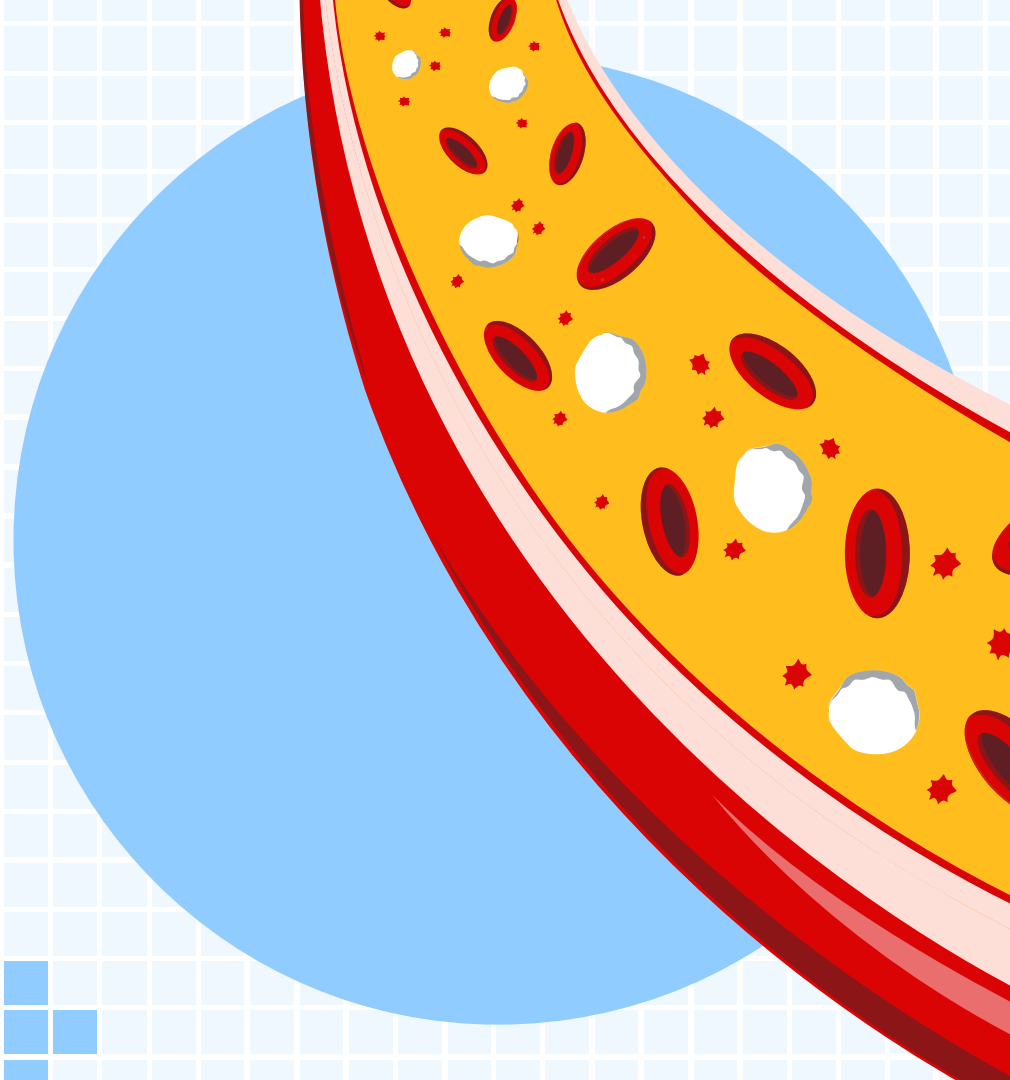
COVID-19-induced coagulopathy.

A review of pathophysiology, diagnosis, management, and prognosis with a focus on von Willebrand's Factor and ADAMTS13.

Presented by Jennifer Mills (21107045)



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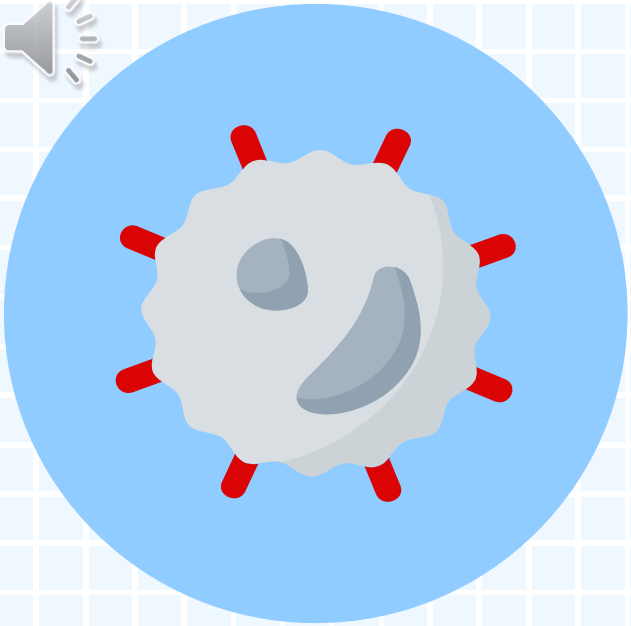


COVID-19: The virus that shook the world.

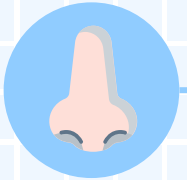
- COVID-19 is caused by the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2.)
- First identified in Wuhan, China in 2019, COVID-19 was declared a pandemic in March 2020.[1]
- It resulted in worldwide lockdowns and restrictions.
- >6 million people have died since Jan 2020[2]
  - 188K deaths occurred in the UK.[3]

The virus is formed of 4 structural components:

- Spike (S)
- Membrane (M)
- Envelope (E)
- Nucleocapsid (N)

COVID-19: Pathophysiology

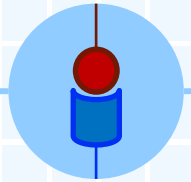
Infection



Airborne

- SARS-CoV-2 is carried in respiratory droplets and aerosols.
- It enters the host through inhalation.
- Initially it infects the nasal epithelium.

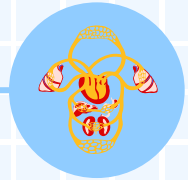
Proliferation



ACE-2

- The virus enters cells via Spike: ACE-2 interactions, triggering endocytosis. [4]
- The virus uses host cell structures to replicate.
- Virus particles are eventually released, often triggering host cell death.

Pathology



Variable Disease States

- **Mild Disease**: The virus is contained in the upper respiratory system. [4-5]
- **Moderate/Severe**: disease is caused by viral spread and can have disseminated effects.
- This is due to ACE-2's physiological distribution and inflammatory sequelae. [4-5]

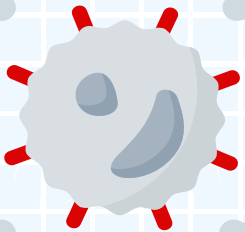
Signs and Symptoms of COVID-19 [6-7]

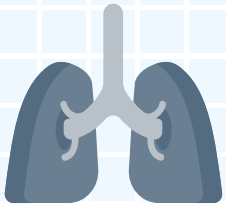
Fever

Fatigue

Anosmia

Continuous cough





Hypoxia/Dyspnoea

Pneumonia

Multi-organ failure.

Acute respiratory distress syndrome

Mild Symptoms

Severe Symptoms

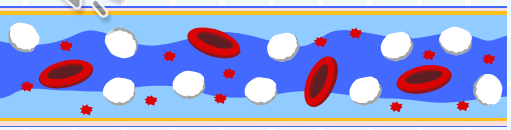
Haemostasis

Primary

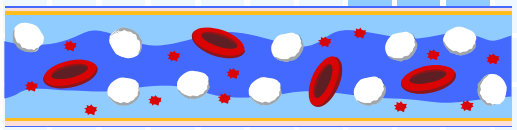
Primary haemostasis forms the initial plug which prevents bleeding and localises further haemostatic interactions.

Secondary

Secondary haemostasis stabilises the clot, forming the “bandage” which supports healing.



Primary Haemostasis



Endothelium

- Cell in constant contact with blood.
- Undamaged=antithrombotic
- When damaged, it becomes prothrombotic via:
  - Collagen exposure.
  - Weibel–Palade bodies (WPB) releasing p-selectin and vWF.
  - Tissue factor release.

Platelets

- Megakaryocytic fragments.
- Activated platelets change shape and degranulate.
- Granules contain prothrombotic agents (positive feedback.)
- With the endothelium, platelets form a negative reaction surface.

Von Willebrand's Factor (vWF)

- vWF is a large, multimeric protein.
- It has many binding sites.
- vWF forms a “bridge” between platelets and collagen.
- vWF also protects VIII.
- vWF size is moderated by ADAMT13 which prevents aberrant activation.

Primary Haemostasis.

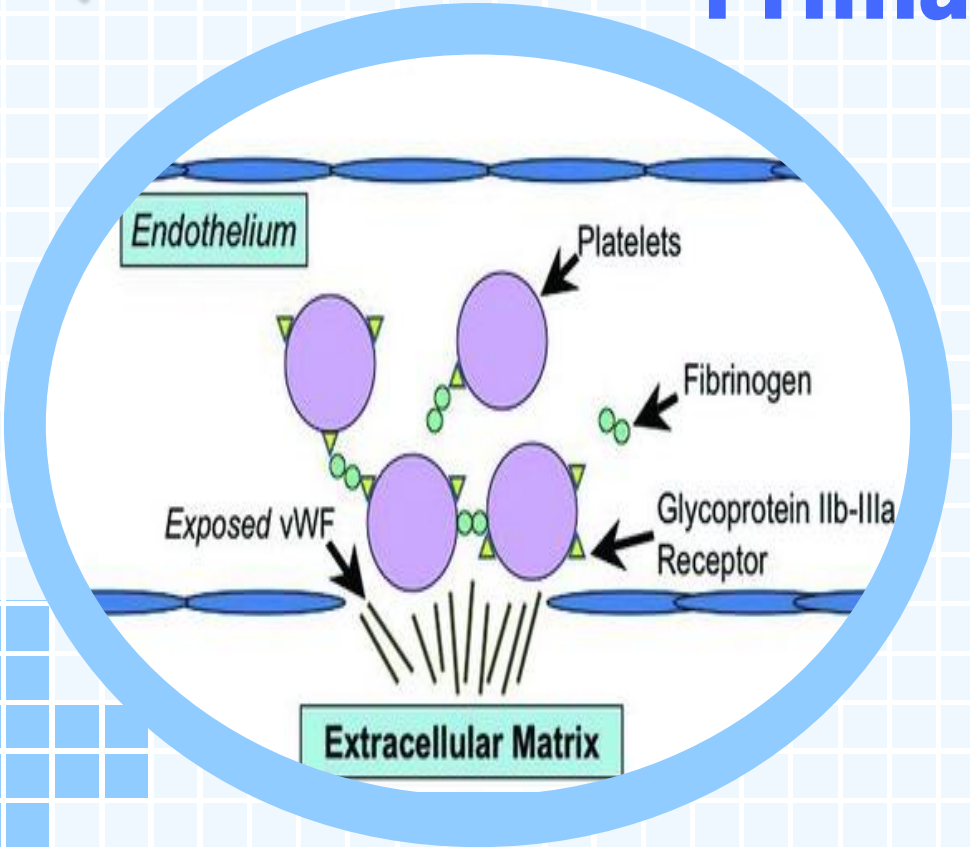


Figure 1: Diagram of initial primary haemostasis initiation.[8]

Injury to the endothelium releases WPB contents and exposes the extracellular matrix.

vWF binds to collagen, and the sheer force of blood flow exposes other bindings sites.

vWF binds to GPIbα receptors on platelets, recruiting them to the site. Platelets are stabilised by complexing with collagen through integrin a2b1/GPVI.

Activated platelets release factors e.g. thromboxane which encourages platelet aggregation (positive feedback loop.)

GpIIb-IIIa on platelets recruits fibrinogen-forming the platelet plug.

Secondary Haemostasis

- The intrinsic cascade initially relies on the extrinsic cascade but once active is more effective at Xa generation

- Secondary haemostasis triggers regulatory pathways e.g. Protein C which prevents overactivation and promotes thrombolysis.

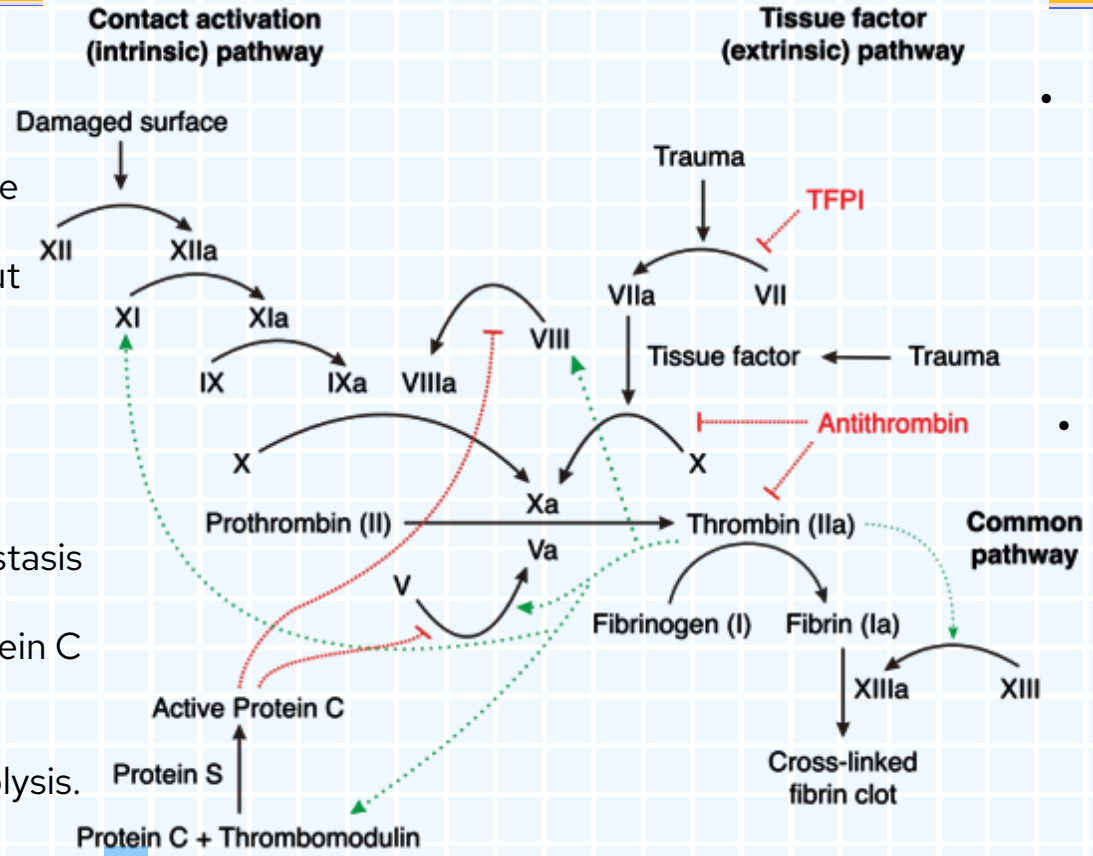


Figure 2: Diagram of Secondary Haemostasis.[9]

- The extrinsic cascade is activated by tissue factor and is the first pathway to activate and produce Xa.

- Both pathways converge on the common pathway, which uses Xa to generate Thrombin, which converts fibrinogen to fibrin.

02

COVID-19 induced coagulopathy and the vWF: ADAMTS13 Axis.

COVID-19 Coagulopathy: A Concerning Complication.

01

Thrombosis was an unexpected COVID-19 feature.

Venous thrombosis (VTE) is a risk of extended hospital stays and immobility but was unexpectedly common in severely unwell COVID-19 patients compared to controls. Up to 34% of COVID-19 ICU patients experience VTE, with a mortality rate of up to 54%.[10]

02

Coagulopathy was associated with worse outcomes.

One study found that 50% of non-surviving patients were procoagulant, compared to only 7% of survivors. Studies suggest it has contributed to up to 10% of COVID-19 deaths. [11-12]

03

Coagulopathy is part of COVID-19 ARDS.

One study found alveolar-capillary thrombi were 9 times more prevalent in COVID-19 ARDS than flu ARDS, and are likely a cause of gas exchanges defects. [12-13]

COVID-19 Coagulopathy: Pathophysiology

Any endothelium expressing ACE-2 receptors can be affected by SARS-CoV-2. Endothelial dysfunction results in the exposure of procoagulant structures and encourages thrombosis. [4-5,12]

Some studies indicate low expression of ACE-2 receptors on the epithelium, so, damage may be mediated by indirect mechanisms. [4]

Disruption to RAAS pathways triggers vessel constriction and permeability. [4,14]

Immune dysfunction creates a procoagulant environment.[4]

vWF antigen including ultra-large forms, soluble P-selectin, and PAI-1 are increased in severe COVID-19 infection and may be released from endothelium. [5,11-12]

Resting platelets express increased P-selectin, which increases sensitivity to activation. [15]

Activated platelets secrete prothrombotic factors, creating a positive feedback loop.

vWF and COVID-19 Coagulopathy.

01

vWF is increased and associated with worse outcomes.

Levels have been recorded as high as 600 U/dL (reference range: 50–200 U/dL). Significantly higher levels were seen in ITU patients and patients with higher hypoxia and mortality rates. [6,17]

02

Distribution of multimers is abnormal.

Studies have shown increased ultra-high molecular weight multimers, while others have shown an increase in intermediate and low molecular weight VWF multimers. In all cases, there is an abnormal multimer distribution. [18]

03

The exact pathology is unknown.

Severe local inflammatory responses may cause vWF release from the endothelium however, Pro-peptide vWF is not increased, suggesting a possible failure of clearance. It is unclear if vWF is a driver of disease severity or a side effect of severe disease pathology.[12,17]

ADAMTS13 and COVID-19 Coagulopathy.

01

In COVID-19, ADAMS13 levels are reduced.

Typical reduction is not lower than 20IU/dL but decreased levels are associated with disease severity. This reduction leads to a deranged function of vWF within haemostasis. [18-19]

02

It is not the same as TTP!

Antibodies are not seen in COVID-19 coagulopathy, and levels do not meet the <10IU/dL threshold for TTP. Thrombocytopenia is not as severe as in TTP.[16]

03

The exact pathology is unknown.

Reduction may be consumptive due to increased vWF (saturation of the enzyme), or liver biosynthesis may be suppressed due to inflammation. [19]

The vWF: ADAMTS13 Axis

vWF is Increased

01

ADAMTS13 is decreased.

In health vWF:ADAMTS13 is 1:1 [16]

↑ Vwf:ADAMTS13

02

Secondary TMA

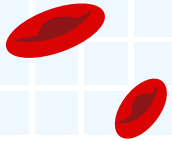
Tilting this ratio in favour of vWF, alongside normal platelets, results in a picture similar to secondary thrombotic microangiopathy.[16]

Procoagulant Enviroment.

03

Increased thrombotic risk.

This creates an environment that promotes clotting, supporting the other procoagulant aspects of COVID-19.[18]



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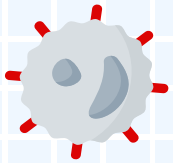
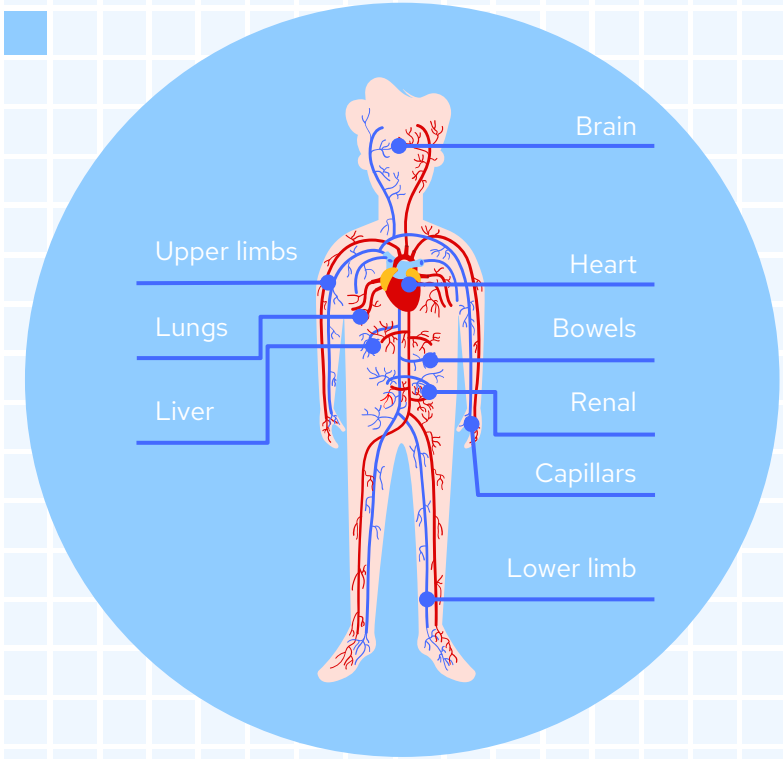


Presentation and Diagnosis.

Signs and Symptoms.



Venous thrombosis is a common feature of COVID-19 coagulopathy.

- Features include leg swelling, hypoxia, and shortness of breath.
- This is more common in ITU patients.[10,20]

Common thromboses include: DVT (11.2%), PE (7.8%) and Arterial thrombosis (3.9%).[20]

Microthrombi have been implicated in disseminated features of COVID-19 including:

- Cardiac injury and necrosis.[21]
- Acute Respiratory Distress Syndrome.[22]
- Autopsies have shown microthrombi in lungs, kidney, heart, and liver.[23]
  - These may contribute to organ failure.

Essential Laboratory Testing

Guidelines recommend these tests for COVID-19 coagulapathy diagnosis [24-26]

Test	Result in COVID-19 coagulopathy.	Contribution to the differential.
D-Dimer	↑↑↑	↑ D-dimers are a VTE feature, but in COVID-19 they are much higher and are diagnostic. ↑ D-dimers are a poor prognostic indicator.
PT/APTT	↑	↑PT/APTT are associated with coagulopathies, commonly bleeding or consumptive pathology, and are non-specific. ↑PT/APTT is a poor prognostic indicator in COVID-19.
Platelets	↓ to normal	Severe thrombocytopenia is expected in DIC/MAHA. In COVID-19, reductions are mild to moderate (>$100x10^9$). The degree of thrombocytopenia appears to correlate with severity.
Fibrinogen	↑↑	↓ Fibrinogen is expected in DIC and other MAHAs. ↑Fibrinogen is seen in all COVID-19 coagulopathy severity states but decreases rapidly at death.

Other Laboratory Testing.

Lupus Anticoagulant

Positive antiphospholipid antibodies in previously unknown/negative patients have been seen. However, there are many confounding factors so the significance is unknown.[25-27]

Neutrophil Lymphocyte Ratio

Neutrophilia with concurrent lymphopenia is seen in severe COVID-19. N:L of >9 is associated with increased mortality.[25]

Lacate Dehydrogenase

Increased levels have been seen in COVID-19 and are associated with increased mortality. However, raised LDH is highly non-specific.[28]

Other abnormal laboratory tests include:
CRP, vWF activity, ADAMTSI3, FVIII, and ROTEM/TEG.[25]

Clinical Assessment.

Assessment of thrombosis relies on VTE assessment tools including:

- Well's Score.
- Doppler Sonography

Suggested clinical assessment tools for COVID-19 coagulopathy management include:

- DIC Score.
  - DIC >5 was seen in 71% of non-survivors vs. 0.6% of survivors, so is associated with mortality.[24]
  - The score appears to increase as the disease progresses.[29-30]
- Sepsis Induced Coagulopathy Score (SIC)
  - Patients with SIC >4 have better outcomes when anticoagulated.[24]
  - SIC >4 is associated with increased ITU mortality.[29]

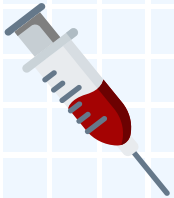
Sepsis Induced Coagulopathy Score

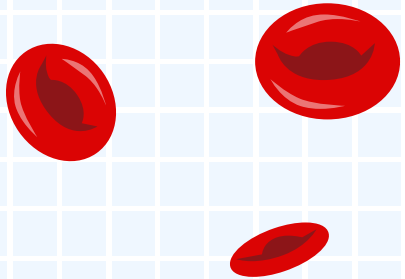
Test	Result	Score
Platelet Count (x109/L)	100-500	1
	<100	2
INR	1.2-1.4	1
	>1.4	1
SOFA Score (Sepsis)	1	1
	>2	2
Positive Score		>4

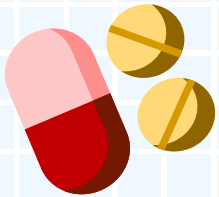
Key differences from the DIC Score include the absence of Fibrinogen, and D-dimer levels and the inclusion of the SOFA score, which is a sepsis assessment tool. [24]

04

Management.







Anticoagulants.

LMWH: More than just an anticoagulant?

Possible non anticoagulant actions of LMWH [35-37]:

- Reducing IL-6.
- Reduced virus shedding (reduced spread).
- Inhibition of heparinase (associated with endothelial leakage)
- Neutralisation of chemokines and histones (NETS)

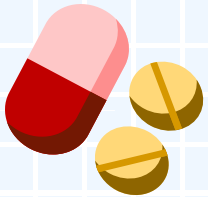
Low Molecular Weight Heparin is recommended by ASH and ISTH guidelines for the management of confirmed VTE in COVID-19 patients. [26,31]

The use of prophylactic anticoagulants comes with variable recommendations in COVID-19.

- Early observation indicated patients may clot despite prophylaxis.[32]
- A clinical trial incorporating REMAP-CAP, ATTACC, and ACTIV-4a showed full dose heparin reduced the need for vital organ support in moderately ill patients.[12,33]
- However, this was not seen in ITU patients, and was outweighed by bleeding risks. [34]
- Currently ASH and ISTH recommend the use of LMWH prophylaxis in critically ill cases. [26]
    - Patients with SIC >4 and D-dimers >6 have reduced mortality when treated with heparin.[29]

Novel Therapeutics.

There are several possible novel therapeutics in the treatment of COVID-19 coagulopathy.



Caplacizumab.

Caplacizumab could be used to remove excess vWF. There are no current ongoing trails, likely due to drug expense.[12-13,38]

Plasma exchange.

Plasma exchange could help restore haemostatic balance and remove excess inflammatory proteins associated with coagulopathy. [12]

Recombinant ADAMTS13

In vitro studies showed that incubation of plasma with rADAMTS13 corrects the abnormal vWF distribution. [13,39]

IL-6 Inhibition

Inhibitors such as tocilizumab have trials underway and data suggests it may help suppress the cytokine storm and reduce mortality [12,40]

Conclusions

COVID-19 triggers a unique coagulopathy.

Coagulopathy occurs in COVID-19 through several postulated mechanisms including vWF: ADAMTS13 derangement, and likely contributes to many of the disseminated disease effects.

Coagulapathy is associated with severity.

Coagulopathy is more common in non-surviving patients and is associated with increased oxygen requirements and organ failure.[41]

Laboratory abnormalities are key in dianosis.

Guidelines recommend D-Dimer, fibrinogen, PT/APTT and platelets testing when evaluating patients for COVID-19 coagulopathy.[41]

Use of anticoagulants is variable across studies.

The use of anticoagulants is essential in confirmed VTE, and prophylactic doses may be beneficial in moderate, but not severe cases according to some studies.

Novel therapeutics are in development.

IL-6 inhibition novel use of LMWH and direct targeting of deranged components may improve COVID-19 coagulopathy.

Thanks!

Do you have any questions?

Jennifer.mills@porthosp.nhs.uk

References.

1. Ghebreyesus T. Who director-general's opening remarks at the media briefing on COVID-19 - 11 march 2020 [Internet]. World Health Organization. World Health Organization; 2020 [cited 2022Apr11]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Worldometers.info. Coronavirus death toll [Internet]. Worldometer. Worldometers.info; 2022 [cited 2022Apr11]. Available from: https://www.worldometers.info/coronavirus/coronavirus-death-toll/
3. UK Health Security Agency. UK summary | Coronavirus (COVID-19) in the UK - data.gov.uk [Internet]. Gov.uk. UK Health Security Agency.; 2022 [cited 2022Apr11]. Available from: https://coronavirus.data.gov.uk/details/
4. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of covid-19 [Internet]. Nature News. Nature Publishing Group; 2020 [cited 2022Apr11]. Available from: https://www.nature.com/articles/s41591-020-0968-3
5. Parasher A. Covid-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgraduate Medical Journal. 2020Sep25;97(1147):312–20.
6. ALIMOHAMADI Y, SEPANDI M, TAGHDIR M, HOSAMIRUDSARI H. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. Journal of Preventative Medicine and Hygiene. 2020Sep;61(3):E304–E312.
7. Berlin DA, Gulock RM, Martinez FJ. Severe Covid-19. The New England Journal of Medicine . 2020Dec17;383:2451–60.
8. Davis JE, Garmel GM. 15 - Bleeding. In: Mahadevan SV, editor. An Introduction to Clinical Emergency Medicine. 2nd ed. Cambridge, UK: Cambridge University Press; 2021. p. 197–206.
9. Medbullets Team. Coagulation Cascade [Internet]. MEDBULLETS. Lineage Medical, Inc; 2019 [cited 2022Apr11]. Available from: https://step1.medbullets.com/hematology/111004/coagulation-cascade
10. Jenner WJ, Gorog DA. Incidence of thrombotic complications in COVID-19. Journal of Thrombosis and Thrombolysis. 2021May28;52(4):999–1006.
11. Seth R, McKinnon TA, Zhang XF. Contribution of the von willebrand factor/ADAMTS13 imbalance to covid-19 coagulopathy. American Journal of Physiology-Heart and Circulatory Physiology. 2022Dec22;322(1).
12. Portier I, Campbell RA, Denorme F. Mechanisms of immunothrombosis in covid-19. Current Opinion in Hematology. 2021Nov;28(6):445–53.
13. Philippe A, Gendron N, Bory O, Beauvais A, Mirault T, Planquette B, et al. Von Willebrand factor collagen-binding capacity predicts in-hospital mortality in COVID-19 patients: Insight from VWF/ADAMTS13 ratio imbalance. Angiogenesis. 2021May11;24(3):407–11.
14. Sriram K, Insel PA. Inflammation and thrombosis in COVID-19 pathophysiology: Proteinase-activated and purinergic receptors as drivers and candidate therapeutic targets. Physiological Reviews. 2021Mar9;101(2):545–67.

References.

15. Agrati C, Sacchi A, Tartaglia E, Vergori A, Gagliardini R, Scarabello A, et al. The role of P-selectin in COVID-19 coagulopathy: An updated review. International Journal of Molecular Sciences. 2021Aug22;22(15):7942.
16. Favaloro EJ, Henry BM, Lippi G. EDITOR'S PICK: VON WILLEBRAND FACTOR AND ADAMTS13 IN COVID-19 AND BEYOND: A QUESTION OF BALANCE. EMJ. 2021;(9):55–68.
17. Ladikou EE, Sivaloganathan H, Milne KM, Arter WE, Ramasamy R, Saad R, et al. Von Willebrand factor (vwf): Marker of endothelial damage and thrombotic risk in COVID-19? Clinical Medicine. 2020Sep21;20(5):e178–e182.
18. Mancini I, Baronciani L, Artoni A, Colpani P, Biganzoli M, Cozzi G, et al. The Adamts13-von Willebrand factor axis in COVID-19 patients. Journal of Thrombosis and Haemostasis. 2020Dec18;19(2):513–21.
19. Hafez W, Ziade MA, Arya A, Saleh H, Ali S, Rao SR, et al. Reduced ADAMTS13 activity in correlation with pathophysiology, severity, and outcome of covid-19: A retrospective observational study. International Journal of Infectious Diseases. 2022Feb12;117:334–44.
20. Tan BK, Mainbourg S, Friggeri A, Bertoletti L, Douplat M, Dargaud Y, et al. Arterial and venous thromboembolism in COVID-19: A study-level meta-analysis. Thorax. 2021;76(10):970–9.
21. Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, et al. Microthrombi as a major cause of cardiac injury in covid-19. Circulation. 2021Jan22;143(10):1031–42.
22. Fahmy OH, Daas FM, Salunkhe V, Petrey JL, Cosar EF, Ramirez J, et al. Is microthrombosis the main pathology in Coronavirus Disease 2019 severity?—a systematic review of the postmortem pathologic findings. Critical Care Explorations. 2021May;3(5).
23. Parra-Medina R, Herrera S, Mejia J. Systematic review of Microthrombi in covid-19 autopsies. Acta Haematologica. 2021;144(5):476–83.
24. Sarkar M, Madabhavi IV, Quy PN, Govindagoudar MB. Covid-19 and Coagulopathy. The Clinical Respiratory Journal. 2021Aug16;15(12):1259–74.
25. Salabei JK, Fishman TJ, Asnake ZT, Ali A, Iyer UG. Covid-19 coagulopathy: Current knowledge and guidelines on anticoagulation. Heart & Lung. 2021;50(2):357–60.
26. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of Coagulopathy in Covid-19. Journal of Thrombosis and Haemostasis. 2020;18(5):1023–6.
27. Favaloro EJ, Henry BM, Lippi G. Is lupus anticoagulant a significant feature of covid-19? A critical appraisal of the literature. Seminars in Thrombosis and Hemostasis. 2021Jun15;48(01):055–71.
28. Martha JW, Wibowo A, Pranata R. Prognostic value of elevated lactate dehydrogenase in patients with COVID-19: A systematic review and meta-analysis. Postgraduate Medical Journal. 2021Jan15;
29. Zheng R, Zhou J, Song B, Zheng X, Zhong M, Jiang L, et al. Covid-19-associated coagulopathy: Thromboembolism prophylaxis and poor prognosis in ICU. Experimental Hematology & Oncology. 2021Feb1;10(1).
30. BSH. The DIC score is of prognostic value in COVID-19 pneumonia. London : The British Society for Haematology; 2020.

References.

31. Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with covid-19. Blood Advances. 2021Feb8;5(3):872–88.
32. Miesbach W, Makris M. Covid-19: Coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clinical and Applied Thrombosis/Hemostasis. 2020Jul17;26.
33. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with covid-19. New England Journal of Medicine. 2021Aug26;385(9):790–802.
34. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with covid-19. New England Journal of Medicine. 2021Aug26;385(9):777–89.
35. Pereyra D, Heber S, Schrottmaier WC, Santol J, Pirabe A, Schmuckenschlager A, et al. Low-molecular-weight heparin use in coronavirus disease 2019 is associated with curtailed viral persistence: A retrospective multicentre observational study. Cardiovascular Research. 2021Oct5;117(14):2807–20.
36. Shi C, Wang C, Wang H, Yang C, Cai F, Zeng F, et al. The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: A retrospective clinical study. Clinical and Translational Science. 2020Nov1;13(6):1087–95.
37. Buijsers B, Yanginlar C, Maciej-Hulme ML, de Mast Q, van der Vlag J. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. eBioMedicine. 2020;59.
38. Ferner RE, Levi M, Sofat R, Aronson JK. Thrombosis in COVID-19: clinical outcomes, biochemical and pathological changes, and treatments. Oxford COVID-19 Evidence Service Team. 2020Jun4;
39. Hafez W, Ziade MA, Arya A, Saleh H, Ali S, Rao SR, et al. Reduced ADAMTS13 activity in correlation with pathophysiology, severity, and outcome of covid-19: A retrospective observational study. International Journal of Infectious Diseases. 2022Feb12;117:334–44.
40. Cortegiani A, Ippolito M, Greco M, Granone V, Protti A, Gregoretti C, et al. Rationale and evidence on the use of tocilizumab in COVID-19: A systematic review. Pulmonology. 2021May1;27(1):52–66.
41. Naqvi IH, Alam MT, Rehan M, Mahmood K, Aurangzeb M, Talib A. Covid-19-associated coagulopathy and thromboembolism: Determination of their patterns and risk factors as predictors of mortality among severe COVID-19 patients. Current Vascular Pharmacology. 2022;20(1):77–86.