COVID-19 Associated Coagulopathy

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Introduction

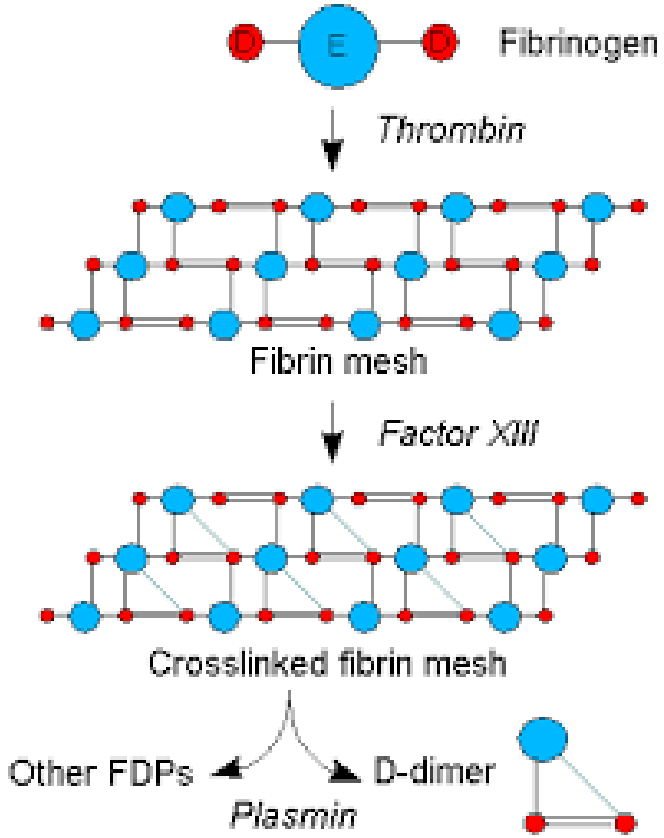
- Individuals with COVID-19 infection have been observed to have changes in a number of haemostatic factors
- Increased risk of VTE, particularly in critically unwell patients
- Haemostatic changes observed appear to lead to a hypercoagulable state with the exact mechanism unclear
  - Has been termed 'COVID-19-associated coagulopathy' (CAC)
- Appropriate evaluations and interventions to prevent or treat thrombosis is not well defined
  - A number of guidelines published
    - International society of thrombosis and haemostasis
    - American college of cardiology
    - Thrombosis and haemostasis society of Australia and New Zealand

Haemostatic Abnormalities

- Disease severity has been associated with
  - Thrombocytopenia
  - Elevated D-dimer
  - Prothrombin time (PT)
- Notable differences observed between survivors and non-survivors
  - Higher D-dimer
  - Prolonged PT
  - Disseminated intravascular coagulation (DIC)
    - 71% of COVID-19 patients who died fulfilled ISTH criteria, compared with only 0.6% among survivors

D-Dimer

- Digestion of cross-linked fibrin by plasmin generates D-dimers
- D-dimers used widely to exclude VTE, i.e. have strong negative predictive value
- Low PPV for VTE as raised in many conditions
  - DIC
  - Sepsis
  - Malignancy
  - Post surgery
  - Liver / cardiac / renal failure



D-Dimer in COVID-19 Infection

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†*

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China

Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, MD

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

BRIEF REPORT

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Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

Ning Tang[1] | Dengju Li[2] | Xiong Wang[1] | Ziyong Sun[1]

D-Dimer in COVID-19 Infection

- Huang et al
  - 41 patients => ICU vs non-ICU
  - 5 fold higher in ICU cohort
- Tang et al
  - 183 patients => Survivors vs non-Survivors
  - 3.5 fold higher in non-Survivors
- Wang et al
  - 138 patients => ICU vs non-ICU
  - 2.5 fold higher in ICU cohort
- Zhou et al
  - 191 patients => Survivors vs non-Survivors
  - 9 fold higher in non-Survivors

D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis

Giuseppe Lippi[1] Emmanuel J. Favaloro[2]

[1] Section of Clinical Biochemistry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy
[2] Department of Haematology, Sydney Centres for Thrombosis and Haemostasis, Institute of Clinical Pathology and Medical Research, NSW Health Pathology, Westmead Hospital, Westmead, New South Wales, Australia

Address for correspondence Giuseppe Lippi, MD, Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, 37134 Verona, Italy (e-mail: giuseppe.lippi@univr.it).

Thromb Haemost

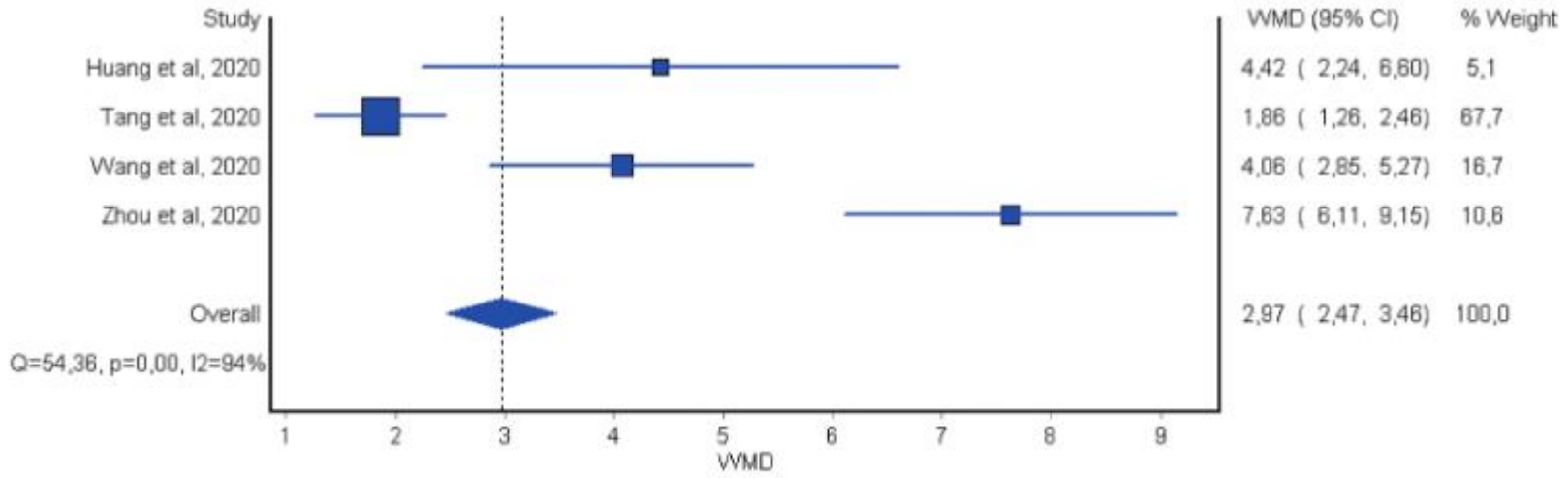


Fig. 1 Weighted mean difference and 95% confidence interval of D-dimer values between patients with or without severe form of coronavirus disease 2019.

Thrombocytopenia

- 5% of patients have platelet count < 100x10^9/L at the time of hospital admission
- 36% have platelet counts < 150x10^9/L at the time of hospital admission
- Aetiology of thrombocytopenia unclear
- Proposed mechanisms
  - Endothelial damage => platelet activation, aggregation and thrombosis
  - Direct viral suppression of megakaryocytes / marrow function
  - DIC

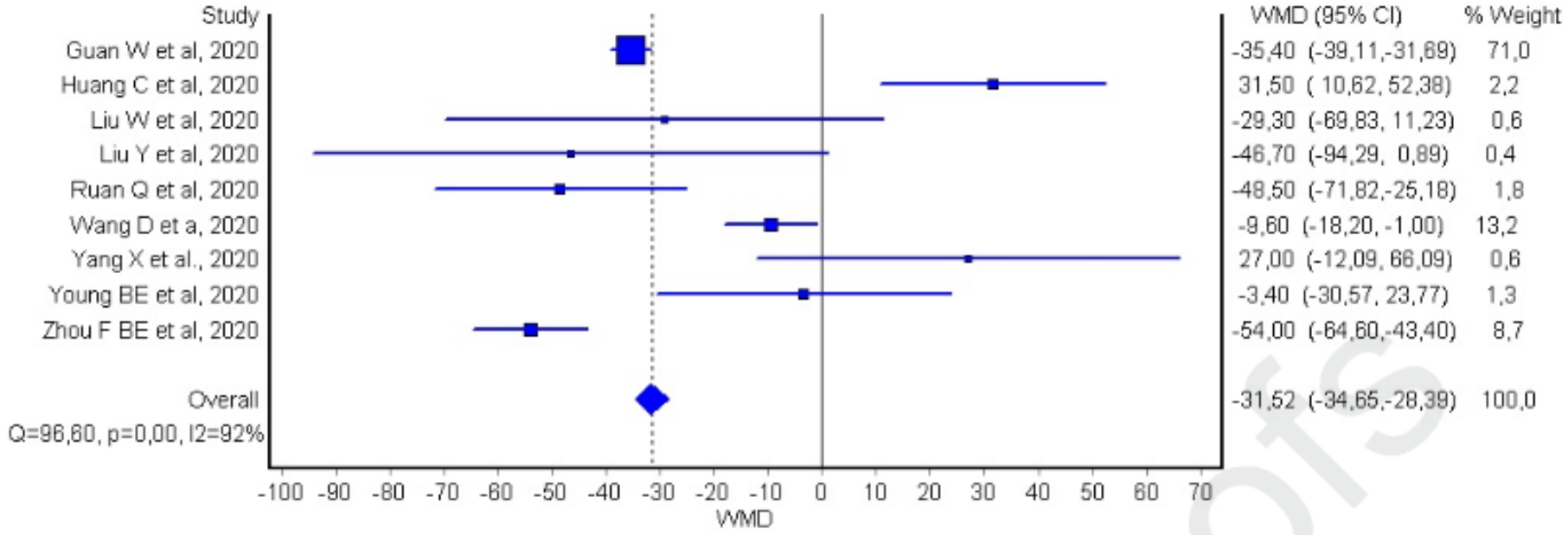
Thrombocytopenia

Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis

Giuseppe Lippi[1], Mario Plebani[2¶], Brandon Michael Henry[3¶]

- Meta-analysis of 9 studies
  - 1779 COVID-19 patients
  - 399 (22.4%) with severe disease
  - platelet count was significantly lower in patients with more severe COVID-19 (WMD -31x10^9/L)

Thrombocytopenia



Study ID	Country	N. Cases	Age	Female (%)	Platelet Count: all x 10^9/L	Platelet Count: Non-Severe x 10^9/L	Platelet Count: Severe x 10^9/L
Guan W et al. [11]	China	1099 (173 severe)	47 (median)	41.9%	168 (132-207)	172 (139-212)	137.5 (99.0-179.5)

Prothrombin Time

BRIEF REPORT

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Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

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- Prothrombin time mildly prolonged in non-survivors and critically ill
  - 15.5 seconds in non-survivors versus 13.6 seconds in survivors
  - 12.2 seconds in the ICU cohort versus 10.7 seconds in the non-ICU cohort at hospital admission

Venous Thromboembolism

- Emerging evidence of high rates of VTE in COVID-19
- Outpatient
  - No published data
- Inpatients (non-ICU)
  - Limited data
  - One case series of 124 patients
  - 4 patients (3%) developed VTE

Venous Thromboembolism

- Inpatients (ICU)
  - A number of case series published
  - VTE incidence 20-43%, mostly pulmonary emboli
  - Often despite thromboprophylaxis
- Series of 184 patients (The Netherlands)
  - Cumulative incidence of VTE of 27%
  - All patients received thromboprophylaxis
- Series of 150 patients (France)
  - VTE in 43%
  - All patients receiving low molecular heparin (70% prophylactic dose and 30% therapeutic dose)
  - Raised vWF Activity, vWF Antigen and FVIII activity in 87% suggesting endothelial dysfunction
  - No patient developed DIC

Is the VTE risk higher than expected?

- Series of 107 ICU patients
  - 21% developed VTE despite thromboprophylaxis
  - Incidence of PE in two matched cohorts of patients with Influenza
    - Same time interval – 6%
    - Previous year – 8%

- Series of 150 patients
  - 77 patients with COVID-19-associated acute respiratory distress syndrome (ARDS)
  - Compared to cohort of non-COVID ARDS patients
  - Rate of thrombotic complications (mostly PE) to be higher in the COVID-19 patients (12 versus 2 percent).

Arterial Events?

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal *has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.*

Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

Arterial Events?

- 5 cases of large vessel strokes over a 2 week period (NYC)
  - Patients less than 50 years of age
- By comparison, every 2 weeks over the previous 12 months, our service has treated, on average, 0.73 patients younger than 50 years of age with large-vessel stroke
- Retrospective study of data from the Covid-19 outbreak in Wuhan, China
  - Incidence of stroke among hospitalized patients with Covid-19 was approximately 5%
  - Youngest patient was 55

Pathogenesis of Thrombosis Risk

- Endothelial Injury
  - Direct invasion of endothelial cells by SARS-CoV-2 virus
  - Mediators of the acute systemic inflammatory response such as cytokines (eg, interleukin [IL]-6) and other acute phase reactants
  - Intravenous catheters
  - Evidence of raised von Willebrand Levels suggests endothelial injury
- Stasis
  - Immobilisation can cause stasis of blood flow in hospitalised and critically unwell patients
- Hypercoagulable State
  - A number of changes in prothrombotic factors have been described
  - Increased FVII activity, high fibrinogen and D-dimers
  - TEG findings => increased early thrombin burst and fibrin generation, and reduced fibrinolysis

Is it CAC or DIC??

COVID Associated Coagulopathy

- Mild thrombocytopenia
  - Typically 100-150x10^9/L
- Mild prolongation in PT and APTT
  - PT typically more prolonged than APTT (likely due to increased FVIII activity)
- D-dimer mild to moderately elevated
- Fibrinogen increased

Disseminated intravascular coagulation

- Moderate to severe thrombocytopenia
  - Typically 50-100x10^9/L
- Markedly prolonged PT and APTT
- D-dimer markedly elevated
- Fibrinogen decreased (<1g/L)

Is the thrombosis risk modifiable?

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Not yet recruiting NEW	Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients	• Covid19	• Drug: Enoxaparin
2	☐	Not yet recruiting NEW	Covid-19 Associated Coagulopathy	• COVID 19 Associated Coagulopathy	• Drug: Intermediate dose thromboprophylaxis • Drug: Standard of Care thromboprophylaxis
3	☐	Recruiting NEW	Preventing COVID-19 Complications With Low- and High-dose Anticoagulation	• COVID • Sars-CoV2	• Drug: Enoxaparin
4	☐	Recruiting NEW	A Randomized Trial of Anticoagulation Strategies in COVID-19	• COVID-19	• Drug: Enoxaparin Higher Dose • Drug: Lower-dose prophylactic anticoagulation
5	☐	Not yet recruiting NEW	Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19	• COVID-19 • Venous Thromboses • Arterial Thrombosis	• Drug: Enoxaparin Prophylactic Dose • Drug: Heparin Infusion • Drug: Heparin SC • Drug: Enoxaparin/Lovenox Intermediate Dose
6	☐	Not yet recruiting NEW	COVID-19 Anticoagulation in Children - Thromboprophlaxis (COVAC-TP) Trial	• Infection Viral • Thromboses, Venous	• Drug: Enoxaparin Prefilled Syringe [Lovenox]
7	☐	Not yet recruiting NEW	Trial Evaluating Efficacy and Safety of Anticoagulation in Patients With COVID-19 Infection, Nested in the Corimmuno-19 Cohort	• COVID19 Pneumonia	• Drug: Tinzaparin or unfractionated heparin
8	☐	Not yet recruiting NEW	Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care	• COVID-19	• Drug: Therapeutic Anticoagulation

Is the thrombosis risk modifiable?

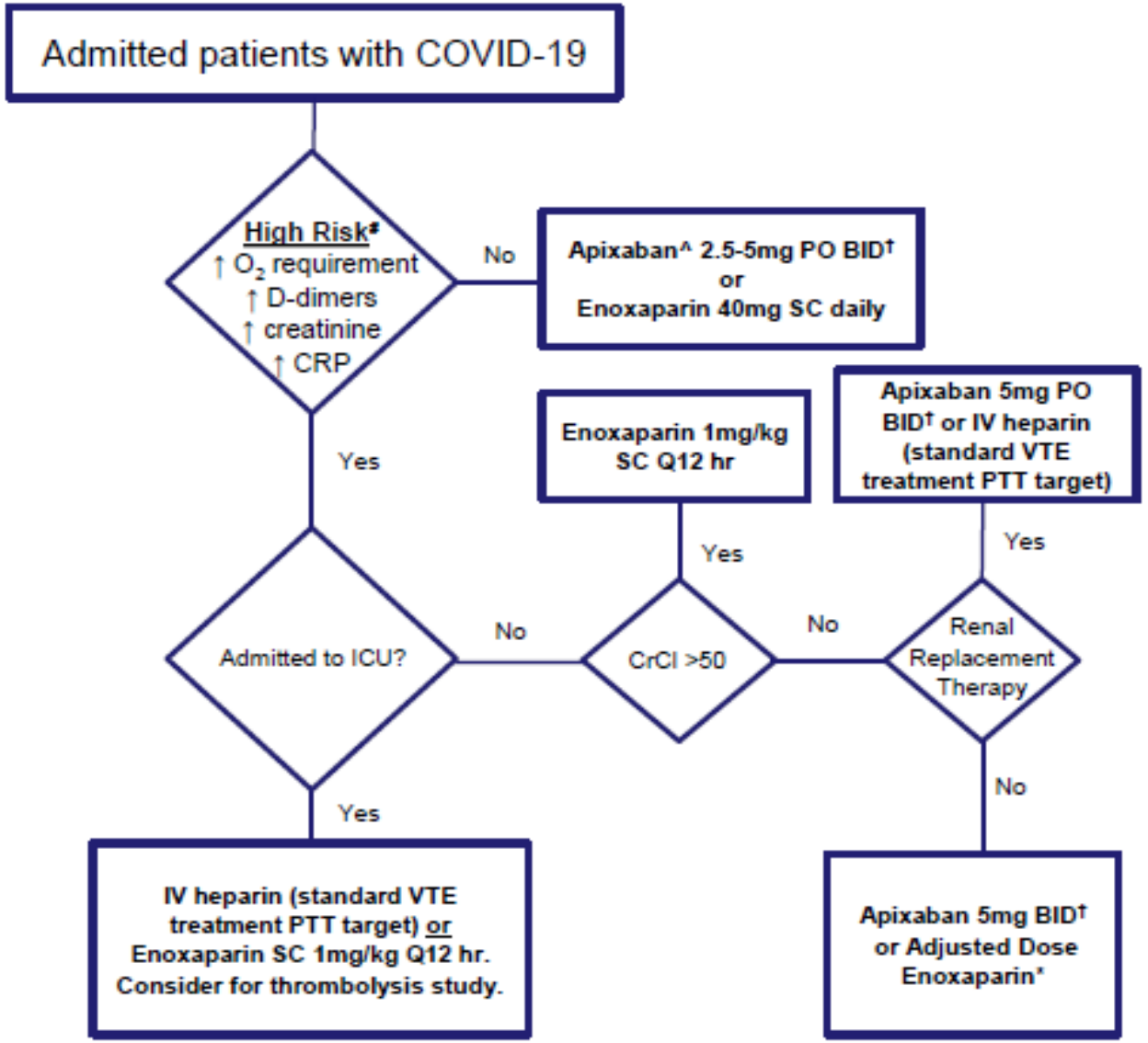
Fibrinolytic Therapy to Treat ARDS in the Setting of COVID-19 Infection: A Phase 2a Clinical Trial

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	60 participants
Allocation:	Randomized
Intervention Model:	Sequential Assignment
Intervention Model Description:	This is a Phase IIa clinical trial, open label, with a modified stepped-wedge design, testing systemic administration of fibrinolytic therapy with alteplase (tPA) versus standard of care for patients infected with COVID-19 resulting in severe respiratory failure. The design is a rapidly adaptive, pragmatic clinical trial, with 3 interim analyses and 1 final look at the data.
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Fibrinolytic Therapy to Treat ARDS in the Setting of COVID-19 Infection: A Phase 2a Clinical Trial
Estimated Study Start Date :	April 2020
Estimated Primary Completion Date :	August 2020
Estimated Study Completion Date :	October 2020

Version: April 15, 2020

Mount Sinai COVID-19 Anticoagulation Algorithm



Inclusion: All admitted patients with COVID-19
Exclusion: High risk of bleeding as judged by treating physician

High-risk for bleeding, consider:
- Platelet count <50,000
- INR >1.5
- Current or recent bleeding

Obtain: Baseline CBC, PT/PTT, D-dimer and daily CBC, D-dimer

Anticoagulant: Rivaroxaban may be used in place of Apixaban if CrCl >50.

Consider treatment-dose AC (Apixaban 5mg PO BID)† for 2 weeks post-discharge for patients on therapeutic anticoagulation while hospitalized

Received: 20 March 2020 | Accepted: 21 March 2020
DOI: 10.1111/jth.14810

RECOMMENDATIONS AND GUIDELINES

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ISTH interim guidance on recognition and management of coagulopathy in COVID-19

AMERICAN SOCIETY OF HEMATOLOGY

COVID-19 and Coagulopathy: Frequently Asked Questions

(Version 2.0; last updated April 14, 2020)

Input from Drs. Agnes YY Lee, Jean M Connors, Lisa Baumann Kreuziger, Mike Murphy, Terry Gernsheimer, Yulia Lin

Feature | Thrombosis and COVID-19: FAQs For Current Practice

Apr 22, 2020

Cardiology Magazine

AMERICAN COLLEGE of CARDIOLOGY

Thromboprophylaxis and thrombosis in COVID 19 infected patients admitted to hospital

16th Apr 20

THANZ
Thrombosis & Haemostasis society of Australia and New Zealand

Coronavirus disease 2019 (COVID-19): Hypercoagulability

Authors: Adam Cuker, MD, MS, Flora Peyvandi, MD, PhD

Section Editor: Lawrence LK Leung, MD

Deputy Editor: Jennifer S Tirnauer, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Apr 2020.** | This topic last updated: **Apr 29, 2020.**

Summary of Guidelines

- Evaluation (all inpatients)
  - Full blood count, PT, APTT, Fibrinogen, D-dimer
  - Monitor over time
- Diagnosis of VTE
  - Normal D-dimer sufficient to exclude VTE
  - DVT – Doppler Ultrasound
  - PE – CTPA (V/Q unlikely to be useful in COVID patients)
- Thromboprophylaxis
  - Recommended for all inpatients admitted with COVID-19
  - Dosing as per THANZ
    - Weight 40-120kg => Enoxaparin 40mg subcut daily
    - Weight > 120kg => Enoxaparin 60mg subcut daily or 40mg BD
    - Weight < 40k or eGFR < 30mL/min => Enoxaparin 20mg subcut daily
  - Consider extended dosing post discharge (immobile patients with low bleeding risk)

Therapeutic Anticoagulation?

- Strong Recommendation
  - Patients with documented VTE
- Weak Recommendation
  - Sudden deterioration in respiratory status in an intubated patient consistent with pulmonary embolism (PE), without another identifiable cause
- Uncertain benefit for commencing intermediate / therapeutic anticoagulation (rather than prophylaxis) in all patients admitted to hospital with COVID-19

Conclusions

- D-dimer, platelet count and PT appear to be prognostic
- Laboratory evidence for coagulopathy associated with COVID-19
- Increased incidence of VTE
  - Particularly in ICU cohort
  - Despite thromboprophylaxis
- Some experts argue for intermediate / therapeutic anticoagulation for ALL inpatients with COVID-19 – no high quality data to support this
- Consensus guidelines recommend standard thromboprophylaxis at this stage

Questions?