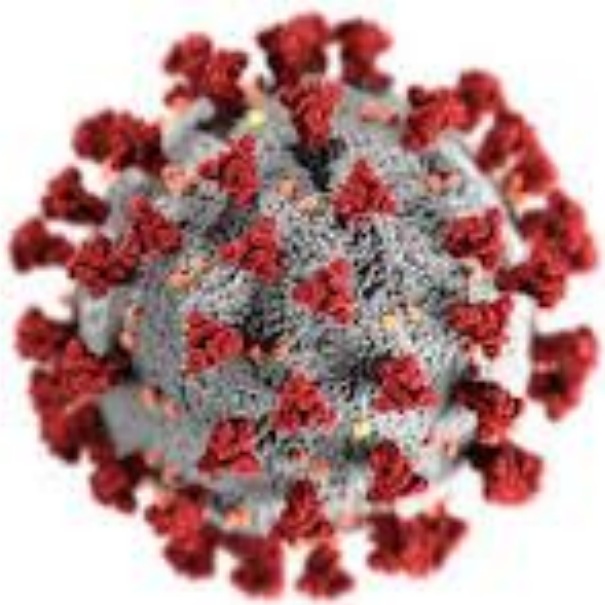
COVID-19 and the Role of Advanced Coagulation Therapy and Monitoring



Galit Frydman, DVM, ScD

Chief Science Officer

Coagulo

Medical Technologies, Inc.

Summary

1. Coagulation and inflammation are intertwined
2. Coagulopathies are common in COVID-19 patients (prothrombotic)
3. Anticoagulation therapy needs further investigation
   - What drug to administer
   - Proper dosage
   - When to start it
4. Coagulation testing currently available is inadequate for effective management of coagulation in COVID-19 patients
5. New diagnostic approaches are required for diagnosis, treatment and research

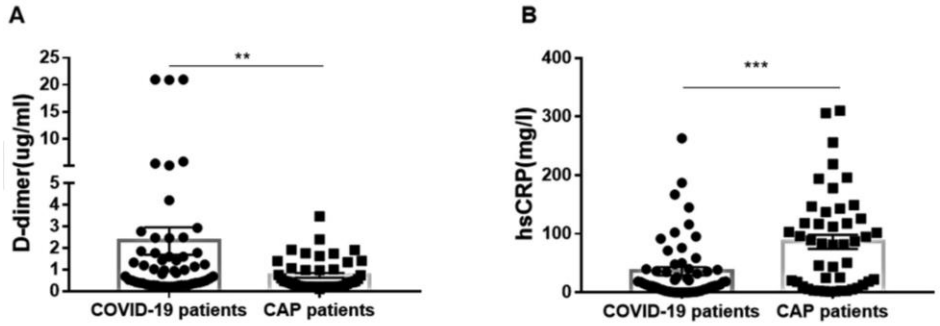
Notes before reading

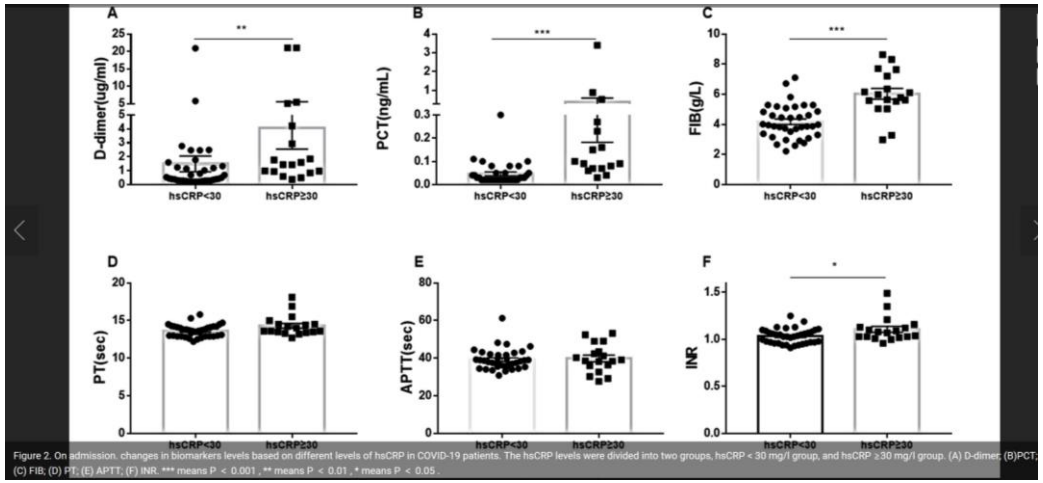
- A large portion of the COVID-19 basic and clinical research has not been peer-reviewed (pre-print) and/or comes from a relatively small number of cases.
- Understanding of COVID-19 will continue to advance and evolve with future scientific research and publications.
- The majority of published reports are from China — different geographies may report contradictory findings due to demographics, divergent health care standard practices and/or natural genetic variation (both in patients and in the virus itself).
- This review does not address all the mechanisms of coagulation and inflammation, such as thrombin, changes in white blood cell counts, endothelial function and platelet function.
- The material that follows is for informational purposes only. Nothing herein is intended to offer medical advice, including for the diagnosis and/or treatment of COVID-19.

Case Reports: COVID-19 and Coagulopathy

- **Multiple case reports confirm a tendency toward a prothrombotic state**

- Specific biomarker and scoring changes consistently appear to be associated with poor prognosis
  - D-dimer is elevated — increases along with inflammatory markers
  - Fibrin degradation products (FDPs) are elevated
  - Fibrinogen is elevated
  - Slight prolongation in PT/aPTT
  - High SOFA scores
  - Detection of anticardiolipen and anti-B2-glycoprotein antibodies (3 cases reported)



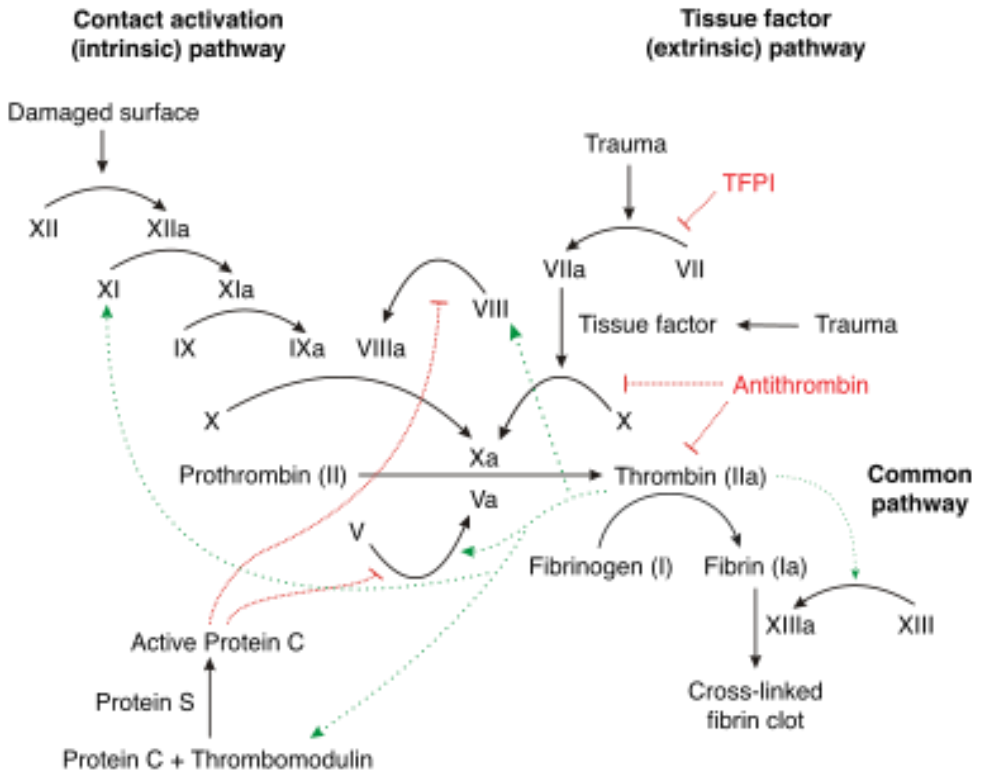


Yu B, 2020

Zhou F, 2020; Yu B, 2020; Tang N, 2020; Zhang Y, 2020

Brief Review: Coagulation and Fibrinolysis

- **PT**
  - Prothrombin Time
  - Extrinsic and common pathway
- **aPTT**
  - Activated Partial Thromboplastin Time
  - Intrinsic and common pathway
- **D-dimer and FDPs** (Fibrin degradation products)
  - Reflects the formation of blood clots as well as activation of fibrinolysis
- **Platelets**
  - Blood cell involved with blood clot formation



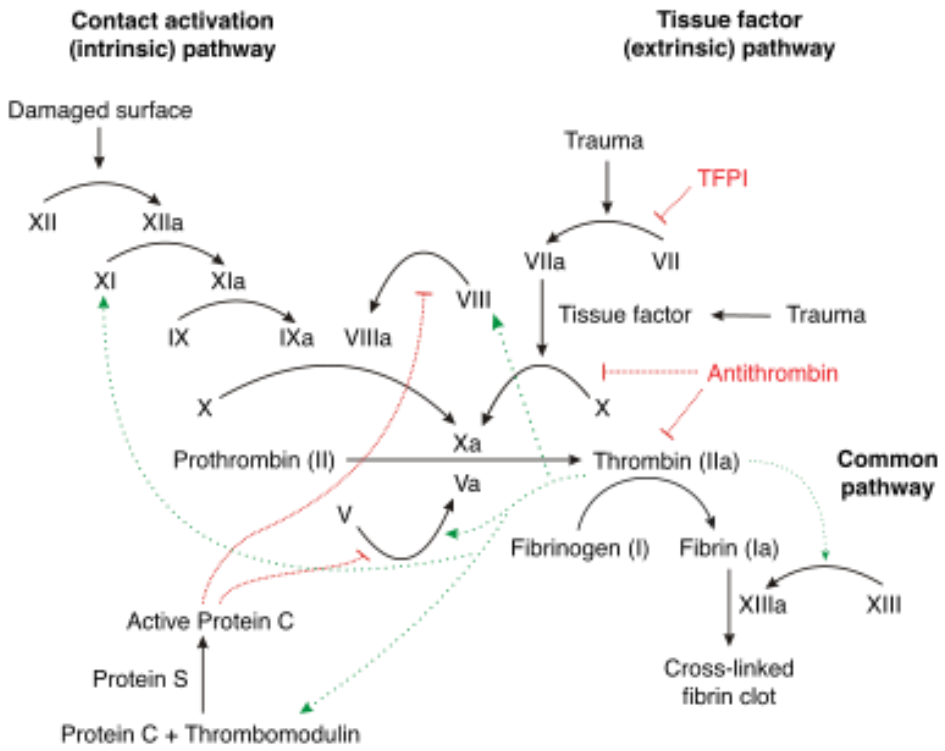
Wikipedia

Brief Review: Coagulation and Fibrinolysis

- **Fibrinogen**
  - Role in blood clot formation
  - Positive acute phase protein — may increase with inflammation

- **Antithrombin III (ATIII)**
  - Inhibitor of Coagulation Factor Xa/IIa
  - Heparin binds to ATIII and promotes inhibition of coagulation
  - Negative acute phase protein

- **Heparanase**
  - Enzyme that can inactivate heparin
  - Commonly located on the cell surface
  - May increase during inflammation

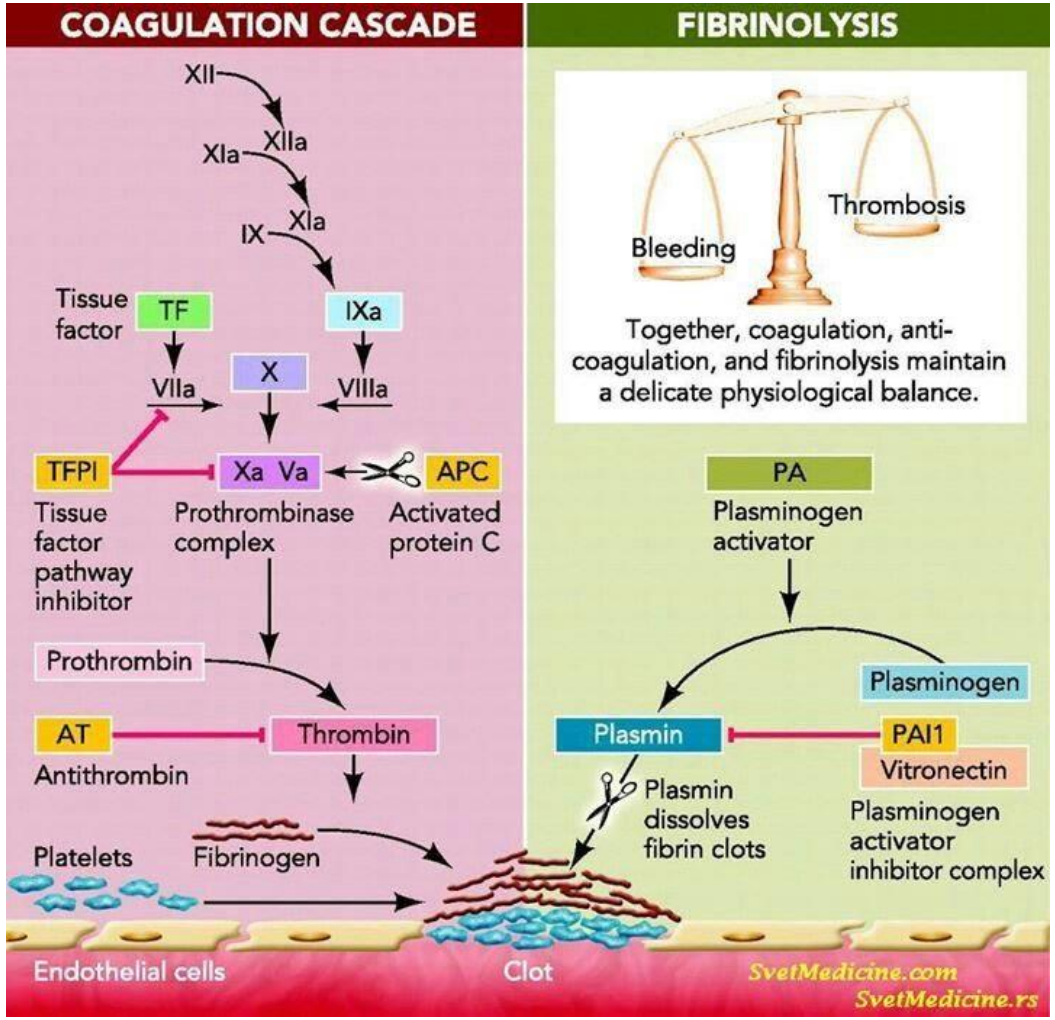


Wikipedia

Disseminated Intravascular Coagulation (DIC)

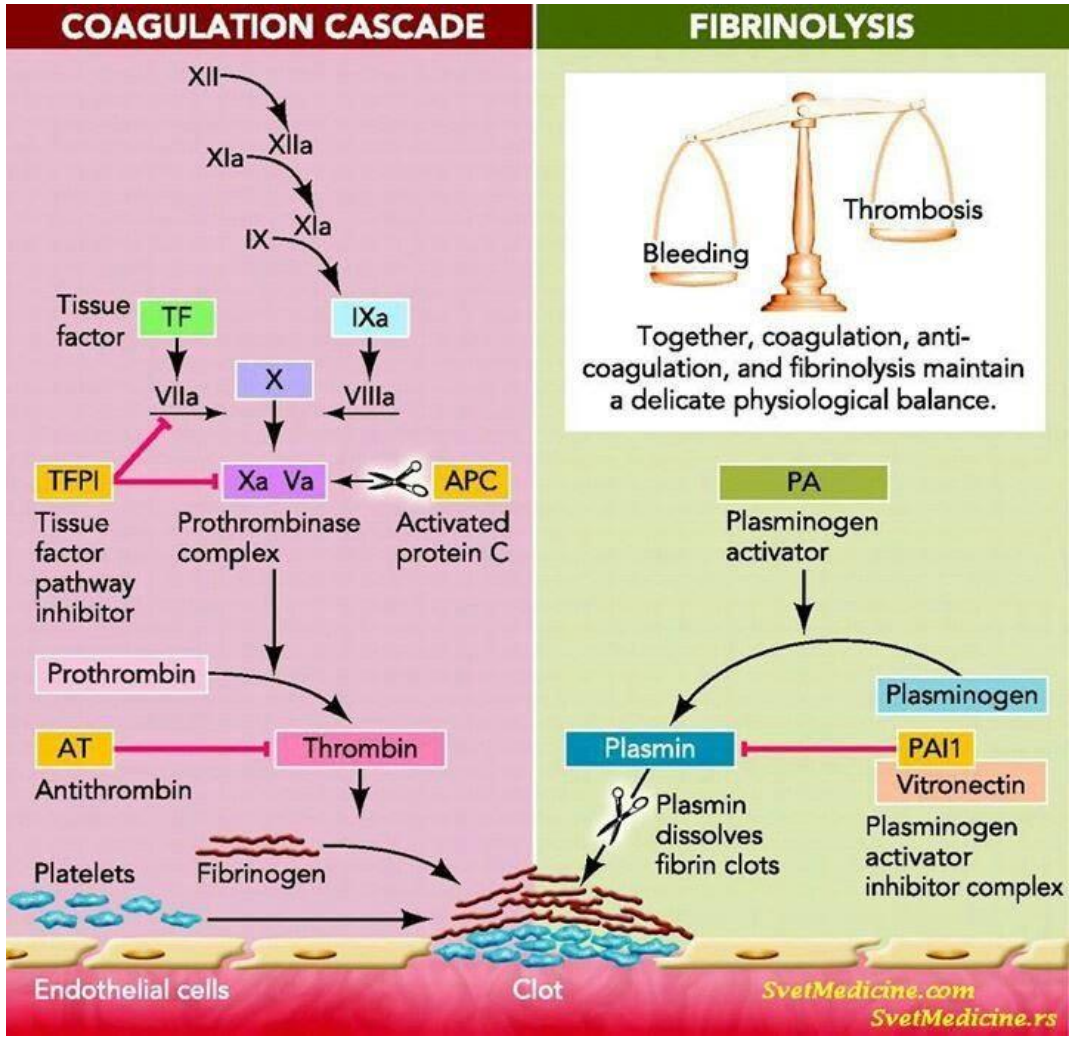
- **Multiple causes**
  - Severe inflammation
  - Trauma
  - Infection
  - Toxin (Snake bite)

- **Two phases**
  1. **Hyper**coagulable phase
     - Increased clot formation
  2. **Hypo**coagulable phase
     - Increased bleeding
     - Usually secondary to consumption of coagulation factors during the hypercoagulable phase



Does COVID-19 Result in DIC?

- Severe COVID-19 infection has been shown to be associated with a prothrombotic state
- Prolongation of PT/aPTT and thrombocytopenia are **NOT** commonly seen in these patients
- Is DIC the incorrect term for these patients?
- Or, is the thrombotic stage so severe that, coupled with the concurrent respiratory distress, patients don't survive to reach the hypocoagulable phase?



(ISTH webinar, 2020)

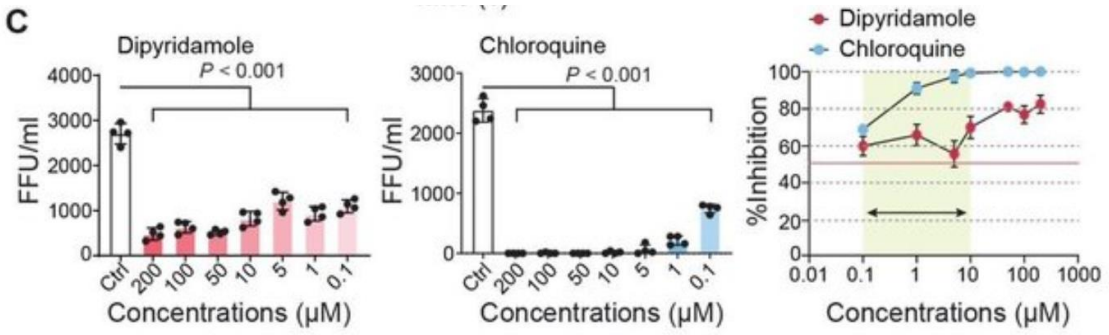
Publications: Anticoagulants in COVID-19 Patients

- **Heparin** (Tang N, 2020)
  - Unfractionated heparin (UFH) and low molecular weight heparin (LMWH)
  - 449 patient evaluated (99 received anticoagulation)
  - No difference in 28-day mortality between heparin and no heparin
  - 28-day mortality of heparin users were lower than non-users in patients with high SIC score or elevated D-dimer

- **Dipyridamole (DIP)** (Liu X, 2020)
  - In vitro studies showed suppression of COVID-19 replication
  - Trial in 12 COVID patients — associated with increased platelet count and decreased lymphocyte count
  - 2 weeks after treatment initiation — 60% of severe cases discharged and 100% of mild cases discharged
  - 1 patient had high D-dimer and lymphopenia and passed away

Table 2. Clinical outcomes of 27 enrolled patients

	Severity of illness — no. (%)	Outcomes (up to 2/26)	Total discharge — no. (%)
Dipyridamole group (n=12)	Mild — 4 (33.3%)	4 discharged (100%)	7 (58.4%)
	Severe — 6 (50.0%)	3 discharged (50%) 2 in remission (33%)	
	Critical ill — 4 (33.3%)	1 in remission (50%) 1 death (2/09)	
Control group (n=10)	Mild — 4 (40.0%)	3 discharged (75%)	4 (40.0%)
	Severe — 4 (40.0%)	1 discharged (25%) 1 in remission (25%)	
	Critical ill — 2 (20.0%)	1 death (2/18)	

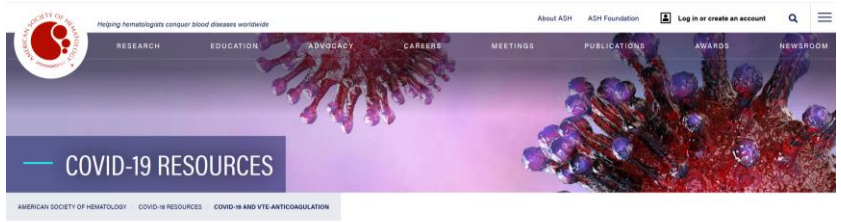


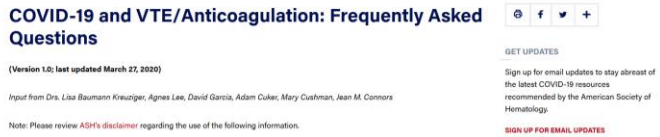
Liu X, 2020

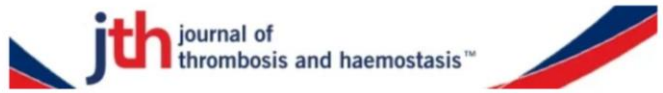
Current Anticoagulation Recommendations

1. **WHAT** to administer
2. **WHEN** to start
3. **HOW** much to administer
4. **HOW** to monitor

- Multiple guidelines
- Lack of consensus
- But, **ALL** agree: coagulation management is warranted







RECOMMENDATIONS AND GUIDELINES | Free Access

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

Jecko Thachil, Ning Tang, Satoshi Gando, Anna Falanga, Marco Cattaneo, Marcel Levi, Cary Clark, Toshiaki Iba

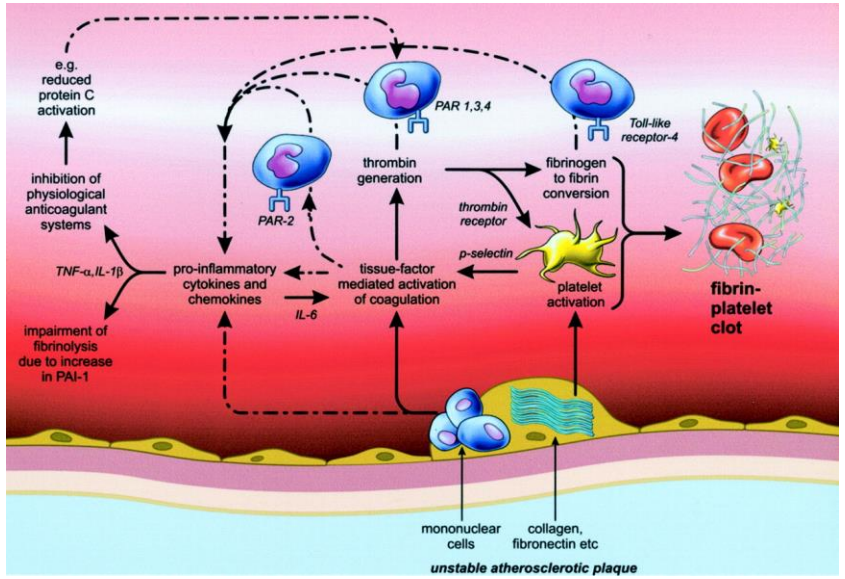
First published:25 March 2020 | https://doi.org/10.1111/jth.14810

MASSACHUSETTS GENERAL HOSPITAL

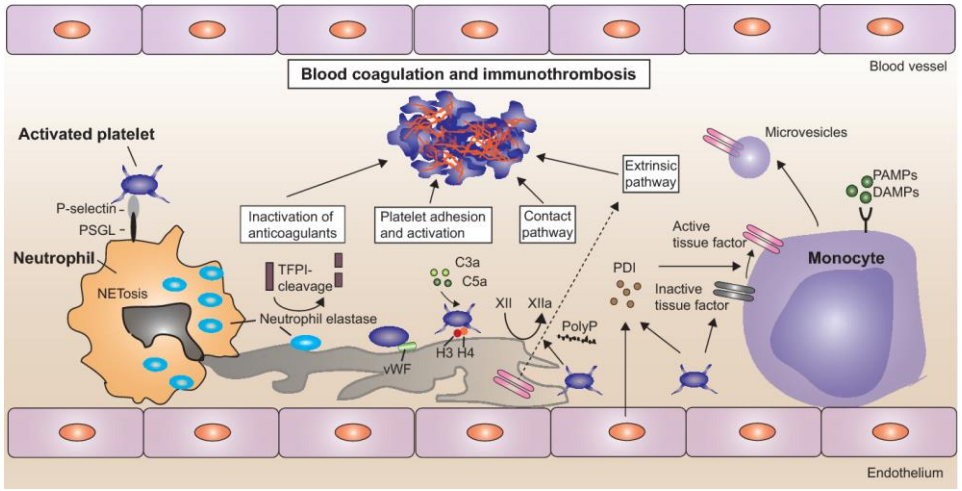
Massachusetts General Hospital COVID-19 Treatment Guidance

Coagulation ⟷ Inflammation

- Inflammation activates coagulation
- Coagulation activates inflammation



(Levi M, 2004)

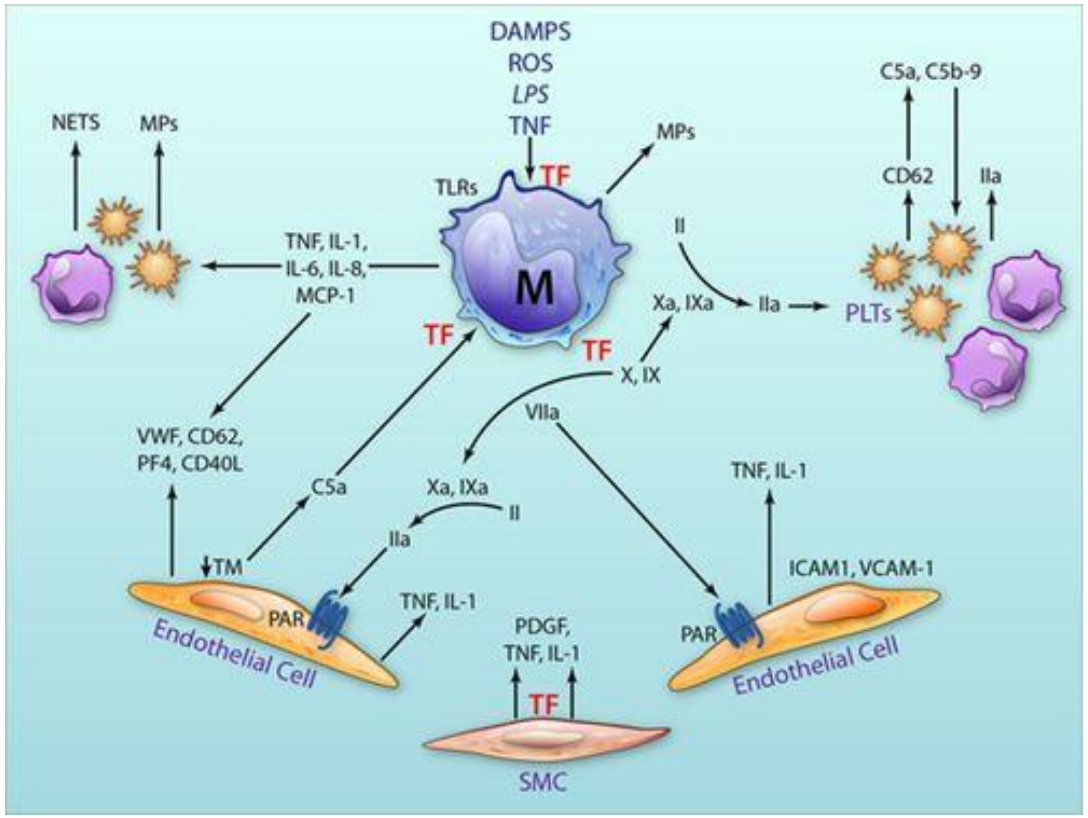


(Gartner F, 2016)

COVID-19 Infection and Severe Inflammation

- COVID-19 infection and disease severity is associated with an **increase in inflammatory biomarkers**
  - IL2R, IL6, IL8, IL10, TNFa, CRP, ferroprotein, procalcitonin, white blood cell counts
  - D-dimer
  - SOFA scores

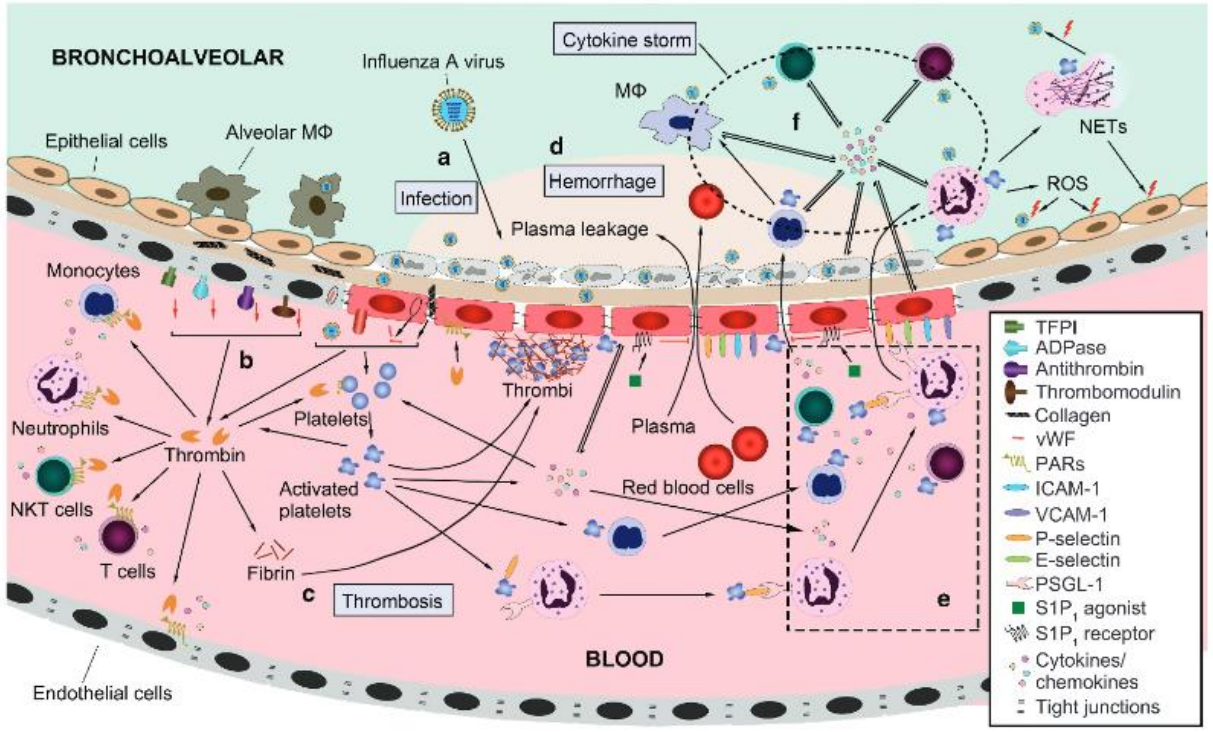
(Gong J, 2020; Zhou F, 2020)



(Foley JH, 2016)

Chicken or Egg: Cytokine Storm or Coagulation

- A Cytokine Storm is a result of severe inflammation
- Cytokine Storm frequently results in the development of pathological blood clots
- Influenza A virus results in uncontrolled coagulation system activation, including both the cellular and protein components (Yang Y, 2016)

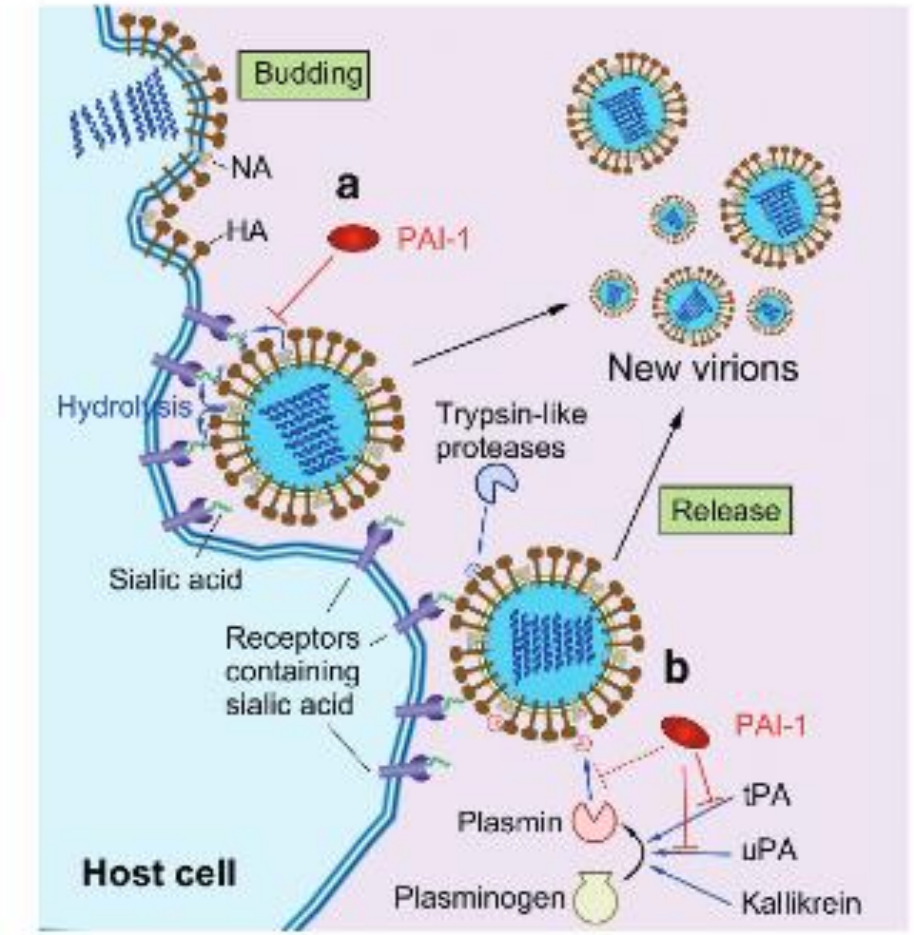


(Yang Y, 2016)

The Role of Fibrinolysis: The Good and the Bad

- **GOOD**
  - Breaks down pathologic clots
  - Can work synergistically with inflammation to resolve thrombi (Mukhopadhyay S, 2019)

- **BAD**
  - Plasminogen and Plasmin are important in the infectivity of Influenza A (Yang Y, 2016)
  - HA requires proteolytic cleavage for the infection of Influenza
  - Influenza uses the conversion of plasminogen into plasmin to aid with this proteolytic cleavage
  - Could this also play a role in COVID infection?
  - FDPs are also pro-inflammatory
    - Have been shown to increase production of IL6, TNF-a and iNOS (Lu PP 2011; Jang M, 2015)

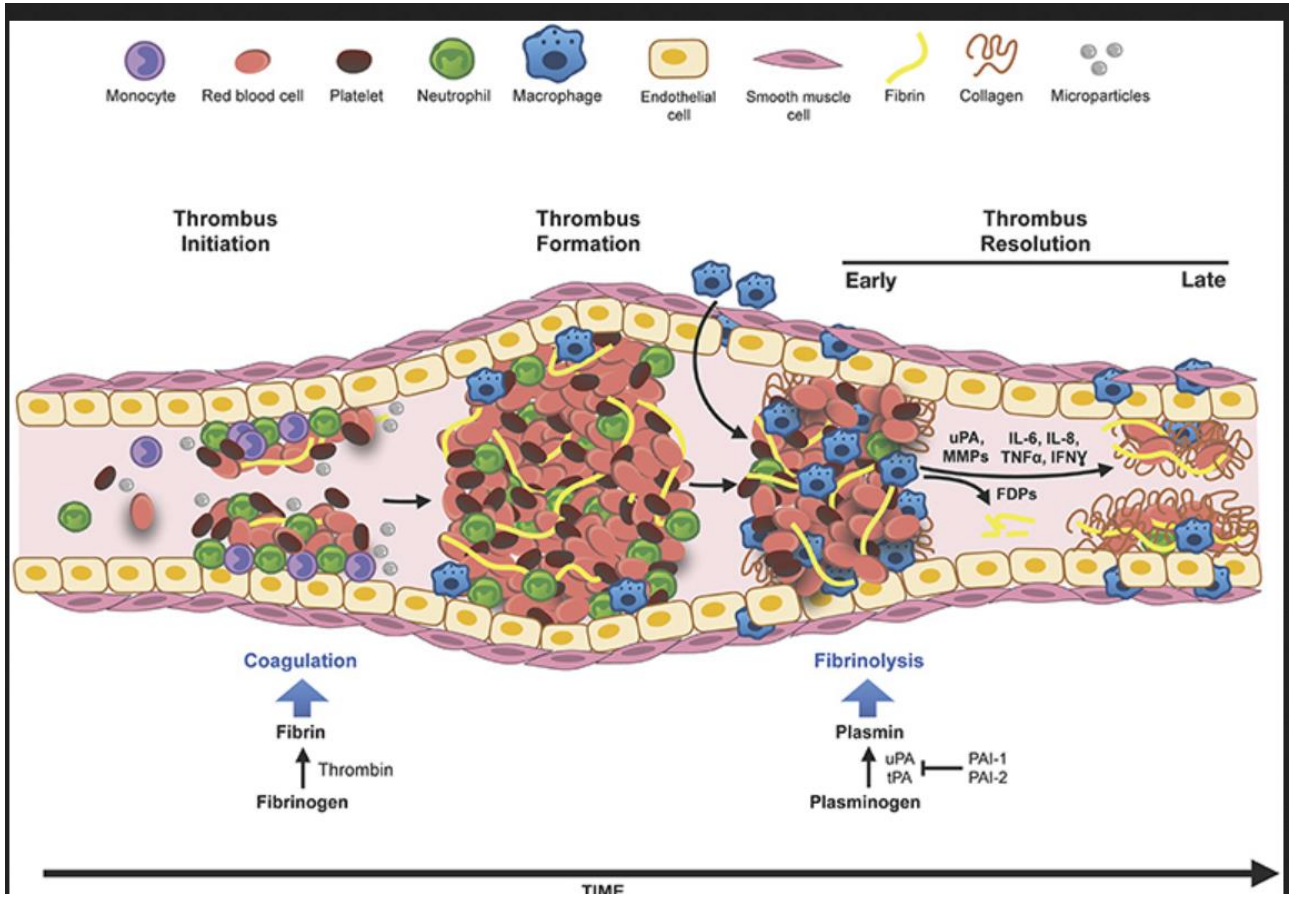


(Yang Y, 2016)

D-dimer: Good? Bad?

- Elevated D-dimer
  - There is increased clot formation and therefore fibrinolysis is activated
  - The fibrinolytic pathway is doing its job by breaking apart the blood clots

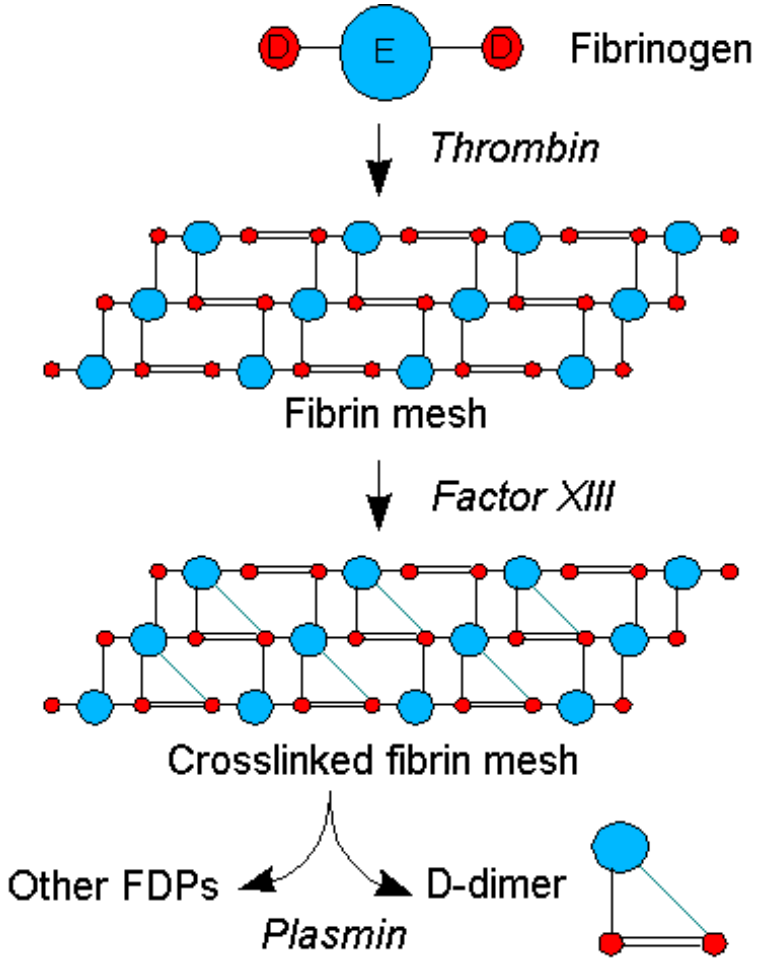
- However, activation of fibrinolysis and the end result of fibrinolysis (FDPs) may play a role in promoting inflammation and, therefore, further coagulation



(Mukhopadhyay, S, 2019)

Fibrinogen and Inflammation

- Fibrinogen is elevated in severe COVID-19
- Fibrinogen is a positive acute phase protein
- Excess fibrinogen can result in increased inflammation and stronger/larger clot formation
    - Increase in FVIII (another positive acute phase protein), increase in endogenous heparanases and decrease in ATIII (a negative acute phase protein) can all contribute to this prothrombotic phenotype
      (Davidson SJ, 2013)



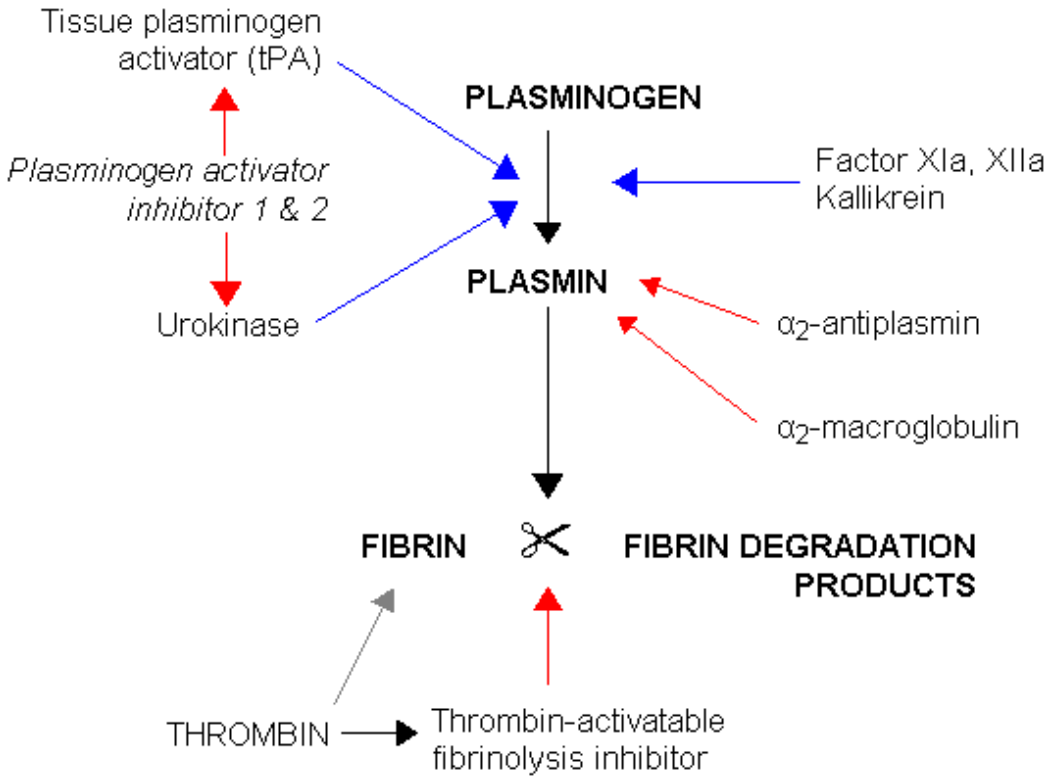
Eclinpath, wikipedia

Urokinase and Plasmin/Plasminogen

- Urokinase (u-PA) is a serine protease and is a positive acute phase protein (Davidson SJ, 2013)

- u-PA is involved in fibrinolysis and inflammation
  - Expressed by macrophages
  - Induces TNF-a and increases IL-6 and IL1B from monocytes and lymphocytes
  - Plays a role in complement pathway activation via C5a/C5aR on alveolar macrophages

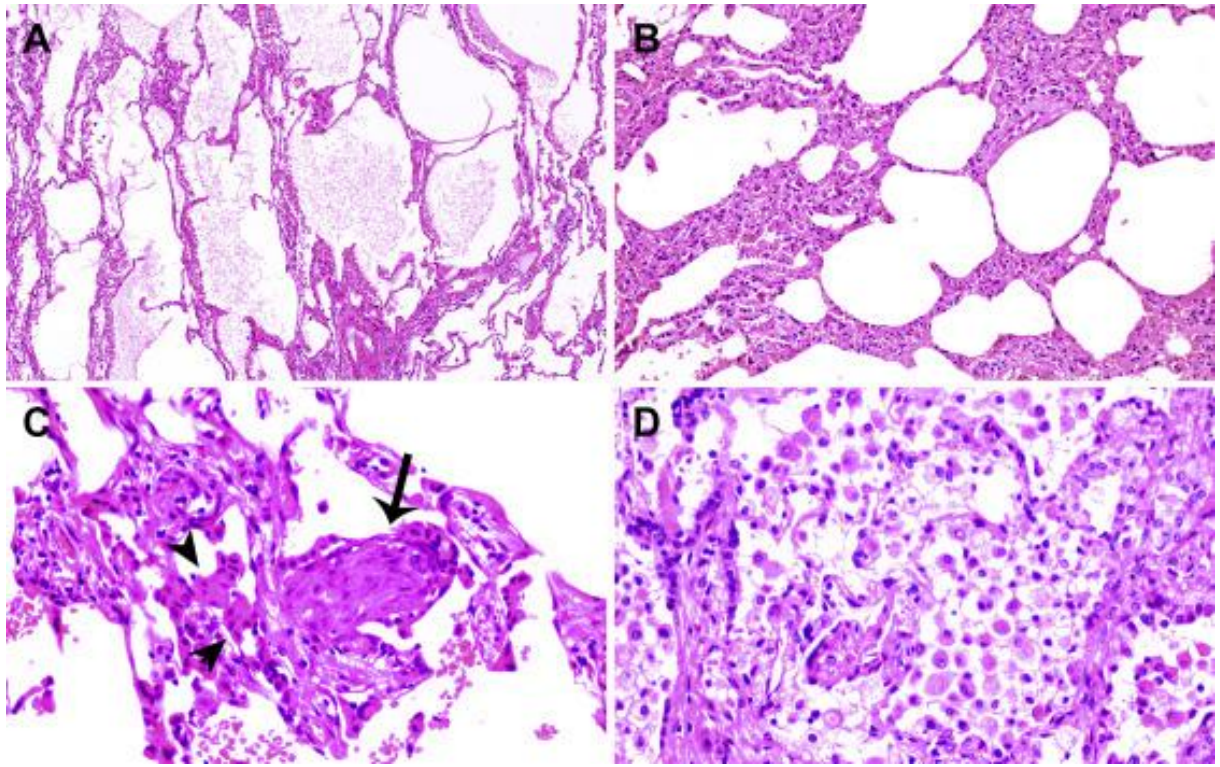
- Plasmin/Plasminogen have also been shown to interact with macrophages (Sugimoto MA, 2017)
  - They are important for the resolving of inflammation



wikipedia

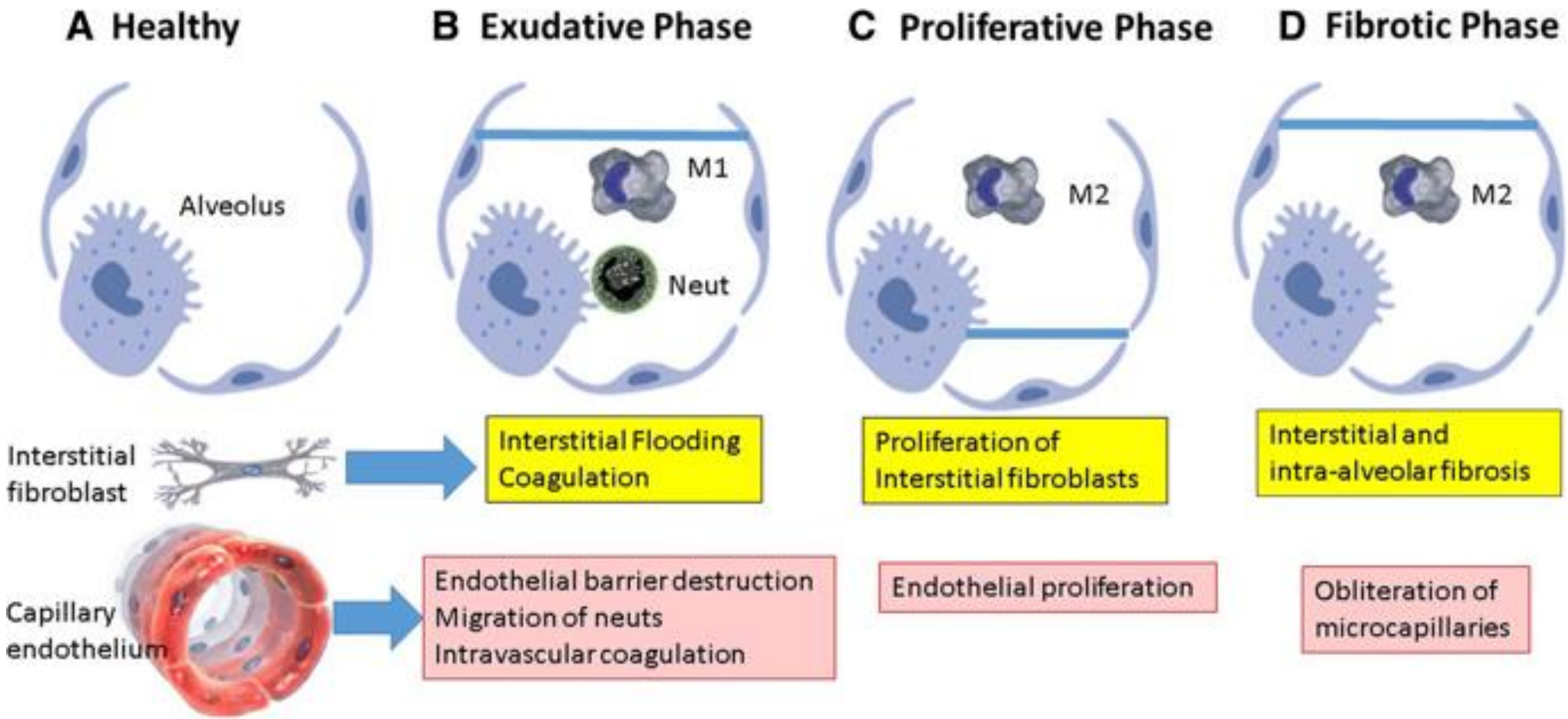
Respiratory Distress During COVID-19 Infection

- Many potential causes of respiratory distress in COVID-19 patients
  - Hypoxia-induced inflammation (Taylor CC, 2016; Frohlich S, 2012)
  - Fibrin deposits along with increased secretions obstructing airways
  - Microthrombi in alveolar capillary beds
  - Macrothrombi in larger pulmonary vessels
  - Alveolar cell stress and death secondary to viral infection, inflammation and coagulation



(Tiang S, 2020)

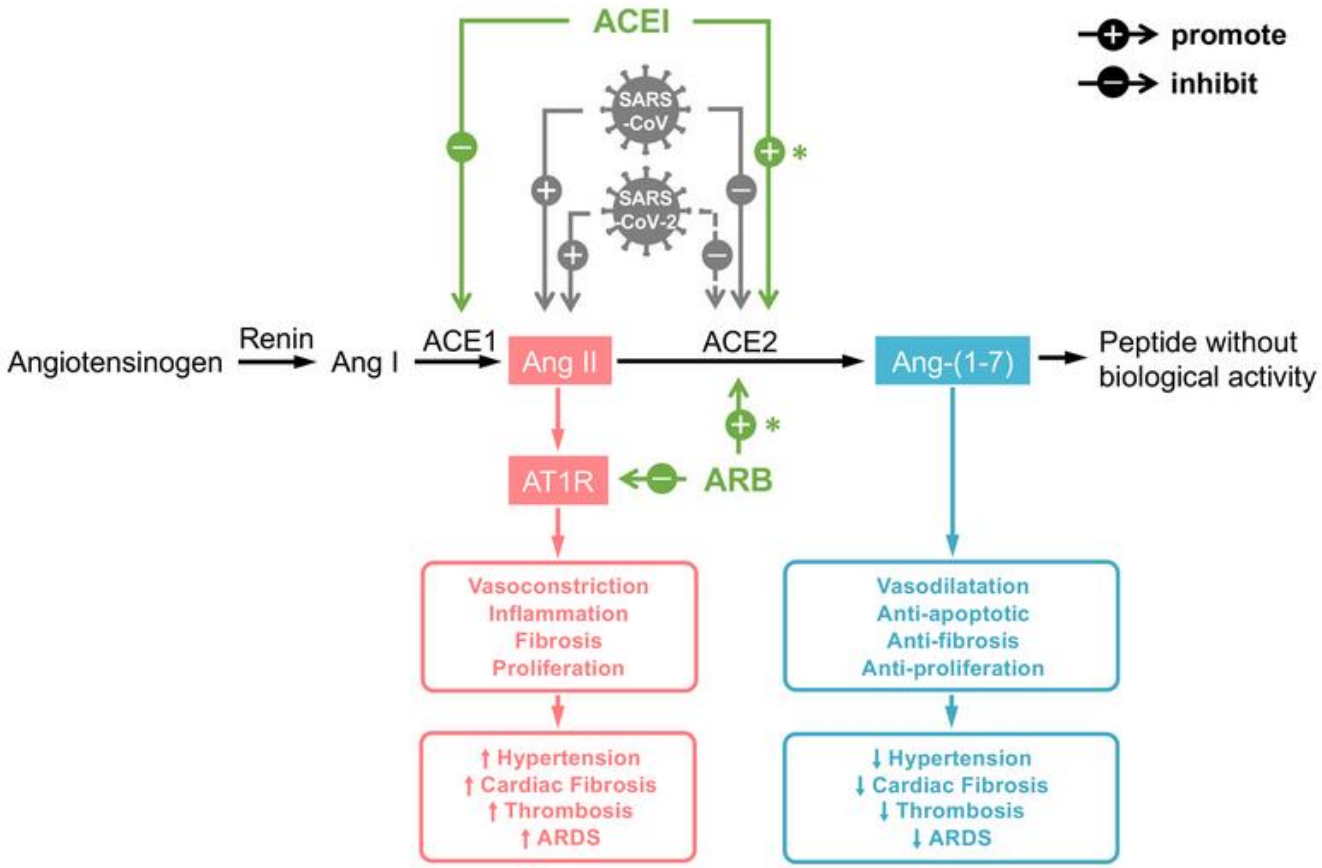
Pre-existing conditions provide a *primed* environment for COVID-19 with elevated inflammation and fibrosis



(Spadaro S, 2019)

COVID-19 Mechanism of Infection: Relationship to Pathogenesis

- COVID-19 binds the ACE2 receptor
- ACE2 plays a role in the renin-angiotensin-system (RAS)
- Decrease of ACE2 via shedding or via binding and blocking results in an increase in Angiotensin II (AngII)
- This results in cell stress, death, inflammation, vasoconstriction and fibrosis

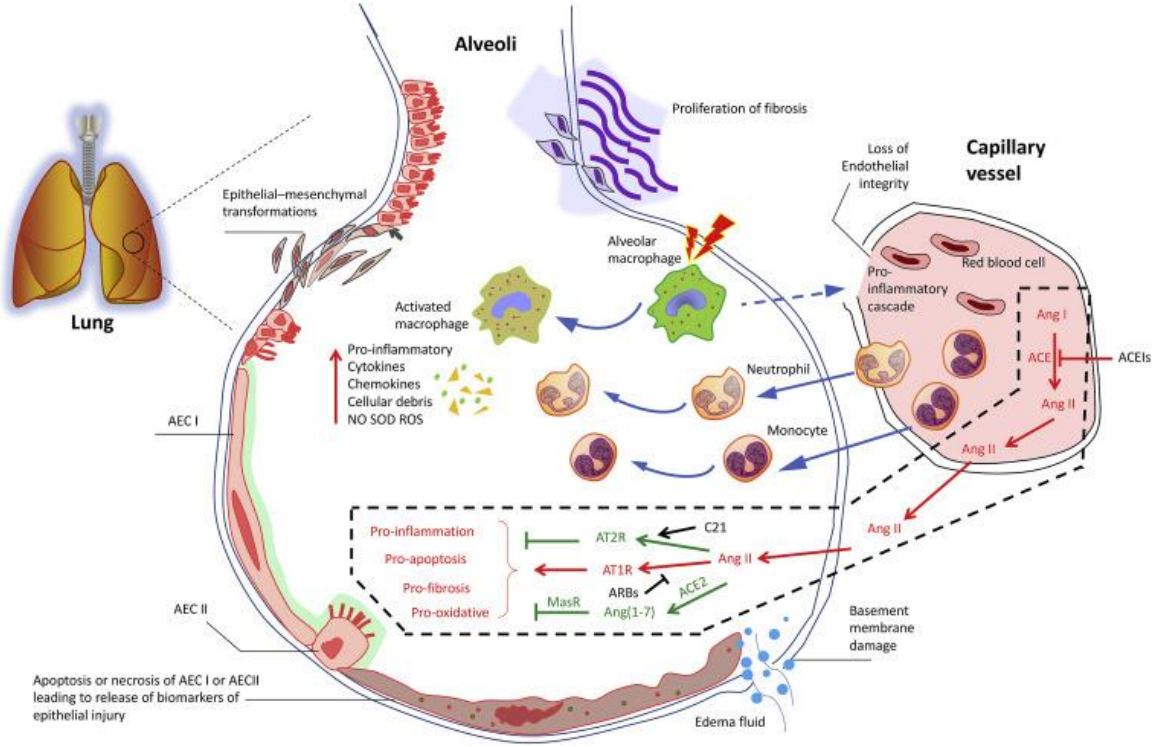


(Guo J, 2020)

(Hoffmann M, 2020; Guo J, 2020)

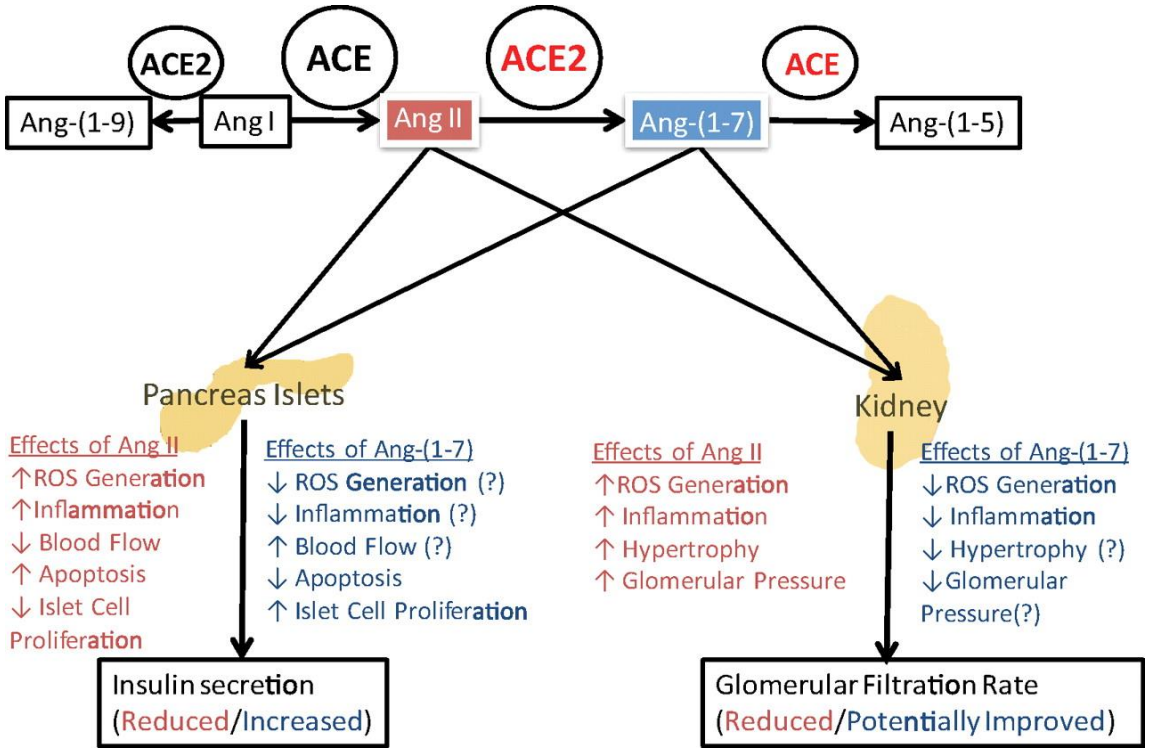
RAS: Key Player in Multiple Conditions

Acute Respiratory Distress Syndrome (ARDS)



(Khan A, 2017)

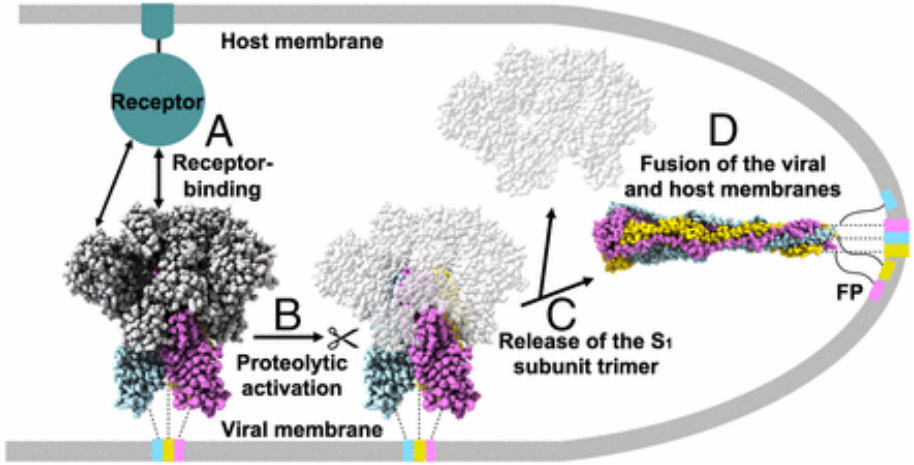
Diabetes Mellitus



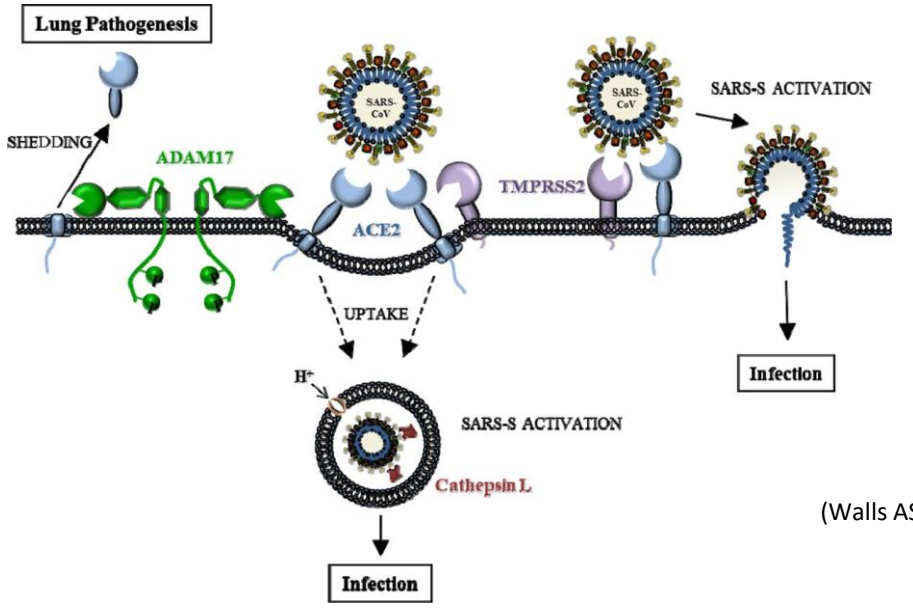
(Battle D, 2010)

COVID-19 Spike Protein Cleavage

- COVID-19 Spike Protein (SP) binds to the host cell receptor, ACE2
- The SP then undergoes one or more proteolytic cleavages, resulting in Spike Protein 1 and 2 (SP1 and SP2)
  - SP1 is then released along with the ACE2 receptor
  - SP2 plays a role in the fusion of the host cell and viral membrane, resulting in cell infection
- TMPRSS2 has been identified as a key protease for SP cleavage



(Walls AS, 2017)

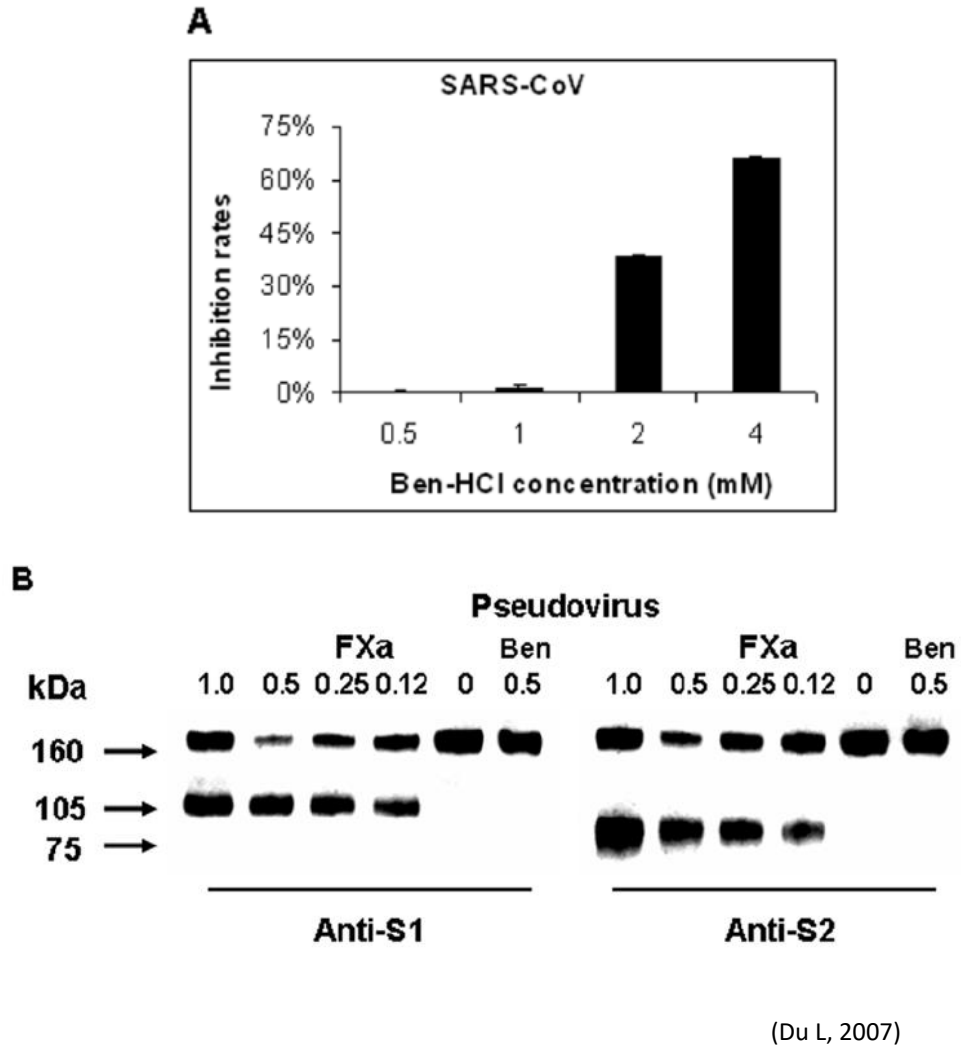


(Walls AS, 2017)

(Wen Shen L, 2017; Esumi M, 2014; Hoffmann M, 2020))

Coagulation Factors: Proteases

- Many coagulation factors are serine proteases
- Inhibition of coagulation factors has been shown to inhibit viral infection and replication in multiple studies:
  - Hepatitis E
  - Coronavirus
  - Influenza
  - Metapneumovirus
  - Respiratory Syncytial Virus
- Factor Xa has been shown to be a protease capable of proteolytic cleavage of SARS Spike Protein (Du L, 2007)



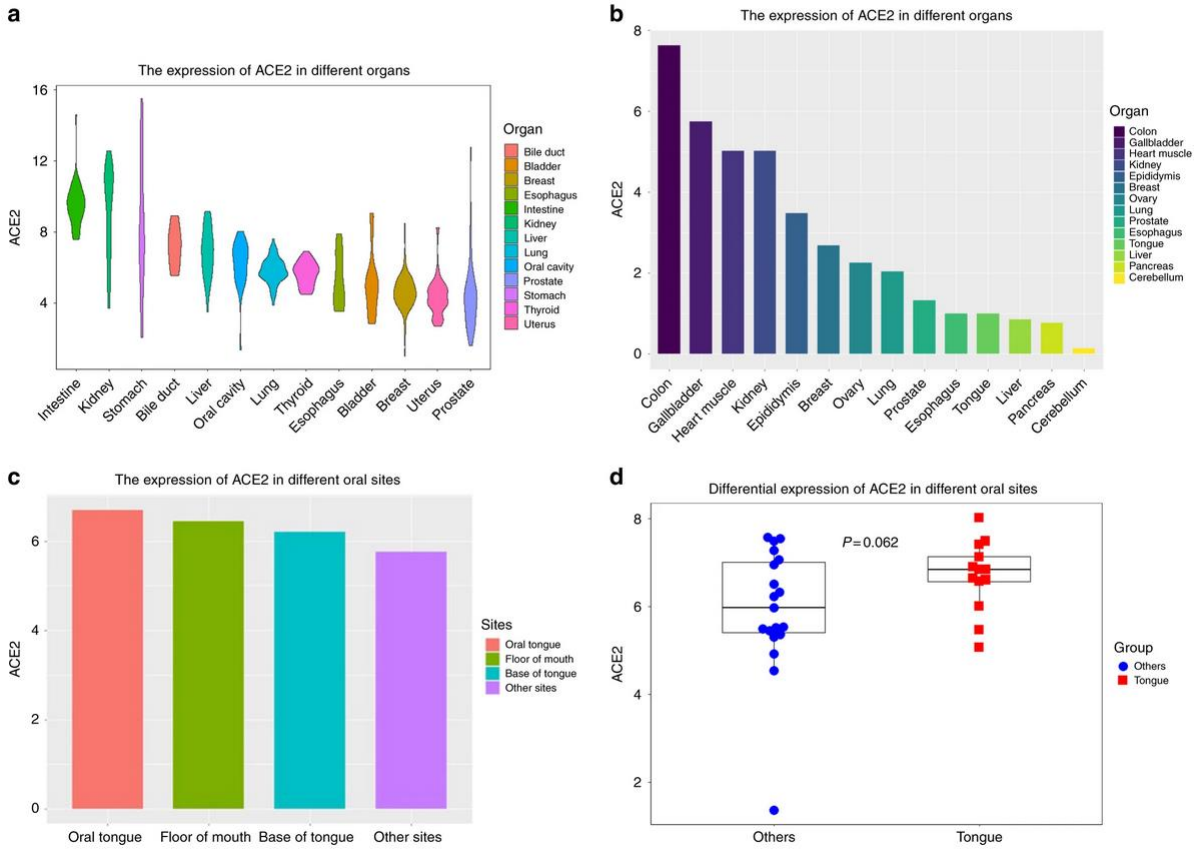
(Du L, 2007)

(Kanade GD, 2004; Le BV, 2018; Howell AL, 1996; Bourgeois C, 1998; Sskidmore MA 2015; Simmons G, 2011))

Coagulation Factor X

- Factor X (FX) is a serine protease
- FX is traditionally known as a coagulation factor that is vitamin K-dependent and is synthesized in the liver
- In addition to hepatocytes, FX has been identified in additional cell types:
  - Alveolar and bronchiolar epithelial cells
  - Cardiac myocytes
  - Macrophages (alveolar macrophages)
  - Brain/CNS
- **These happen to be cells that co-express ACE2**

From: High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa

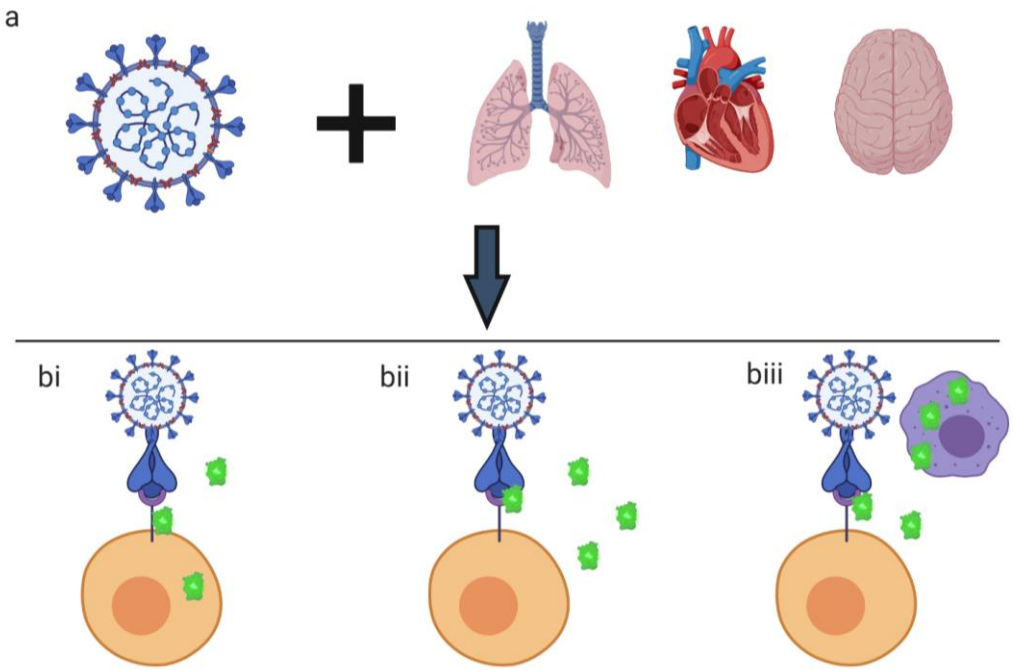


(Xu H, 2020)

Scotton CJ, 2009; Bastarche JA, 2007; Osterud B, 1980; McGee MP, 2989)

FX and COVID-19 Infection

- In organs that co-express ACE2 and FX/FXa, there is the possibility that FX serves as one of the proteases cleaving SP
- Additional sources of FX include the circulatory system as well as localized, activated macrophages
- Factor X may play a role in the infectivity and viral load of COVID-19



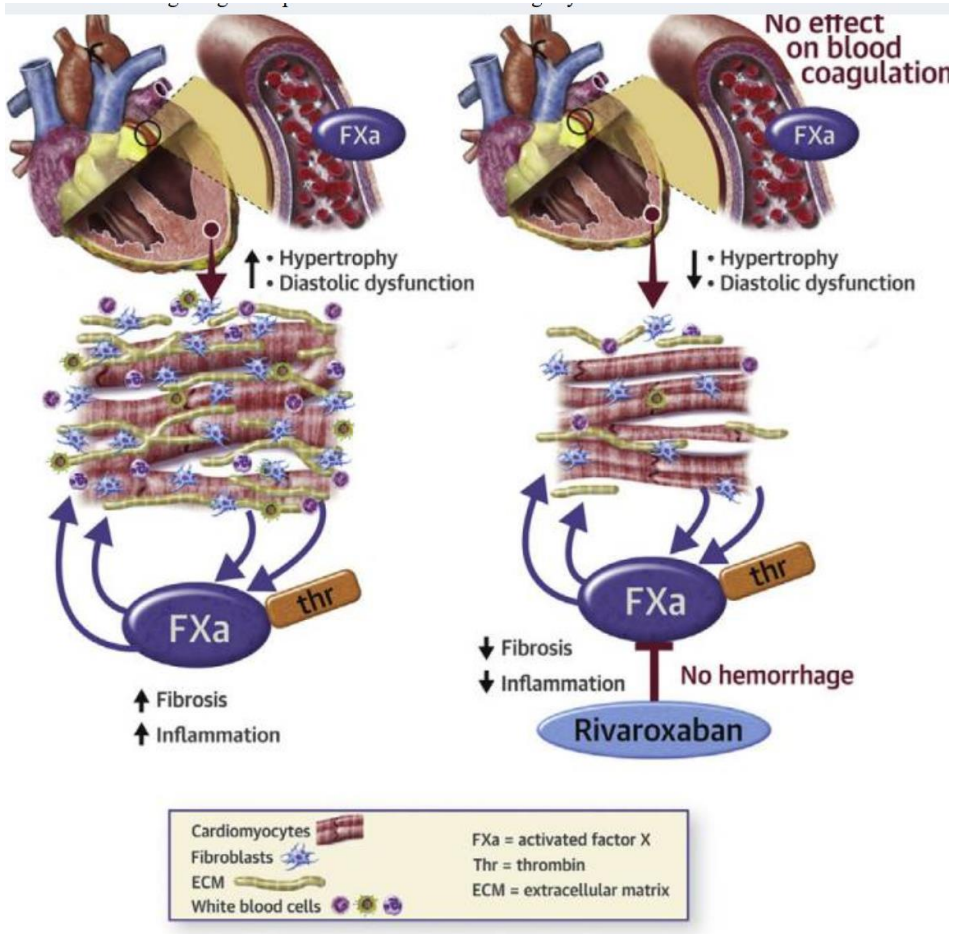
(Frydman GH, 2020)

ACE2 and FX in Cardiac Disease

- ACE2 has been shown to be increased in patients with heart disease (Epelmam S, 2008; Raizada M, 2007)

- Increased expression of FX in cardiac myocytes has been shown in patients with heart disease
  - Associated with cardiac dysfunction
  - Inhibition of FX was shown to decrease FX expression in cardiac myocytes, improving cardiac function and reducing fibrosis

- Could the increased expression of ACE2 and FX in patients with heart disease be a predisposing factor for myocardial injury in COVID-19 infection?

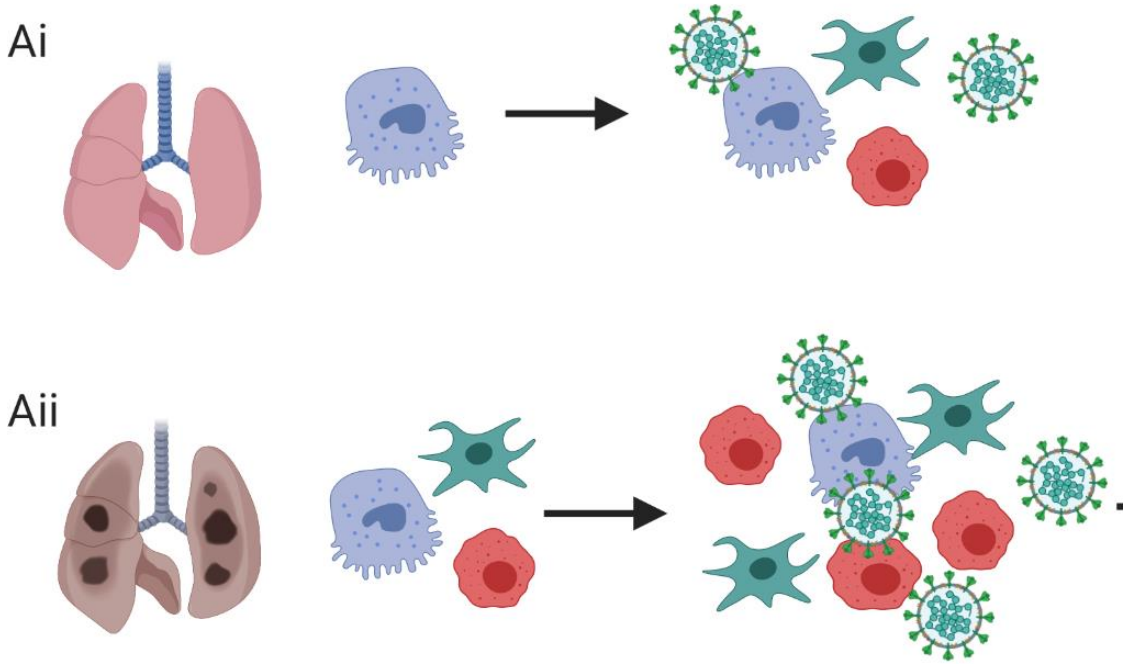


(Guo X, 2020)

Pre-existing Conditions and COVID-19 Outcomes

- The presence of inflammatory cells and fibroblasts in lung and heart disease sets the stage for severe inflammation in response to COVID-19 infection

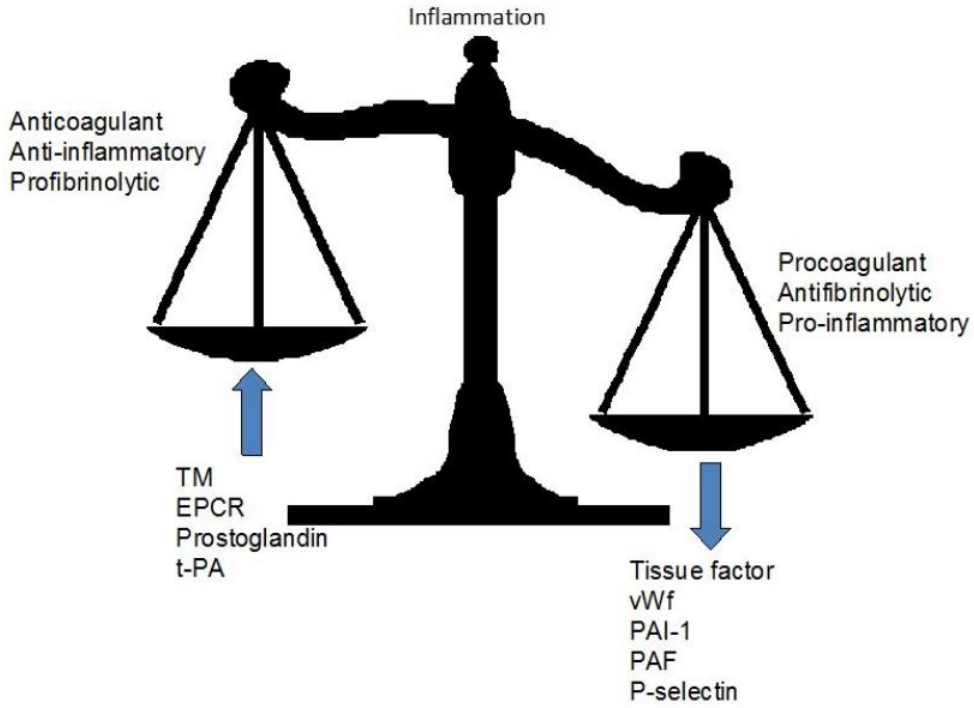
- This leads to the development of systemic inflammation, cytokine storm and coagulopathies as well as long-term organ damage



(Frydman GH, 2020)

Anticoagulants: Role in COVID-19 Infection

- Anticoagulants may serve multiple roles in the treatment of COVID-19:
  - Anticoagulation
  - Reduction in inflammation
  - Improvement in cardiac function
  - Reduction in fibrosis
- Anticoagulants come with risks, such as adverse bleeding events
- Dosing likely needs to be customized in the critical care setting to account for concurrent kidney/liver disease and other medications

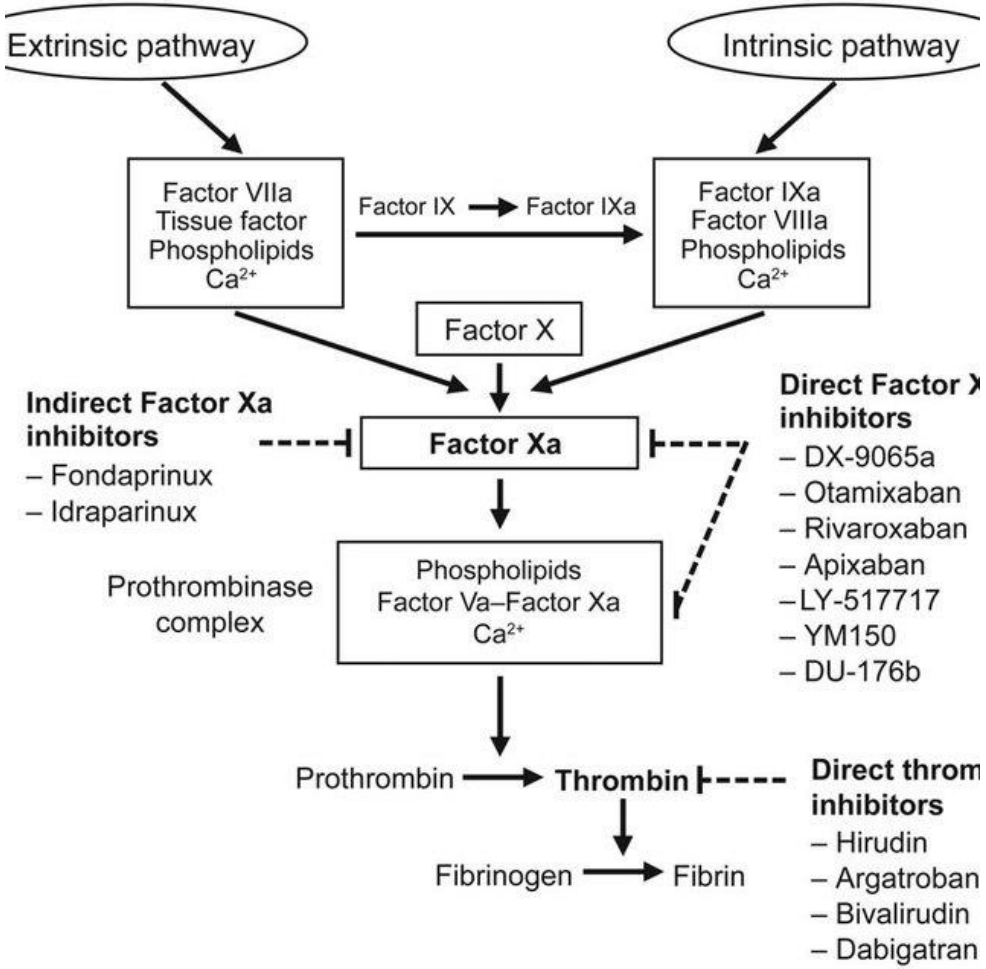


(Davidson SJ, 2013)

How to Manage Coagulation in COVID-19

1. **WHAT** to administer
2. **WHEN** to start
3. **HOW** much to administer
4. **HOW** to monitor

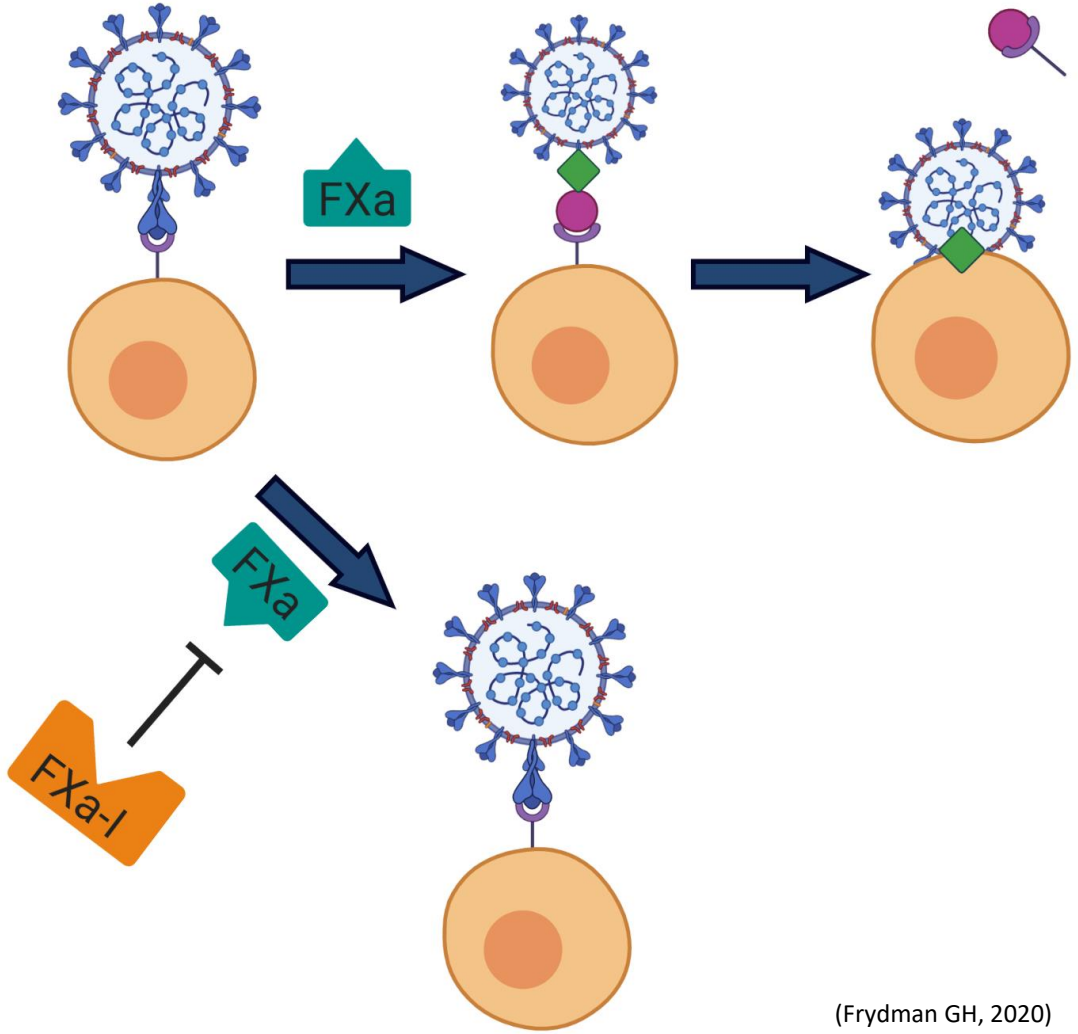
- Evidence-based research is limited
- Likely not “one dose fits all”
- Coagulation is dynamic and monitoring with appropriate diagnostics will be essential for clinical management and research



(Burghaus R, 2011)

A Possible Role for FX Inhibitors in COVID-19?

- Factor Xa inhibitors are common anticoagulants
- Potential role for FX inhibitors:
  - Reducing SP cleavage, therefore resulting in decrease cell infection and overall viral load
  - Improving cardiac function/cardio-protective
  - Reduction in inflammation
- Is there a potential role for these drugs to be administered prophylactically?
- Direct FXa inhibitors may be preferred to heparin in some cases
  - Increased heparinase and decreased ATIII may result in “heparin resistance”
  - Oral administration



(Frydman GH, 2020)

Does Race or Ancestry Affect Coagulation Management in COVID-19 Patients?

- There are over 6 million patients in the US on anticoagulants
- African Americans have a lower rate of Afib, but a higher rate of thromboembolic events
- African American women are at a higher risk of clots than African American men
- Potential causes for hypercoagulable state:
  - Increased levels of Factor VIII, D-dimer and Plasmin-antiplasmin complex
  - Sickle cell disease (trait present in up to 8%)
  - Chronic conditions — hypertension, diabetes mellitus, chronic kidney disease
  - Possible changes in RAS

Arteriosclerosis, Thrombosis, and Vascular Biology
Volume 37, Issue 11, November 2017, Pages 2220-2227
https://doi.org/10.1161/ATVBAHA.117.310073

CLINICAL AND POPULATION STUDIES

D-Dimer in African Americans

Whole Genome Sequence Analysis and Relationship to Cardiovascular Disease Risk in the Jackson Heart Study

Laura M. Raffield, Neil A. Zakai, Qing Duan, Cecelia Laurie, Joshua D. Smith, Marguerite R. Irvin, Margaret F. Doyle, Rakhi P. Naik, Ci Song, Ani W. Manichaikul, Yongmei Liu, Peter Durda, Jerome I. Rotter, Nancy S. Jenny, Stephen S. Rich, James G. Wilson, Andrew D. Johnson, Adolfo Correa, Yun Li, Deborah A. Nickerson, Kenneth Rice, Ethan M. Lange, Mary Cushman, Leslie A. Lange, and Alex P. Reiner

THE LANCET

Log in

ARTICLES | VOLUME 382, ISSUE 9894, P790-796, AUGUST 31, 2013

Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study

Minoli A Perera, PharmD † • Larisa H Cavallari, PharmD † • Nita A Limdi, PharmD † • Eric R Gamazon, MS • Anuar Konkashbaev, MS • Roxana Daneshjou, BS • et al. Show all authors • Show footnotes

Open Access • Published: June 05, 2013 • DOI: https://doi.org/10.1016/S0140-6736(13)60681-9 • Check for updates

PlumX Metrics

(Raffield LM, 2017; Magnani JW, 2016; Roberts LN, 2013; Janbain M, 2014; Buckner TW, 2014; Perera MA, 2013; Kanuri SH, 2018)

Could Differences in Anticoagulation Play a Role in COVID-19 Disease Trends?

- Differences in coagulation management in African Americans:
  - Those with Afib were less likely to be prescribed an anticoagulant
  - Less likely to be prescribed a Direct Oral Anticoagulant (DOAC)
  - Tend to require higher doses of warfarin than Caucasians
  - DOAC clinical trials only had between 1–4% African Americans enrolled

African Americans have a propensity to be prothrombotic, yet they are less likely to be on an anticoagulant. Does that predispose them to coagulopathies during COVID-19 infection?

(Essien UR, 2018; Akinboboye O, 2016; Nathan AS, 2019; FDA)

Current COVID-19 Treatment Trials and Coagulation

- Hydroxychloroquine trials
  - In addition to its anti-malarial mechanism of action, hydroxychloroquine has been investigated as a potential platelet inhibitor
  - PT/INR increases when hydroxychloroquine is administered along with warfarin
- Inhaled UFH/N-acetylcysteine
  - UFH is an indirect FXa/FIIa inhibitor via the binding of ATIII; N-acetylcysteine helps loosen secretions
- Inhaled Tissue Plasminogen Activator (tPA)
  - tPA functions similarly to uPA in the fibrinolytic pathway
  - This is targeted for patients that already have pathologic clot formation and fibrin deposition in the lungs

More Studies Needed!!!!!!

Need to explore the prevention of clots in addition to the treatment of them.

Coagulation Monitoring in COVID-19 Patients

- Currently-available coagulation assays and testing systems are not adequate
- Few coagulation tests are able to detect HYPERcoagulability
- No single coagulation test is able to identify the specific source of coagulation abnormality
- Diagnostic monitoring tools for all anticoagulants (and especially DOACs) are severely lacking
- Most tests require multiple blood tubes in order to perform complete coagulation profiling

Coagulo is currently using its technology, which can identify factor-specific inhibition, to study the effect of anticoagulants in COVID-19 patients

Currently-Available Coagulation Tests

- **PT**
  - Shown to be slightly elevated in COVID-19 patients (so slight that INR may seem normal)
  - Readily-available and point-of-care (POC)
- **aPTT**
  - Shown to be elevated in patients with end-stage DIC (along with thrombocytopenia)
  - Some reports of near-normal/normal aPTT even on heparin (UFH and LMWH) (not published)
  - Readily available and POC
- **D-dimer**
  - D-dimer is traditionally used to detect pathologic clot formation (such as pulmonary embolism)
  - COVID-19 patients have such elevated D-dimers that this marker is not useful to detect PE/DVT
  - Readily available — qualitative can be POC, but quantitative is usually lab-based
- **Fibrinogen**
  - Fibrinogen will likely be elevated in COVID-19 patients due to severe inflammation
  - Readily available— usually lab-based assay; can perform an ESR POC if needed

Rapid tests that are available at most hospitals

Currently-Available Coagulation Tests

Coagulo Medical Technologies, Inc.

- **Anti-Xa levels**
  - Level of Xa inhibition (used to monitor heparins/DOACs)
  - This is not a functional test — may not reflect that actual level of anticoagulation the patient is exhibiting
  - Many Anti-Xa tests add in ATIII — this would result in false elevation of FXa inhibition in patients that have lower values of ATIII
  - Not available at all labs or in smaller hospitals
- **ATIII levels**
  - COVID-19 patients tend to trend lower — may be helpful in identifying some heparin resistance
  - Not available at all labs or in smaller hospitals
- **Viscoelastic testing**
  - Reported that COVID-19 patients tend to have shortened clotting times and larger MA, potentially due to the increase in fibrinogen levels
  - Can show that a patient is prothrombotic, but not useful in detecting cause or in selection of type of anticoagulant
  - More common in research and large hospitals; POC versions available, but not common in most small hospitals
- **Factor VIII levels**
  - Likely elevated in patients that are exhibiting systemic inflammation
  - Questionable utility in light of other inflammatory biomarkers
  - Not available at all labs or in smaller hospitals

Laboratory tests that are only available at some hospitals

Laboratory Tests

- COVID-19 patients are likely to be hospitalized for prolonged periods of time (up to multiple weeks) and will require many blood tests, including coagulation, blood gases, chemistries and CBCs

- In particular, be mindful of the coagulation tests that you order, their limitations and what question you are trying to answer by ordering that specific test

Laboratory Tests

- **Don’t** subject the patient to the **Anemia of Chronic Investigation**
- Patients that are systemically inflamed are already prone to anemia (Hayden SJ, 2012)
- COVID-19 is suspected to effect hemoglobin: anemia would further exacerbate hypoxia (Liu W, 2020)
- Most research hospitals are paying attention to this and are instituting sample sharing between researchers to minimize blood volume drawn

Key Takeaways

1. **Inflammation and coagulation go hand-in-hand**
   - Successful treatment of COVID-19 disease will likely include a combination of anti-inflammatory and anticoagulant medications.

2. **Disease is dynamic and treatment should be tailored to the patient's stage of inflammation/coagulation**
   - Dosing and selection of anticoagulant needs to be tailored for the patient. It is likely that patients with moderate to severe COVID-19 disease are in a pro-thrombotic state.
   - This will require coagulation monitoring (with diagnostics) as well as appropriate dose adjustment (i.e., a prophylactic dose may not be sufficient to anticoagulate a patient that is in a severe prothrombotic state).
   - Drug selection may need to change during disease (i.e., in severe inflammation, changes in coagulation factor expression may result in a "heparin resistance").

3. **There is room to be proactive in patients that are at high-risk for severe COVID-19 disease**
   - There may be a place for patients that have pre-existing conditions, such as heart and lung disease, diabetes, autoimmune disease or cancer to be placed on prophylactic anticoagulation in a confirmed case of COVID-19 infection (this may reduce inflammation and coagulation prior to systemic elevation and activation).

4. **More advanced testing techniques are desperately needed**

What Coagulo is doing to advance the battle against COVID-19:

1. Coagulo is addressing the emergent need for more advanced diagnostics to support tailored anticoagulation therapy in COVID-19 patients.

2. Collaborating with leading hospitals and research institutions to elucidate the mechanisms of thrombosis in COVID-19 patients and help identify optimal treatments for those requiring coagulation management.

3. Exploring studies of direct FXa inhibitors in patients with COVID-19.

Thank you to all the healthcare workers and researchers banding together on the frontlines to tackle COVID-19!

Coagulo
Medical Technologies, Inc.

www.coagulomed.com

References

1. Zhou F, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet, 2020; 395:1054-1062.
2. Yu B, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. Research Square, Preprints: doi: 10.21203/rs.3.rs-20056/v1.
3. Zhang Y, et al. Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. Xhonghua Xue Ye Xue Za Zhi, 2020; 41(0):E006.
4. Tang N, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus. J Throm Haemost, 2020; doi: 10.1111/jth.14768.
5. Zhang Y, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. NEJM, 2020;doi: 10.1056/NEJMc2007575.
6. Tang N, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients and coagulopathy. JTH, 2020; doi: 10.111/JTH.14817
7. Liu X, et al. Therapeutic effects of dipyridamole on COVID-19 patients with coagulation dysfunction. medRxiv, 2020; doi: doi.org/10.1101/2020.02.27.20027557.
8. Thachil J, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. JTH, 2020; doi:10.1111/jth.14810.
9. ISTH Webinar: https://academy.isth.org/isth/2020/covid-19/291581/marcel.levi.26.beverley.jane.hunt.thrombosis.thromboprophylaxis.26.coagulopathy.html?f=menu%3D8%2Abrowseby%3D8%2Asortby%3D2%2Alabel%3D19794.
10. Foley JH, et al. Cross talk pathways between coagulation and inflammation. Circ Research, 2016;118:1392-1408.
11. Gartner F, et al. Blood coagulation in immunothrombosis-at the frontline of intravascular immunity. Semin Immunol, 2016;28(6):561-569.
12. Levi M, et al. Bidirectional relationship between inflammation and coagulation. Circ, 2004;109:2698-2704.
13. Gong J, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pnuemonia. medRxiv, 2020: doi: 10.1101/2020.02.25.20025643.
14. Yang Y, et al. Aberrant coagulation causes a hyper-inflammatory response in severe influenza pneumonia. Cellular & Molecular Immunology, 2016;13:432-442.
15. Lu PP, et al. Pro-inflammatory effect of fibrinogen and FDP on vascular smooth muscle cells by IL6, TNF-a and iNOS. Life Sci, 2011;88:839-845.
16. Kang M, et al. FDP-E induces adipocyte inflammation and suppresses insulin-stimulated glucose disposal: effect of inflammation and obesity on fibrinogen Bbeta mRNA. Am J Physiol Cell Physiol, 2015;309(11):C767-774.
17. Mukhopadhyay S, et al. Fibrinolysis and inflammation in venous thrombus resolution. Front Immunol, 2019;10:1348.
18. Davidson SJ. Inflammation and acute phase proteins in haemostasis. Intechopen, 2013; doi: 10.5772/55998.
19. Sugimoto MA, et al. Plasmin and plasminogen induce macrophage reprogramming and regulate key steps in inflammation resolution via annexin A1. Blood, 2017;129(21):2896-2907.
20. Frohlich S, et al. Hypoxia-induced inflammation in the lung A potential therapeutic target in acute lung injury? AM J Resp Cell and Mol Biol, 2012;doi: 10.1165/rcmb.2012-0137TR.
21. Taylor CC, et al. Hypoxia-dependent regulation of inflammatory pathways in immune cells. JCI, 2016; doi: 10.1172/JCI84433.
22. Tian S, et al. Pulmonary pathology of early-phase 2019 Novel Coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol, 2020;S1556-0864(20):30132-30135.
23. Spadaro S, et al. Biomarkers of acute respiratory distress syndrome and prospects for personalized medicine. Journal of Inflammation, 2019;16:1.
24. Guo J, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. JAHA, 2020;9:e016291.
25. Hoffmann M, et al. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. BioRxiv, 2020; doi.org/10.1101/2020.01.31.929042
26. Batlle D, et al. ACE2 and diabetes: ACE or ACEs? Diabetes, 2010; doi.org/10.2337/db10-1205
27. Haga S, et al. Modulation of TNF-a-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-a production and facilitates viral entry. PNAS, 2008;105(22):7809-7814.
28. Imai Y, et al. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Exp Physiol, 2008;93(5):543-548.
29. Wang D, et al. Renin-angiotensin-system, a potential pharmacological candidate, in acute respiratory distress syndrome during mechanical ventilation. Pulmonary Pharm & Ther, 2019;58:101833.
30. Glowacka I, et al. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. J. of Virol, 2009; doi.org/10.1128/JVI.01248-09.
31. Khan A, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care, 2017;21(1):234.
32. Walls AC, et al. Tectonic conformational changes of a coronavirus spike glycoprotein promote membrane fusion. PNAS, 2017;114(42):11157-11162.
33. Heurich A, et al. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. JVI, 2014;88(2):1293-1307.

References (continued)

34. Esumi M, et al. Transmembrane serine protease TMPRSS2 activates hepatitis C virus infection. Hepatology, 2014; 16(2):doi.org/10.1002/hep.27426
35. Wen Shen L, et al. TMPRSS2: a potential target for treatment of influenza virus and coronavirus infections. Biochimie, 2017;142:1-10.
36. Du L, et al. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. Biochem Biophys Res Common, 207;359(1):174-179.
37. Kanade GD, et al. Activities of thrombin and Factor Xa are essential for replication of hepatitis E virus and are possibly implicated inVicenzi E, et al. Coronaviridae and SARS-associated coronavirus strain HSR1. Emergeing Infectious Diseases, 2004;10(3).
38. Lê BV, Jandrot-Perrus M, Couture C, et al. Evaluation of anticoagulant agents for the treatment of human metapneumovirus infection in mice. J Gen Virol. 2018; 99(10):1367-1380.
39. Howell AL, Taylor TH, Miller JD. Inhibition of HIV-1 infectivity by low molecular weight heparin. Results of in vitro studies and a pilot clinical trial in patients with advanced AIDS. Int J Clin Lab Res, 1996;26(2):124-131.
40. Bourgeois C, Bour JB, Lidholt K, et al. Heparin-like structures on respiratory syncytial virus are involved in its infectivity in vitro. Journal of Virol, 1998:7221-7227.
41. Skidmore MA, Kajaste-Rudnitski A, Wells NM, et al. Inhibition of influenza invasion by modified heparin derivatives. MedChemComm, 2015;6:640.
42. Simmons G, Bertram S, Glowacka I, et al. Different host cell proteases activate the SARS- coronavirus spike-protein for cell-cell and virus-cell fusion. Virology, 2011;413(2):265-274.
43. Xu H, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. IJOS, 2020;12.
44. Scotton CJ, et al. Increased local expression of coagulation factor X contributes to the fibrotic response in human and murine lung injury. JCI, 2009; doi: 10.1172/JCI33288.
45. Bastarche JA, et al. The alveolar epithelium can initiate the extrinsic coagulation cascade through expression of tissue factor. Thorax, 2007;62(7):608-616.
46. Guo X, et al. Cardiac expression of factor X mediates cardiac hypertrophy and fibrosis in pressure overload. JACC, 2020; doi: 10.1016/j.acbts.2019.10.006.
47. Osterud B, et al. Macrophages produce blood coagulation factors. FEBS Letters, 1980; 120(1).
48. McGee MP, et al. Initiation of the extrinsic pathway of coagulation by human and rabbit alveolar macrophages: a kinetic study. Blood, 1989;74(5):1583-1590.
49. Frydman GH, et al. The potential role of coagulation factor Xa in COVID-19: Anticoagulants as multi-modal therapeutics. Under Review (Am J Resp and Crit Care), 2020.
50. Epelman S, et al. Detection of soluble angiotensin-converting enzyme 2 in heart failure. J Am Coll Cardiol, 2008;52(9):750-754.
51. Raizada M, et al. ACE2: a new target for cardiovascular disease therapeutics. J of Cadio Pharm, 2007;50(2):112-119.
52. Burghaus R, et al. Evaluation of the efficacy and safety of rivaroxaban using computer model for blood coagulation. PLoS ONE, 2011;6(4):e17626.
53. Raffield LM, et al. D-dimer in African americans. Arteriosclerosis, thrombosis and vascular biology, 2017;37(11):2220-2227.
54. Essien UR, et al. Race/ethnicity and oral anticoagulation use in AF patients. ACC, 2018; https://www.acc.org/latest-in-cardiology/journal-scans/2018/11/29/08/12/association-of-race-ethnicity-with-oac-use.
55. Akinboboye O. Use of oral anticoagulants in African-american and Caucasian patients with atrial fibrillation: is there a treatment disparity? J Multidiscip Healthc, 2015;8:217-228.
56. Magnani JW, et al. Racial differences in atrial fibrillation-related cardiovascular disease and mortality. JAMA Cardiol, 2016;1(4):433-441.
57. FDA. Clinical trials for multiple DOAC studies. Accessdata.fda.gov.
58. Roberts LN, et al. African-caribbean ethnicity is associated with a hypercoagulable state as measured by thrombin generation. Blood Coagul Fibrinolysis, 2013;24(1):40-49.
59. Janbain M, et al. Analysis of racial disparity in plasma of healthy volunteers using rotational thromboelastography reveals higher prothrombotic profile in African americans. Blood, 2014;124(21):5972.
60. Buckner TW, et al. Venous thrombosis in blacks. Circ, 2012;125:837-839.
61. Nathan AS, et al. Racial, ethnic and socioeconomic inequities in the prescription of direct oral anticoagulants in patients with venous thromboembolism in the united states. Circ: Cardiovascular quality and outcomes, 2019. Penn LDI: https://ldi.upenn.edu/publication/racial-ethnic-and-socioeconomic-inequities-prescription-direct-oral-anticoagulants.
62. Perera MA, et al. Genetic variants associated with warfarin dose in African-american individuals: a genome-wide association study. The Lancet, 2013; doi: 10.1016/S0140-6736(13)60681-9.
63. Kanuri SH, et al. Pharmacogenomics of novel direct oral anticoagulants: newly identified genes and genetic variants. Journal of Personalized Medicine, 2018; doi: 10.3390/jpm9010007.
64. Liu W, et al. COVID-19 attaches the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv, 2020; https://chemrxiv.org/articles/COVID-19_Disease_ORF8_and_Surface_Glycoprotein_Inhibit_Heme_Metabolism_by_Binding_to_Porphyrin/11938173.
65. Hayden SJ, et al. Anemia in critical illness. Am J Resp Crit Care, 2012;185(10):1049-1057.