Consensus Statement for Pharmacological Management of Coronavirus Disease 2019 (COVID-19): A Pragmatic Approach

Jain R, Javeri Y, Nasa P, Kashyap R, Khanna A, Tayar A, Bhaskar B, Jagiasi B, Juneja D, Lipman J, Ng J, Portila JLP, Zippe K, Popugaev KA, Hashmi M, Malbrain MLNG, Kirkman MA, Chan MTV, Turkoglu M, Mer M, Singer M, Harriss M, Rangappa P, Piacevoli Q, Mani RK, Mishra RC, Garg R, Yadav R, Bagdia S, Donovan S, Reza ST, Yeh TY, Videtta W.

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Abstract

Introduction: In the absence of high-quality evidence for Coronavirus disease-2019 (COVID-19), supportive care is advocated during this pandemic. We aim to develop a consensus statement from global experts for pharmacological management, based on the pathophysiology of COVID-19.

Material and Methods: We used a modified Delphi methodology in three steps: 1) Formulation of the steering committee and questionnaire; 2) Delphi methodology and selection of experts; 3) Final meeting of the steering committee and analysis, discussion, preparation, and presentation of captured data.

Results: 34 (73.9%) experts accepted the invitation for the study. We conducted two rounds of Delphi and consensus (>70% votes) was achieved on 11 out of 24 statements after the end of round two.

Conclusion: This global consensus suggests that “Anti-viral therapy should be administered in the early infection phase of COVID-19 followed by low dose steroid therapy in pulmonary phase. Prophylactic dose anticoagulation should be used in hospitalized, mild to moderate COVID-19 patients. We make no suggestions for the use of immune modulation therapy”.

Keywords
Consensus Statement, COVID-19, Modified Delphi Method, Pharmacologic Management
Introduction

Coronavirus disease 2019 (COVID-19) has taken the world by storm with more than 45 million cases and 1.2 million deaths (as of November 1, 2020) globally. Hospitalization and intensive care unit (ICU) admission rates vary widely, ranging from 15-30% and 4-12% respectively. Critically ill COVID-19 patients have unusually high mortality rates, leaving the clinician with a short window of opportunity to act [1,2]. Despite desperate efforts in search of effective pharmacotherapeutic agents, with over 3600 listed clinical trials underway according to ClinicalTrials.gov (last accessed October 15, 2020), the ongoing lack of concrete evidence has impelled authorities and professional bodies to predominantly recommend supportive care [3-5]. There is a paucity on a global consensus for a pragmatic pharmacological management protocol. We brought together global experts and developed a consensus view that would act as an interim guide for managing COVID-19 patients until ongoing research studies provide more definitive evidence.

Methodology

A modified Delphi methodology was used to generate a consensus statement involving a three-step approach.

Step-1: Formation of the steering committee, literature review, and preparation of focused questionnaire:

Seven critical care physicians who are currently managing of COVID-19 formed a steering committee.

Literature Search Strategy:

We searched various electronic databases including Google Scholar, PubMed, and Embase for literature published since the start of the pandemic and July 10, 2020, using keywords, such as “COVID-19”, “pharmacological management”, “consensus statement”, “modified Delphi methodology” “epidemiology”, “pathophysiology”, “anti-viral”, “anticoagulation”, “immune modulation” and “adjunctive therapies”. Non-English articles, animal studies, and articles for pharmacological management in the pediatric population were excluded from this search. Major contemporary guidelines by the World Health Organization (WHO), US Centers for disease control and prevention (CDC), European Society of Intensive Care Medicine (ESICM), Indian Council for Medical Research (ICMR), Society of Critical Care Medicine (SCCM) were also reviewed. A final pool of 209 relevant articles related to COVID-19, were created and stored in an online cloud forum to facilitate the generation of a focused questionnaire for the first round.

After discussions among the steering committee, a set of cornerstone therapies and their timing in relation to disease pathophysiology, and various biomarkers for starting and monitoring treatment response were identified. On review of the literature, the pathophysiological model of the disease includes three different phases of illness [6]. Each stage lasts for approximately five days and has a particular presentation related to virus and host interaction. Targeting these phases differently may lead to successful management of COVID-19 disease.

Based on these inputs, five sections of experimental therapies including anti-viral agents, anticoagulation, steroids, immunomodulators, antibiotics, and adjuvant therapies were identified a preliminary questionnaire for the Delphi survey was framed, discussed among the steering committee, and validated.

Step-2: Delphi methodology and selection of experts:

Delphi Methodology:

The Delphi methodology was selected for this project as it is a reliable instrument for developing consensus especially when evidence is lacking or limited [7]. The modified Delphi was used to involve experts within the field of intensive care and using their “collective intelligence” to develop a consensus pharmacological management. There are different rounds of iterative discussion among experts to achieve consensus. COVID-19 pandemic is an appropriate problem because of the lack of available effective treatment options. The statement which reached desired consensus during the first round were removed and the left-over statement circulated during the second round. We planned to have two to three
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![Diagram](image)

**Fig-1:** Illustration of modified Delphi methodology flow and 3 step wise approach.

Rounds of the survey (Fig-1).

A thorough search of experts involved in the management of severe to critical COVID-19 patients was undertaken by the steering committee members. 46 experts from all affected regions of the world were selected and invited to participate. After receiving confirmation of participation, these members were provided with the first round of the questionnaire. To avoid dominance, conflicts of interest, and group pressures, the expert panel was strictly anonymized throughout the process. Experts could communicate only with the steering committee. Consent for using their opinions for research and publication purposes was obtained concurrently. A panel of 30 experts participated in the first round, and 27 in the second round.

The first-round questionnaire had five sections with 23 questions, 13 of which were multiple choices, and ten with ordinal qualitative responses on a five-point Likert scale. This form was generated on the “Google Forms” platform. A free text space for comments was provided after each section to incorporate suggestions for the subsequent round questionnaire. Experts were asked to provide their opinion on these practice points within 72 hours. A brief report on the first-round result was generated, without disclosing the identity of the experts. This feedback report and a modified second-round questionnaire were sent to the experts in round two (Table-1). This questionnaire had 24 questions, 14 had multiple choices and 10 were Likert scale. In this round, identity capturing was mandatory to enable communication with experts. A free text space was provided after each question to explain the extreme position of an expert regarding any particular statement.

**Statistics**

Captured data from both rounds of questionnaires were analyzed to evaluate the consensus level. For statements with responses on an ordinal Likert scale, consensus was defined when >70% of participants agreed/strongly agreed or disagreed/strongly disagreed with a statement in round two. To calculate the central tendency of response and dispersion along

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the central value, a median and interquartile range (IQR) descriptor was used. A similar level of agreement has been considered appropriate in previous studies [7]. For multiple-choice type questions, a consensus for a particular option was considered to be generated when it reached >70% of the vote. In the absence of substantial evidence in a particular area, subjective opinions were likely hence unanimous consent was not expected for all recommendations. Therefore, a predefined threshold to mark consensus was established among the steering committee, with good consensus achieved if agreement was >70%, and strong if > 90%. For questions not reaching a consensus level, data is presented in ranking order of votes for each option.

| Table-1: Final Results on Consensus After Round Two |
|-----------------------------------------------|
| Clinical statements                           | Agreement | Disagreement | Median (IQR) |
| **Section-1: Early anti-viral therapy**       |           |              |              |
| 1: The best window of opportunity for anti-viral therapy is | | | |
| Early infection phase (0 to 5 days)-          | 22 (81.5%) | | |
| Pulmonary phase (5 to 15 days of symptoms onset) | 5 (18.5%) | | |
| 2: In which phase of COVID-19 does hydroxychloroquine (HCQ) therapy work best? | | | |
| Early infection phase (0 to 5 days)           | 13 (48.1%) | | |
| Unlikely to benefit                           | 14 (51.9%) | | |
| 3: Anti-viral therapy may be useful when applied early in COVID-19 and defer further progression. | 74.00% | 3.70% | 4(1.5) |
| 4: Which of the following anti-viral therapy/therapies would be most beneficial? | | | |
| Remdesivir                                     | 14 (51.9%) | | |
| Favipiravir                                     | 3 (11%) | | |
| HCQ+ azithromycin                              | 3 (11%) | | |
| None                                           | 5 (18.5%) | | |
| 5: Would benefit outweigh harm with the compassionate use of experimental anti-viral therapy. | 51.50% | 14.80% | 4(1.5) |
| **Section-2: Anticoagulation therapy**         |           |              |              |
| 6: Anticoagulation prophylaxis should be administered to mild to moderate cases of COVID-19 | 70.30% | 22.20% | 4(2) |
| 7: There is a need for clinical picture and laboratory parameters related guidance for aggressive anticoagulation | 100% | - | 5(0) |
| 8: What may be the best markers for starting anticoagulation therapy? | | | |
| Sepsis Induced Coagulopathy (SIC) score related criteria | 3 (11.5%) | | |
| D-dimer levels                                  | 17 (65.4%) | | |
| Worsening hypoxia levels                       | 3 (11.5) | | |
| Worsening organ dysfunction                    | 2 (7.7) | | |
| 9: The use of one of bleeding prediction scores for anticoagulation [used in venous thromboembolism (VTE) (e.g. VTE-BLEED, HAS-BLED, RIETE score)] improves safety. | 44.40% | 7.40% | 3(1) |
**10:** Which anticoagulation strategy would you prefer in your clinical practice?

| Strategy                      | Percentage |
|-------------------------------|------------|
| Unfractionated heparin (UFH)  | 11 (11.1%) |
| Low molecular weight heparin (LMWH) | **92 (92.6%)** |

**Section-3: Low dose steroid therapy**

**11:** The best window of opportunity for the use of steroids is?

| Phase                        | Percentage |
|-------------------------------|------------|
| Pulmonary phase (5 to 15 days of symptoms onset) | **74 (74.1%)** |
| Hyperinflammation phase (10 to 20 days of symptoms onset) | 25 (92.6%) |

**12:** The side effects commonly noticed in practice with the use of low dose steroid therapy in patients with COVID-19 are?

| Side effect                              | Percentage |
|------------------------------------------|------------|
| Secondary infections                      | 40 (40.7%) |
| Delayed viral clearance                   | 22 (22.2%) |
| Hyperglycemia/loss of glycemic control    | 70 (70.4%) |
| Leukocytosis                              | 14 (14.8%) |
| None                                      | 14 (14.8%) |

**13:** Which of the following steroid therapy you would prefer to use in moderate and severe COVID-19.

| Steroid Therapy | Percentage |
|-----------------|------------|
| Methylprednisolone | 25 (25.9%) |
| Hydrocortisone   | 11 (11.1%) |
| Dexamethasone    | 63 (63%)   |

**Section-4: Immune Modulation Therapy**

**17:** Which is the best window of opportunity for using immune modulation therapy?

| Phase                        | Percentage |
|-------------------------------|------------|
| Early infection phase (0 to 5 days) | 18 (18.5%) |
| Pulmonary phase (5 to 15 days of symptoms onset) | 44 (44.4%) |
| Hyperinflammation phase (10 to 20 days of symptoms onset) | 37 (37%) |

**18:** Which immune modulation therapies you find most effective?

| Therapy                  | Percentage |
|--------------------------|------------|
| HCQ based combination therapy | 7 (7%)     |
| Tocilizumab              | 48 (48.1%) |
| Convalescent plasma therapy | 11 (11%)  |
| Cytokine filtration therapy | 7 (7%)    |
| Steroid therapy          | 29 (29.6%) |
Results

**Expert panel selection and preparation of questionnaire:**

34 (73.9%) experts accepted the invitation and agreed to participate in the study. Thirty (88.2%) completed the first-round questionnaire: 18(60%) from Asia, 6(20%) from Europe, 2(6%) each from North and South America, and 1(3.3%) each from Africa and Oceania. For the second round, 27 (90%) of the 30 experts completed the survey.

**Results of Round 1 and 2:**

In the first round, only four of 13 multiple choice questions and only two of ten Likert scale statements received consensus (Table-2). In the second round, a modified questionnaire was prepared based on the responses and comments from the first round. Multiple-choice qualitative questions were now changed to a single best response system. Least responded options from the first round were eliminated. One new question was added after reviewing comments from the first round.
Among the 24 statements in the second round, eleven could reach the pre-determined level of consensus (two multiple-choice type questions, four agreements, and one strong disagreement on Likert scale questions) (Table-1). A strong consensus (>80%) was achieved for two qualitative questions and two strong agreements (Table-1).

### Table-2: Responses that achieved consensus votes in round one

| Section; Statement Number | Question Asked in Questionnaire | Response | Votes (%) |
|---------------------------|---------------------------------|----------|-----------|
| S·1; 4                    | Which of the following anti-viral therapy/therapies would be most beneficial? | Remdesivir | 22(73.3%) |
| S·2; 3                    | What may be the best markers for starting anticoagulation therapy? | D-dimer levels | 26(86.7%) |
| S·2; 5                    | Which anticoagulation strategy would you prefer in your clinical practice? | Low molecular weight heparin | 27(90%) |
| S·4; 3                    | Which laboratory parameter you prefer for immune modulation therapy use in your institute? | C-Reactive Protein | 21(72.4%) |
| S·2; 2                    | There is a need for clinical picture and laboratory parameters related guidance for aggressive anticoagulation. | Agreement | 28(93.4%) |
| S·5; 4                    | Antibiotics should be used only for patients with suspected co-infections/secondary infections. | Agreement | 26(86.7%) |

Consensus is considered achieved when >70% votes on Likert scale or multiple-choice question

### Anti-Viral Therapy:

On a question related to specific anti-viral agents, round one had consensus on Remdesivir (73.3% votes) but opinion was divided when experts were asked to rank the best anti-viral agent: Remdesivir (51.9%), no anti-viral therapy (18.5%), Favipiravir (11.1%), and a Hydroxychloroquine (HCQ)-Azithromycin combination (11.1%) (Table-1) and Table-2). The question relating to compassionate use of experimental therapy showed opinion remained widely divided (disagreement: 14.8%, neutral: 29.6%, agreement: 51.5 % [median:4 IQR:1.5]) (Table-1).

### Anticoagulation Therapy:

In the first round, two answers reached consensus, namely using D-Dimer levels as the biomarker of choice to guide anticoagulation therapy [26 votes (86.7%)] and low molecular weight heparin (LMWH) as the choice of anticoagulant [27 votes (90%)]. There was strong agreement on need for clinical and laboratory parameter-related guidance for aggressive anticoagulation therapy (100% agreement). In the second round, we were able to reach consensus on one new question, namely the anticoagulation prophylaxis in mild-to-moderate COVID-19 (70.3% agreement; median 4 IQR:2).

### Steroid Therapy:

In round one, there was no agreement but consensus (74.1% of votes) was achieved on the use of low dose steroids during the pulmonary phase (5-15 days from symptom onset) in round two. Adverse reactions with steroids were hyperglycemia and loss of glycemic control (70.4% votes), secondary infections (40.7% votes), and delayed viral clearance. Experts also agreed that steroid use may lead to oxygenation improvement (70.4%) and recommended inflammatory marker-guided use to enhance patient safety (70.4%). A new question regarding the choice of steroid received split results among Dexamethasone (63%) and Methylprednisolone (25.9%). CRP (33.3%), Ferritin (22.2%), and Procalcitonin (18.5%) were
Considered the biomarkers that can most help in guiding steroid therapy.

Immuno-Modulation Therapy:
Only CRP to guide immunomodulation therapy

| Table-3: Consensus statement for pharmacologic management of COVID-19: A pragmatic Approach |
|---------------------------------------------------------------|
| Section | Therapies             | Statement                                                                 |
|---------|------------------------|---------------------------------------------------------------------------|
| Section-1 | Early anti-viral therapy | 1. Anti-viral therapy should be given in early infection phase of COVID-19 (0-5 days of symptoms onset. |
|          |                        | 2. If applied early anti-viral therapy may defer further progression also. |
|          |                        | 3. Remdesivir followed by favipiravir seems to be the top two choices for anti-viral therapy. |
|          |                        | 4. There is almost equal divide among experts for utility of HCQ and Azithromycin and no conclusion can be made |
|          |                        | 5. Opinion is also split for compassionate use of anti-viral therapy. |
| Section-2 | Anti-coagulation therapy | 1. Prophylactic dose anticoagulation should be used in every hospitalized mild to moderate COVID-19 patient. |
|          |                        | 2. A clinical and lab parameter related guidance is always necessary for aggressive anticoagulation in COVID-19 |
|          |                        | 3. D-dimer levels followed by SIC score and worsening hypoxia levels are the most reliable guide for aggressive anticoagulation therapy. |
|          |                        | 4. Low molecular weight heparin therapy is the most used anticoagulation therapy worldwide. |
| Section-3 | Low dose steroid therapy | 1. Best window of opportunity for low dose steroid therapy is in pulmonary phase (5-15 days of symptoms onset) |
|          |                        | 2. Oxygenation improves with use of steroid therapy in COVID-19. |
|          |                        | 3. Inflammatory marker guided steroid therapy seems to enhance patient safety, and to guide steroid therapy CRP>Ferritin>Procalcitonin are the most preferred biomarkers. |
|          |                        | 4. Dexamethasone>solumedrol are the most preferred steroid therapy for COVID-19. |
|          |                        | 5. Hyperglycemia/loss of glycemic control> secondary infections> delayed viral clearance is the most frequently noticed side effects of steroid therapy. |
| Section-4 | Immune-modulation therapy | 1. There seems to be no consensus for use of immune modulation therapy, however tocilizumab is certainly most voted therapy among all, and IL-6 is the biomarker of choice for use of immune modulation therapies followed by CRP levels and ferritin. |
|          |                        | 2. There is split opinion for window of opportunity for immune modulation therapy, where pulmonary phase followed by hyper inflammation phase are the most voted phases for its use. |
| Section-5 | Antibiotics and adjuvant therapies | 3. There is no need for routine initial antibiotic therapy. |
|          |                        | 4. Antibiotics are needed for suspected co infections or super infections ONLY. |
|          |                        | 5. Most experts voted for use of antibiotics as per standard ICU protocol only. |
|          |                        | 6. There is no consensus for any adjuvant therapy however, almost half of the experts believe none needed followed by Vitamin C and zinc supplementations. |
**General Care:**

This section dealt with antibiotics and adjuvant therapies in critically ill COVID-19. There was disagreement (77-8%) on routine antibiotics use in COVID-19 and strong agreement (92-6%) votes for antibiotics use only in suspected co-infections or secondary infections. No consensus was reached for any specific initial antibiotic therapy, with most of the experts (40-7%) advocating routine ICU protocol-based antibiotics. With regard to adjuvant therapies, there was no consensus agreement in any round; on request from the experts for an additional choice ("none of the above") in the second round garnered 51-9% of votes (Table-1 and Table-2).

The study was concluded at round two, as the steering committee felt that opinion on unresolved questions remained too widely divided to generate consensus in the absence of new substantial evidence. The results of these questions are projected as received (Table-1).

**Discussion**

**Consensus Statement:**

The global consensus states that “anti-viral therapy should be given in the early infection phase of COVID-19 followed by low-dose steroid therapy in the pulmonary phase. Prophylactic dose anticoagulation should be used in hospitalized, mild-to-moderate COVID-19 patients. Consensus for the use of immune modulation therapy is low, with tocilizumab being the most voted agent.”

COVID-19 is a novel disease stimulating global medical collaboration. Many pathophysiological models and studies have been published but we still lack a specific treatment regimen. The respiratory system is commonly involved but increased thrombotic potential with both systemic and pulmonary thrombi, and multi-organ involvement, affecting predominantly kidneys, heart, and brain, are noted [1,2,6]. Simultaneously, an exaggerated pro-inflammatory response and types of cytokine release syndromes have been described in critically ill patients, especially in those with fatal outcomes [6,8,9]. It is common to observe elevated levels of D-Dimer, inflammatory biomarkers such as C-reactive protein (CRP), Ferritin, interleukin (IL)-6, IL-1and raised Neutrophil-lymphocyte ratio in severe COVID-19 disease [6,10]. Activation of self-perpetuating inflammatory and coagulation pathways, similar to but more virulent than more traditional sepsis phenotypes, likely plays a role in disease progression [6,10].

A Delphi methodology was adopted because of evidence-based on good controlled trials is expected to take time. The experience of experts who are actively involved in the clinical care of COVID-19 and also involved in research was valuable to develop consensus on available treatment options for COVID-19 and will guide the clinicians till evidence emerge from the trials.

**Early Anti-Viral Therapy:**

Anti-viral therapy should be administered in the early infection phase of COVID-19 (0-5 days of symptoms onset) to defer further progression. There was no consensus however could be achieved on best anti-viral agent. However, in round one experts were favoring Remdesivir. This may reflect the changing evidence during the survey and experts own experience with anti-viral drugs.

At present, no trials have showed direct efficacy in terms of mortality with any anti-viral agent. Results from the Adaptive COVID-19 Treatment Trial (ACTT) with more than 1000 patients enrolled, found patients who received Remdesivir had a significantly faster time to recovery (31%) as compared with those who received placebo (P < 0.001) [11]. Remdesivir group had a shorter time to recovery than those in the placebo group (median 11 days vs. 15 days, p<0.001, odds ratio 1.32, 95% confidence interval (CI) 1.02-1.55) however mortality benefit was non-significant in Remdesivir group [11]. The data on compassionate use of Remdesivir for COVID-19 patients reported 62% reduction in the risk of mortality as compared to standard treatment without Remdesivir. There was a significant reduction in mortality rate in patients treated with Remdesivir (7.6% versus 12.5% at day 14) (adjusted OR, 0.38; 95% CI, 0.22-0.68, P = 0.001) [12]. Recently, the preliminary results from WHO Solidarity trial on antiviral agents reported no overall...
reduction in mortality duration and initiation of invasive mechanical ventilation [13]. Favipiravir was compared with a Lopinavir/Ritonavir (historical controls) combination in an open label nonrandomized controlled study and found a shorter viral clearance time with Favipiravir (median (IQR) 4 (2.5–9) days versus 11 (8–13) days; p<0.001) but no mortality benefit [14]. Similarly, a Lopinavir/Ritonavir combination used in an RCT also failed to show statistically significant mortality improvements (HR 1.24; 95% CI, 0.90 to 1.72) [15].

A question related to the use of HCQ and Azithromycin gathered split votes. This divergence reflects current practice and the lack of a strong evidence base [16]. Small observational studies reported good viral clearance or improved outcomes, but had methodological and statistical limitations [17]. Larger randomized study (including RECOVERY trial) show no outcome benefit in terms of need for ventilation or mortality [16].

**Anticoagulation Therapy:**

Diffuse endothelium damage and hypercoagulability is a common finding in severe COVID-19 illness [2,6,9,18].

Study reported that patients requiring anticoagulation were more likely to require invasive mechanical ventilation (29.8% vs. 8.1%, p<0.001) and decreased mortality [19,20]. Experts agreed that anticoagulation prophylaxis has to be considered for mild-moderate COVID-19 disease. The role of higher doses of anticoagulation in selected COVID-19 patients is to be considered and expert agreed that can be guided by clinical and laboratory parameters. D-Dimer received consensus as the biomarker of choice to guide anticoagulation therapy (86.7%) and low molecular weight heparin (LMWH) as the choice of anticoagulant (90%). Similar strategic biomarker-based inclusion has been suggested by the American College of Cardiology [21].

**Steroid Therapy:**

This section was the most debated section among experts and the steering committee with maximum inconsistency between rounds. A prominent "bandwagon effect" was obvious from second-round responses [7,22].

In the first round, no consensus could be reached for any of the five questions, but as the preliminary results of the Dexamethasone arm of the RECOVERY trial were released [22], a significant shift in opinion was evident. Consensus (74.1%) was achieved on the use of low dose steroids during the pulmonary phase (5-15 days from symptom onset) however this vote occurred before the publication of the pre-print showing benefit only in those starting treatments after seven days of symptom onset.

Preliminary results of the RECOVERY trial suggest that dexamethasone 6 mg once daily for up to ten days reduces death by a third in mechanically ventilated patients and by a fifth in patients on oxygen support alone, but had no effect in patients not receiving any respiratory support [22]. Recently published meta-analysis by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group suggests that corticosteroid use in Critically sick COVID-19 patients was significantly associated with lower 28-day all-cause mortality [23].

**Immunomodulation Therapy:**

CRP was the only biomarker target which expert agreed, can guide immunomodulation therapy. There was no support for immunomodulator therapy, albeit a minority view (48.1%), for IL-6 inhibitor, tocilizumab and its use in either the pulmonary (44.4%) or hyper inflammation (37%) phase. The majority (63%) considered that IL-6 levels, followed by CRP levels (44-4%) would be useful in identifying the hyperinflammatory stage. The recently published studies RCT and largest observational studies had conflicting results on the use of Tocilizumab in COVID-19 [24-27]. This may reflect the overall role of tocilizumab in the management of severe COVID-19 is very doubtful and to be considered only in a very small subgroup of patients [28].

**General Care:**

With regard to adjuvant therapies, there was no consensus agreement in any round. This underlines the view that adjuvant therapies need to prove their...
worth as guided by the dictum "primum non nocere".

**Strengths:**

The Delphi method has well-recognized benefits and pitfalls [7]. It helps find a set of commonly agreed-upon statements without bringing experts physically together. It allowed us to combine quantitative and qualitative approaches and ensure good quality feedback from experts for Delphi rounds. This was imperative in an emerging scenario like the COVID-19 pandemic where the current evidence-based on pathophysiology is limited. The strength of the study is the multinational expert panel. We attempted to include experts from across the globe, especially working in countries actively reeling under the pandemic. The timelines were maintained despite their busy schedule. Anonymity was preserved to avoid dominance, conflict of interest, and group pressures that are potentially inherent biases when using the Delphi methodology. We were thus able to describe qualitative best practice points from the compiled opinions of worldwide experts. This format will help clinician in taking a pragmatic approach towards the management of COVID-19 pandemic as the treatment can be chosen based on the phase of disease till further evidence is available.

**Limitations**

This study has several limitations:

1. Identity capture was not compulsory in the first round, so we are unable to report any inconsistency and heterogeneity in individual responses.
2. As the study was time-sensitive it was concluded in two rounds and stability of responses was not compared.
3. In some sections, a "significant bandwagon effect" was seen. For example, the steroid questions in the second-round had many more positive responses than in the first round. A contrast effect cannot be ruled out in the second round as the "immune-modulatory therapies" section was followed by "low dose steroid therapy."
4. The distribution of experts is skewed to Asia because of the narrow timeframe for participation and completion of survey and inclusion of experts. There was the unavailability of few experts who were invited based on the criteria decided by steering committee because of the unprecedented situation of the COVID-19 pandemic. There were some additional dropouts of experts in round two. We tried to minimize this by actively engaging the experts and minimized the time frame of the process (three weeks). A summary of the results of the first round was included with individualized covering letters in the second round to raise their interest.
5. Other factors that may have affected consensus were the uneven responses of experts, non-availability of specific treatment options in some countries, and variable government health policies.
6. Lastly, this is only a contemporary best qualitative opinion of experts and may change with evolving evidence; it also needs quantitative inputs from well-structured intervention studies.

**Conclusions**

Global Experts gave consensus on use of anti-viral therapy in the early infection phase of COVID-19 followed by low-dose steroid therapy in the pulmonary phase. Prophylactic dose anticoagulation should be used in mild-to-moderate COVID-19. This document can also be used to generate hypotheses for future trials and protocol based therapy till further evidence evolve.

**Contributors**

RJ, YJ conceived the idea for this paper. RJ and PN wrote and prepared original draft with figures tables and panel. RJ, YJ, PN, RK prepared Delphi questionnaire, coordinated and conducted Delphi process and critically evaluated the prepared draft, and made substantial editorial contributions to the final document. All the co-authors (experts) participated in Delphi process, reviewed, and made substantial critical comments for preparation of the final draft of the document. All authors approved the final version for submission.
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Declaration of Interest

MLNGM is a member of the medical advisory Board of Pulsion Medical Systems (now fully integrated into Getinge, Solna, Sweden) and Serreno Medical (Tel Aviv, Israel), consults for Baxter, Maltron, ConvaTec, Acelity, Spiegelberg, and Holtech Medical.

All other authors declare that they have no competing interests in relation to the content published in this manuscript.

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