

# Review of current clinical management guidelines for COVID-19 with special reference to India

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**SUMMARY** The healthcare sector has been overwhelmed by the global rise in the number of COVID-19 cases. The primary care physicians at the forefront of this pandemic are being provided with multiple guidelines (state, national, international). The aim of this review was to examine the existing guidelines for congruence and critically analyze them in light of current evidence. A discordance was noted between the national and state guidelines with respect to indication, duration and dosage of antivirals, steroids/immunomodulators, anticoagulation and convalescent plasma. The lack of concordance between various guidelines mandates the need for a unified national guideline that is regularly updated.

**Keywords** Coronavirus disease 19, hydroxychloroquine, remdesivir, dexamethasone, tocilizumab, convalescent plasma

## 1. Introduction

The current coronavirus disease 2019 (COVID-19) pandemic has put a challenging situation in front of an already overburdened health care system with an inadequate doctor to patient ratio. The primary care physicians are at the front line of this pandemic and are not only dealing with an increased number of patients but are also facing difficulties in the management of critically ill patients. To fill the current knowledge gap and guide the management plans of primary care physicians, several guidelines have been published all over the world. In a review by Kow *et al.*, inconsistencies and lack of consensus have been reported in recommendations given by several global bodies (1). The aim of this review was to compare and critically analyze the current existing guidelines for congruency.

## 2. Review strategy

The websites of Infectious Disease Society of America (2), World Health Organisation (3) and the Ministry of Health and Family Welfare of the central and state governments of India (4) were searched for the last available guidelines on COVID-19 as on 25.06.2020.

The guidelines from the following states were available- Kerala (5), Karnataka, Maharashtra and West Bengal (6). These guidelines were reviewed independently by three reviewers. The data extracted from these guidelines are compiled according to severity (mild, moderate, severe) and are discussed under the following headings (Table 1).

## 3. Anticoagulation

Concerns on the possible role of coagulopathy in moderate-to-severe COVID-19 were raised in the initial reports from China. Raised D-Dimer was found as one of the predictors of mortality (7). A descriptive study by Carsana *et al.*, on post-mortem lung specimens of COVID-19 cases revealed the presence of microthrombi (8). Similar observations were reported in other histopathological studies as well (9). Based on these observations, a possible role of anticoagulation in prophylactic or therapeutic dose in moderate to severe illness has been proposed. However, the evidence suggesting the benefit of anticoagulant therapy is still weak. A retrospective observational study by Tang *et al.* revealed no overall benefit of heparin on 28-day-mortality. However, when adjusted for D-Dimer values, heparin prophylaxis was associated with a

Table 1. Comparison of national and state management guidelines (as on 25.06.2020)

National/ state (DOP)	Anti-coagulation	Antivirals	Steroids/ immunomodulators	Antibiotic at presentation	Convalescent plasma
WHO (27.05)	No recommendation	Not recommended outside clinical trial	Not recommended	Not recommended	Not recommended outside clinical trial
ISDA (25.06)	No recommendation	Not recommended outside clinical trial	Not recommended	No recommendation	Not recommended outside clinical trial
India (13.06)	Not recommended	HCQ recommended if high risk features*	Not recommended	Not recommended	Not recommended
Maharashtra (22.06)	If high risk features <sup>#</sup> - LMWH OD	If high risk <sup>#</sup> -HCQ or Favipiravir	No recommendation	If high risk <sup>#</sup> - Cefixime or Amoxicillin-clavulanate	No recommendation
Karnataka (15.05)	LMWH OD (If d-dimer > 1000ng/ml or ground glass opacities)	Oseltamivir plus Azithromycin plus HCQ	Not recommended	Not recommended	Not recommended
Kerala (24.03)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
West Bengal	No recommendation	HCQ for high risk**	No recommendation	No recommendation	No recommendation
WHO (27.05)	No recommendation	Not recommended outside clinical trial	Moderate- Pneumonia with Spo2 90-94% on room air Tocilizumab not recommended outside clinical trial. Steroids not recommended	Not recommended	Not recommended outside clinical trial
ISDA (25.06)	No recommendation	Not recommended outside clinical trial	Tocilizumab not recommended outside clinical trial. Steroids use recommended (Dexa 6 mg daily or equivalent)	No recommendation	Not recommended outside clinical trial
India (13.06)	LMWH OD	HCQ and/or remdesivir for those on oxygen	If oxygen requirement progressively increasing MPS 0.5 – 1 mg/Kg for 3 days If not improving on steroids-Tocilizumab	Older people, immunocompromised patients, and children < 5 years of age	If oxygen requirement progressively increasing despite use of steroids
Maharashtra (22.06)	LMWH OD	HCQ or favipiravir or remdesivir If HCQ contraindicated – Ivermectin plus doxycycline	MPS 0.5-1 mg/Kg for 3 days followed by oral pred tapered over 5 days If MPS not available, Dexa 6 mg OD for 10 days If oxygen requirement progressively increasing-Tocilizumab	Ceftriaxone	1.IFP/F between 200-300 OR 2.Respiratory rate > 24/min, Sao2 < 93% on room air

Abbreviations: DOP, date of publication in date/month format; LMWH, low molecular weight heparin; HCQ, hydroxychloroquine; CQ, chloroquine; LPV/r, lopinavir/ritonavir; OD, once daily; BD, twice daily; Dexa, dexamethasone; Pred, prednisolone; MPS, methylprednisolone; 3GC, 3<sup>rd</sup> generation cephalosporins; AG, aminoglycosides; PT, piperacillin-tazobactam; NAC, N-acetyl cysteine; ULN, upper limit of normal; ARDS, acute respiratory distress syndrome. <sup>#</sup>High risk features, obesity, age > 60 yrs, DM, HTN, COPD/chronic lung disease, immunocompromised state, CKD. <sup>\*\*</sup>Patients with age > 60 years; chronic lung diseases; chronic liver disease; chronic kidney disease; hypertension; cardiovascular disease; cerebrovascular disease; diabetes; HIV; cancers; on immunosuppressive drugs.

Table 1. Comparison of national and state management guidelines (as on 25.06.2020) (continued)

National/ state (DOP)	Anti-coagulation	Antivirals	Steroids/ immunomodulators	Antibiotic at presentation	Convalescent plasma
Karnataka (15.05)	LMWH OD	Osetamivir plus Azithromycin plus HCQ	No recommendation	Recommended according to local antibiogram	Not recommended
Kerala (24.03)	No recommendation	HCQ plus Azithromycin plus Osetamivir	Systemic steroids and Tocilizumab not recommended.	Not recommended	Not recommended
West Bengal	LMWH OD (if d-dimer > 6ULN)	HCQ plus Osetamivir (when suspected)	Progressive deterioration of oxygenation, rapid worsening on imaging- MPS 1- 2mg/kg/day X 3-5 days. Tocilizumab - If IL-6 is more than 5 times of ULN	3GC / PT / Carbapenem +/- AG + Azithromycin	No recommendation on CP (Recommends therapeutic plasma exchange)
WHO (27.05)	LMWH OD	Antivirals not recommended outside clinical trial	Severe- pneumonia with Spo2 < 90% in room air AND Critical- ARDS, hypotension, worsening mental status, MODS Tocilizumab not recommended outside clinical trial. Steroids not recommended	Not recommended	Not recommended outside clinical trial
IDSA (25.06)	No recommendation	Remdesivir recommended	Tocilizumab not recommended outside clinical trial. Steroids use recommended (Dexa 6 mg daily or MPS 40 mg or Pred 32 mg)	No recommendation	Not recommended outside clinical trial
India (13.06)	LMWH BD	HCQ use is to be avoided	MPS 1-2 mg/Kg for 5-7 days. No recommendation on tocilizumab	Older people, immunocompromised patients, and children < 5 years of age	No recommendation
Maharashtra (22.06)	LMWH OD If D-Dimer is raised 3-fold, then BD	Remdesivir may be considered	MPS 0.5-1 mg/Kg for 5-7 days and duration can be extended based upon D-dimer. If MPS not available, Dexamethasone 6 mg OD for 10 days. Tocilizumab can be considered	Meropenem or as per local antibiotic policy	May be considered
Karnataka (15.05)	LMWH BD days	Osetamivir plus Azithromycin plus HCQs. Lopinavir/ritonavir on compassionate grounds. Remdesivir if patient progress to ARDS or septic shock.	Tocilizumab and/or steroids- if patient progresses to ARDS or septic shock Sepsivac recommended in septic shock	Ceftriaxone	Can be tried if patient progress to ARDS or septic shock
Kerala (24.03)	No recommendation	Osetamivir plus Azithromycin plus HCQ. LPV/r can be added if HCQ contraindicated or progressive disease	Steroids for septic shock, macrophage activation syndrome. For grade 3 or 4 cytokine release syndrome- Tocilizumab (or steroids)	Not recommended	No recommendation
West Bengal			Same as moderate		

Abbreviations: DOP, date of publication in date/month format; LMWH, low molecular weight heparin; HCQ, hydroxychloroquine; CQ, chloroquine; LPV/r, lopinavir/ritonavir; OD, once daily; BD, twice daily; Dexa, dexamethasone; Pred, prednisolone; MPS, methylprednisolone; 3GC, 3<sup>rd</sup> generation cephalosporins; AG, aminoglycosides; PT, piperacillin-tazobactam; NAAC, N-acetyl cysteine; ULN, upper limit of normal; ARDS, acute respiratory distress syndrome. <sup>#</sup>High risk features, obesity, age > 60 yrs, DM, HTN, COPD/chronic lung disease, immunocompromised state, CKD. <sup>\*\*</sup>Patients with age > 60 years; chronic lung diseases; chronic liver disease; chronic kidney disease; hypertension; cardiovascular disease; cerebrovascular disease; diabetes; HIV; cancers; on immunosuppressive drugs.

statistically significant reduction in 28-day-mortality (10). There is a need to assess the safety and efficacy of anticoagulation in large scale prospective studies (11). Based on these observations, a possible role of anticoagulation has been proposed in patients requiring oxygen therapy. While most guidelines recommend the use of anticoagulation in patients with moderate/severe disease, there are some differences with respect to indication for a higher prophylactic dose (Table 1). Although the evidence to use anticoagulants in mild disease is lacking, some of the state guidelines have recommended thromboprophylaxis in this category as well (Table 1).

#### 4. Antivirals

##### 4.1. Hydroxychloroquine (HCQ)

HCQ was touted as the wonder drug at the beginning of the pandemic based on small observational studies. Although a recent study from Michigan showed decreased mortality in the HCQ arm, several confounders were not taken into account (12). Based on the preliminary results of the RECOVERY and SOLIDARITY trial, the HCQ arm was discontinued in both the trials. In a randomized controlled trial, HCQ did not substantially reduce the severity of symptoms in patients with mild COVID-19 (13). Studies have also highlighted that adverse events such as arrhythmia are higher in the HCQ arm when compared to standard of care. Based on some observational studies, it was initially recommended to combine azithromycin with HCQ for a potential synergistic effect; however, it did not stand the test of time (14). This combination may be potentially harmful because of the increased risk of QT prolongation. An observational study published from India showed that although the use of HCQ prophylaxis, on the whole, was not associated with decreased infection rate, > 4 doses were associated with a decreased chance of infection (15). A randomized controlled trial showed that receipt of post-exposure prophylaxis with HCQ within four days of exposure did not decrease infection rates (16). Despite the lack of evidence, the national and state guidelines have retained HCQ with/without azithromycin as the preferred antiviral for clinical management in mild with/without risk factors and moderate illness. While the national guideline mentions that HCQ should be avoided in severe cases, other states continue to recommend and enforce the use of HCQ (Table 1).

##### 4.2. Favipiravir

Favipiravir is an RNA polymerase inhibitor that has been marketed in India for treatment of mild COVID-19. A very small study compared favipiravir versus lopinavir/ritonavir in patients with the non-severe disease and

showed faster viral and radiographic clearance in patients on favipiravir (17). Although this study mandates need for larger studies, the evidence to use outside the purview of a clinical trial is not there.

##### 4.3. Lopinavir/ritonavir

Lopinavir/ritonavir is a protease inhibitor that was initially tried for use in patients with SARS-COV-2. However, a randomized trial of 199 patients with severe COVID-19 showed that it did not help in improving the clinical outcomes and was also removed from the SOLIDARITY trial (18). Despite a lack of clear evidence, lopinavir/ritonavir has been recommended by some of the state guidelines.

##### 4.4. Remdesivir

Remdesivir is a novel nucleotide analogue that is recommended for use in patients with COVID-19 requiring oxygen. In a multinational, randomized, placebo-controlled trial of around a thousand patients with confirmed COVID-19 pneumonia, remdesivir resulted in a faster time to recovery. There was a trend towards lower 14-day mortality in patients in the remdesivir arm (19). In another study with a smaller sample size from China, time to clinical improvement and mortality was not statistically different with remdesivir compared with placebo. However, in patients who received remdesivir within ten days of symptom onset, there was a trend to shorter time to improvement and lower mortality rates (20). While the national and some state guidelines have incorporated remdesivir into their management algorithms, some states are yet to update theirs.

##### 4.5. Others

Despite very poor evidence that supports the use of agents like doxycycline and ivermectin, they have found a place in management algorithms and clinical practice. It is therefore important that management guidelines are updated frequently and are based on the most recent scientific evidence.

#### 5. Steroids

The controversy around the use of steroids was somewhat mitigated with results of RECOVERY trial. Dexamethasone (6 milligrams once daily for ten days) was found to be useful as it decreased 28-day mortality in patients requiring oxygen or invasive ventilation. It did not show any benefit in patients not requiring oxygen (21). No increase in the adverse effects or secondary infections was noted with dexamethasone. While most guidelines have adopted steroids in clinical management, there is wide variability in the formulation

(dexamethasone, methylprednisolone, hydrocortisone), dose (as high as 2 milligrams per kilograms of methylprednisolone) and duration of steroids, creating a lot of confusion.

## 6. Immunomodulators

### 6.1. Tocilizumab

Tocilizumab is an interleukin-6 receptor inhibitor that is now being used for the management of hyperinflammation in COVID. Pending randomized controlled trial, some observational studies have shown some benefit with tocilizumab. In a study of patients with severe COVID-19, tocilizumab was associated with a reduced risk of invasive mechanical ventilation or death (22). In another study of ventilated patients with COVID-19, tocilizumab was associated with lower mortality (23). Both the studies were associated with higher rates of superinfection. Although tocilizumab remains an investigational therapy, it has been recommended by some of the guidelines (Table 1).

### 6.2. Sepsivac

Sepsivac is a heat-killed *Mycobacterium W* that was developed as an immunomodulator for treating gram-negative sepsis. It has been proposed as a drug for COVID-19, but there are no published studies supporting this claim. However, it has been incorporated into the Karnataka state guidelines for patients of COVID-19 progressing into septic shock without much justification.

## 7. Antimicrobials

Although a possible coinfection in a patient with proven COVID-19 cannot be ruled out without doing microbiological tests, preliminary data indicates that coinfection with other pathogen is not very common in patients with COVID-19 (24). Blanket antibiotics in all patients with COVID-19 seems to be counterintuitive and goes against the principle of antimicrobial stewardship. Antibiotics should be used only in patients where bacterial infection is suspected (*e.g.* shock, new-onset consolidation after improvement, *etc.*). Empiric antibiotics, when initiated, should be promptly de-escalated based on microbiological cultures and/or negative procalcitonin reports. Despite India being a hub of antimicrobial resistance, several guidelines have recommended the use of prophylactic antibiotics in patients with moderate and severe disease (Table 1).

## 8. Convalescent plasma

Convalescent plasma has received much attention from the media and the public. It has been tried in the past

for the treatment of various infectious diseases where no definitive therapy was available. It acts by acting as a source of neutralizing antibodies and inhibiting the replication of the virus (25). Since no single effective antiviral therapy is available, it may be a potentially effective therapeutic option for COVID-19. Use of convalescent plasma in the current pandemic is guided by experience from previous influenza and coronavirus epidemics (26). There has been limited published data for its use in COVID-19, mostly in the form of case reports or case series (27-29). In a Cochrane analysis, no conclusion could be drawn on the overall efficacy of convalescent plasma (30). Pending the results of few ongoing large-scale trials, most guidelines support the use of convalescent plasma only as an investigational therapy.

## 9. Conclusion

Due to the sheer numbers of people affected by the illness, the systems are moulding themselves and evolving in order to rise to the challenges thrown at them by the pandemic. In such a situation, having state, national and international guidelines that do not agree on recommendations can cause undue confusion. There is a need to have a unifying national guideline with ongoing appraisal and recommendations that are updated on the basis of evolving data. Similar incongruencies should be identified and addressed at the level of other countries as well to aid the clinical practice of physicians globally.

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