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

Jain R[1], Javeri Y[2], Nasa P[3*], Kashyap R[4], Khanna AK[5], Tayar AA[6], Bhaskar B[7], Jagiasi BG[8], Juneja D[9], Lipman J[10,11], Ng J[12], Portilla JLP[13], Zirpe K[14], Popugaev KA[15], Hashmi M[16], Malbrain MLNG[17,18], Kirkman MA[19], Chan MTV[20], Turkoglu M[21], Mer M[22], Singer M[23], Harriss M[24], Rangappa P[25], Piacevoli Q[26,27,28,29,30], Mani RK[31], Mishra RC[32], Garg R[33], Yadav R[34], Bagdia S[35], Donovan S[36], Reza ST[37], Yeh TY[38,39,40,41], Videtta W[42]

[1]*Consultant Critical Care, Nayati Healthcare, Mathura, Uttar Pradesh, India*

[2]*Head CCM and Emergency Medicine, Regency Super Specialty Hospital, Lucknow, India*

[3]*Specialist and Head Critical Care Medicine, Head -Prevention and Control of Infection, NMC Specialty Hospital, Al Nahda 2, Dubai, UAE*

[4]*Assistant Professor of Anesthesiology, Department Of Anesthesia and Critical Care Medicine, Mayo Clinic, USA*

[5]*Associate Professor, Section Head for Research, Department of Anesthesiology, Wake Forest University School of Medicine, Cleveland, OH, USA*

[6]*Consultant, Head of ICU at Security Forces Hospital, Dammam, Saudi Arabia*

[7]*Director of the Intensive Care Services, Chair Intensive Care Committee, American Hospital Dubai, UAE*

[8]*Head of Critical Care Department, Reliance Hospital, Navi Mumbai, India*

[9]*Associate Director, Institute of Critical Care Medicine, Max Super Specialty Hospital, Saket New Delhi, India*

[10]*The University of Queensland, Australia*

[11]*Scientific Consultant, Nimes University Hospital, University of Montpellier, France*

[12]*Department of Anaesthesiology, Intensive Care and Pain Medicine, Tan Tock Seng Hospital, Singapore*

[13]*Medicina Intensiva, Coordinador Neuro UCIN, Jefe del Servicio de Cuidados Intermedios, Hospital Nacional Almanzor Aguinaga Asenjo, EsSalud, Perú*

[14]*Prof and Head of Department Neuro Intensive Care Unit, Ruby Hall Clinic, Grant medical Foundation, Pune, India*

[15]*Deputy Director, Head of Regional Vascular Centre, Sklifosovsky Research Institute of Emergency Medicine, Bolshaya Sukharevskaya Square, Russia*

[16]*Professor and Head of Department, Critical Care Medicine, Ziauddin University, Karachi, Pakistan*

[17]*Department Intensive Care Medicine, University Hospital Brussel (UZB), Brussels, Belgium*

[18]*Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel (VUB), Brussels, Belgium*

[19]*Atkinson Morley Regional Neurosciences Centre, St George's Hospital, London, UK*

[20]*Professor, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China*

[21]*Associate Professor, Department of Internal Medicine, Medical İntensive Care Unit, Gazi University Faculty of Medicine, Turkey*

[22]*Clinical Head Adult Multidisciplinary Intensive Care Unit, Department of Medicine, Divisions of Critical Care and Pulmonology, University of the Witwatersrand, Johannesburg, South Africa*

[23]*Professor of Intensive Care Medicine, Director, Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, London, UK*

[24]*Pulmonologist, Medcare Hospital Sharjah and Dubai London Clinic and Hospital, Dubai, UAE*

[25]*Consultant Intensive Care Physician, Columbia Asia Hospitals, Bangalore, India*

[26]*Professor and Head Department of Anaesthesia and Intensive Care, Rome, Italy*

[27]*Member of the Board of the FEDERATION EUROPEEN des MEDICINE, Brussels, Belgium*

[28]*P. Member of the World Commission on Safety and Quality WFSA, WHO*

[29]*Visiting Professor, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia, Greece*

[30]*Visiting Professor, Campus Bio Medico University, Rome, Italy*

[31]*Director, Strategy and COVID-19 Management, Yashoda Super Specialty Hospital, Kaushambi, Ghaziabad, UP, India*

[32]*Honorary Consultant Intensivist & Internist, Ahmedabad, India*

[33]*Additional Professor of Anaesthesiology, Critical Care, Pain and Palliative Medicine, All India Institute of Medical Sciences, New Delhi, India*

[34]*Senior Consultant Critical Care Medicine, Nayati Healthcare, Mathura, UP, India*

[35]*Pulmonologist, NMC Royal Hospital DIP, Dubai, UAE*

Original Article

[36]*Clinical Professor of Medicine, UCLA School of Medicine, USA*

[37]*Assistant Professor, Critical Care Medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh*

[38]*Clinical Associate Professor, Attending Anesthesiologist and Intensivist, Department of Anesthesiology, National Taiwan University Hospital (NTUH), Taiwan*

[39]*Chair, Scientific Committee, Taiwan Society of Emergency & Critical Care Medicine (TSECCM), Taiwan*

[40]*Vice-Chair, Research Committee and International Affairs, TSECCM, Taiwan*

[41]*Secretary General, Taiwan Society of Critical Care Medicine (TSCCM), Taiwan*

[42]*Hospital Posadas, Buenos Aires, Argentina*

Corresponding Author: **Prashant Nasa, MD** [ORCID ID]

Address: Specialist and Head Critical Care Medicine, Head -Prevention and Control of Infection, NMC Specialty Hospital, Al Nahda 2, Dubai, UAE.

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".

Original Article

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
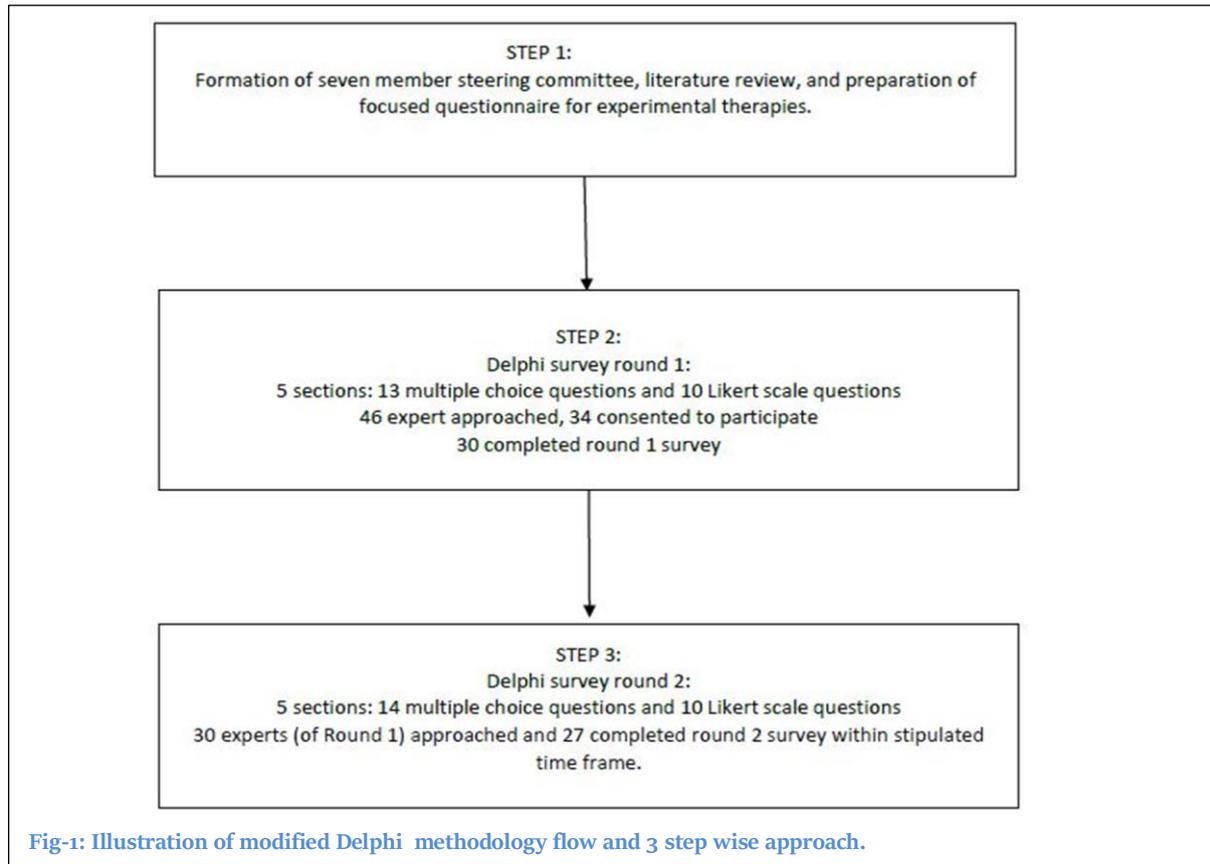
Original Article

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

Original Article

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(11·1%)		
HCQ+ azithromycin	3(11·1%)		
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)

Original Article

10: Which anticoagulation strategy would you prefer in your clinical practice?			
Unfractionated heparin (UFH)	3(11·1%)		
Low molecular weight heparin (LMWH)	**25(92·6%)**		
Section-3: Low dose steroid therapy			
11: The best window of opportunity for the use of steroids is?			
Pulmonary phase (5 to 15 days of symptoms onset)	**20(74·1%)**		
Hyperinflammation phase (10 to 20 days of symptoms onset)	7(25·9%)		
12: The side effects commonly noticed in practice with the use of low dose steroid therapy in patients with COVID-19 are?			
Secondary infections	11(40·7%)		
Delayed viral clearance	6(22·2%)		
Hyperglycemia/loss of glycemic control	**19(70·4%)**		
Leukocytosis	4(14·8%)		
None	4(14·8%)		
13: Which of the following steroid therapy you would prefer to use in moderate and severe COVID-19.			
Methylprednisolone:	7(25·9%)		
Hydrocortisone	3(11·1%)		
Dexamethasone	17(63%)		
14: Oxygenation improves with the early use of steroid use.	**70.40%**	7.40%	4(0.5)
15: Inflammatory marker guided use of steroids can enhance patient safety	**70.40%**	3.70%	4(0.5)
16: Which of the following inflammatory biomarkers would you suggest guiding steroid therapy?			
C- Reactive Protein (CRP)?	9(33·3)		
Ferritin	6(22·2%)		
Interleukin- 6 (IL-6)	4(14·8%)		
Procalcitonin	5(18·5%)		
None	3(11·1%)		
Section-4: Immune Modulation Therapy			
17: Which is the best window of opportunity for using immune modulation therapy?			
Early infection phase (0 to 5 days)	5(18·5%)		
Pulmonary phase (5 to 15 days of symptoms onset)	12(44·4%)		
Hyperinflammation phase (10 to 20 days of symptoms onset	10(37%)		
18: Which immune modulation therapies you find most effective?			
HCQ based combination therapy	1(3·7%)		
Tocilizumab	13(48·1%)		
Convalescent plasma therapy	3(11·1%)		
Cytokine filtration therapy	2(7·4%)		
Steroid therapy	8(29·6%)		

Original Article

19: Which laboratory parameter you prefer for immune modulation therapy use in your institute?			
C- Reactive Protein (CRP)	12(44·4%)		
Ferritin	9(33·3%)		
Interleukin- 6 (IL-6)	17 (63%)		
D-Dimer	4(14·8%)		
Procalcitonin	4(14·8%)		
None	2(7·4%)		
Section-5: Antibiotics and Adjuvant Therapies			
20: Routine initial antibiotic therapy is needed for COVID-19.	14.80%	77.80%	1(1)
21: Initial Antibiotics therapy should be guided based on procalcitonin based algorithms.	55.60%	18.50%	4(1)
22: Which initial antimicrobial agent you prefer in practice for COVID-19.			
Azithromycin	5(18·5%)		
B-lactam antibiotics	7(25·9%)		
As per routine ICU protocol	11(40·7%)		
No routine antibiotics used	4(14·8%)		
23: Antibiotics should be used only for patients with suspected co-infections/ secondary infections.	92.60%	3.70%	5(0)
24: Which adjuvant therapies do you find most effective for COVID-19?			
Vitamin C	8(29·6%)		
Vitamin C and thiamine combination	5(18·5%)		
Vitamin D supplementation	4(14·8%)		
Zinc supplementation	6(22·2%)		
None	14 (51·9%		
* Highlighted statements in grey have approached consensus.			
COVID-19 coronavirus disease 2019, CRP- C-reactive protein, HCQ- hydroxychloroquine, IL-Interleukin, ICU-intensive care unit SIC- Sepsis Induced Coagulopathy			

Results

Expert panel selection and preparation of questionnaire:

34 (73·9%) experts accepted the invitation and agreed to participation 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.

Original Article

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**).

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%)

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

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

Original Article

considered the biomarkers that can most help in guiding steroid therapy.

reached consensus (72·4%) in the first round. In the second round, none of the three statements could reach consensus (**Table-3**).

Immuno-Modulation Therapy:

Only CRP to guide immunomodulation therapy

Section	Therapies	Statement
Table-3: Consensus statement for pharmacologic management of COVID-19: A pragmatic Approach		
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.

Original Article

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) 1·12-1·55) 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

Original Article

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

Original Article

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 the 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.

Original Article

Acknowledgement

Declaration of Interest

MLNGM is a member of the medical advisory Board of Pulsion Medical Systems (now fully integrated into Getinge, Solna, Sweden) and Serenno 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.

References

[1] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-42. [**PMID**: 32091533]

[2] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020 May 22;369:m1966. [**PMID**: 32444366]

[3] ClinicalTrials.gov. NIH U.S. National library of medicine. [Cited 2020 Oct 30]. Available from: https://clinicaltrials.gov/ct2/results?cond=COVID19&term=&cntry=&state=&city=&dist

[4] National Institutes of Health (NIH). COVID-19 treatment guidelines. NIH; 2020 [updated 2020 Nov 3; cited 2020 Oct 30]. Available from: https://www.covid19treatmentguidelines.nih.gov/introduction

[5] Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020 May;46(5):854-87. [**PMID**: 32222812]

[6] Romagnoli S, Peris A, De Gaudio AR, Geppetti P. SARS-CoV-2 and COVID-19: From the Bench to the Bedside. Physiol Rev. 2020 Oct 1;100(4):1455-66. [**PMID**: 32496872]

[7] Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, Wales PW. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014 Apr;67(4):401-409. [**PMID**: 24581294]

[8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. [**PMID**: 31986264]

[9] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. [**PMID**: 32171076]

[10] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Jul 1;180(7):934-43. [**PMID**: 32167524]

[11] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY,

Original Article

Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Nov 5;383(19):1813-26. [**PMID**: 32445440]

[12] Gilead. Gilead presents additional data on investigational antiviral remdesivir for the treatment of COVID-19. Gilead Sciences, Inc.; 2020 Jul 10 [cited 2020 Oct 15]. Available from: https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19

[13] WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2020 Dec 2. [**PMID**: 33264556]

[14] Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C, Li X, Peng L, Huang D, Zhang J, Zhang S, Wang F, Liu J, Chen L, Chen S, Wang Z, Zhang Z, Cao R, Zhong W, Liu Y, Liu L. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020 Oct;6(10):1192-98. [**PMID**: 32346491]

[15] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 May 7;382(19):1787-99. [**PMID**: 32187464]

[16] RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse T, Felton T, Williams J, Faccenda J, Underwood J, Baillie JK, Chappell LC, Faust SN, Jaki T, Jeffery K, Lim WS, Montgomery A, Rowan K, Tarning J, Watson JA, White NJ, Juszczak E, Haynes R, Landray MJ. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Nov 19;383(21):2030-40. [**PMID**: 33031652]

[17] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Jul;56(1):105949. [**PMID**: 32205204]

[18] Fogarty H, Townsend L, Ni Cheallaigh C, Bergin C, Martin-Loeches I, Browne P, Bacon CL, Gaule R, Gillett A, Byrne M, Ryan K, O'Connell N, O'Sullivan JM, Conlon N, O'Donnell JS. COVID19 coagulopathy in Caucasian patients. Br J Haematol. 2020 Jun;189(6):1044-49. [**PMID**: 32330308]

[19] Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, Charney AW, Narula J, Fayad ZA, Bagiella E, Zhao S, Nadkarni GN. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020 Jul 7;76(1):122-24. [**PMID**: 32387623]

[20] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019

Original Article

patients with coagulopathy. J Thromb Haemost. 2020 May;18(5):1094-99. [**PMID**: 32220112]

[21] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quéré I,Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Jun 16;75(23):2950-73. [**PMID**: 32311448]

[22] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020 Jul 17:NEJMoa2021436. [**PMID**: 32678530]

[23] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin PF, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, Meziani F, Møller MH, Perner A, Petersen MW, Savovic J, Tomazini B, Veiga VC, Webb S, Marshall JC. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Oct 6;324(13):1330-41. [**PMID**: 32876694]

[24] Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P; CORIMUNO-19 Collaborative Group. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2020 Oct 20:e206820. [**PMID**: 33080017]

[25] Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turrà C, Ballerini PF, Sciascia R, Zammarchi L, Para O, Scotton PG, Inojosa WO, Ravagnani V, Salerno ND, Sainaghi PP, Brignone A, Codeluppi M, Teopompi E, Milesi M, Bertomoro P, Claudio N, Salio M, Falcone M, Cenderello G, Donghi L, Del Bono V, Colombelli PL, Angheben A, Passaro A, Secondo G, Pascale R, Piazza I, Facciolongo N, Costantini M; RCT-TCZ-COVID-19 Study Group. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2020 Oct 20:e206615. [**PMID**: 33080005]

[26] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Dec 10;383(24):2333-44. [**PMID**: 33085857]

[27] Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava A, Zhou Y, Finkel D, Green A, Mallappallil M, Faugno AJ, Zhang J, Velez JCQ, Shaefi S, Parikh CR, Charytan DM, Athavale AM, Friedman AN, Redfern RE, Short SAP, Correa S, Pokharel KK, Admon AJ, Donnelly JP, Gershengorn HB, Douin DJ, Semler MW, Hernán MA, Leaf DE; STOP-COVID Investigators. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med. 2020 Oct 20:e206252. [**PMID**: 33080002]

Original Article

[28] Parr JB. Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia. JAMA Intern Med. 2020 Oct 20. [**PMID**: 33079980]