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THROMBOSIS AND ANTICOAGULATION IN COVID-19

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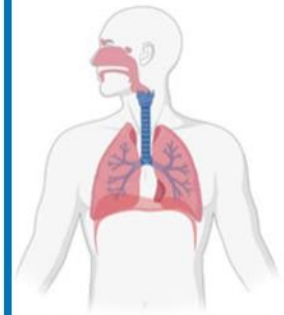
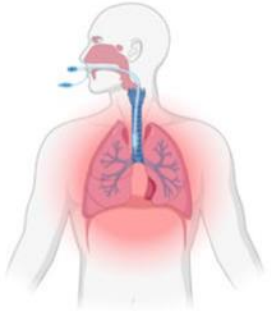
NATF North American Thrombosis Forum

GLOBAL THROMBOSIS FORUM

Introduction

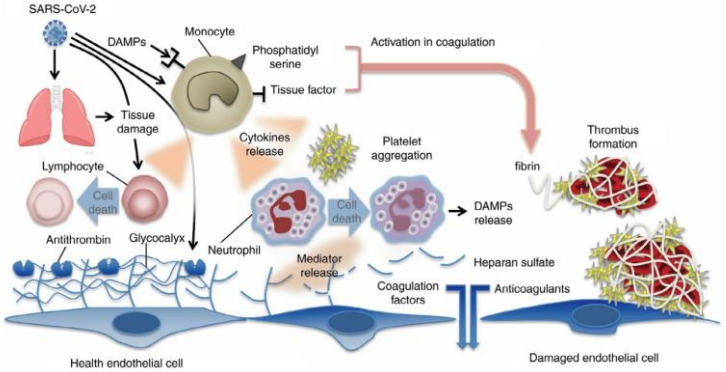
- Covid-19 disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Doctors began to notice changes in the coagulation system in severe cases of Covid-19.
- When SARS-CoV-2 enters the host cell, the coagulation system and inflammatory tissues are activated, leading to thrombotic events.
  - Pulmonary embolism (PE)
  - Deep vein thrombosis (DVT)
  - Myocardial infarction (MI)
  - Stroke
- These events can be detected and measured through biomarkers of coagulopathy.
- Antithrombotic agents and anticoagulants are needed to address this problem.
- Many international and national institutions have conducted studies to evaluate each antithrombotic therapy.

Stages of Covid-19 Associated Coagulopathy

	STAGE 1	STAGE 2	STAGE 3
			
Symptoms	Mild symptoms, no need for respiratory support	More severe symptoms, need for oxygen therapy	Critical illness, mechanical ventilation and organ support
Inflammation	Mild, local	Moderate, local +/- systemic	Hyperinflammation, systemic

Coagulation Abnormalities

- Endothelial Dysfunction
  - Much of the thrombotic issues that those with Covid-19 encounter, root from endothelial cell (EC) dysfunction; when these cells are disrupted, by SARS-CoV-2, they may be aggravated, which will result in signs of thrombotic events and an activated coagulation cascade.
  - Severe Covid-19 with cytosine release signals the body to activate the endothelial cells which also induce antigen presenting cells which regulate other inflammatory cells such as neutrophils, lymphocytes, and platelets.
- Proinflammatory Cytokines
  - Due to the increasing levels of pro-inflammatory cytokines post SARS-CoV-2 infection, the coagulation cascade and clotting factors will also be functioning abnormally and even dysfunctioning.
  - Many pro-inflammatory cytokines (IFN-ɣ, TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, MCP-1, G-CSF, GM-CSF, and MIP-1α) are increased during Covid-19 infection.
  - IL-6 is the most important regulator for coagulation activation through cytokines. Increased IL-6 levels is associated with severe thrombotic events and mortality in Covid-19 patients.



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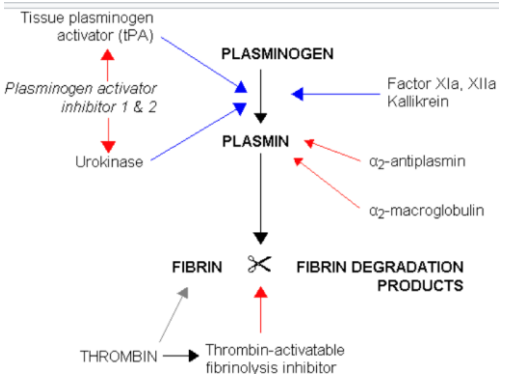
Coagulation Abnormalities

- D-dimer
  - D-dimer is the most comprehensive biomarker and has been found higher in critical patients who had thrombotic events and acute kidney injury, and those who are deceased.
  - Elevated D-dimer levels have shown correlation with the levels of inflammatory markers, including C-reactive protein and ferritin, supporting an association with the inflammatory state of COVID-19.
  - High D-Dimer levels have been reported to be used to screen for thrombosis to identify patients with COVID-19 who needed CT pulmonary angiography to diagnose pulmonary embolism.
- Fibrinolytic System
  - Studies have found that in the majority of Covid-19 patients with thrombotic events, they have fibrinolytic shut down.
  - This was primarily mediated by overexpression of plasminogen activator inhibitor 1 (PAI-1) from endothelial cells and activated platelets.
  - Markedly elevated PAI-1, tPA, and TAFI levels have been reported in patients with COVID-19.



Clinical Manifestations of Thrombotic Events

- Myocardial Infarction
  - Myocardial infarctions are associate with the Covid-19 diagnosis because entry of SARS-CoV-2 results in an immune response which releases cytokines which promote coagulation leading to increasing D-dimer levels and a hypercoagulable state,
  - This state and the increasing number of clots with vasoconstriction leads to inhibition in the path of oxygen to reach the heart resulting in a myocardial infarction.
- Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT)
  - The most common thrombotic event occurring in Covid-19 with 87% of patients with thrombotic events experiencing PE.
  - Since severe Covid-19 results in increased coagulopathy, these newly formed blood clots often become stuck in arteries, blocking blood flow, resulting in a pulmonary embolism. In many cases, these blocks occur in the legs which is called deep vein thrombosis (DVT).

Clinical Manifestations of Thrombotic Events

- Stroke
  - After entry of SARS-CoV-2, the hyper-reactive immune response leads to an exaggerated inflammatory reaction in COVID-19 patients; coagulation occurs, forming increased clots
  - These clots can thus become stuck in the blood vessel and restrict the flow of blood to the brain, causing a stroke.
- Bleeding
  - Bleeding in Covid-19 patients is very rare; these cases are characterized by being difficult to control and having microvascular damage.
  - Bleeding may occur after SARS-CoV-2 enters the body, ACE-2 receptors' activity decreases, resulting in an immune response which leads to an increase in blood pressure, resulting in endothelial dysfunction and bleeding.
  - It is recommended that if falling D-dimer and fibrinogen levels are noted while are anticoagulant therapy, doses should be adjusted in line with these changes to prevent overdose and bleeding.

Antithrombotic Agents

	Classification	Mechanism	Half-life	Therapeutic Dosing	Prophylactic Dosing
Unfractionated Heparin	Heparin	Binds to thrombin and Factor Xa, inhibiting progression of coagulation cascade and inactivating thrombin	60-90 minutes	Heparin drip with a bolus injection of 80 units/kilogram intravenously> continuous infusion rate of 18/units/kilogram/hours	5000 units subcutaneously, 2 or 3 times a day
LMWH	Heparin	Enhances antithrombin effects to be more selective on Factor Xa rather than on thrombin.	Depends on specific LMWH le: enoxaparin: 4.5-7 hours Dalteparin: 2-5 hours	1 mg/kg twice daily	Enoxaparin: creatinine clearance>30 mL/min, 40 mg once daily Dalteparin: 5000 units once daily
Apixaban	DOAC	Inhibits free and clot-bound FXa as well as prothrombinase activity. Indirectly inhibits platelet aggregation	12 hours	10 mg twice daily for a week> 5 mg twice daily	2.25 mg PO bid
Rivaroxaban	DOAC	Directly inhibits Factor Xa in coagulation	5-9 hours hours (depend	15 mg twice daily for one week to 20 mg	10 mg daily
		cascade.	ent on renal function)	once daily	

Antithrombotic Agents

	Classification	Mechanism	Half-life	Therapeutic Dosing	Prophylactic Dosing
Warfarin	Vitamin K antagonist	Competitively inhibits vitamin K epoxide reductase complex 1, thus reducing synthesis of clotting factors	20-60 hours	Once a day, depending on INR adjustment	Not applicable
Sulodexide	Heparin: mixture of dermatan sulfate and fast moving heparin	Inhibits thrombin generation by catalysis of heparin cofactor II by dermatan sulfate and antithrombin	18.7 +/- 4.1 hours after 50 mg 25.8 +/- 1.9 hours after 100 mg	Intravenous 1000-1200 Lipase Releasing Units (LRU) or 500 LRU orally twice daily	250 Lipase Releasing Units (LRU) twice daily
Aspirin	Antiplatelet agent	Inhibits platelet aggregation through inhibition of platelet thromboxane A2 synthesis	Irreversible actions, 1 week	80 to 500 mg/day	Not applicable/ low dose (80-150 mg/day)

ISTH Recommendations

Table 1: ISTH 2022 Recommendations for Antithrombotic Therapy in Covid-19		
Antithrombotic Therapy in Non-hospitalized COVID-19 Patients. (stage 1)		
Class of Recommendation	Level of Evidence	Recommendation
3) No benefit	B-R) Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	Antiplatelet therapy is proven to be ineffective in reducing risk of hospitalization, venous or arterial thrombosis, or mortality
3) No benefit	B-R) Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	DOAC therapy is proven to be ineffective in reducing risk of hospitalization, arterial or venous thrombosis, or mortality.
2b) Weak Benefit≥**risk**	B-R) Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	Oral sulodexide therapy within 3 days of symptoms onset may be considered in order to reduce risk of hospitalization.

ISTH Recommendations

Antithrombotic Therapy in Non-critically-ill Hospitalized COVID-19 patients. (stage 2)		
Class of Recommendation	Level of Evidence	Recommendation
1) Strong Benefit>>>risk	B-R) Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	Low (prophylactic) dose LMWH or UFH recommended in comparison to no LMWH or UFH to effectively reduce risk of thromboembolism and mortality.
1) Strong Benefit >>>risk	A) High-quality evidence from more than 1 RCT Meta-analyses of high-quality RCT One or more RCT corroborated by high-quality registry studies	Therapeutic dose LMWH or UFH recommended in comparison to low (prophylactic) or intermediate dose LMWH or UFH to effectively reduce risk of thromboembolism and end organ failure.
3) No benefit	B-R) Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	Intermediate dose LMWH or UFH is not recommended in comparison to low (prophylactic) dose LMWH or UFH to reduce risk of thromboembolism and other adverse outcomes such as death.
3)Harm (strong) risk> benefit	A)High-quality evidence from more than 1 RCT Meta-analyses of high-quality RCT One or more RCT corroborated by high-quality registry studies	Add-on treatment with an antiplatelet agent is potentially harmful and is advised against.
3) No benefit	B-R) Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	Therapeutic dose DOAC is proven ineffective in reducing risk of thromboembolism and other adverse outcomes such as death.

ISTH Recommendations

Antithrombotic Therapy in Critically-ill Hospitalized COVID-19 patients. (stage 3)		
Class of Recommendation	Level of Evidence	Recommendation
3) No benefit	B-R)Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	Intermediate dose LMWH/heparin is not recommended in comparison to prophylactic dose LMWH/heparin in reducing risk of adverse events, including mortality and thromboembolism.
3) No benefit	B-R)Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	Therapeutic dose LMWH/heparin is not recommended over usual or prophylactic dose LMWH/UFH.
2b) (weak) Benefit≥ risk	B-R)Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	In certain critically ill patients who are hospitalized, add on treatment with an antiplatelet agent to prophylactic dose LMWH. Heparin is not fully established but potentially could reduce mortality.

ISTH Recommendations

Antithrombotic Therapy in Patient Discharged from the Hospital.		
Class of Recommendation	Level of Evidence	Recommendation
2b) (weak) Benefit≥ risk	B-R) Moderate-quality evidence from 1 or more RCTs Meta-analyses of such studies	In certain patients who have been discharged from the hospital, prophylactic dose rivaroxaban for about 30 days potentially will reduce risk of venous thromboembolism.

Conclusion

- COVID-19 induced coagulopathy results in many critical thrombotic events which result in changes in the coagulation and fibrinolytic system.
- There are many antithrombotic agents and anticoagulants which provide treatment for and prevent COVID-19 induced thrombosis and coagulopathy.
- National and international institutions are providing updated recommendations and guidelines on these agents which should be abided by, should conditions allow.

Future Plans

- Review manuscript will be submitted to the Journal of *Clinical and Applied Thrombosis/Hemostasis*.
- Abstract will be submitted for Experimental Biology meeting and publication.

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Thank You