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

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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

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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.[1] 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.[1] The exact pathophysiology of this syndrome is not completely understood and extends beyond the direct virus-mediated injury of the lung parenchyma.[2] 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.[2-5]

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.[6-9] 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.

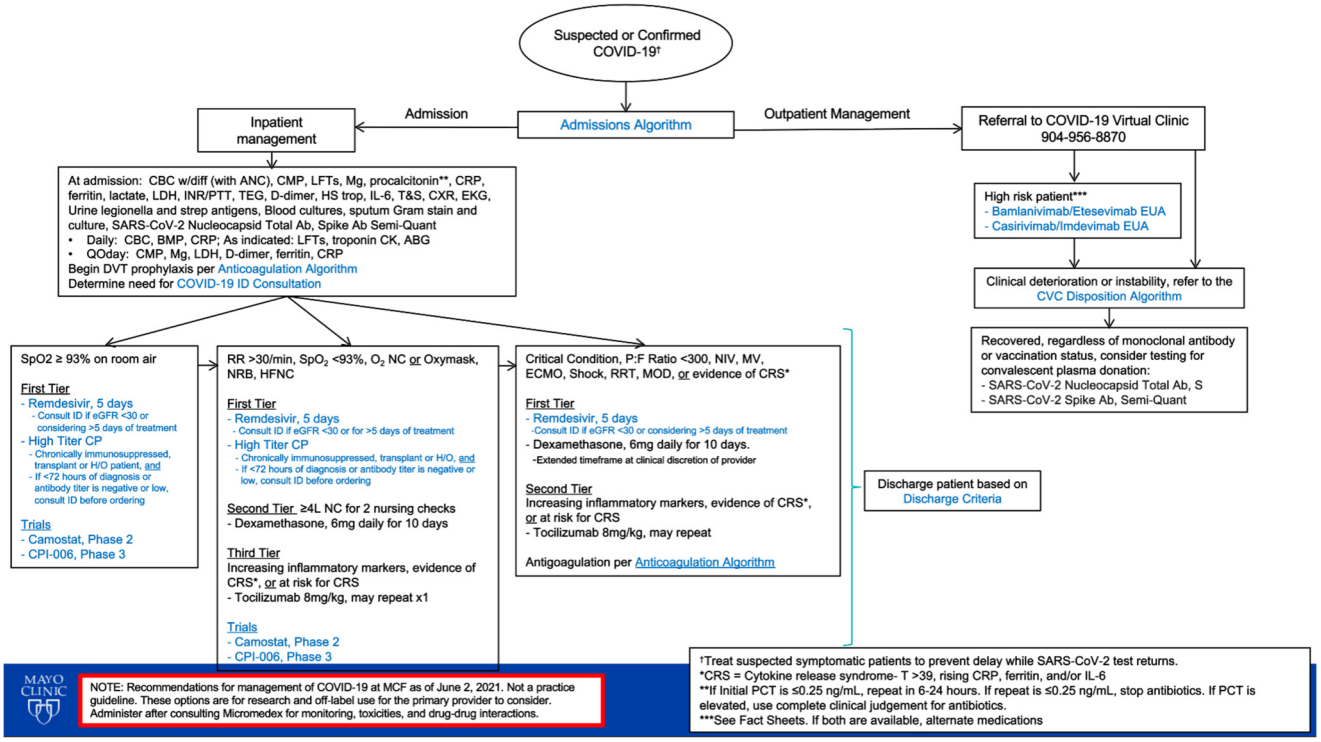

Figure 1: . Treatment review panel algorithm for inpatient management of COVID-19. This algorithm can be used to determine the appropriate inpatient treatment based on the severity of illness. This algorithm is updated periodically based on the inputs of the Treatment Review Panels team member after reviewing the available research articles and supporting data.

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 to 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.[10] 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,

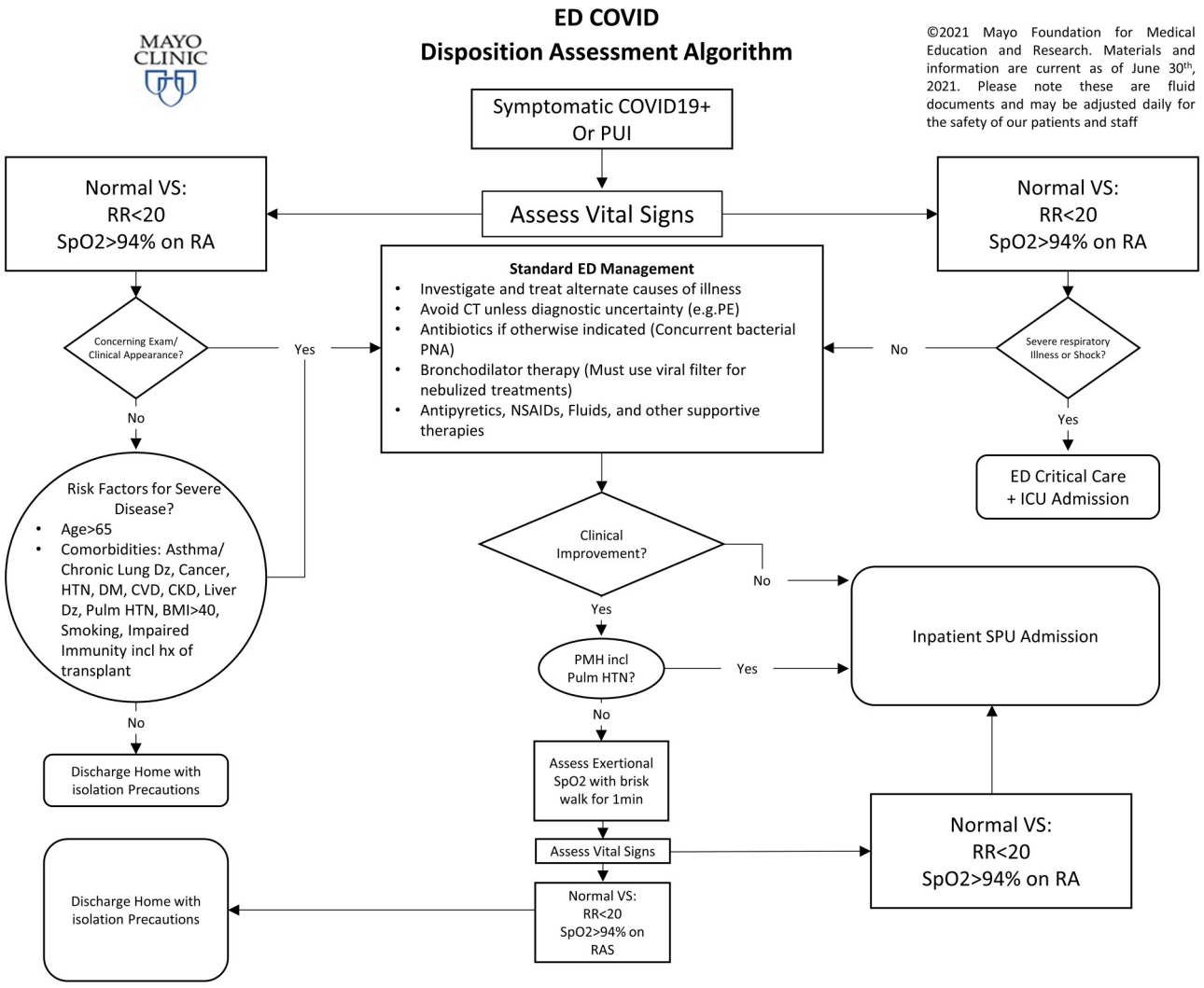

Figure 2: . Emergency Department COVID Disposition Assessment Algorithm. This algorithm can be used to determine the disposition of patients with COVID-19 in the emergency department. This algorithm is updated periodically based on the inputs of the Treatment Review Panels team member after reviewing the available research articles and supporting data.

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 website[11] (https://www.ncbi.nlm.nih.gov/research/coronavirus/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 hypoxemic respiratory failure associated with ARDS is exacerbated by hypervolemia.[14] 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 euvolemia 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.[15-17]

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.

I) 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.[18,19] 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[20-30] and in case of dexamethasone, improve survival.[6] 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.[31] 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

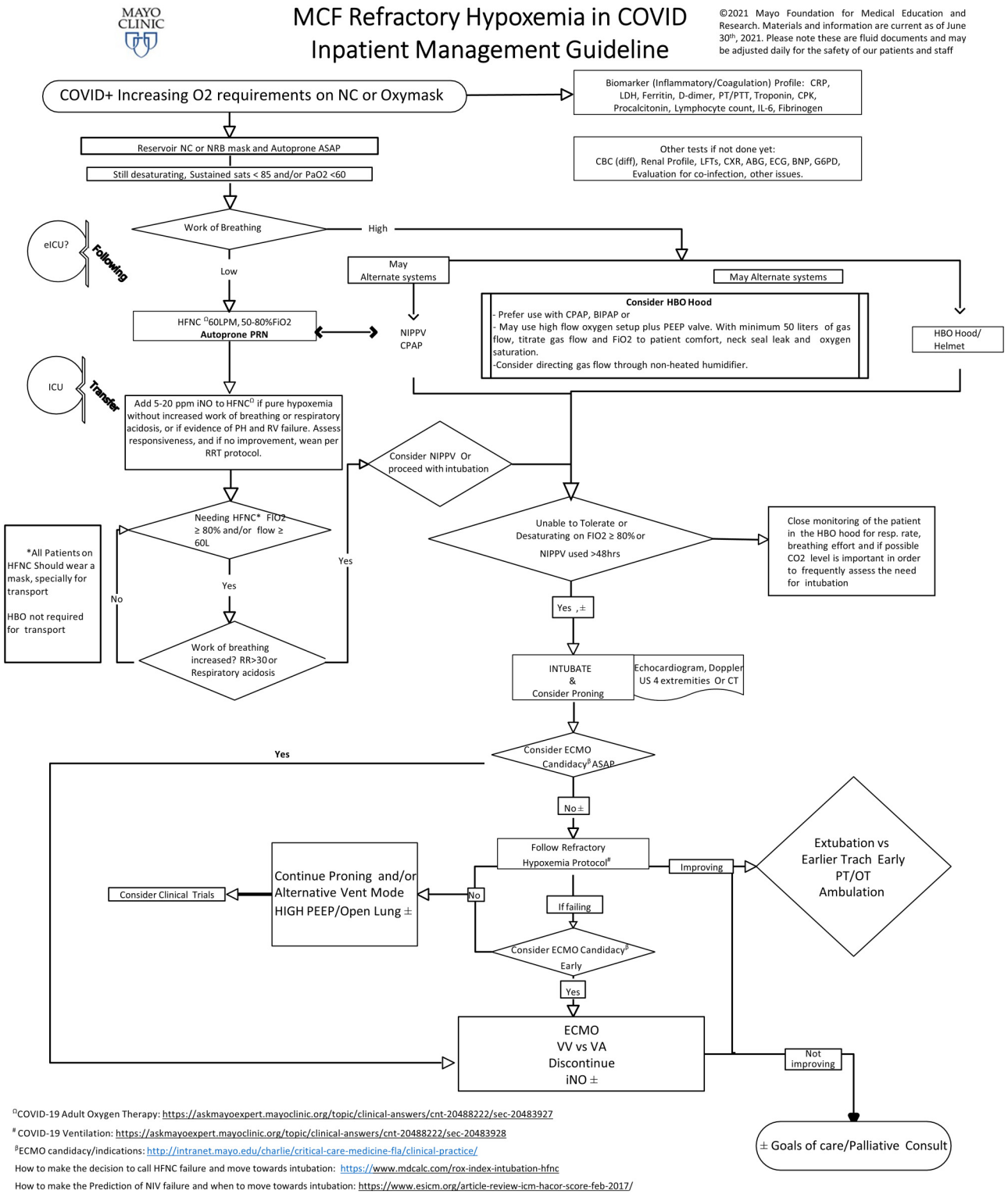

Figure 3: . Refractory Hypoxemia in COVID inpatient Management Protocol. This algorithm can be used to determine the appropriate management of refractory hypoxemia in inpatients with COVID-19. This algorithm is updated periodically based on the inputs of the Treatment Review Panels team member after reviewing the available research articles and supporting data.

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

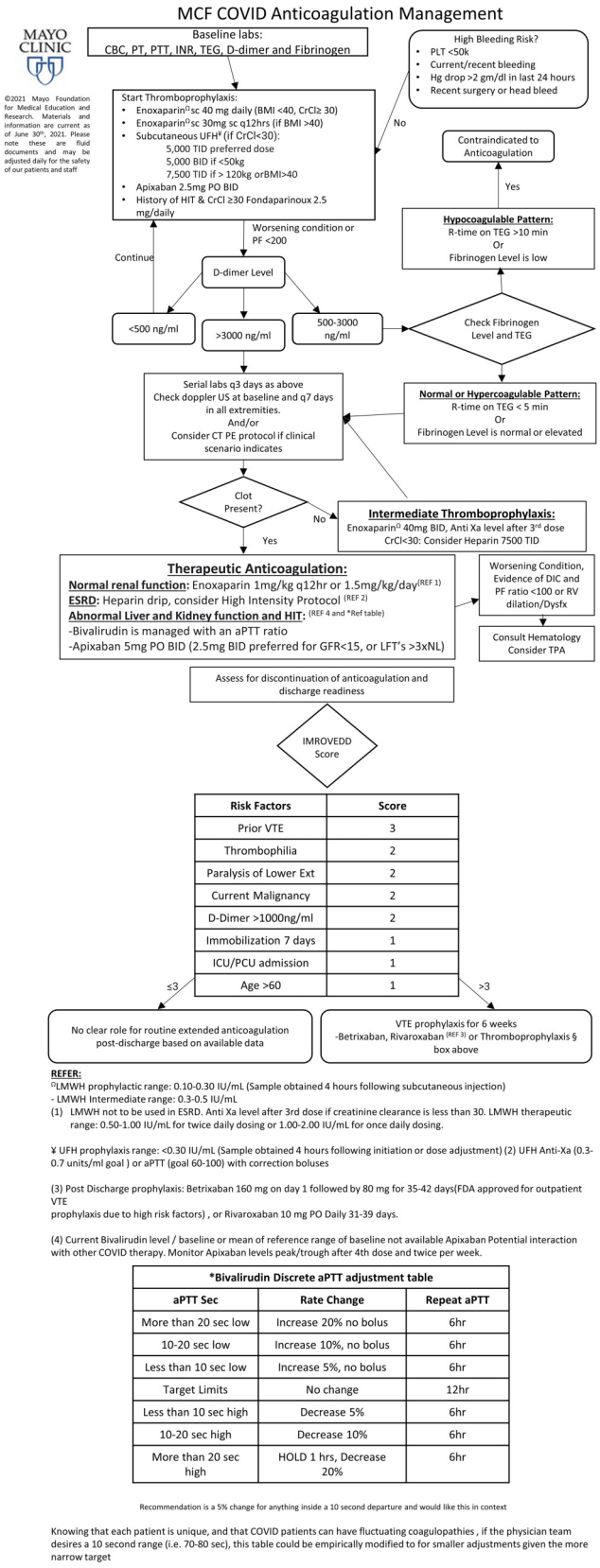

Figure 4: . Anticoagulation in COVID inpatient Management Protocol. This algorithm can be used to determine the appropriate anticoagulation therapy in inpatients with COVID-19. This algorithm is updated periodically based on the inputs of the Treatment Review Panels team member after reviewing the available 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)
Total Leukocyte Count (x10^6/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)

Table 1: . Continued.

Volume Fluid Balance/ Weight				
Pulmonary V/Q Scan				
Treatment	Day			
Enoxaparin/ Alternative Agent				
Alveolar Recruitment and Oxygenation Strategy				
	Frequency			
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				

deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with COVID-19.[32] Additional literature suggests that the hypercoagulable state seen in COVID-19 has led to cases of disseminated intravascular coagulation, intussusceptive angiogenesis, endothelialitis and microvascular thrombosis of the pulmonary capillaries without the presence of DVT or PE.[33] 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.[32] 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.[34] 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.[35-37] 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.[16,38,39] 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

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 oxygenation and alveolar recruitment, one the most essential components in managing a patient affected by COVID-19 associated pneumonia.

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.

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. Given the scarcity of the available data surrounding various therapeutic options, most of the guidelines presented here are not supported by high quality of evidence and are mostly conditionally 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.

Conclusion:

In this unprecedented pandemic, there is a vast amount of literature and information that emerges daily regarding the

Table 2: . Level of evidence adapted from Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95:2S–4S. Levels I (large RCTs with clear cut results), II (small RCTs with unclear results), III (cohort and case-control studies), IV (historical cohort or case-control studies), and V (case series or studies with no controls). Grades of recommendation adapted from the American Society of Plastic Surgeons Evidence-Based Clinical Practice Guideline Methodology. Available at: https://www.plasticsurgery.org/documents/medical-professionals/quality-resources/ASPS-Evidence%E2%80%90Based-Clinical-Practice-Guideline-Methodology.pdf Accessed on June 25, 2021. Grades A (strong recommendation), B (moderate recommendation), C (weak recommendation), and D (optional recommendation).

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

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)
pulmonary ventilation	(V)
perfusion	(Q)
positive expiratory pressure	(PEP)
fraction of inspired oxygen	(FiO2)
positive end-expiratory pressure	(PEEP)
methicillin resistant staphylococcus aureus	(MRSA)

Financial Support Information/ Conflicts of Interest

All authors declare no competing interests and none of the authors have any financial interests which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work presented in this manuscript. There was no funding for the work associated with this publication. None of the authors have been paid by any agency or pharmaceutical company to write this article. All authors have full access to the manuscript and all the data in the study, and the corresponding author has the final responsibility for the decision to submit for publication. All authors declare that this study is an original work and has not been published or presented in any capacity elsewhere.

Data Availability Statement

The authors confirm that all the data supporting this study are available within the article.

Ethics Approval

The Mayo Clinic Institutional Review Board (IRB) acknowledges that based on the responses submitted for this new activity through the Mayo Clinic IRBe Human Subjects Research Wizard tool, and in accordance with the Code of Federal Regulations, 45 CFR 46.102, the above noted activity does not require IRB review.

Author Contributions

Ethical Approval

Informed Consent

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Trial Registration

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