


The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

COVID-Coag

What is "Immuno-thrombo-inflammation?"



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The Fritsma Factor
Your Interactive Hemostasis Reference
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Bottom Line at the Start [BLAST]

Keep it Short and Simple [KISS—no hope]
Immuno-thrombo-inflammation

The participant...

- Proposes the pathophysiology and comorbidities associated with COVID.
- Applies relevant COVID progression laboratory assays results.
- Aligns COVID laboratory results and pathophysiology with disease progress.
- Discusses possible COVID vaccine adverse events.





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32 YO Biker With Shortness of Breath

A motorcyclist who attended the Sturgis, SD 8-8-2020 rally appears at his local ED experiencing a sore throat, cough, fever, and shortness of breath, O₂ sat. 88%. The physician suspects COVID-19. A lab scientist collects a nasopharyngeal specimen and employs a Cepheid GeneXpert® POC RT-PCR, which detects the SARS-Cov-2 virus in less than one hour. The patient is placed in isolation.

Smithgal, MC, Dowlatshahi M, Spitnik SL, Hod EA, Rai AJ. Types of assays for SARS-CoV-2 testing: a review. Lab Med 2020 DOI: 10.1093/labmed/lmaa039

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COVID-19 Symptoms

- Coronaviridae varieties: respiratory infections; the common cold
- The third Coronaviridae epidemic since 2000
 - Severe acute respiratory syndrome [SARS] 2002–3.
 - Middle East respiratory syndrome [MERS] 2012
- SARS and MERS: Interstitial pneumonia with progression to acute respiratory distress syndrome
- COVID: multisystem disorder: hyperimmune, inflammatory, progressing to profound hemostatic disturbance
 - High rates of pulmonary embolism and deep venous thrombosis
 - Smaller component of stroke, myocardial infarction
 - Mortality greatest over 60, males, hypertension, diabetes, obesity, cancer, pulmonary, renal, cardiovascular, liver, and neurological disorders

Lippi G, Sanchis-Gomar F, Favaloro EJ, Lavie CJ, Henry BM. Coronavirus disease 2019-associated coagulopathy. Mayo Clin Proc 2021; 96:203–17

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Symptoms Specified in Vaccine Clinical Trials to Define COVID Infection

- Pfizer BioNTec, Moderna, Astra Zeneca, J&J/Janssen
- No minimum duration: fever, dyspnea, shortness of breath
- Minimum 2 days' duration: Chills, cough, fatigue, muscle or body aches, headache, loss of taste and/or smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea
- Confirm by reverse transcriptase polymerase chain reaction [RT-PCR] SARS-Cov2

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Meta-analysis of 17,052 Patients

- RT-PCR Positive
- Severe [3664]: respiratory frequency >30/min; O₂ sat 93% at rest; artery PP of O₂/inspired O₂, [PaO₂/PiO₂] 300 mmHg
- Mild [13,388]: Hx of exposure, fever, pneumonia

Chaudhary R, Garg J, Houghton DE. Thrombo-inflammatory biomarkers in COVID-19: systematic review and meta-analysis of 17,052 patients. Mayo Clin Proc pre-press 4-21

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Conditions for 17,052 Patients

Condition	Severe	Mild
Death	32%	1%
Age	64 Y	53 Y
Male sex	65%	54%
Hypertension	45%	23%
Diabetes	28%	16%
Cardiac/stroke	23%	8%
Chronic kidney disease	9%	3%
Chronic liver disease	5%	4% [NS]
Malignancy	10%	7%
COPD	9%	3%

Chaudhary R, Garg J, Houghton DE. Thrombo-inflammatory biomarkers in COVID-19: systematic review and meta-analysis of 17,052 patients. Mayo Clin Proc pre-press

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COVID Diagnostic Assays

- RT-PCR: false negatives [FN] <2%
 - High throughput
 - Pooled specimens
 - Limit of detection [LOD]
 - Not employed to confirm recovery
 - POC: FN rates 2–15% depending on LOD
- Antigen: 16% FN rate
 - confirm pos with RT-PCR
 - If negative but symptomatic reflex to RT-PCR
- Antibody assay not diagnostic
 - IgM & IgG recovery data for public health

Smithgal, MC, Dowlatshahi M, Spitalnik SL, Hod EA, Rai AJ. Types of assays for SARS-CoV-2 testing: a review. Lab Med 2020 DOI: 10.1093/labmed/lmaa039

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SARS-CoV-2 Diagnostic Assays

- Molecular—NP or nasal swab, saliva: definitive assays
<https://www.afhl.org/programs/preparedness/Crisis-Management/COVID-19-Response/Pages/Lab-resources.aspx>
- Antibody—serum or plasma <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html>
- Antigen tests—POC whole blood lateral flow immunoassays detect ~84% of RT-PCR positives
<https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html>

Courtesy of Andrew J. Goodwin, MD

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COVID Progression: What is it?

A hemostasis abnormality unmistakably associates with COVID infection progression, but what is the abnormality? VTE? DIC? LAC? HIT? TMA? TTP? ITP? PLT activation? Sepsis? Hypofibrinolysis?

It has earned a new name, “immuno-thrombo-inflammation.”

We apply routine and specialized laboratory assay results to attempt a model and to develop COVID antithrombotic therapy.

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COVID Infection Progression Recommended Onset Assays

- PT and PTT
- CBC: PLT count
- Fibrinogen
- D-dimer [FDP?]
- CRP
- LDH

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32 YO Biker with SOB

Mean coagulation labs of 94 COVID patients Vs 40 healthy controls

Assay	Patients	Control	p-value
PTT	29.01 s	28.65 s	0.518
PT	12.43 s	12.08 s	0.678
TT	18.00 s	18.34 s	0.137
D-dimer	1036 ng/mL	260 ng/mL	<0.001
Fibrinogen	502 mg/dL	290 mg/dL	<0.001
AT	85.46%	98.83%	<0.001

Patient Onset Labs

- D-dimer: 854 ng/mL
- FIB: 405 mg/dL
- PT: 12.5 s
- PTT: 31 s
- PLT: 170,000/uL

Han H et al. Clin Chem Lab Med. 2020;58:1116–20. Courtesy of Andrew J. Goodwin, MD.

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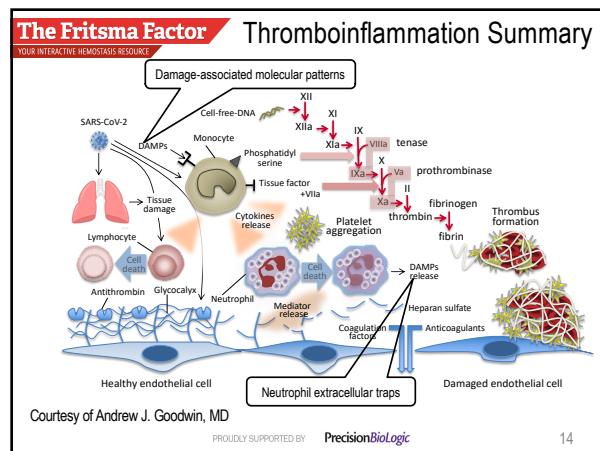
The Fritsma Factor Labs: 17,052 Patients

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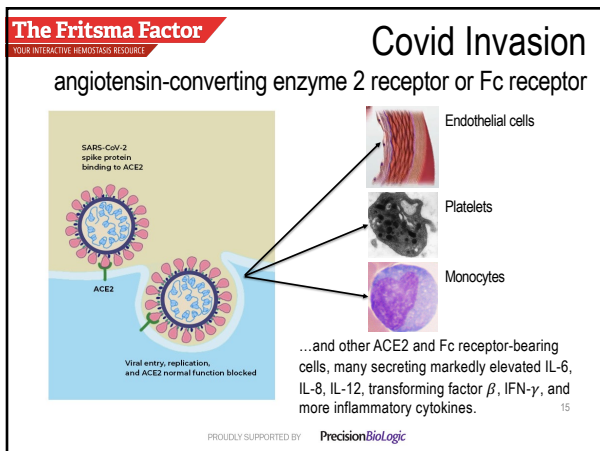
	Severe	Mild
Platelet count	17,100/uL	197,000/uL
D-dimer [FEU]	2900 ng/mL	800 ng/mL
Prothrombin time	13.9 s	12.7 s [NS]
PTT	36.6 s	35.1 s [NS]
Fibrinogen	440 mg/dL	400 mg/dL
CRP	92.6 mg/L	22.9 mg/L
IL-6	49.6 pg/L	12.5 pg/L
Ferritin	1367 ng/mL	635 ng/mL
Troponin-I	36.4 pg/mL	5.7 pg/mL
LDH	448.6 U/L	267.5 U/L

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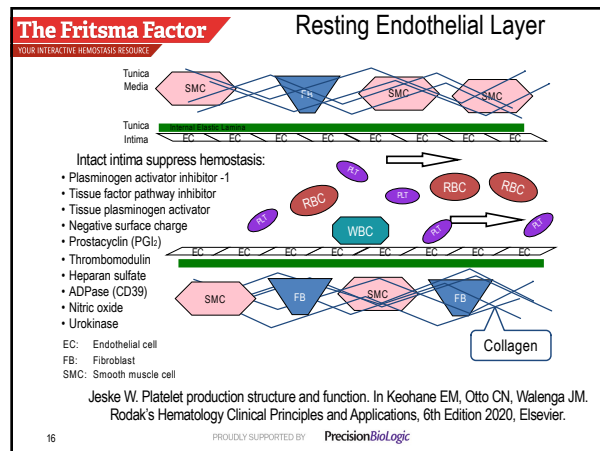
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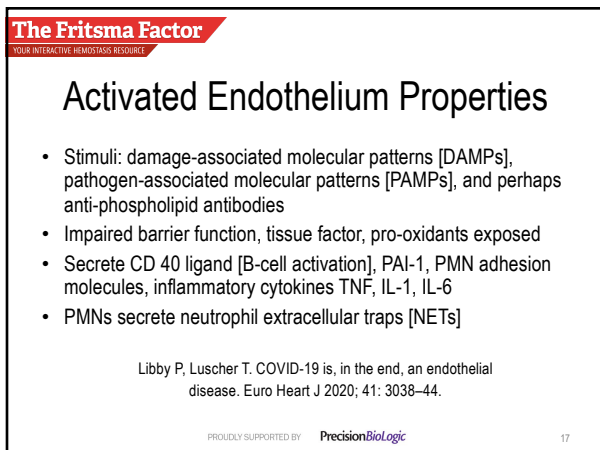
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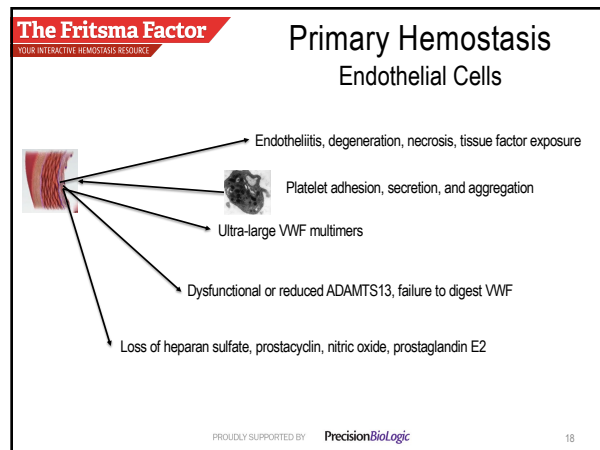
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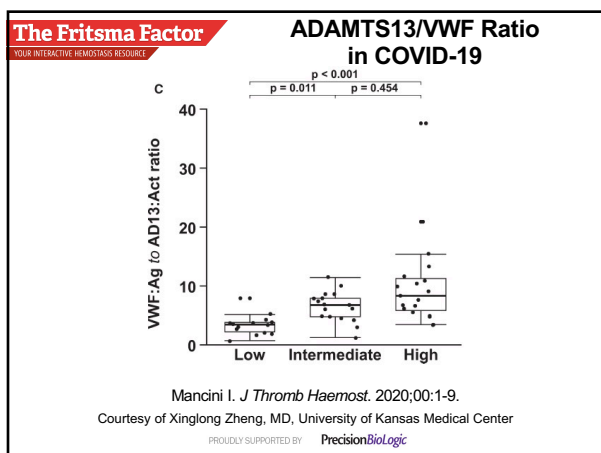
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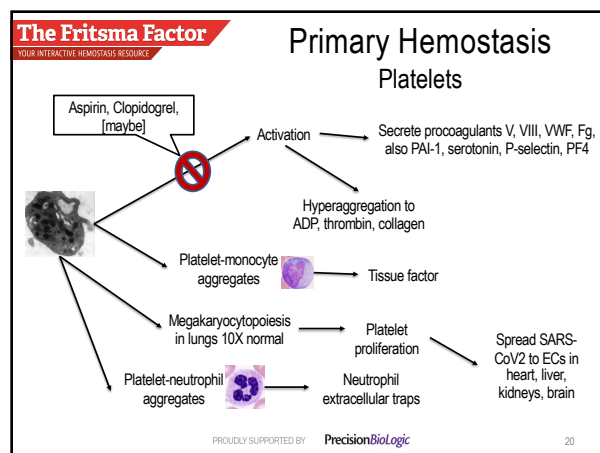
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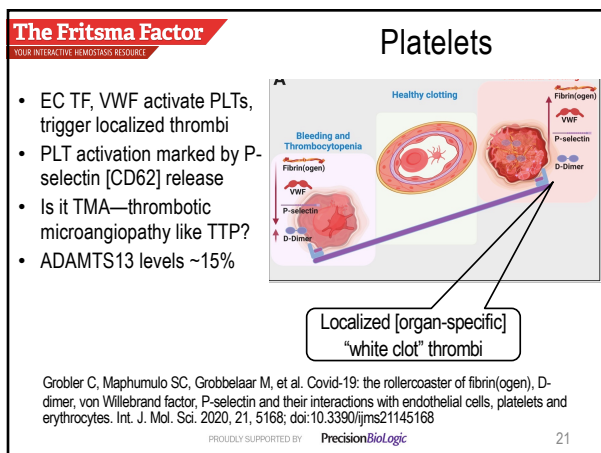
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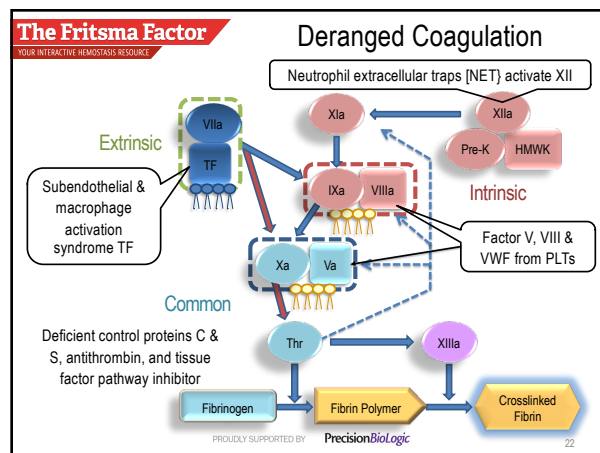
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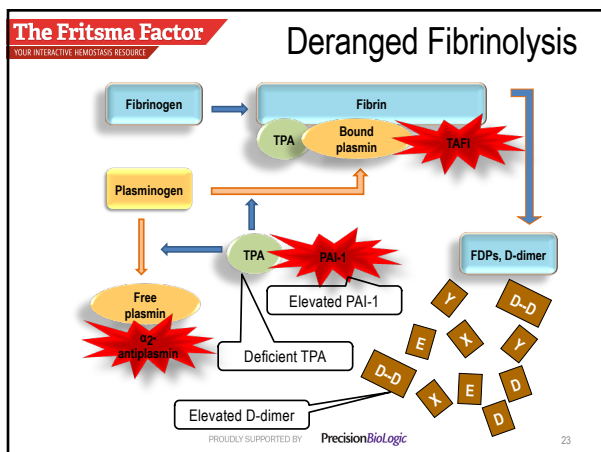
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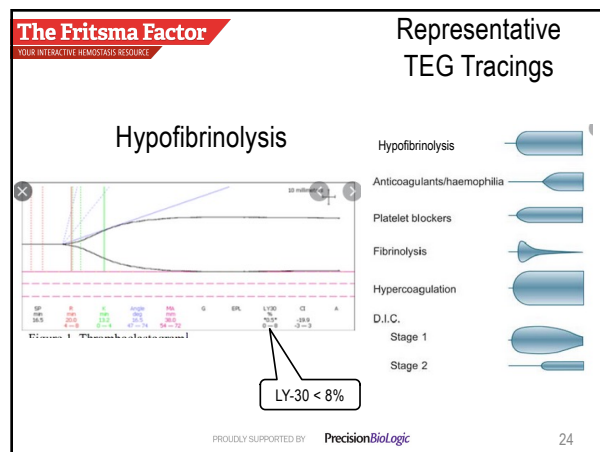
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24 YO Biker: SARS-CoV-2 Tracing = Hypofibrinolysis

Fibrinolysis Shutdown Correlates to COVID-19 Associated Thromboembolic Events

Wright, et al. J Am Coll Surg. April 2020.

Reduced LY-30 and markedly elevated D-dimer associate with VTE and renal insufficiency.

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Courtesy of Andrew J. Goodwin, MD

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D-dimer Correlated to Severity

Assay	Mean	Onset	Intermediate	Severe
D-dimer [ng/mL]	260 ng/mL	2140 ng	19,110 ng	20,040 ng
FDP [mg/L]	1.55 mg/L	7.93 mg	60.01 mg	69.15 mg

Courtesy of Andrew J. Goodwin, MD

- FDP used in China—automated, not in North America
- D-dimer units [DDUs]
 - Normal limit per manufacturer <240 ng/mL or 0.24 mg/L or ug/mL
- Fibrinogen equivalent units [FEUs]
 - Normal limit per manufacturer <500 ng/mL or 0.5 mg/L or ug/mL
- Most research reports fail to specify FEUs or DDUs; and fail to specify units
- Favaloro EJ, Thachil J. Reporting of D-dimer data in COVID-19: some confusion and potential for misinformation. Clin Chem Lab Med 2020; 58: 1191–9.
- Han H et al. Clin Chem Lab Med. 2020;58:1116–20.

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The D-dimer Assay

- "Promiscuous"
 - Screening is ineffective
 - Baseline necessary when there are indications
 - R/O DVT or PE when there is low pre-test probability
- Normal limits are age-adjusted
 - If over 50, multiply age by 10 ng/mL FEUs
 - For example, age 60 = <600 ng/mL FEUs, age 70 = <700 ng/mL FEUs
- Marked elevation implies DIC
- Tang: "Recent studies described that severe COVID-19 is commonly complicated with coagulopathy, DIC may exist in the majority of deaths."

Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease. JTH 2020 as doi: 10.1111/JTH.14817

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Courtesy of Dave McGlasson, DiaPharma Clot Club

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32 YO Biker: Is it DIC?

ISTH Overt DIC Score		
Assay	DIC	Score
PLT	<50,000/uL	2
PLT	50–100,000/uL	1
PT	Prolonged >6 s	2
PT	Prolonged 3–6 s	1
D-dimer	Marked increase	2
D-dimer	Moderate increase	1
Fibrinogen	<100 mg/dL	1
Overt DIC when total = 5 or more		

- Mild thrombocytopenia
- No schistocytes
- PT prolonged to 16.2 s
- PTT unaffected
- Coag factors normal
- No bleeding
- Thrombosis
- D-dimer: 4300 ng/uL

Iba et al. J Thromb Haemost. 2019;17:1989–94.

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32 YO Biker, 5 Days: Is it SIC?

Assay	Score	ISTH DIC	SIC
PLT	2	<50,000/uL	<100,000/uL
PLT	1	50–100,000/uL	100–150,000/uL
PT/PT Ratio	2	> 6 s	> 1.4
PT/PT Ratio	1	3–6 s	1.2–1.4
D-dimer	2	Marked increase	–
D-dimer	1	Moderate increase	–
Fibrinogen	1	< 100 mg/dL	–
SOFA Score	2	–	2 or more
SOFA Score	1	–	1
Overt DIC when total = 5 or more		4 or more	

- SIC = sepsis-induced intravascular coagulation
- SOFA = sequential organ failure assessment; respiratory, cardiovascular, renal, hepatic

Iba et al. J Thromb Haemost. 2019;17:1989–94.

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Sepsis: Infection Response

Endothelium normally releases cytokines to fight infection. Sepsis occurs when cytokine response is out of balance, damaging multiple organs. If sepsis progresses to shock, BP drops.

Organ failure accompanies severe sepsis. Livedo reticularis, anuria, thrombocytopenia, dyspnea, abnormal heart rhythm, chills, weakness, loss of consciousness.

Treat with fluids, antibiotics, norepinephrine and vasopressin. Target a mean arterial pressure of 65 mm Hg.



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The Fritsma Factor 24 YO Biker, Sepsis Lab Assays

Courtesy of Dave McGlasson
Dialpha Ciot Club

Assay	Patient	Reference Interval
PMNs	750/uL	17–7500/uL
Pelgeroid	10%	
Lymphs	900/uL	1000–11500/uL
Reactive	15%	
PLTs	65,000/uL	150–450,000/uL
CRP	1425 ug/dL	< 820 ug/dL
Serum ferritin	850 ng/mL	40–400 ng/mL
IL-6	28.2 pg/L	12.5 pg/L
Procalcitonin	1.6 ug/L	< 0.5 ug/L
Anti β-2-glycoprotein 1	Positive	Negative
Antithrombin, PC, PS	< 60%	> 60%

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The Fritsma Factor Localized Inflammation--Lungs

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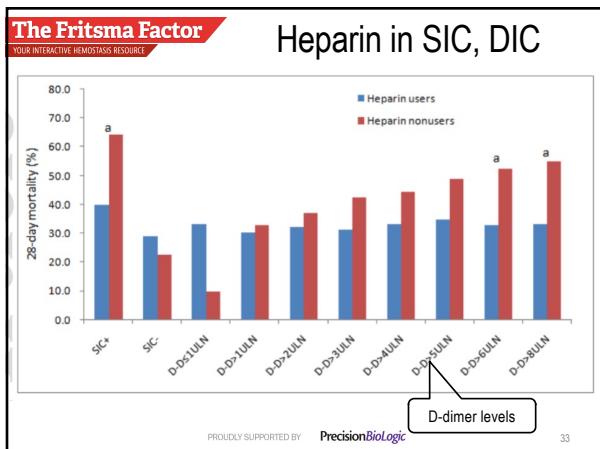
- COVID: 15 inpatients, 15 outpatients, 8 controls
- COVID: elevated TF, reduced protein S, remains post-Rx
- Monitor long-term therapy with TF, PS
- But—also hepatic, renal, CNS, cardiac, and intestinal localization
- How to treat?

What do they have in common? Endothelium

University of Kentucky COVID-19 Unified Research Experts (CURE) Alliance, 9-17-20

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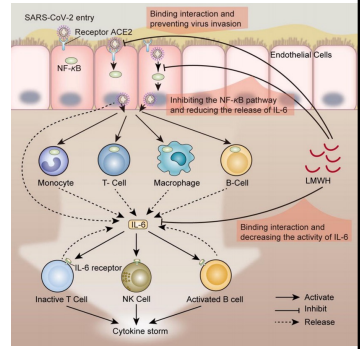


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The Fritsma Factor LMWH Anti-inflammatory

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- Animal studies: Heparin reduces pulmonary microvascular EC barrier dysfunction via microtubule stabilization in a sepsis mouse model and *in-vitro* human ECs
- Retrospective study in COVID-19 patients: LMWH reduced nuclear factor κB reduces IL-6 & increases lymphocyte %
- Heparin reduces expression of VWF and fibrinogen in animal lung injury models




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The Fritsma Factor Thrombosis with Thrombocytopenia Syndrome [TTS]

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- Concerns for clotting events documented after “replication-defective” COVID-19 adenovirus vector vaccines
 - Autoantibody response with PF4-specificity
 - Resembles heparin-induced thrombocytopenia with thrombosis [HIT] Ab
 - J&J human adenovirus 26 vector
 - AZ chimp adenovirus vector
 - No similar events for Pfizer-BioNTec & Moderna mRNA-based vaccines
- Adverse events documented 6–20 days after exposure



Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination [Letter]. NEJM 2021; DOI: 10.1056/NEJMc2105869

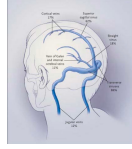
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The Fritsma Factor Astra-Zeneca Thrombosis with Thrombocytopenia Syndrome [TTS] Incidence

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- EU: 18 fatalities
 - 62 cases of cerebral venous sinus thrombosis [CVST] with thrombocytopenia
 - 24 cases of abdominal vein thrombosis with thrombocytopenia
 - Most in females <60 years of age
 - Variant data collection, cannot exclude age/gender as risks
- UK: 20.2 million doses, 19 fatalities
 - Incidence ~4/million, slightly higher in younger age
 - 79 cases of TTS
 - 44 cases of CVST [14 fatalities]
 - 35 cases of other clots [DVT/PE, 5 fatalities]
 - 51 [65%] of cases were female



Schultz NH, Sorvall IH, Michelson AE, et al. Thrombosis and thrombocytopenia after CHAdOx1 nCoV19 vaccination [brief report, Norway. NEJM 2021; DOI 10.1056/NEJMoA2104882.

Greinecher A, Thiele T, Warkentin TE et al. Thrombotic thrombocytopenia after CHAdOx1 nCoV19 vaccination [Germany. NEJM 2021; DOI 10.1056/NEJMoA2104840.

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J&J Vaccine TTS

- CDC and FDA: 8 million doses as of 4-23-21
 - 13 females TTS 18–49, report rate 7/million
 - 3 females TTS 50+ YO, report rate 1/million
 - No TTS males
 - Risk factors: obese [7], OC, hypothyroid, hypertension [2 each]
- CVST, DVT/PE, abdominal vein, acute myocardial infarction
- Strongly positive in EIA PF4/polyvinyl sulfonate fixed target
- Responds adversely to heparin therapy as though it is HIT, use alternate such as argatroban, fondaparinux, DOACs

This is an official CDC HEALTH ALERT

Strieff MB. Pathogenesis and management of thrombosis with thrombocytopenia syndrome. Presented 4-23-21 at CDC conference

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ISTH Vaccine-induced Immune Thrombocytopenic Purpura [VITT] Guidance

- Watch for fever, chills, nausea, headache, vision change, seizures, leg pain, chest pain, SOB, abdominal pain
- Clots on imaging and PLT count <150,000/uL
 - Mean nadir 27,000/uL
- PT, PTT, D-dimer, Fg, immunoassay for anti-PF4 AB
- Ivlg infusion, steroids, PLEX, Fg concentrate, no PLT concentrate
- Non-heparin AC: fondaparinux, argatroban, DOACs
 - Heparin OK if anti-PF4-negative

isth
International Society on Thrombosis and Haemostasis

ISTH interim guidance for the diagnosis and treatment on vaccine-induced immune thrombotic thrombocytopenia. 4-21-21

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J&J: 4–10/million

Risk of Blood Clots

AstraZeneca Vaccine	Birth Control Pill	Smoking	COVID Infection
			
4 cases in 1,000,000 Vaccines	500 - 1200 cases in 1,000,000 women	1,763 cases in 1,000,000 Smokers	165,000 cases in 1,000,000 Cases
0.0004%	0.05% to 0.12%	0.18%	16.5%

Harid Leonor Ramos | Médica Interna de Medicina Geral e Familiar

Forbes, Hyatt, European de Hematology, Sub VJ, Hong K, Shao H et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. Pathology 2021; Cheng, Yan-Ju & Liu, Shi-Hua & Yao, et al. (2021). Current and Future Smoking and Risk for Venous Thromboembolism: A Systematic Review and Meta-Analysis.

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Ongoing COVID-Coag Challenges

- Is COVID-coagulopathy a form of DIC? Is it SIC?
- Is it platelet-triggered thrombotic microangiopathy?
- Should patients be treated with A/Cs for COVID-coagulopathy?
- Control platelets with antiplatelet drugs such as aspirin or clopidogrel?
- Is monitoring UFH & LMWH required in COVID-coagulopathy?
- What is the target therapeutic level of anticoagulation?
- Are vaccines the cause of TTS?
- Report adverse events to Vaccine Adverse Event Reporting System [VAERS] at [vars.hhs.gov](https://www.hhs.gov), 800-822-7967, info@vaers.org

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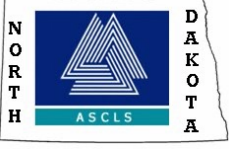
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Bottom Line at the End [BLEAT]

Kept it Short and Simple [KISS—nope]

The participant...

- Proposes the pathophysiology and comorbidities associated with COVID.
- Applies relevant COVID progression laboratory assays results.
- Aligns COVID laboratory results and pathophysiology with disease progress.
- Discusses possible COVID vaccine adverse events.

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