamethasone This is the mainstay treatment for patients with COVID-19 and respiratory failure because it has demonstrated a reduction in mortality.[12,13] The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial and the COVID-19 Dexamethasone (CoDEX) trial both found lower 28-day mortality and more ventilator-free days for patients with COVID-19 and respiratory failure.[12,13] Patients who did not require respiratory support had no benefit from dexamethasone.[12]

Patients who were started early on dexamethasone had a lower incidence of requiring high-flow oxygen or ventilator support as well as a shorter duration of hospitalization.[14] For this reason, many patients with marginal oxygen saturations (Spo_2 levels of 92% and below) are started on dexamethasone in the hospital.

Questions remain whether there is any increased benefit to higher dexamethasone dosing or use of other glucocorticoids. Two randomized controlled trials did not find any statistically significant difference between the standard 6-mg dose of dexamethasone compared with 12-mg daily or a taper of 20 mg followed by 10 mg.[15,16]

Remdesivir This drug often is used in conjunction with dexamethasone for patients with severe or critical illness. It also can be used as prophylaxis for patients without hypoxia with risk factors for severe disease. Remdesivir is given once daily for 5 days (200 mg on day 1 followed by 100 mg on subsequent days) but may be extended to 10 days for patients with continued or worsening respiratory status.[17,18]

The first stage of the Adaptive COVID-19 Treatment Trial (ACTT-1) concluded that remdesivir reduced the duration of illness but did not affect mortality.[17] Patients receiving remdesivir had a mean recovery of 10 days compared with 15 days in the usual care group.

A subsequent randomized controlled trial evaluated the duration of treatment with remdesivir and found no significant difference between 5- and 10-day courses.[18] Patients randomly assigned to the 10-day group had significantly worse clinical status compared with those in the 5-day group.

Tocilizumab and baricitinib Patients with rapidly worsening respiratory status may be candidates for tocilizumab or baricitinib in addition to dexamethasone and remdesivir. Elevated inflammatory markers such as C-reactive protein or D-dimer levels may help guide initiation. Tocilizumab is given once weekly via infusion. Baricitinib is given orally at 4 mg/day for 14 days. The drugs can be used interchangeably but should not be used together. Both interfere with the inflammatory pathway and reduce the occurrence of cytokine storm.

The RECOVERY trial found that patients with hypoxia and systemic inflammation had reduced risk for requiring mechanical ventilation and improved survival rate when treated with tocilizumab in conjunction with systemic corticosteroids.[19] The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial found similar results with an improved survival rate for patients in the ICU who required organ support.[20]

The Efficacy and Safety of Baricitinib for the Treatment of Hospitalized Adults with COVID-19 (COV-BARRIER) clinical trial investigated the use of baricitinib with dexamethasone and found that one additional death was prevented per 20 baricitinib-treated patients.[21] The ACTT-2 trial, the second stage of ACTT-1, concluded that baricitinib in conjunction with remdesivir was superior to remdesivir alone in reducing recovery time, which was most pronounced among patients who required high-flow oxygen.[22]

Anticoagulants Prophylactic anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) may be used. NIH guidelines recommend LMWH such as enoxaparin over UFH.[8] Prophylactic dose (enoxaparin 40 mg SC daily) can be used in most patients; a therapeutic dose may be used in nonpregnant patients with elevated D-dimer levels without increased bleeding risk.[8] Contraindications include recent bleeding, history of a bleeding disorder, patients already on anticoagulation, or thrombocytopenia.[8]

Other treatments Hydroxychloroquine, ivermectin, azithromycin, and high-dose vitamins are not recommended.[23] Two separate randomized controlled trials evaluated 800 mg of hydroxychloroquine on day 1 followed by 400 to 600 mg daily for 6 days in patients with confirmed COVID-19 with symptom duration of fewer than 5 days.[24,25] Results demonstrated no reduction in risk of hospitalization or duration of illness compared with the control cohort.[24]

RECOVERY trial results demonstrated that hydroxychloroquine use in hospitalized patients did not affect 28-day mortality compared with usual care.[26] Secondary outcomes also suggested that the intervention group had a longer hospitalization (16 days compared with 13 days) and increased risk for mechanical ventilation or death compared with the usual care group.[26]

TABLE 1. NIH guidelines for treating hospitalized patients with COVID-19[8]

Disease severity	Oxygen therapy	Treatment
Asymptomatic, mild, or moderate	Not required	If asymptomatic, monitor without treatment. If asymptomatic but at high risk, consider prophylaxis with Paxlovid or remdesivir.
Severe	Requires up to 6 L/min of supplemental oxygen	Dexamethasone and remdesivir
Critical	Requires high-flow supplemental oxygen via nasal cannula or noninvasive ventilation	Dexamethasone and remdesivir plus baricitinib or tocilizumab

The Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease (ORCHID) trial concluded that hospitalized patients with respiratory failure did not have significant improvement in their clinical status at day 14 when treated with hydroxychloroquine versus placebo.[25]

The Ivermectin to Prevent Hospitalizations in Patients with COVID-19 (IVERCOR-COVID-19) trial found that ivermectin for mild to moderate COVID-19 infection had no significant effect on preventing hospitalization.[27] An additional finding from this trial was that patients who received ivermectin required mechanical ventilation significantly earlier.[27]

Another study evaluated ivermectin use in hospitalized patients who received 12 mg/day of the drug for 3 days.[28] No statistically significant difference was found in mortality, length of stay, or need for mechanical ventilation compared with patients in the usual care group.[28]

Convalescent plasma was used in hospitalized patients early in the pandemic but is no longer used. The RECOVERY trial found no significant difference in 28-day mortality in patients receiving convalescent plasma compared with usual care alone.[29] Multiple other trials, including the CONvalescent Plasma for Adults with COVID-19 Respiratory Illness (CONCOR-1) and Convalescent Plasma in the Management of Moderate COVID-19 in Adults in India (PLACID) trials, concluded that convalescent plasma use did not reduce 28-day mortality or progression to severe disease.[30-32]

DISCUSSION

Treatment of COVID-19 in the hospital has changed dramatically since the beginning of the pandemic. Multiple novel therapies have been trialed and subsequently recommended against, including hydroxychloroquine, ivermectin, convalescent plasma, high-dose vitamin C, and zinc. Early on, corticosteroids were not recommended and patients were placed on ventilators early. Now, corticosteroids are the mainstay of treatment in patients with respiratory failure and have been shown to reduce mortality, and patients are treated with noninvasive ventilation unless mechanical ventilation is absolutely necessary. Many clinical trials involving treatment regimens will continue to be conducted, and new publications will likely alter treatment plans for hospitalized patients.

Variants likely will result in future surges of COVID-19. Cases and hospitalizations have come in waves as variants with increased transmissibility or disease severity became prevalent. The second half of 2021 was initially dominated by the Delta variant, which was rapidly replaced by the Omicron variant.[33] Delta has increased transmissibility and severity, resulting in hospital systems being strained with very ill patients at its height. Omicron has significantly higher transmissibility; however, illness severity generally is lower. Omicron was the first significant variant that did

TABLE 2. IDSA recommended treatments

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Class	Medication	Disease severity	Duration	Route
Antivirals	Remdesivir	3 days for up to moderate illness; 5 (vs. 10) days in severe illness	3, 5, or 10 days	IV
	Nirmatrelvir/ ritonavir	Within 5 days of symptoms for high-risk ambulatory patients up to moderate illness	5 days	Oral
	Molnupiravir	Within 5 days of symptoms for high-risk ambulatory patients who have no other treatment options	5 days	Oral
Immunomodulators	Dexamethasone	Severe or critical illness (respiratory failure)	10 days	Oral or IV
	Tocilizumab	Severe/critical illness with elevated inflammatory markers and high oxygen requirements	2 doses (second dose at least 8 hours after first)	IV
	Baricitinib	Severe illness with high oxygen requirements	14 days	Oral
Antithrombotic	LMWH or UFH	Prophylaxis dose in most, therapeutic dose in severe/ critical elevated high D-dimer	Until discharge	SC

not have a correlation of case rate to hospitalization rate. Both of these variants quickly became dominant strain after being identified.

Vaccination remains the best protection against COVID-19. Variants have led to a decrease in the effectiveness of vaccination, but vaccination continues to offer patients significant protection from contracting COVID-19, from severe disease, and reduced mortality compared with unvaccinated patients.[4]

Mortality in patients with COVID-19 has directly correlated with age. However, during the Delta wave, significant illness was seen in unvaccinated patients ages 40 to 65 years; meanwhile, older vaccinated patients were more likely to have mild illness.[34] Additionally, consider that most adults have been at least partially vaccinated. CDC reports that 88% of patients over age 65 years received the initial vaccination series.[3] Even with nearly 9 out of 10 patients in this demographic being vaccinated, the majority of hospitalized patients with COVID-19 are unvaccinated.[4]

Compared with previous variants, Omicron has caused more cases of COVID-19 in vaccinated patients.[33] However, unvaccinated patients were three times more likely to test positive than vaccinated patients and five times more likely to test positive than patients who had been vaccinated and received the first booster.[3]

Remaining current with published literature is difficult for clinicians, whose workloads were dramatically increased by the pandemic. The pandemic has uniquely compounded this as the public has sought information, much being anecdotal or low quality, or politicized illness or treatments. Many patients continue to downplay the severity of COVID-19 even as they are being treated in the hospital with moderate or worse illness. Others refuse medications such as remdesivir because of things they have read or what others have said to them. Educating patients about the potential benefits of treatments is key to helping them make informed decisions.

The Infectious Diseases Society of America (IDSA) recommendations for treating patients with COVID-19 cover postexposure prophylaxis, ambulatory care, and hospitalized care (**Table 2**).[23] The IDSA website provides a summary of the studies, conclusions, and recommendations for further research and is a useful tool to help clinicians stay up-to-date on COVID-19 therapies.

The IDSA recommends a 3-day course of remdesivir prophylaxis in both ambulatory and hospitalized patients with mild to moderate disease who do not need supplemental oxygen.[23] Antivirals including nirmatrelvir/ritonavir (Paxlovid) and molnupiravir are recommended in ambulatory care for patients with mild to moderate disease.[23] These medications also are being used in patients at greater risk for severe complications secondary to COVID-19 infection.[35]

CONCLUSION

COVID-19 has been a disruptive force and will continue to be widely discussed as cases, hospitalizations, and mortality accumulate. Hopefully, future variants will be less likely to cause severe illness and mortality, helping to lead to herd immunity. Until then, studies will continue to evaluate the most effective treatment for patients with COVID-19. **JAAPA**

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