

Basic Critical Care for Management of COVID-19 Patients: Position Paper of Indian Society of Critical Care Medicine, Part-I

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ABSTRACT

With more than 23 million infections and more than 814,000 deaths worldwide, the coronavirus disease-2019 (COVID-19) pandemic is still far from over. Several classes of drugs including antivirals, antiretrovirals, anti-inflammatory, immunomodulatory, and antibiotics have been tried with varying levels of success. Still, there is lack of any specific therapy to deal with this infection. Although less than 30% of these patients require intensive care unit admission, morbidity and mortality in this subgroup of patients remain high. Hence, it becomes imperative to have general principles to guide intensivists managing these patients. However, as the literature emerges, these recommendations may change and hence, frequent updates may be required.

Keywords: Antivirals, Corticosteroids, COVID-19, Critical care, Intensive care, SARS-CoV-2.

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INTRODUCTION

Since December 2019, coronavirus disease-2019 (COVID-19) has swept over the world, causing more than 23 million infections and more than 814,000 deaths. Although most of the patients remain asymptomatic or develop mild symptoms, up to 30% of these patients develop severe symptoms necessitating intensive care unit (ICU) admission.¹⁻³ Morbidity and mortality in this subgroup of patients remain high and may reach up to 80%, especially in those who require invasive mechanical ventilation (IMV).^{2,4-7} Because of lack of any specific therapy, high-quality intensive care remains the cornerstone of management in these patients to improve patient outcomes. Tremendous amount of literature is being added regarding the management of these patients, making it difficult to keep pace in these changing times. Hence, it becomes imperative to have general principles to guide intensivists managing these patients. To aid in understanding the level of evidence, the recommendations were accorded as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) basic approaches and rules.⁸ In absence of direct clinical evidence, grade of useful practice point (UPP) was awarded by consensus of the working group based on clinical experience and expertise.⁸ As the literature emerges, these recommendations may change and hence, frequent updates may be required.

GENERAL MANAGEMENT PRINCIPLES

The COVID-19 pandemic has posed a big challenge to the healthcare community and many stakeholders, exposing gaps in resource, knowledge, and infrastructure. Different ICU models, therapeutic strategies, and community health practices have surfaced during this period. The guidelines below are an attempt to conglomerate best available evidence to optimize ICU management of the COVID-19 patients.

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Intensive Care Unit Admission Criteria

Recommendations

- Every institution should develop its own ICU admission criteria based on severity of illness, clinical frailty and patient preferences to suit available infrastructure. (UPP)
- Modified EWS >6, qSOFA ≥2, or NEWS2 ≥5 can be recommended as a screening tool to identify patients who would benefit from closer monitoring and intensive treatment. (UPP)
- The need for ICU transfer and likely clinical outcomes should be discussed with the patient or his representatives and their preference is to be incorporated into decision-making. (UPP)
- Critical Care Team should be involved in the decision to transfer a patient from ER or wards to the ICU. (UPP)
- Complex decision-making should involve a multi-disciplinary approach. (UPP)
- There should be periodic audit and review of criteria to make it best suited to each individual setting. (UPP)

Rationale

ICU admission criteria for COVID-19 patients should be based on acuity of illness, comorbid conditions, physiologic reserve, metabolic factors, likely outcomes, availability of resources including personnel, and end-of-life care (EOLC) decisions if any.^{9,10} This is no different from the criteria employed in a non-COVID setting,¹¹ and there is no single model that includes all these components. Care should be taken to confine these patients to specified areas in order to safeguard the uninterrupted care of non-COVID patients as well as to contain the spread of infection.¹²

The abovementioned factors are variably incorporated into some of the commonly employed scoring systems such as the modified Early Warning Score (mEWS),¹³ revised National Early Warning Score (NEWS),¹⁴ Acute Physiology and Chronic Health Evaluation (APACHE) score, Sequential Organ Failure Assessment (SOFA) score, qSOFA, etc. Although none of these have shown to have high sensitivity or specificity for predicting transfer to ICU or subsequent outcomes, they add an element of objectivity to physician intuition. Every institution should develop their own ICU admission criteria for patients with COVID based on each of their unique infrastructure.¹⁵ The tools for resource allocation and admission prioritization proposed by the Society of Critical Care Medicine (SCCM) for the ICU can be extrapolated to this setting.¹⁶ The position statement on COVID-19 management by the Indian Society of Critical Care Medicine (ISCCM) also gives a detailed outline for ICU admission and infection control planning.¹⁷

Basic Laboratory Investigation

Recommendations

- Baseline laboratory assessment including complete blood count, coagulation profile, renal and liver function tests, serum electrolytes, arterial blood gas, chest X-ray, and ECG should be done in all patients upon ICU admission. (GRADE IIB)
- Investigations should be repeated if clinically warranted and not as a scheduled routine. (GRADE IIB)
- Neutrophil to lymphocyte ratio (NLR) can be used as a screening tool to identify patients who may benefit from more intense monitoring. (GRADE IIB)

Rationale

Apart from the basic laboratory tests, additional investigations may be ordered based on individual assessment. The frequency of lymphopenia, thrombocytopenia and prognostic role of raised NLR in COVID-19 has been well observed and reported.² While other hematological ratios such as platelet–lymphocyte, lymphocyte–monocyte, and lymphocyte–CRP have been studied, none have compared well with NLR.^{18,19} Similarly, raised serum levels of lactate dehydrogenase (LDH), aspartate amino transferase, alanine amino transferase, bilirubin, gamma glutamyl transpeptidase (GT), and serum creatinine have all been observed.^{20,21} Deranged coagulation parameters have also been a common occurrence, especially in severe disease.²²

While a baseline chest X-ray is needed for assessment of extent of disease, the practice of routine and repeated imaging in patients with acute respiratory failure should be discouraged.²³ Cardiac manifestations of COVID-19 have been commonly reported,²⁴ and several ECG manifestations of arrhythmia, strain, injury, inflammation, and infarction have been observed. Additional attention is also warranted for ECG intervals in the context of drug therapy.

Biomarkers

Recommendations

- We recommend measuring levels of C-reactive protein (CRP), LDH, ferritin, and D-dimer upon ICU admission. (GRADE IIB)
- These may be repeated if clinically warranted to assess disease progression. (UPP)
- IL-6 level can be monitored where available in severe disease to guide anti IL-6 therapy. (UPP)
- Cardiac troponin (hs-Tnl) may be done when myocardial injury is suspected and not as a routine. (UPP)

Rationale

Several biomarkers of injury, inflammation, and coagulation have been proposed as tools for prognostication and treatment guidance. Some of these commonly used include CRP, IL-6, LDH, D-dimer, ferritin, cardiac troponin, etc. CRP, a non-specific acute-phase reactant, is produced by the liver under the influence of inflammatory mediators. Significantly elevated values have been reported in COVID-19 patients with higher severity of illness.²⁵ One retrospective observation suggested that patients with CRP values >41.8 mg/L were more likely to deteriorate.²⁶ CRP levels have also been reported to correlate positively with computed tomography (CT) severity scores.²⁷ Given the relative ease of analysis and available database, CRP can be considered a valuable biomarker for prognostication.

IL-6 is a pro-inflammatory cytokine released by activated macrophages. An exaggerated release has been observed in severe disease during the so-called cytokine storm or cytokine release syndrome (CRS). Mean levels were noted to be 2.9 times higher in patients with severe disease compared to milder forms in one meta-analysis.²⁸ Similarly, higher values were observed in nonsurvivors than survivors.²⁹ Ferritin, an iron storage protein located within the cells, causes activation of macrophages upon release. Hyperferritinemia, as a marker of immune dysregulation was therefore commonly observed in patients³⁰ and high levels were shown to correlate with disease severity.²⁹

LDH is an important enzyme in glucose metabolism. High levels have been observed in COVID-19 patients and are thought to be

released from damaged cell membranes. A multicenter study has revealed a strong correlation between high LDH levels and severity of COVID-19.¹ LDH levels have also been shown to correlate with CT severity.³¹

COVID-19 is known to be associated with widespread activation of coagulation and fibrinolysis. This raises the possibility of D-dimer being a potential marker for extent of the disease considering that it is a breakdown product of cross-linked fibrin. Levels of D-dimer have been reported to be higher in those with greater disease severity and in nonsurvivors.³² Levels more than 1 µg/mL were significantly associated with higher mortality.³²

Myocardial injury and an associated higher mortality have been observed in patients with COVID-19.³³ High-sensitivity Troponin I (hs-TnI), a cardiac biomarker, has therefore been studied as a test for severity and mortality prediction. One retrospective study suggested a univariate odds ratio for death at 80.1 for hs-TnI.²⁸ Another study reported high values in 20% of patients upon presentation, and these were more likely to require ICU care.³⁴ Elevated cardiac troponins together with NT-pro BNP have been reported often in patients with COVID-19 myocarditis.³⁵

Other biomarkers such as serum amyloid A and markers of glomerular filtration have also been studied but are not available for routine analysis. Novel biomarkers such as homocysteine, angiotensin II, ang (1–7), ang (1–9), and alamandine have also been proposed as markers of vascular damage and endothelial dysfunction; however, their role in COVID-19 is yet to be evaluated.

Cultures

Recommendation

- Microbial cultures should be ordered based on clinical suspicion. (UPP)
- Precautions against infection transmission are to be strictly adhered to during sampling. (UPP)

Rationale

Data regarding coinfections and secondary infections in patients with COVID-19 are emerging. While viral coinfections at presentation have been reported, bacterial and fungal infections are often secondary and the consequence of reduced immunity secondary to COVID pneumonia or nosocomial in onset.³⁶ The need for microbial cultures shall therefore follow established principles based on clinical suspicion either upon admission or whenever indicated. Utmost infection control precautions should be adhered to, especially with reference to lower respiratory culture sampling.

Computed Tomography Scan

Recommendations

- CT chest may be considered as a screening tool for isolating suspected patients. (UPP)
- We recommend against routine CT chest in patients in the ICU unless an alternate pathology is suspected. (UPP)
- Strict infection control precautions are to be adhered to during intra-hospital transport in case a CT chest is warranted. (UPP)

Rationale

CT chest findings in COVID-19 may manifest in the asymptomatic or the pre-symptomatic patients and typically evolve over 1–3 weeks. Varying features have been reported including bilateral,

multifocal patchy ground-glass opacities, or segmental and sub-segmental consolidation with interlobular and vascular thickening (crazy paving pattern) in a predominant peripheral distribution.³⁷ These findings, although highly sensitive, are not specific and are also seen with other viral pneumonias. The chest CT has hence assumed importance, more as a rapid screening tool, to aid in isolation of suspects. Consensus recommendations are against the use of CT-scan as a rapid diagnostic tool as against the gold standard RT-PCR,^{38,39} despite a lower sensitivity of the latter. The COVID-19 Reporting and Data System (CO-RADS) classification developed by the Dutch radiological society, which assesses the suspicion for COVID-19 (category 1 = no suspicion through category 5 = very high and category 6 = PCR positive), has been shown to have substantial interobserver agreement and can be considered for standardized reporting.⁴⁰ CT chest may also find a role in assessing the evolution of the disease as well as in gauging clinical severity using the CT severity score (CT-SS). A CT-SS <19.5 has been shown to rule out severe disease with a negative-predictive value of 96.3%.⁴¹ They have also been incorporated in mortality prediction models.⁴²

Despite the abovementioned applications, the role of CT chest in the ICU is rather limited. Treatment strategies in the critically ill COVID-19 patients are not guided by CT chest findings unless an alternate pathology is suspected. The widespread availability and application of bedside chest X-ray and ultrasound in the ICUs can further avert the need for CT chest in acute respiratory failure.^{43,44}

Positioning of Patients (Awake Prone Positioning)

Recommendation

- Awake patients with normal sensorium requiring supplemental oxygenation, noninvasive ventilation (NIV), or high-flow nasal cannula (HFNC) therapies and in the absence of contraindications can be considered for awake prone positioning (PP). (GRADE IIB)
- PaO₂:FiO₂ 150 to 300 (or) SpO₂:FiO₂ 140 to 315 can be a reasonable threshold for attempting awake PP in patients not in distress. (GRADE IIB)
- General contraindications for prone ventilation apply for awake PP as well. (UPP)
- Prone sessions of 1–3 hours can be tried with attempts to maximize duration based on patient tolerance and benefit. Multiple sessions can be attempted each day. (GRADE IIB)
- Awake PP can be continued until there is sustained and satisfactory improvement in oxygenation or until intubation when promptly indicated due to futility of PP. (UPP)
- Lateral positioning may be attempted in those who do not tolerate PP. (UPP)
- There should be strict vigilance for patient discomfort and failure with emphasis on timely intubation where appropriate. (UPP)
- General principles for PP such as care for skin, eyes and invasive devices, prevention of neuropathy and abdominal compression etc. apply. (UPP)
- There is no evidence to recommend the use of any gadgets or special mattress at this time point. (UPP)

Rationale

Acute respiratory distress syndrome (ARDS) has been reported in 20–41% of patients with severe COVID-19.⁴ The physiologic and mortality benefit of prone ventilation in intubated patients with moderate to severe ARDS is well established.⁴⁵ The same benefit was not observed in milder forms of the disease albeit

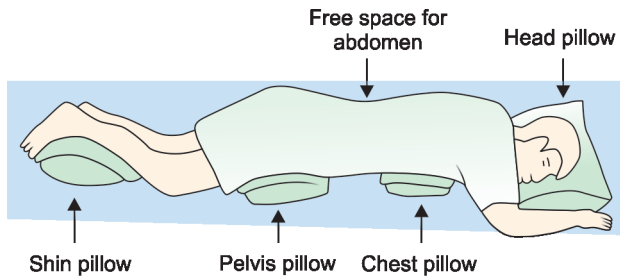


Fig. 1: Positioning for awake proning

improvement in oxygenation. However, such a physiologic benefit may still be welcome considering the magnitude and resource consumption of the present pandemic. Small prospective trials^{46–48} and case series⁴⁹ have studied the application of PP in non-intubated patients with mild to moderate COVID-19 receiving supplemental oxygen, NIV, and HFNC therapies (Fig. 1). These have demonstrated feasibility in a good proportion of patients and a greater than 20% improvement in oxygenation for proning periods of 1–3 hours. Lateral positioning (LP) has been tried for patients not tolerating PP (Fig. 2). Several important questions such as who will benefit, what constitutes an optimal technique and duration of PP, safety issues, and whether this will translate in terms of avoidance of intubation and enhanced survival remain unanswered. While $\text{PaO}_2:\text{FiO}_2$ has been the traditional threshold for PP, there are newer insights into the use of $\text{SpO}_2:\text{FiO}_2$ for ease of use in resource limited settings.⁵⁰ Likewise, there is emphasis for a protocolized approach for ease, standardization, and better performance.⁵¹

While awaiting better evidence, it may not be wrong to adopt awake proning of non-intubated patients with mild to moderate COVID-19 as a rescue measure in an attempt to ease resource constraints. Nevertheless, the choice of patients, post prone monitoring for tolerance, safety and benefit and the avoidance of delay in intubation are paramount.

Discharge from Intensive Care Unit

Recommendations

- Prompt discharge from ICU should be considered once the patient has stabilized and no longer needs ventilator support or more than one organ support. (UPP)
- In the event of limitation of care based on futility and due consent from patient or family, a transfer out of ICU to a stepdown unit or room with facilities for continued palliative care should be considered keeping infection control aspects in mind. (UPP)
- Every institution should develop its own ICU discharge criteria to allow for safe and timely transfer out from ICU. (UPP)
- The decision for ICU discharge should be validated by the treating intensivist. (UPP)
- Complex decision-making should involve a multidisciplinary approach. (UPP)
- A hospital bed management system may help in smooth coordination of ICU admission and discharge during bed shortage. (UPP)
- There should be periodic audit and review of ICU readmissions and post ICU discharge mortality to identify areas of improvement. (UPP)

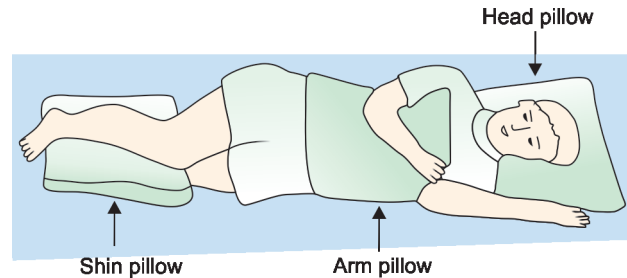


Fig. 2: Lateral positioning

Rationale

Discharge of critically ill patients with COVID from ICU shall typically follow clinical recovery. The criteria for this recovery however can be modified depending on the availability of high-dependency or stepdown units. The emphasis should be on timely and safe discharge from ICU to avoid resource constraints. This is especially true considering the typically prolonged length of stay of patients with severe COVID requiring ventilatory and other organ supports. Further compounding this problem is the fact that rehabilitation of such patients often continues in the ICU due either to non-availability of such specialized units or for infection control reasons. Criteria should also account for patient preference, futility of care, and EOLC decisions, where appropriate. Viral clearance using RT-PCR should not be a criterion for discharge from ICU considering the demand for acute-care beds.

While there are many ICU discharge models based on prioritization, physiological stability, laboratory criteria, or diagnosis, none of them are validated.¹¹ United Kingdom (UK) guidelines^{52,53} and the SCCM task force for ICU admission, discharge, and triage⁵⁴ provide useful information to design an institute-specific discharge criteria. A checklist-based approach may come in useful in timely and safe discharge from ICU.⁵⁵

THERAPEUTIC OPTIONS

No therapy till date has shown to improve survival of patients with COVID-19. Several drugs are under scrutiny, and many antiviral, anti-inflammatory drugs, and antibiotics are currently being prescribed, despite dearth of evidence. To have maximum efficacy, antivirals should be used in the first 7–10 days of symptom onset with an aim to reduce the viral load.

Hydroxychloroquine and Chloroquine

Recommendation

Currently no robust evidence regarding the efficacy of CQ and HCQ for either prophylaxis or treatment of COVID-19. (GRADE IIB)

Rationale

Chloroquine (CQ), used to treat malaria and amebiasis, and hydroxychloroquine (HCQ), used as a disease-modifying rheumatoid arthritis drug, are 4-aminoquinoline derivatives. Both drugs act as a weak base that change the pH of acidic intracellular organelles, thereby interfering with membrane fusion of viruses and have shown *in vitro* activity against corona viruses.⁵⁶ Other mechanisms of action include interference with the cellular receptor ACE2 (making it particularly effective against coronavirus) and impairment of acidification of endosomes which interfere with virus trafficking within cells.^{57,58} Yao et al. found that the HCQ was

much more potent than CQ at inhibition of COVID-19 in cell lines.⁵⁸ HCQ additionally has immunosuppressive properties, and activity against many pro-inflammatory cytokines (e.g., IL-1 and IL-6) might be helpful in prevention or treatment of cytokine storm.^{59,60}

Chloroquine is recommended as 1 g on day 1 and 500 mg daily, while HCQ, 800 mg on day 1 and then 400 mg daily for 4–7 days for patients weighing more than 50 kg.^{61,62} ICMR recommends oral HCQ as 400 mg twice daily on day 1 and then 200 mg twice daily on days 2–5. Majority of data till date involve patients with mild to moderate COVID-19 with very limited clinical data in severe disease. A small, randomized study in hospitalized adults in China comparing chloroquine with lopinavir/ritonavir showed that all patients treated with chloroquine had negative RT-PCR by day 13 and were discharged compared to 92% treated with lopinavir/ritonavir were negative, and only 50% were discharged from the hospital by day 14.⁶³

National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of chloroquine for the treatment of COVID-19.⁶⁴ Infectious Disease Society of America (IDSA) recommends that a combined regimen of chloroquine and azithromycin be used for the treatment of COVID-19 only in the context of a clinical trial.⁶⁵

Food and Drug Administration (FDA) issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, and ventricular fibrillation) with use of CQ/HCQ and cautioned against its use outside of a clinical trial or hospital setting.⁶⁶

Preliminary results of the RECOVERY trial, which evaluated the efficacy of 6 different treatment arms for prevention of death in hospitalized patients with COVID-19, indicated that HCQ did not provide a significant difference in 28-day mortality. In addition, there was no evidence of beneficial effects on duration of hospitalization or other outcomes.^{67,68}

Role of Prophylaxis⁶⁹

The Joint Monitoring Group and National task force have now recommended the prophylactic use of HCQ in the following categories:

- All asymptomatic healthcare workers involved in containment and treatment of COVID-19 and asymptomatic healthcare workers working in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks.
- Asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19 related activities.
- Asymptomatic household contacts of laboratory confirmed cases.

Dose for prophylaxis as per ICMR is 400 mg 12th hourly for first 2 doses the 400 mg once a week for 5 weeks, extendable to 8 weeks (if well tolerated and no risk for QTc prolongation) under medical supervision.

NIH does not recommend the use of any agent for pre-exposure or post-exposure prophylaxis of COVID-19 infection outside of clinical trials.⁶⁴

Azithromycin

Recommendations

Current data is insufficient to establish the role of adjunctive use of azithromycin in management of COVID-19. (GRADE IIB)

Rationale

Azithromycin, a macrolide antibiotic with immunomodulatory and anti-inflammatory actions additionally, has some *in vitro* activity against viruses such as Influenza-A, H1N1, and Zika.^{70,71} There is no data on its *in vitro* activity against COVID-19. A dose of 500 mg on day 1 and 250 mg once daily on days 2–5 has been tried in conjunction with a 5–10-day regimen of HCQ.

Azithromycin has been used for antibacterial coverage in conjunction with HCQ in hospitalized patients with COVID-19 in several French studies, but current data are insufficient to evaluate clinical benefits.^{72,73} Data from two retrospective studies indicate that use of HCQ with or without azithromycin was not associated with decreased in-hospital mortality.^{74,75}

NIH and IDSA recommend against the use of a combined regimen of HCQ and azithromycin for the treatment of COVID-19, except in the context of a clinical trial.^{64,65} Because both azithromycin and HCQ are associated with QT prolongation, and caution is advised when considering the combination, especially in outpatients who cannot be closely monitoring and in those at risk for QT prolongation or receiving other arrhythmogenic drugs.⁷⁶

Remdesivir

Recommendations

Available evidence suggests that benefits likely outweigh risks for the use of remdesivir in hospitalized COVID-19 patients without renal insufficiency. (GRADE IC)

Rationale

Remdesivir is a broad-spectrum antiviral, nucleotide analog prodrug, with activity against coronaviruses. Preliminary data analysis of the ACTT-1 trial indicated shorter median time to recovery with remdesivir vs placebo and suggested that remdesivir treatment may have provided a survival benefit.⁷⁷ This trial used a 10-day regimen, but a more recent RCT suggested that a 5-day course was sufficient.⁷⁸

It remains unclear whether remdesivir might affect long-term outcomes. Emergency Use Authorization (EUA) dosage recommended by FDA for patients weighing >40 kg is a loading dose of 200 mg by IV infusion on day 1, followed by 100 mg IV once daily on days 2–5 with option to extend treatment up to day 10 if needed (for patients requiring ventilator support).⁷⁹

Lopinavir/Ritonavir

Recommendations

No strong evidence to support routine use for treatment in COVID-19 patients, the side effect profile is significant and the drug should only be used in context of clinical trials. (GRADE IIC)

Rationale

Lopinavir/ritonavir is a combination of protease inhibitor antiretroviral drugs (lopinavir is the actual antiviral agent, with ritonavir functioning to inhibit metabolism of lopinavir). This combination has *in vitro* activity against SARS-CoV-1 and functions synergistically with ribavirin (the addition of ribavirin increases lopinavir's potency fourfold). Compared to remdesivir, lopinavir/ritonavir has the advantage that it is widely available and has an established toxicity profile.

Available human data on SARS and MERS have combined these three agents together.⁸⁰ For lopinavir/ritonavir, standard dose is 400 mg/100 mg PO BID. Crushing and administering tablets via a

nasogastric tube may decrease absorption by ~50%.⁸¹ Ribavirin is given as 4 g oral loading dose followed by 1.2 g PO q8hr (or 8 mg/kg IV q8hr) for 14 days.⁸²

A randomized, open-label trial in hospitalized adults with severe COVID-19 compared lopinavir/ritonavir with standard care vs standard care alone. The primary end point, time to clinical improvement, was not shorter with lopinavir/ritonavir; however, 28-day mortality rate was numerically lower.⁸³ No significant differences in reduction of viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death was observed. Even the RECOVERY trial reported no clinical benefit from using lopinavir/ritonavir in hospitalized COVID-19 patients.⁸⁴ NIH and IDSA recommend against the use of lopinavir/ritonavir or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial.^{64,65}

Favipiravir (Avigan)

Recommendations

Efficacy and safety of favipiravir for treatment of COVID-19 is not established. Given the lack of pharmacokinetic and safety data for the proposed high dosages, the drug should be used with caution. (UPP)

Rationale

Favipiravir is a broad-spectrum antiviral with *in vitro* activity against various viruses, including coronavirus.^{85,86} Favipiravir was developed by Fujifilm Toyama Chemical in 2014 in Japan for the treatment of avian influenza or novel influenza resistant to neuraminidase inhibitors. Its antiviral activity is exhibited through selectively targeting RNA-dependent RNA polymerase (RdRp), interrupting the nucleotide incorporation process during viral RNA replication. The dysregulation in viral RNA replication induces destructive mutagenesis in RNA viruses including COVID-19.

Favipiravir was used in a dose of 1,600 mg twice daily on day 1 followed by 600 mg twice daily for 7–14 days in several open-label COVID-19 studies in China.⁸⁷ Another ongoing trial specifies a Favipiravir dosage of 1,800 mg on day 1 and 800 mg twice daily on days 2–10.

In a small, open-label, nonrandomized study in patients with non-severe COVID-19 in China, Favipiravir was associated with decreased median time to viral clearance and higher improvement rate on chest CT imaging on day 14 compared to the control group receiving lopinavir/ritonavir. Both groups also received aerosolized interferon α -1b.⁸⁸

Ivermectin

Recommendations

Currently no recommendation can be made for or against ivermectin use in COVID-19 due to lack of data regarding efficacy and safety profile. (UPP)

Rationale

Ivermectin, an antiparasitic agent, has broad-spectrum *in vitro* antiviral activity from inhibition of viral replication. The effective *in vivo* dose is not known, and pharmacokinetic modeling predicts that plasma concentrations attained with dosages up to 10 times higher than usual dosage are also substantially lower than concentrations associated with *in vitro* inhibition of the virus.⁸⁹

Single dose 200 μ g/kg once (12 mg for upto 80 kg and 18 mg for >80 kg) or 600 μ g/kg (up to 60 mg once a day for 3 days) have been used. Currently, there are no known published data regarding efficacy or safety in COVID-19. A retrospective cohort study in hospitalized COVID-19 patients showed significantly lower mortality rates in those who received ivermectin compared with usual care. The mortality rate was also lower among patients with severe pulmonary disease treated with ivermectin although the rate of successful extubation did not differ significantly.⁹⁰

ROLE OF STEROIDS

Use of corticosteroids in Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS) have been associated with adverse effects including delayed viral clearance and increase risk of mortality.⁹¹ Hence, earlier recommendation for use of corticosteroids in COVID-19 was only for patients with obstructive lung disease, adrenal insufficiency, or refractory septic shock. Emerging evidence however suggests potential benefit of corticosteroids in COVID-19.⁹²

Which Steroids to Use?

Recommendations

- Use of dexamethasone may be recommended as the steroid of choice and methylprednisolone and prednisolone can be substituted. (GRADE IIA)
- Use of hydrocortisone may be recommended in case of vasopressor refractory shock in severe COVID-19 infections. (GRADE IIIB)

Rationale

Glucocorticoids reduce inflammation by inhibition of genes regulating expression of most inflammatory cytokines. In COVID-19 infection, an anti-inflammatory effect is desired to decrease the host inflammatory response. Regimens of corticosteroids in COVID-19 infection have studied methylprednisolone^{93–97} and dexamethasone⁹² mostly. Previously in ARDS Villar et al.⁹⁸ had shown beneficial effect of dexamethasone. Theoretically, dexamethasone may be a better steroid because of long half-life, which allows it to be abruptly stopped and superior CNS penetration. Dexamethasone has little mineralocorticoid activity, which may decrease fluid retention and hypernatremia. Also, there is some evidence that mineralocorticoid stimulation might be harmful in ARDS.⁹⁹

Data from studies on methylprednisolone are also favoring its use, but there is no head-to-head comparison between the various steroids. Hydrocortisone may be considered when there is a concomitant vasopressor refractory shock in severe COVID-19 infections.¹⁰⁰

When to Start Corticosteroids?

Recommendations

- Use of steroids are recommended in the pulmonary phase of the illness, i.e., when requiring oxygen (GRADE IA)
- Use of steroids in early ARDS may be beneficial (GRADE IB).

Rationale

The ideal time to start corticosteroids would be at the onset of pulmonary involvement when patients start requiring oxygen.

Early steroids before the onset of hypoxia may not be beneficial.⁹¹ Steroids after onset of ARDS can also be advocated based on the previous ARDS studies; however, its role in the fibroproliferative phase is controversial.

From a cell biology perspective, infection with SARS-CoV2 can be divided into three phases that correspond to different clinical stages of the disease. The initial viral replication is in the nasal epithelium, where there is minimal innate immunity and patients are asymptomatic. Subsequently, in the stage 2, there is involvement of the conducting airways, and the patient is symptomatic with fever and cough. In the stage 3, the type II alveolar cells of the peripheral alveolar units are affected leading to dyspnea. It is in this stage that there is a vigorous response from the alveolar macrophages and dendritic cells to create a proinflammatory environment that can progress to ARDS and MODS due to immune mediated inflammation and cytokine storm.¹⁰¹ A clinical therapeutic staging proposal by Siddiqi et al.¹⁰² also divides COVID-19 infection into three stages, wherein, as the viral response phase wanes, the inflammatory phase worsens to produce a pulmonary phase, and a hyperinflammatory phase leading to ARDS and MODS. Early use of corticosteroids during the asymptomatic to mild illness has a potential fear of worsening viral shedding, as noted in the SARS epidemic. Ling et al.¹⁰³ showed that the duration of viral RNA for oropharyngeal swabs and feces was almost doubled in corticosteroids group than controls. The first major study to suggest benefit from steroid in COVID-19-induced ARDS was a retrospective study by Wu et al.⁹⁶ They included 201 participants and reported 62% reduction in risk of death with methylprednisolone.⁹⁶ The RECOVERY trial⁹² showed that dexamethasone treatment initiated in patients requiring oxygen conferred a mortality benefit.

The use of steroids in non-COVID ARDS is controversial. In a large RCT, mortality was significantly higher when steroid therapy was started 2 weeks after the onset of symptoms.¹⁰⁴ Perhaps steroids are more efficient at reversing the inflammatory process in early ARDS but ineffective once fibrosis is established. Extension of non-COVID ARDS data for treatment of ARDS due to Covid-19 has led to the use of steroids early in the course of illness.

Dose of Corticosteroids

Recommendations

Use of steroids at doses of ≤ 30 mg prednisone equivalent (PE) a day are beneficial in COVID-19 infection causing hypoxia (GRADE IA).

Rationale

Low-dose corticosteroids started early after the onset of hypoxemia or ARDS has shown both mortality benefit and outcome benefit in terms of faster clinical improvement, resolution of fever, improved oxygenation, faster radiological improvement, shorter length of stay, and less days on ventilation.

Dosage of corticosteroids are described with reference to PE to make comparison between steroid drugs easier (Table 1). The dose of steroids implies the glucocorticoid receptor saturation and hence its effects. Doses of corticosteroids have been classified as: low dose ≤ 7.5 mg/day PE, medium dose 7.5–30 mg/day, high dose 30–100 mg/day, very high dose >100 mg/day, and pulse therapy ≥ 250 mg/day PE.¹⁰⁵ In non-COVID ARDS, studies have shown beneficial effect with low-dose steroids.¹⁰⁶ All the studies in COVID-19 infection have used doses of ≤ 100 mg/day PE. The RECOVERY trial used ≤ 30 mg/day PE in the form of dexamethasone.

Table 1: Relative potencies and duration of action of therapeutic corticosteroids

Agent	Relative glucocorticoid potency	Relative mineralocorticoid potency	Duration of action
Hydrocortisone (cortisol)	1	1	Short
Prednisolone	4–5	0.25	Short
Methylprednisolone	5–6	0.25	Short
Dexamethasone	18	<0.01	Long
Fludrocortisone	10	125	Short

Duration of Therapy

Recommendations

Use of steroids should be limited to less than 10 days in COVID-19 infection. (GRADE IA)

Rationale

Corticosteroids at doses of ≤ 30 mg/day PE for a duration of less than 10 days seem to have a faster clinical improvement, with resolution of fever, improvement in oxygenation, faster radiological improvement, and mortality benefit.

In non-COVID ARDS, the Corticosteroid Guideline Task Force of the SCCM and the European Society of Intensive Care Medicine based its recommendations for corticosteroid treatment for a duration of at least 7 days. There was evidence for a reduction in the duration of MV and improved survival.¹⁰⁷ Wang et al.⁹³ used methylprednisolone for 5–7 days, the RECOVERY trial used dexamethasone for 10 days, while showing significant decrease in mortality from 28 to 23% in the oxygen/ventilation cohort.⁹² Duration of therapy did not exceed 10 days in any of the other studies reviewed.

CONCLUSION

By and large, the basic management of COVID-19 patients requiring ICU admission shall abide by the general and well-established principles of critical care. Despite the outburst of literature, most of which are observational or low-quality RCTs, there has been no path-breaking discovery. Likewise, it needs to be stressed that a “one-size-fits-all” approach has never benefitted the critically ill. The recommendations discussed therefore are based on a summary of available evidence and expert opinion in order to provide a standard framework for care.

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