V.I.T.A.M. in COVID 19: A Systematic Approach to a Global Pandemic

Siva Naga S. Yarrarapu, MBBS1, Pankaj Bansal, MD2, David Abia-Trujillo, MD3, Austin Cusick, DO4, Megan Melody, MD MS1, Varun Moktan, MD1, Andrea Rivero, DO1, Tara J. Brigham, AHIP5, Claudia Libertin, MD6, Lisa Brumble, MD6, J O’brein Jennifer, MD7, Augustine Lee, MD8, Torp Klaus, MD9, Christian Santos, APRN10, Candido Rivera, MD11, Jason Siegel, MD10, Pramod Guru, MBBS, MD10, Pablo Moreno Franco, MD12 and Devang Sanghavi, MBBS, MD10

1Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 2Mayo Clinic Health System. 1400 Bellinger Street, Eau Claire, WI – 54701. 34500 San Pablo Rd S, Jacksonville, FL 32224. 4535 Olentangy River Rd. Columbus, OH 43214. 5Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 6Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 7Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 8Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 9Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 10Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 11Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224. 12Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224.

ABSTRACT

INTRODUCTION: In the unprecedented era of COVID-19, ongoing research and evolution of evidence has led to ever-changing guidelines for clinical monitoring and therapeutic options. Formulating treatment protocols requires the understanding and application of the evolving research.

OBJECTIVE: The primary objective of this study is to present a systematic evidence-based approach to synthesize the necessary data in order to optimize the management of COVID-19.

METHODS: At Mayo Clinic Florida, we developed a multidisciplinary centralized COVID Treatment Review Panel (TRP) of expert pulmonologists, intensivists, infectious disease specialists, anesthesiologists, hematologists, rheumatologists, and hospitalists that in real-time reviews the latest evidence in peer-reviewed journals, the available clinical trials, and help guide the rapid application of therapeutics or interventions to the patient and the bedside provider.

RESULTS/CONCLUSIONS: The multi-disciplinary team approach of synthesizing clinical data and coordinating care is effective in responding to rapidly evolving and changing evidence. Systematic data collection and evidence-based treatment algorithms enable physicians to rapidly translate the current literature to clinical practice, and improve care and outcomes of patients.

KEYWORDS: COVID-19, inflammatory, thrombotic, oxygenation, microbiological

Introduction:

Coronavirus Disease 2019 (COVID-19), a pandemic with over 203 million cases diagnosed worldwide as of August ninth, 2021, has left a lasting impact on the delivery of healthcare. The hypoxemic respiratory failure associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is associated with high morbidity and mortality, and more than 4 million deaths have been reported worldwide due to COVID-19. The exact pathophysiology of this syndrome is not completely understood and extends beyond the direct virus-mediated injury of the lung parenchyma. Multiple pathways including but not limited to direct injury to the lung parenchyma by microbiological organism, overwhelming inflammation and cytokine release syndrome (CRS), hyperemia, atelectasis, and thrombotic events have been implicated in impairing the oxygenation and ventilation at the alveolar level.

The rapid evolution of this multifaceted disease has led to an influx of literature regarding disease processes and potential interventions and treatment modalities including formally tested options, off-label drugs, and ongoing trials. It seems as if we are suffering from cognitive overload of muddy data, social media, personal testimonials, preprints and publications of numerous poor-quality research trials leading to an “Infodemic” of therapeutic options on how to deal with the pandemic of COVID-19 affecting our patients. In this era where the clinicians are being overworked in the COVID unit, it is often difficult to sift through the immense literature and determine the clinical significance of new data.
The Mayo Clinic Florida (MCF) created a multidisciplinary COVID-19 Treatment Review Panel (TRP) consisting of various physicians from different medical specialties to decipher the plethora of information. Based on the guidance of the TRP we have created a method to summarize the most up-to-date therapeutic options and the daily variables that are assessed and monitored in the setting of these treatments. We have found that this presentation of data is easily updated daily and has allowed our clinicians to comprehensively assess the patient’s disease status and ensure optimal application of current treatment modalities. In this commentary, we share the systematic approach developed by our COVID TRP, its application and positive impact on the management of patients infected with COVID-19.

Methods:
Treatment review panel
The Mayo Clinic Florida (MCF) COVID-19 Treatment Review Panel (TRP) is a multidisciplinary team consisting of pulmonologists, intensivists, infectious disease specialists, anesthesiologists, hematologists, rheumatologists, pharmacists, research coordinators and hospitalists. The role of the panel is to continually review the available literature and open trials to create and endorse treatment algorithms (Figure 1, Figure 2) for use by MCF hospitalist and intensive care unit (ICU) teams.

All members of the TRP meet three times a week to discuss the recent research and literature, and to form a consensus about any desired changes to the treatment algorithms and research protocols if felt appropriate by the group. The TRP Chair meets with the clinical team to discuss and guide the management of specific patients such as decisions about specific antimicrobial and immunosuppressive therapies. It aims to assess the potential for research protocol following the criteria for individual drug research studies, while restricting each individual patient to a single research study, and while maintaining the standard of care.

Search strategies
TRP clinicians enlisted the help of a librarian (TJB) to send regular literature updates on relevant COVID-19 therapeutic strategies. COVID-19 therapeutic articles with citation counts were identified by the librarian developing and running searches in the Scopus (Elsevier) database. Although two other well-known platforms, Google Scholar (Alphabet) and Web of Science (Clarivate Analytics) also provide article-level metrics, Scopus was chosen due to its advanced searching capabilities and ease of exporting citation metrics, as well as its wide inclusion of citations for the field of Health & Medical Sciences. Filters to identify English-language studies and to remove articles older than 1 January 2020 were included. The search strategies were created using a combination of COVID-19 keywords and these 11 therapies: Hydroxychloroquine, Remdesivir, Dexamethasone, Heparin,
Azithromycin, Tocilizumab, LPV/RTV, Zinc, Convalescent Plasma, Nitric Oxide, Colchicine. The full search strategies are available here: https://osf.io/qzy6u.

Evidence collection

The literature updates were sent by email to the TRP team and consisted of two components:

(a) a link to the Treatment section of NLM LitCovid website11 (https://www.ncbi.nlm.nih.gov/research/corona-virus/docsum?filters=topics.Treatment)
(b) updated, evidence synthesis documents from the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery’s COVID-19 Rapid and Systematic Reviews Repository.12

Review of evidence

Adapted from Sackett DL,13 the quality of evidence was assessed and classified into various levels, and are as follows:

- Levels I (large RCTs with clear cut results)
- Level II (small RCTs with unclear results)
- Level III (cohort and case-control studies)
- Level IV (historical cohort or case-control studies)
- Level V (case series or studies with no controls).

The recommendations for the clinical management of the patients were devised from the American Society of Plastic Surgeons Evidence-Based Clinical Practice Guideline Methodology. Key factors involved in the grading of the recommendations include level of evidence, patient preferences, and...
benefits versus harm evaluation. (Available at: https://www.plasticsurgery.org/documents/medical-professionals/quality-resources/ASPS-Evidence%E2%80%90Based-Clinical-Practice-Guideline-Methodology.pdf)

- Grades A (strong recommendation)
- Grade B (moderate recommendation)
- Grade C (weak recommendation)
- Grade D (optional recommendation)

**Updating evidence**

Evidence-based algorithms have been formulated including protocols for inpatient management of refractory hypoxemia and use of anticoagulation in COVID-19. (Figure 3, Figure 4) A table organizing the pertinent clinical information and current therapeutic interventions in an individual patient has been formulated to be used and updated on a daily basis. (Table 1) The treatment algorithms are updated periodically based on the inputs of the Treatment Review Panels team member after reviewing the available research articles and supporting data. The NIH, CDC and IDSA guidelines and recommendations are incorporated into our practice.

**Results and Discussion:**

The TRP in collaboration with the MCF Department of Critical Care Medicine (CCM) and other experts has formulated recommendations and guidelines for management of COVID-19 patients at our institution. These guidelines are specific for COVID-19 patients and are in addition to the standard ABCDE Bundle guidelines by the Society of Critical Care Medicine for intubated patients and ARDSNET protocol for ARDS patients.

Through this document, we have presented a comprehensive approach in the management of COVID-19 patients that provided readily accessible, institution endorsed guidelines when clinicians were overwhelmed with patient responsibilities. Our approach enables the practicing clinicians to readily incorporate these evidence-based guidelines in managing COVID-19 patients. The algorithms and table presented here encompass our treatment algorithms which enable us to manage the multifaceted involvement in COVID-19 which includes management of Volume status, inflammatory cascade, Thrombotic disease, Alveolar recruitment and oxygenation, and Microbiologic strategies (V.I.T.AM).

**V) Volume status:** The hypoxic respiratory failure associated with ARDS is exacerbated by hypervolemia. There is an increased fluid leak mediated by the increased hydrostatic pressure in the pulmonary capillaries caused by the alveolar injury and the local inflammatory reaction. Furthermore, the endothelial and epithelial layers damage to the alveolar surface and pulmonary capillaries translates into filtration of protein-poor fluid into the interstitial and alveolar spaces leading to alveolar flooding and augmented interstitium thickness resulting in subsequent decrease in gas exchange. Daily monitoring of the patient’s volume status allows the clinician to maintain euvo-lemia and, if needed, promote negative balance to facilitate and optimize gas exchange. There is no direct evidence regarding benefits of a conservative fluid strategy over a liberal fluid strategy in patients with COVID-19. However, data from indirect evidence from patients who are critically ill with ARDS and shock favors conservative fluid strategy.

As part of our standard ICU care, we begin our patient assessment by summarizing net volume status over the past 24 h and over the total hospitalization along with the daily weight and net weight change since admission. Following this information, the current diuretic regimen (if applicable) is documented and, subsequently, the most recent electrolytes affected by aggressive diuresis (Table 1). Our initiative to reduce cognitive overload by summarizing the information to allow providers to more quickly assess volume status and determine whether the patient may benefit from additional diuresis while balancing risk of acute kidney injury and electrolyte abnormalities.

1) **Inflammatory cascade:** Elevated serum levels of inflammatory markers including ferritin, C-reactive protein (CRP) and interleukin 6 (IL-6) are seen in patients who test positive for COVID-19. An upward trend in these biomarkers is associated with inflammatory-induced lung injury from sepsis, pneumonia, aspiration, shock and death. Targeting this inflammatory cascade can potentially benefit a decompensating patient with hypoxic respiratory failure. In the treatment of COVID-19, drugs such as Dexamethasone, and Tocilizumab (humanized recombinant monoclonal antibody against IL-6 receptor) have been shown to modulate the systemic inflammation associated with COVID-19 and in case of dexamethasone, improve survival. The RECOVERY trial has inferred that Tocilizumab decreases the duration of hospitalization, reduces the need for mechanical ventilation, and when used in combination with dexamethasone, improves survival in critically-ill COVID patients with increased C-Reactive Protein levels. The National Institute of Health COVID Management Guidelines have also recommended adding Tocilizumab to dexamethasone in hospitalized patients with respiratory decompensation. Close monitoring of serum inflammatory markers over the course of the patient’s hospitalization may allow the clinician to initiate anti-inflammatory treatment like Tocilizumab in case of persistent rise in these parameters.

The second component of our suggested method for compiling necessary clinical data in patients affected by COVID-19 includes the current daily value and most recent trends of the inflammatory markers most frequently associated with CRS: ferritin, CRP and IL-6. Subsequently, the treatments to augment this inflammatory cascade available at our institution are clearly listed directly below these data, providing
clinicians not only with the administered treatments over the course of the hospitalization, but also the current duration of therapy. The inclusion of this information allows the clinician to accurately assess the trend of serum inflammatory markers and additional treatment modalities that can be added or removed from a patient’s therapeutic regimen.

T) Thrombotic disease: Early reports have suggested an increased incidence of thromboembolic phenomenon including
Figure 4: Anticoagulation in COVID inpatient Management Protocol. This algorithm can be used to determine the appropriate anticoagulation therapy in inpatients with COVID-19. This algorithm is updated periodically based on the inputs of the Treatment Review Panels team member after reviewing the available research articles and supporting data.

Table 1: Summary table which synthesizes volume status, inflammatory markers, thrombotic risk, alveolar recruitment/oxygenation strategies, and anti-microbial/viral work-up with associated therapeutic options.

| Volume | Fluid Balance/ Weight |
|--------|-----------------------|
| Over the last 24 h | Weight in kg: |
| Since Admission | Net change in weight: |

| Current Diuretic Regimen |
|--------------------------|
| Electrolytes | Level |
| Potassium (mmol/L) |
| Magnesium (mg/dL) |
| BUN (mg/dL) |
| Creatinine (mg/dL) |

| Inflammatory Cascade | Date | Level | (Trend) |
|----------------------|------|-------|---------|
| Date | Level | (Trend) |

| Total Leukocyte Count (x10^9/L) |
| Interleukin 6 (pg/mL) |
| Ferritin (mcg/L) |
| C-Reactive Protein (mg/L) |
| Treatment | Day |
| Dexamethasone |
| Tocilizumab |
| Other |

| Thrombotic Disease | Date | Level | (Trend) |
|-------------------|------|-------|---------|
| D-Dimer (ng/mL) |
| Fibrinogen (mg/dL) |
| Platelet Count (10^9/L) |

| Imaging | Date | Results |
|---------|------|---------|
| Lower Extremity Doppler |
| CT Angiography (chest) |

(continued)
deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with COVID-19. Additional literature suggests that the hypercoagulable state seen in COVID-19 has led to cases of disseminated intravascular coagulation, intussusive angiogenesis, endothelialitis and microvascular thrombosis of the pulmonary capillaries without the presence of DVT or PE. Prevention of these hematological complications becomes a crucial part of a resultant positive outcome in the management of COVID-19. In a study describing the rate and severity of hemostatic and thrombotic complications in 400 COVID-19 inpatients, overall thrombotic complications were seen in 9.5% of the patients and overall bleeding was seen in 4.8% of the patients. Thus far, serum markers that have been associated with this hypercoagulable state are D-dimer, fibrinogen, and platelet count. A rise in these markers is suggestive of an increased risk of thrombosis. Trending these serum markers allows the clinicians to obtain imaging studies to detect thrombotic events that were not clinically evident and proceed with empiric therapeutic dosing of anticoagulation if no significant risk of bleeding is suspected.

Thus, the third component outlined in our suggested strategy (Table 1) includes the daily values of D-dimer, fibrinogen, and platelet counts. In addition, any imaging that has been obtained to assess for thrombosis (lower extremity doppler, computerized tomography angiography of the chest, and pulmonary ventilation [V] and perfusion [Q] scan, the dates obtained, and subsequent results are listed in this compiled table. Following this clinical information, we follow the anticoagulation management in COVID-19 patients formulated by the experts at our facility. [Figure 4] Potential therapies [including standard prophylactic anticoagulation], dosage, and duration of therapy are detailed for the clinician’s easy reference. This summarization of data and treatment modalities allows the clinician to make appropriate decisions regarding potentially beneficial therapeutic anticoagulation and, although no data is yet available for discontinuing anticoagulation in a patient infected with COVID-19, when to discontinue this therapy. This standardizes the treatment and decreases the inappropriate use of potentially dangerous medication, chances of error and thus decreases potential harm to patients.

A) Alveolar recruitment and oxygenation: The most prominent symptom of the severe acute respiratory syndrome secondary to COVID-19 is profound hypoxia. The mechanism of this hypoxia is most likely attributed to high levels of inflammation causing direct endothelial damage and increased hydrostatic pressures which promote alveolar collapse. These patients also suffer from decreased lung compliance, retained airway secretions and impaired ventilation. Treatment strategies for this syndrome have been extrapolated from the management of acute respiratory distress syndrome (ARDS) and include methods for alveolar recruitment and increased oxygenation. CCM along with the other experts have formulated the refractory hypoxemia protocol for COVID-19 inpatient management (Figure 3) and strategies such as high flow nasal cannula, oxygen hood therapy, non-invasive positive pressure ventilation and, when necessary, lung protective mechanical ventilation (6 mL/kg) have been used to improve oxygenation in these patients. VV ECMO can be considered in patients with resistant hypoxemia despite mechanical ventilation and other rescue measures if they meet the criteria for ECMO. The addition of nitric oxide has also been shown to improve gas exchange by causing pulmonary vasodilatation to the appropriately ventilated portion of the lung, thereby decreasing V/Q. However, there is no data showing mortality benefit in COVID-19 patients. There are multiple clinical trials underway which will define its role in the treatment of COVID-19 patients better. Until more data

Table 1: Continued.

| Volume Fluid Balance/ Weight | Pulmonary V/Q Scan | Treatment Day | Enoxaparin/ Alternative Agent | Alveolar Recruitment and Oxygenation Strategy |
|-----------------------------|-------------------|---------------|-------------------------------|-----------------------------------------------|
| Positive Expiratory Pressure | Proning           | Device Settings | FiO2 | SpO2/ PaO2 (Trend) | High Flow |
| Ventilation                 | Nitric Oxide      | PH p CO2 pO2 | HCO3 |                      |
| Arterial Blood Gas          |                   | Date Result Treatment Day |

| Microbiologic Strategies | Viral PCR | Bacterial | Blood Cultures | MRSA Nares | Pro-calcitonin |

Yarrapu et al
is available, a trial of inhaled nitric oxide as a “rescue” medication for short term to improve oxygenation can be considered. Methods to improve alveolar recruitment such as proning, incentive spirometer and Positive Expiratory Pressure (PEP) have also proved effective in improving alveolar recruitment.40,41

Due to the complexity of the management of hypoxia in patients infected with COVID-19, our proposed method (Table 1) summarizes the most relevant portions of data pertaining to alveolar recruitment, oxygenation and ventilation in these patients. Initially, the proposed table focuses on the two most identified methods for improved alveolar recruitment (proning and PEEP) and the schedule and duration of this treatment regimen. Our method then outlines the current strategies for oxygenation to include the method of delivery, fraction of inspired oxygen (FiO2), and current settings including liters of oxygen delivered, positive end-expiratory pressure (PEEP), and the ratio of mean airway pressure to peak airway pressure. In addition to the interventions utilized in the management of these patients, our table also identifies the current oxygen saturation to partial pressure of oxygen ratio and the current trend in patient’s oxygenation status over the past 24 h. Lastly, the remaining portion of this section includes the most recent arterial blood gas. In this manner, clinicians have the most essential data available to them in a clear and concise manner to help manage patient’s condition. COVID-19 is a virally mediated illness by us are based on the most up-to-date literature and can serve any frontline clinician. However, the guidelines and algorithms presented here are based on the most updated research and literature by a panel inclusive of leaders from several specialties in the TRP. Given the scarcity of the available data surrounding various therapeutic options, most of the guidelines presented here are additionally recommended. (Table 2) Further, there was a lack of high-quality of peer-reviewed evidence early on in the pandemic and as the pandemic evolved, the recommendations were adjusted based on the best available data after committee discussion. Given the evolving nature of COVID-19, more changes in may be indicated in some of these recommendations as new and more literature becomes available in the future. A critical role of the TRP is to continuously review the new literature and modify the recommendations as and when indicated. Secondly, Mayo Clinic Florida is a large multi-specialty tertiary care center with access to several specialists. We understand this may not be the case with many care settings, especially with limited availability of specialists across the nation, limiting their ability to review the evolving literature and form practice guidelines. However, the guidelines and algorithms presented by us are based on the most up-to-date literature and can serve any frontline clinician.

### Limitations:
There are some limitations with our approach. The data and algorithms presented in this document are based on a comprehensive review of the most updated research and literature by a panel inclusive of leaders from several specialties in the TRP. The viral component of the syndrome, the acquired ciliary dysfunction in combination with prolonged hospitalizations and other host defense impairments, predispose patients infected with COVID-19 to bacterial coinfection.

**M) Microbiologic strategies:** The final component of our suggested method of management in patients affected by COVID-19, is the antiviral and antimicrobial component of the disease management. Concomitant diseases both bacterial and viral are ruled out by appropriate testing based on the patient’s condition. COVID-19 is a virally mediated illness and a wide range of medications have been tried as armament to fight viral replication and other viral cycle processes. While their true efficacy has not yet been validated in large prospective studies, due the severity of this widespread pandemic, the most promising treatments are being used in an attempt to decrease disease burden. In addition to the viral component of the syndrome, the acquired ciliary dysfunction in combination with prolonged hospitalizations and other host defenses impairments, predispose patients infected with COVID-19 to bacterial coinfection.

Our suggested algorithm (Table 1) lists the patient’s most recent antiviral and antimicrobial testing as well as current therapeutic options. The viral component allows clinicians to confirm the most recent date of positive viral PCR and subsequent management (such as remdesivir and convalescent plasma) as well as the duration of therapy.6,7,42-51 The antimicrobial portion documents the most recent date of positive culture, both sputum and blood cultures; procalcitonin level, utilized to help determine the need for the addition of antibiotics in a rapidly deteriorating patient even if cultures have resulted negative; and the results of methicillin resistant staphylococcus aureus (MRSA) culture, used to determine the necessity of MRSA coverage should the patient require empiric antibiotic coverage. While there is limitation of data about the use of procalcitonin as a surrogate marker for bacterial infection, it can serve as a negative predictor when normal, and can assist in antimicrobial stewardship. As some of this data (such as blood cultures, viral PCR, or MRSA swab) are often obtained at the time of hospital presentation rather than on a daily basis, the initial completion of this documentation allows the clinician to promptly assess current microbiology testing and the subsequent management of these results without searching through the electronic medical record for testing performed at the beginning of the hospitalization. This is particularly useful in patients who continue to deteriorate despite the appropriate therapies outlined in the sections above.

### Conclusion:
In this unprecedented pandemic, there is a vast amount of literature and information that emerges daily regarding the
pathophysiology of COVID-19 and the management of patients infected with this disease. In this article, we have presented our novel evidence-based approach to utilize this data. In our institution we have created a multidisciplinary team to synthesize this information daily and determine the appropriate impact this data should have on patient care. Through this team of clinicians, we have been able to develop treatment algorithms and a systematic method for data collection and presentation. It is through this method we are able to rapidly translate the most current literature and information to our busy clinical staff and the treatment of our patients affected by COVID-19. In doing so, our goal and overall objective of minimizing unestablished therapies, maximizing clinical trial enrollment, and providing biologically grounded interventions from available data even in the absence of definitive clinical trials will improve the care and outcomes of our patients.

### Abbreviations

- Coronavirus Disease 2019 (COVID-19)
- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
- Cytokine release syndrome (CRS)
- Mayo Clinic Florida (MCF)
- Treatment review panel (TRP)
- Intensive care unit (ICU)
- Critical care medicine (CCM)
- C-reactive protein (CRP)
- Interleukin 6 (IL-6)
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Positive end-expiratory pressure (PEEP)
- Methicillin-resistant Staphylococcus aureus (MRSA)

### Table 2

| RECOMMENDATION | Level of Evidence | Grade of recommendation |
|----------------|-------------------|-------------------------|
| **VOLUME STATUS** | | |
| Maintain a negative fluid status in critically ill patients | II | B |
| **INFLAMMATORY CASCADE** | | |
| Dexamethasone 6 mg daily for 10 days in patients needing oxygen | I | A |
| Tocilizumab in patients needing oxygen and evidence of, or at risk of cytokine release storm | I | A |
| **THROMBOTIC DISEASE** | | |
| Prophylactic anticoagulation in all inpatients without any risk factor for high bleeding | I | A |
| Therapeutic anticoagulation in inpatients in the presence of DVT and/or PE | I | A |
| **ALVEOLAR RECRUITMENT AND OXYGENATION** | | |
| High flow nasal cannula in patients with increasing oxygen requirement on nasal cannula, oxymask or NRB mask and low work of breathing | II | B |
| Oxygen helmet, NIPPV or CPAP in patients with increasing oxygen requirement on nasal cannula, oxymask or NRB mask and high work of breathing | III | B |
| Inhaled nitric oxide in intubated patients as rescue therapy to improve oxygenation | IV | C |
| VV ECMO in patients with hypoxemia despite ventilation and other rescue therapies | IV | C |
| **MICROBIOLOGIC STRATEGIES** | | |
| Remdesivir for 5 days in all inpatients | I | A |
| Convalescent Plasma in non-intubated patients | II | C |
REFERENCES

1. Johns Hopkins University of Medicine Coronavirus Resource Center. Johns Hopkins Coronavirus Resource Center. Accessed August 9, 2021. https://www.coronavirus.jhu.edu/.

2. Kashani KB. Hypoxia in COVID-19: sign of severity or cause for poor outcomes. Mayo Clin Proc. 2020;95(6):1094-1096. doi:10.1016/j.mayocp.2020.04.021

3. DhoST, Derom E, Van Brackel D, Depuydt P, Lambrecht BN. The pathophysiology of “hypo” hypoxemia in COVID-19. Respir Res. 2020;21(1):198. doi:10.1186/s12931-020-01462-5

4. Russo B, Salton F, Braga L, et al. The history and mystery of alveolar epithelial type II cells: focus on their physiologic and pathologic role in lung. JIMIS. 2021;22(5):2566. doi:10.3390/jimis2025266

5. Elia S, Rossana B, Fabrizio Z, et al. Radiological-pathological signatures of patients with COVID-19-related pneumonia: is there a role for sonic-hedgehog and Wnt5a pathways? EJCR. Open Res. Published online June 25, 2021;7(3):00346-002021. doi:10.1186/s13210-021-00346-6

6. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764

7. Meyhoff TS, Møller MH, Hjortrup PB, Cronhjort M, Perner A, Wetterslev J. Unconventional anakinra to treat acute respiratory distress syndrome secondary to cytokine storm: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43-49. doi:10.1016/j.ejim.2020.05.021

8. Colaneri M, Bogliolo L, Valecchi P, et al. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SM/AtmIo Covi19 Registry (SMACCORE). Microorganisms. 2020;9(5):695. doi:10.3390/microorganisms9050669

9. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19: acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Respir Med. 2020;2(6):325-331. doi:10.1016/S2665-9913(20)30127-2

10. Temesgen Z, Assi M, Merydès P, et al. First clinical use of leucrinolide to neutralize GM-CSF in patients with severe COVID-19 pneumonia. medRxiv. Published online June 14, 2020. doi:10.1101/2020.06.08.20125369

11. Iglesia-Julian E, Lopez-Veloso M, de-la-Torre-Ferrera N, et al. High dose subcutaneous anakinra to treat acute respiratory distress syndrome secondary to cytokine storm among severely ill COVID-19 patients. J Autoimmun. Published online August 20, 2020;115:102537. doi:10.1016/j.jaut.2020.102537

12. Huert T, Beausir H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Respir Med. 2020;2(27):e293-e400. doi:10.1016/S2665-9913(20)30164-8

13. Aouba A, Baldoli A, Geoffroy L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. BMJ. 2020;369:m1970. doi:10.1136/bmj.m1970

14. Stone JH, Frighault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with covid-19. N Engl J Med. Published online October 21, 2020;383(24):2333-2344. doi:10.1056/NEJMoa2028836

15. Temesgen Z, Assi M, Shweta FNU, et al. GM-CSF Neutralization With leucrinolide in reducing severe COVID-19 mortality: a systematic review. PeerJ. 2020;8:e10322. doi:10.7717/peerj.10322

16. Farnati M, Khorana A, Joffe M, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500. doi:10.1182/blood.202006520

17. Al-Samkari H, Karaf Leaf RS, Dhill On, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500. doi:10.1182/blood.202006520

18. Al-Samkari H, Karaf Leaf RS, Dhill On, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500. doi:10.1182/blood.202006520

19. Tan X, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(5):844-847. doi:10.1111/jth.14768

20. Tan X, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. doi:10.1111/jth.14817

21. Moushi L, Walkey A, Goligher E, Pham T, Uhegy EM, Fan E. Venous extra-corporeal membrane oxygenation for acute respiratory distress syndrome: a
systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(2):163-172. doi:10.1016/S2213-2600(18)30452-1

36. Mclaren G, Fisher D, Brodie D. Preparing for the most critically Ill patients With COVID-19: the potential role of extracorporeal membrane oxygenation. *JAMA*. 2020;323(13):1245-1246. doi:10.1001/jama.2020.2342

37. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post Hoc Bayesian analysis of a randomized clinical trial. *JAMA*. 2018;320(21):2251-2259. doi:10.1001/jama.2018.14276

38. Tavaazzi G, Marco P, Mongodi S, Dammassa V, Romito G, Mojoli F. Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19 pneumonia. *Crit Care*. 2020;24(1):508. doi:10.1186/s13054-020-03222-9

39. Abou-Arab O, Huette P, Debouvries F, Dupont H, Jouneaux V, Mahjoub Y. Inhaled nitric oxide for critically ill covid-19 patients: a prospective study. *Crit Care*. 2020;24(1):645. doi:10.1186/s13054-020-03371-x

40. Kacmarek RM. Strategies to optimize alveolar recruitment. *Curr Opin Crit Care*. 2001;7(1):15-20. doi:10.1097/00075198-200102000-00003

41. Reychler G, Uribe Rodriguez V, Hickmann CE, et al. Incentive spirometry and positive expiratory pressure improve ventilation and recruitment in postoperative recovery: a randomized crossover study. *Physioter Theory Pract*. 2019;35(3):199-205. doi:10.1080/09593985.2018.1443185

42. Kow CS, Aldayah M, Hasan SS. Effect of remdesivir on mortality in patients with COVID-19: a meta-analysis of randomized control trials. *J Med Virol*. Published online October 29, 2020;93:1860-1861. doi:10.1002/jmv.26638

43. Spiller CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir versus standard care on clinical Status at 11 days in patients With moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. doi:10.1001/jama.2020.16349

44. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9

45. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe covid-19. *N Engl J Med*. Published online May 27, 2020;383(19):1827-1837. doi:10.1056/NEJMoa2015301

46. Jiang Y, Chen D, Cai D, Yi Y, Jiang S. Effectiveness of remdesivir for the treatment of hospitalized COVID-19 persons: a network meta-analysis. *J Med Virol*. Published online August 19, 2020;93(2):1171-1174. doi:10.1002/jmv.26443

47. Salazar E, Christensen PA, Gravis EA, et al. Significantly decreased mortality in a large cohort of COVID-19 patients transfused early with convalescent plasma containing high titer anti-SARS-CoV-2 spike protein IgG. *Am J Pathol*. Published online November 3, 2020;191(1):90-107. doi:10.1016/j.ajpath.2020.10.008

48. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID trial). *Br Med J*. 2020;371:m3939. doi:10.1136/bmj.m3939

49. Gemild A, Hu B, ErdoGAN C, et al. A single center cohort of 40 severe COVID-19 patients who were treated with convalescent plasma. *Turk J Med Sci*. Published online November 20, 2020;50(8):1781-1785. doi:10.3906/sag-2009-77

50. Chai KL, Valk SJ, Pochtotta V, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev*. 2020;7(7):CD013600. doi:10.1002/14651858.CD013600.pub3

51. Mair-Jenkins J, Sarvedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80 to 90. doi:10.1093/infdis/jiu396