Viral Coagulopathy in Patients With COVID-19: Treatment and Care

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Abstract
COVID-19 has proven to be particularly challenging given the complex pathogenesis of SARS-CoV-2. Early data have demonstrated how the host response to this novel coronavirus leads to the proliferation of pro-inflammatory cytokines, massive endothelial damage, and generalized vascular manifestations. While SARS-CoV-2 primarily targets the upper and lower respiratory tract, other organ systems are also affected. SARS-CoV-2 relies on 2 host cell receptors for successful attachment: angiotensin-converting enzyme 2 and transmembrane protease serine 2. Clinicopathologic reports have demonstrated associations between severe COVID-19 and viral coagulopathy, resulting in pulmonary embolism; venous, arterial, and microvascular thrombosis; lung endothelial injury; and associated thrombotic complications leading to acute respiratory distress syndrome. Viral coagulopathy is not novel given similar observations with SARS classic, including the consumption of platelets, generation of thrombin, and increased fibrin degradation product exhibiting overt disseminated intravascular coagulation–like syndrome. The specific mechanism(s) behind the thrombotic complications in COVID-19 patients has yet to be fully understood. Parenteral anticoagulants, such as heparin and low-molecular-weights heparins, are widely used in the management of COVID-19 patients. Beyond the primary (anticoagulant) effects of these agents, they may exhibit antiviral, anti-inflammatory, and cytoprotective effects. Direct oral anticoagulants and antiplatelet agents are also useful in the management of these patients. Tissue plasminogen activator and other fibrinolytic modalities may also be helpful in the overall management. Catheter-directed thrombolysis can be used in patients developing pulmonary embolism. Further investigations are required to understand the molecular and cellular mechanisms involved in the pathogenesis of COVID-19-associated thrombotic complications.

Keywords
COVID-19, coagulopathy, thrombosis, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS)

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Introduction

There are more than 3.8 million COVID-19 cases identified globally, and the race to develop possible vaccines is more important than ever before. However, it will be some time before a vaccine candidate(s) has been evaluated in well-designed clinical trials. More importantly, immunization would only protect against the spread of new cases, whereas treatment options for current and future cases are limited to supportive care and experimental therapies.

Early reports on the clinical course of hospitalized patients suffering from COVID-19 indicate the empiric utilization of various pharmacologic treatments.[1,2] These treatments include antivirals that may block viral binding (eg, monoclonal antibodies, Angiotensin Receptor Blockers, angiotensin-converting enzyme-2 [ACE-2] inhibitors, transmembrane protease serine 2 [TMPRSS2] inhibitors), inhibit viral RNA production (ie, direct antiviral agents), or inhibit the release of mature virion particles (eg, hydroxychloroquine). Other treatments include immunosuppressants aimed at mitigating the autoimmune-type reactions involved in acute respiratory distress syndrome (ARDS) with pneumonitis.

Recently, studies of the clinical course of COVID-19 patients have demonstrated a concerning incidence of viral coagulopathy. The aim of this article is to provide an updated review on the coagulopathies present in COVID-19 patients with reference to their impact on molecular, cellular, and organ targets. Additionally, the current approaches in the anticoagulant management and other supportive therapies are also addressed.

Pathogenesis of SARS-CoV-2 Infection (COVID-19)

COVID-19 appears to mainly affect the upper and lower respiratory tract, though newer reports also implicate other organ systems (ie, cardiovascular, digestive, renal, and nervous systems) in certain subgroups. It has been demonstrated that the virus may rely on 2 host cell receptors for successful attachment, ACE-2 and TMPRSS2.[3]

Previous studies have shown that ACE-2 is highly expressed in the endothelial cells of arteries and veins, arterial smooth muscle cells, and type I and type II alveolar epithelia cells in human lung tissue.[4] Despite the large distribution of ACE-2 expression in human tissues, preliminary analysis of clinical specimens indicates that there is little evidence for profound infectious reaction at a systemic level.[5] Similarly, human tissue specimen analysis of TMRPSS2 has revealed the expression of TMPRSS2 in lung tissue.[6] Therefore, the convergent distribution of these 2 factors in the respiratory system may explain SARS-CoV-2 pathogenesis in the lungs. COVID-19 targets pulmonary endothelial lining and, besides the receptor remodeling, stimulates angiogenesis and upregulates localized inflammatory responses resulting in severe ARDS.[7,8] It is likely that other target organs may also be infiltrated by SARS-CoV-2 and exhibit localized pathogenesis as

gastrointestinal tract, kidneys, heart, and brain. A recent study reporting on the postmortem examination of COVID-19 patients also suggested the involvement of multiple organs including central nervous system.[9]

COVID-19-Associated Viral Coagulopathy

Although COVID-19-associated illness mainly presents itself in the lungs, COVID-19 has been shown to manifest in other organ systems. Recent clinical and pathological data demonstrate an association between COVID-19 and coagulopathies that may manifest as pulmonary embolism (PE) or venous, arterial, and/or microvascular thrombosis which are associated with severe viral injury of lung endothelium. In light of these findings, several professional groups have recommended anticoagulation in all hospitalized patients with COVID-19.[10] Viral infections may cause prothrombotic states through the modulation of various coagulation proteins. SARS-CoV-1 and several other viral respiratory infections have demonstrated increased intravascular thrombi and fibrin deposition in the lungs.[11] Pulmonary infarcts and thrombocytopenia were observed in SARS-CoV-1 cases.[11,12]

It was previously demonstrated that in patients with H1N1, ARDS had significantly increased risk of venous thrombotic complications. The 2009 H1N1 pandemic (pH1N1/09 virus or swine flu) was estimated to have claimed as many as 575 000 lives.[13] Although pH1N1/09 (*Orthomyxoviridae*) and SARS-CoV-2 (*Coronaviridae*) originate from different viral families, both are highly pathogenic, cause viral pneumonia, and exhibited viral coagulopathy. Several postmortem, retrospective, pathological studies during the H1N1 pandemic revealed alveolar septal edema, hyperplasia of type II pneumocytes, fibrin thrombus in the vascular lumen, necrosis of the bronchiolar walls, diffuse alveolar damage, intra-alveolar hemorrhage, necrotizing bronchiolitis, microthrombi, thrombosis of the large pulmonary arteries, and hemophagocytosis.[14-18] A retrospective cohort study on 119 H1N1 cases revealed that almost 6% of patients developed thrombotic vascular events (either in the venous circulation or arterial thrombi). H1N1 thrombotic events were associated with an increased length of stay and increased mortality. Patients who developed thrombi had no underlying conditions that would predispose them to developing thrombi.[19]

SARS-induced platelet depletion was believed to be caused by the direct infection of the hemopoietic stem/progenitor cells and megakaryocytes.[12] Consumption of platelets due to overt disseminated intravascular coagulation (DIC)–like syndrome may also be a contributing factor for the observed thrombocytopenia in COVID-19 patients. Additionally, platelet sequestration and splenic regulation due to viral infection should be explored for potential involvement in these processes. Similar pathogenesis in SARS-CoV-2 has yet to be determined; however, clinical course follow-up has demonstrated thrombocytopenia in hospitalized patients. Specifically, thrombocytopenia was more prominent in nonsurvivors (20%) versus survivors in one study.[20]

The extent of coagulopathies in various coronavirus-associated infections widely vary in terms of pathogenesis and severity outcomes.[21] The association of bleeding and thrombotic complications with viral infections has been investigated extensively, and the mechanism involved is well understood. These mechanisms include multiple processes involving coagulation and fibrinolytic network, platelets, endothelial cells, and leukocytes. Fibrinolytic dysregulation and imbalance of serine proteases are also contributory to the fibrinolytic deficit in these patients.[22] Viral infections has also been associated with the generation of antiphospholipid antibodies. Recent publication has reported the association of antiphospholipid antibodies with thrombotic complications observed in COVID-19 patients.[23] It is likely that certain additional mechanisms also contribute to the pathogenesis of vascular and hemostatic imbalance observed in COVID-19-associated bleeding and thrombotic disorders. Additional investigations are needed to further elucidate these processes.

The International Society on Thrombosis and Hemostasis (ISTH) released interim guidance on the management of coagulopathy in COVID-19 patients. The ISTH advises for the use of prophylactic doses of a low-molecular-weight heparin (LMWH) unless there is active bleeding or a platelet count of $<25 \times 10^9$/L. Additionally, periodic monitoring of D-dimer, prothrombin time, platelet counts, and fibrinogen levels are recommended.[10] Reportedly, high D-dimer levels appear to correlate with mortality in patients with severe COVID-19; however, currently, it is not defined if this correlation is specific and/or significant for COVID-19 patients; hence, previously, a similar relationship has been demonstrated in critically ill patients.[24] Moreover, elevated D-dimer cannot be envisioned as a guide for initiation and dose escalation for anticoagulation. Although bleeding is rare, in instances where it is present, the ISTH panel advises on maintaining platelet counts $>50 \times 10^9$/L (and $>20 \times 10^9$/L goal in nonbleeding patients), fibrinogen >2.0 g/L, and the international normalized ratio <1.5. In many patients, these measures may prove inadequate to predict coagulopathies. In these cases, higher doses of anticoagulants and/or the incorporation of nonpharmacologic approaches may be warranted.

Currently, several other groups are developing consensus statement and guidelines for the prevention and treatment of venous thromboembolism (VTE) associated with COVID-19 infection. A preguideline consensus statement is recently published on behalf of various international investigators.[25] This statement provides practical recommendations for the diagnosis and treatment of COVID-19-associated VTE for clinicians. Additionally, in this document, risk assessment, prevention of VTE in various risk groups, and the use of anticoagulant are detailed. It is expected that several other guidelines on behalf of various groups will also be introduced in due time. Periodic update for these guidelines may be needed as additional data on the pathogenesis and outcome on COVID-19 become available.

The specific mechanism(s) accounting for the increased incidence of venous thrombosis among COVID-19 patients has not been fully elucidated. This heightened risk may be just part of the series of events that led up to DIC typical of any critical illness. Alternatively, there may be a direct effect of the virus on the endothelium or coagulation cascade.

Unfractionated heparin (UFH) and LMWH are widely used in the management of COVID-19 patients.[26-29] Besides possessing anticoagulation and antithrombotic properties, these agents produce other pharmacologic effects including antiviral, anti-inflammatory, and cytoprotective effects.[30-33] Parenteral UFH at therapeutic dosage has been used for the anticoagulant management of COVID-19 patients. Individual dosage adjustment to achieve therapeutic anticoagulation requires frequent monitoring. Low-molecular-weight heparin such as enoxaparin at 40 mg or higher is widely used in COVID-19 patients.[34] Low-molecular-weight heparins are now widely used and do not require monitoring. Low-molecular-weight heparin also have a lower potential to induce bleeding and thrombocytopenia in comparison to UFH. The current use of both the UFH and LMWH is empirical and will require clear recommendations based on the outcomes observed in the ongoing studies. Harmonized guidelines need to be developed for the use of not only heparins but other anticoagulants used in COVID-19 patients.

Unfractionated heparin has been used for intrapulmonary administration by several investigators utilizing different approaches.[35-37] A pilot study of nebulized UFH for the prevention of ventilator-induced lung injury has been reported.[38] Inhaled prophylactic UFH has also been shown to be effective for the prevention and management of pneumonia and ventilated intensive care unit patients. A phase 1 trial of nebulized heparin in acute lung injury demonstrated better outcomes in heparin-treated groups.[39] Other reports on nebulized heparins have demonstrated improved outcomes in chronic obstructive pulmonary disease and other lung diseases such as inhalation injury.[40-42] As the COVID-19 viral infection results in significant pulmonary injury, the inhaled forms of heparins that reach lung tissue may be effective in through anti-inflammatory and antiviral effects.

Unfractionated heparin is a heterogenous mixture of glycosaminoglycans, and only 30% of its component produce anticoagulant effects. The other 70% have multiple pharmacological properties including the release of tissue factor pathway inhibitor (TFPI) from the endothelium, direct interactions with vascular surface, cytoprotective effects, interactions with growth factors, and modulation of cellular regulatory processes.[29] The LMWH represents depolymerized heparin derivatives with molecular weight in the range of 4 to 6 kDa. Like UFH, only 30% of the components of these drugs interact with AT to produce their pharmacologic effects. The LMWHs have a much longer biologic half-life and produce lesser adverse effects. Comparable to UFH, these agents also exhibit anti-inflammatory effects and are capable of downregulating inflammatory cytokines.

There are several other types of anticoagulant and antithrombotic agents worthy of clinical investigation in COVID-19 patients. This includes the parenteral antithrombin agents (argatroban, bivalirudin), direct oral anticoagulants (DOACs), danaparoid, and sulodexide. The DOACs, including factor Xa

and IIa inhibitors, may provide advantages including their oral route of administration. However, patient risk stratification, bioavailability at specific sites of action, and onset of action needed to be studied in this unique patient population. Likewise, for danaparoid and sulodexide, the determination of optimal dosage, duration of therapy, and monitoring parameters in COVID-19 patients require much further investigation. Defibrotide, a nucleic acid–derived antithrombotic agent with additional pharmacological effects, is currently undergoing clinical trials at the fixed dosage and continuous infusion protocols. Tissue plasminogen activator (tPA) has been used for COVID-19-associated ARDS and patients with refractory microthromboembolic complications.[43,44]

It is not always possible to achieve desirable outcome with pharmacological agents, and patients may carry contraindications to pharmacologic approaches. In these patients, especially those with concerns of bleeding complications, other modalities such as nonpharmacologic approaches must be considered. Dependent on risk status of the patient, and the concerns of bleeding especially ischemic stroke, nonpharmacologic approaches with or without concomitant pharmacologic treatments should be considered.

The primary action of nonpharmacologic modalities is to reduce the stasis component of Virchow's triad (stasis, endothelial injury, prothrombotic blood factors).[45] Nonpharmacologic approaches include thromboprophylatic stockings, mechanical compression devises, calf compression pumps, and electrical neuromuscular stimulation devices. Compression stockings protect against venous stasis by a mechanical manipulation in the nonparalyzed or nonanesthetized patient. Venous flow induced by involuntary or habitual muscle movement is augmented by the external compressive counterforce.[46] Stockings also reduce venous volume and, in consequence, the venous load available for thrombosis. Sequential intermittent pneumatic compression devices, applied around the calf and foot, protect against DVT by pumping venous blood toward the heart.[47] The calf muscles can be induced to contract by electrical stimulation applied directly over the muscle bellies of gastrocnemius or indirectly over the common peroneal nerve.[48,49] These nonpharmacologic modalities may play a vital role in VTE prophylaxis in patients infected with COVID-19.

Catheter-Directed Thrombolysis

Recent data have suggested an increased incidence of PE in COVID-19 patients.[50] It is therefore important to identify the risk of PE in COVID-19 patients in order to optimize treatment modalities and clinical outcome. Intravenous administration of antithrombotic and thrombolytic therapy has been anecdotally used, with scattered reports of acute improved oxygenation. A more localized approach is warranted: catheter-directed thrombolysis (CDT) may prove to be effective with the use of a Swan-Ganz catheter in the pulmonary arteries. Catheter-directed thrombolysis can be performed bedside, and imaging is not required to successfully complete the procedure. Adjunct

local delivery of antivirals and/or interleukin 6 inhibitors is feasible. Additionally, the use of catheter-based mechanical thrombectomy devices also needs to be considered when PE is present.

However, these approaches do pose several logistical and clinical challenges. During the prodromal period or period of illness, patients with COVID-19 are highly contagious in which the virus may spread via droplets or become aerosolized during intubation or other aerosol-producing conditions. Therefore, the physical movement and intervention of these patients in interventional radiology suites need to be highly controlled to minimize the risk of nosocomial transmission. Feasibility studies will help determine the safety and preliminary efficacy of local thrombolytic delivery.

Other Considerations

Convalescent Plasma

Several studies have reported on the successful use of plasma obtained from recently recovered patients to treat the COVID-19 patients. This plasma was referred to as convalescent plasma that contains neutralizing antibodies capable of reducing viral load and associated pathogenesis. Food and Drug Administration has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19.[51] Several recent reports have provided evidence for improved outcome in patients treated with convalescent plasma.[52-55] Various national and international studies are ongoing on the use of convalescent plasma in the management of COVID-19 patients.

Transarterial Drug Delivery

Transarterial drug delivery to the lungs could prove to be another avenue for local drug delivery to combat coagulopathies with specific agents. Acute respiratory distress syndrome likely leads to blood delivery decrease from the pulmonary circulation as well as the bronchial circulation. The former may be partially overcome by intrapulmonary delivery. The latter leads to dilation of the bronchial arteries, thereby allowing easy cannulation and rendering them an alternative venue for local drug delivery. Transarterial local drug delivery is a well-established procedure, including drug therapy/delivery in the lungs via the bronchial arteries using microcatheters. The physician is free to choose their therapeutic of choice, given that many identified COVID-19 drug candidates can be administered through a catheter or may be easily formulated in the pharmacy for this purpose.

Hyperbaric Oxygen Therapy

Several studies have suggested that hyperbaric oxygen therapy can effectively restore systemic hypoxia in COVID-19 patients. Early hyperbaric oxygen therapy may improve the

overall systemic supportive treatment, reduce the use of mechanical ventilation, and improve the outcome in critically ill COVID-19 patients. Preliminary evidence strongly suggest that hyperbaric oxygen therapy is useful in severely hypoxemic COVID-19 pneumonia patients.[56,57]

Primary and Secondary Prevention

Another vexing problem is how to provide primary and secondary prevention in COVID-19 patients with coronary artery disease (CAD). Specifically, the role of antiplatelet agents (ie, clopidogrel, prasugrel, ticagrelor, and cilostazol) with SARS-CoV-2 pathogenesis needs to be further investigated. There are some evidence phosphodiesterase inhibitors such as dipyridamole are effective in patients with severely ill COVID 19.[58] Additionally, there is little understanding on the possible interactions of these pharmaceuticals with the current drugs being evaluated for COVID-19 treatment.

Acute Heart Injury

There is no consensus on the approach to treat the COVID-19 patients with acute heart injury, which occurs in 6% to 18% of cases.[59] The variability in the proportion of acute heart injury may be explained by many factors including insufficient data collection, lack of biomarkers, and other suitable testing capabilities. Currently, we are limited to using treatment strategies based on etiology of the heart injury.[59,60]

SARS-CoV-2 itself is a likely culprit to produce acute heart injury. However, difficulties to perform magnetic resonance imaging, myocardial biopsy, and computed tomography angiography, have made the diagnosis and understanding of the mechanism of injury complicated and empirical. One potential mechanism could be acute coronary syndrome in the absence of CAD in anamnesis. Several groups have suggested the use of systemic tPA in cases of progression of existing cardiovascular disease; however, perhaps PCI may be an optimal strategy. Further investigation and standardization are required prior to recommending any of the traditional anticoagulant treatments.

Risk of Stroke in Younger Patients

There is a concerning number of strokes in younger patients with COVID-19. Aggressive investigation is required to better understand this phenomenon. Intravenous administration of tPA and more aggressive interventional approaches using catheter-based mechanical thrombectomy devices may be warranted in these patients with serious disease.

Conclusion

The burden and reach of COVID-19 continues to grow, though early public health interventions may have flattened the curve. However, there remains a large population, globally, hospitalized from COVID-19 with many more anticipated to be hospitalized. There is no singular treatment shown to be effective in combatting COVID-19 and vaccines are currently being investigated. COVID-19 is largely localized to the lungs, and the development of COVID-19 coagulopathies is a real concern. There is much more research that is required to be performed.

Based upon the evidence we currently have, the heparins and other anticoagulants may provide effective prophylaxis against clinical deterioration. The dosage regimen of the heparins requires further investigation for optimization. The role of antiplatelet therapy as preventive measure also needs to be addressed. Patients currently on antiplatelets may require special attention, as well as those developing acute heart injury. Finally, local drug delivery of any of the identified COVID-19 drug candidates in combination of anticoagulation and antithrombotic therapies may increase treatment efficacy.

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