The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

COVID-Coag
What is "Immuno-thrombo-inflammation?"

George A. Fritsma, MS MLS
The Fritsma Factor, Your Interactive Hemostasis Resource
www.fritsmafactor.com ~ george@fritsmafactor.com

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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 was at the Sturgis, SD 8-8-2020 rally. He appears at his local ED experiencing a sore throat, cough, fever, and shortness of breath, O_2 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, 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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COVID-19 Symptoms

- Coronaviridae varieties: respiratory infections; the common cold
- COVID-19: 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 RT-PCR Positive Patients

- Mild [13,388]: Hx of exposure, fever, pneumonia
- Severe [3664]; all the above plus…
  - Respiratory frequency ≥30/min
  - O_2 sat ≤93% at rest
  - "Horowitz" index; arterial PP of O_2/percent inspired O_2, [PaO_2/PiO_2]; ≤300 mmHg

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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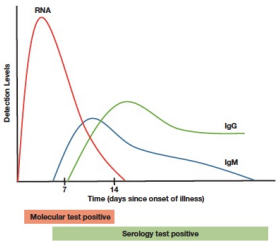
COVID Diagnostic Assays

- RT-PCR: false negatives [FN] <2%
  - High throughput, pooled specimer
  - Limit of detection [LOD]
  - Not used to confirm recovery
  - POC: FN rates 2–15% re LOD
- Antigen: 16% FN rate
  - confirm pos with RT-PCR
  - If neg but symptomatic reflex to RT-PCR
- Antibody assay not diagnostic
  - IgM & IgG recovery data
  - Population data
- 2021: Nex-gen T-cell response
  - Recent or prior infection



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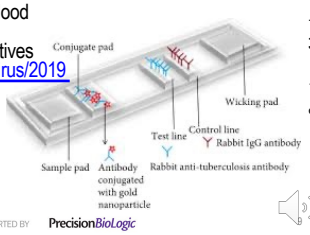
SARS-CoV-2 Diagnostic Assays

- Molecular—NP or nasal swab, wet or dry, saliva: definitive assays https://www.aphl.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
- 2021: T-detect COVID test®, Adaptive Technologies
- 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
- 2021: Abbott Binax-NOW® OTC 15" COVID test
- Flu combo tests: 20 viruses



Courtesy of Andrew J. Goodwin, MD

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COVID Progression: What is it?

- A hemostasis abnormality 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 name, "immuno-thrombo-inflammation.
- We apply routine and specialized laboratory assay results to attempt a model and to develop 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

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

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

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

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Labs: 17,052 Patients

	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 [NS]
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

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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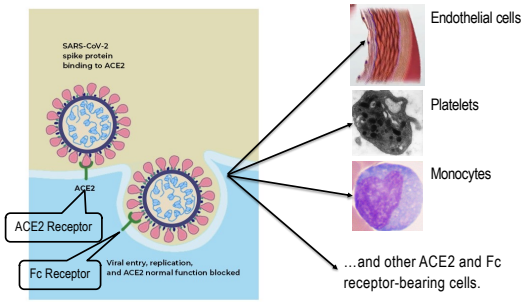
Covid Invasion

angiotensin-converting enzyme 2 receptor or Fc receptor



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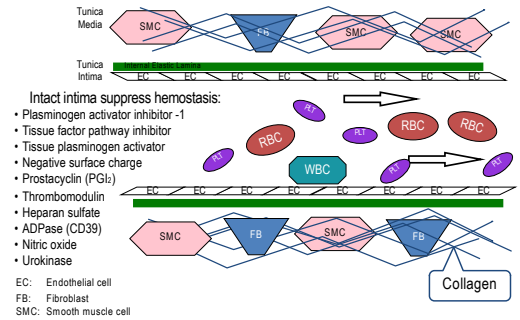
Intact Endothelium



Jeske W. Platelet production structure and function. In Keohane EM, Otto CN, Walenga JM. Rodak's Hematology Clinical Principles and Applications, 6th Edition 2020, Elsevier

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DAMPs, PAMPs, NETs, & APLs

- **Damage**-associated molecular patterns [DAMPs] or **pathogen**-associated molecular patterns [PAMPs]
  - Array of pro-oxidant cytosolic proteins & nucleic acids released from damaged or pathogen-invaded cells.
  - Activate inflammatory cells such as T-cells and macrophages
- PMNs secrete neutrophil extracellular traps [NETs]
  - Nucleic acids and cytoplasmic granule enzymes
  - "Lasso" and destroy pathogens and foreign materials extracellularly
- Anti-phospholipid antibodies [APLs, lupus anticoagulants, LACs] that interact with endothelium [some studies claim 60% of patients]

Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. Euro Heart J 2020; 41: 3038–44.

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Activated Endothelium Properties

- Impaired barrier function exposes TF and pro-oxidants
- Release ultra-large von Willebrand factor [ULVWF]
- Depleted ADAMTS13 [VWF-cleaving protease]
- Activates lymphocyte nuclear factor κB [NFKB]
- Induces T cells and monocytes to secrete CD 40 ligand [B-cell activation], PAI-1, PMN adhesion molecules and NETs, inflammatory cytokines TNF, IL-1, IL-6, IL-8, IL-12, transforming factor β, IFN-γ, and more inflammatory cytokines

Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. Euro Heart J 2020; 41: 3038–44.

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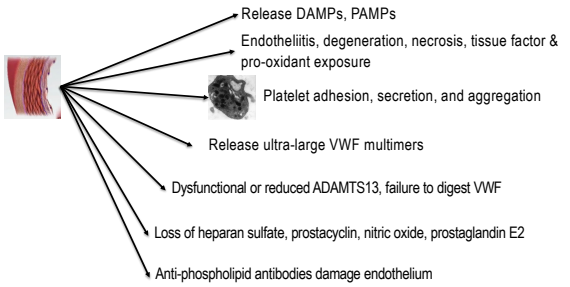
Primary Hemostasis

Endothelial Cells



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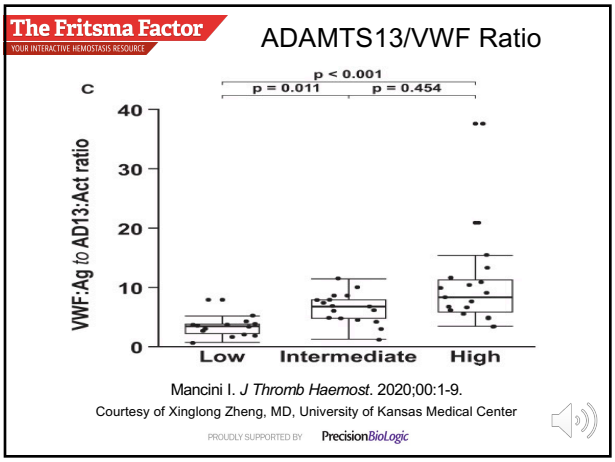

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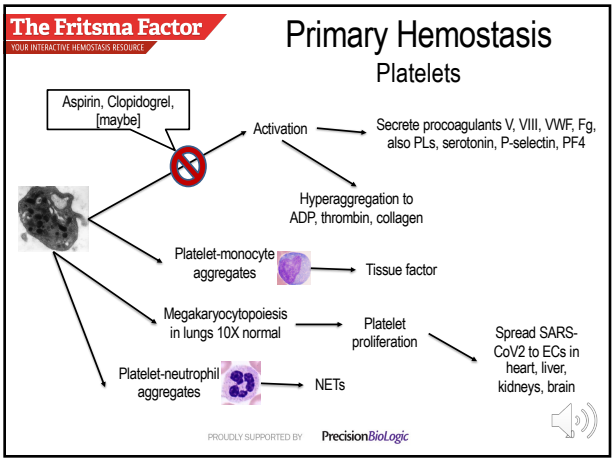

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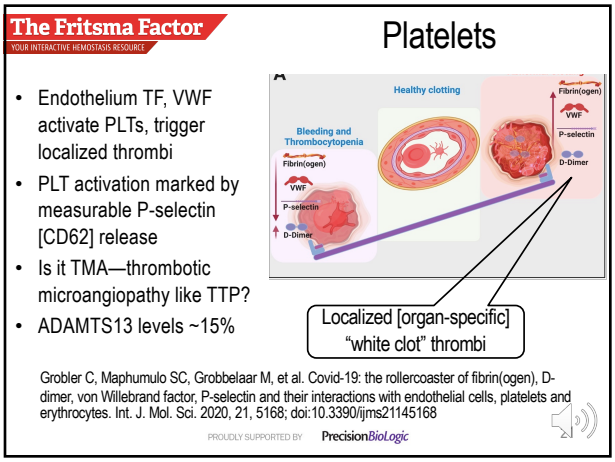

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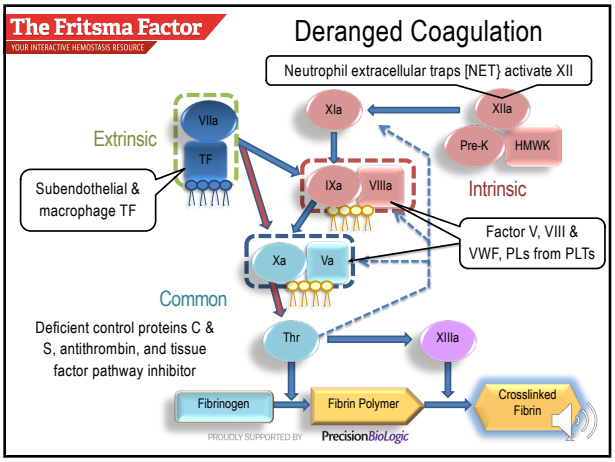

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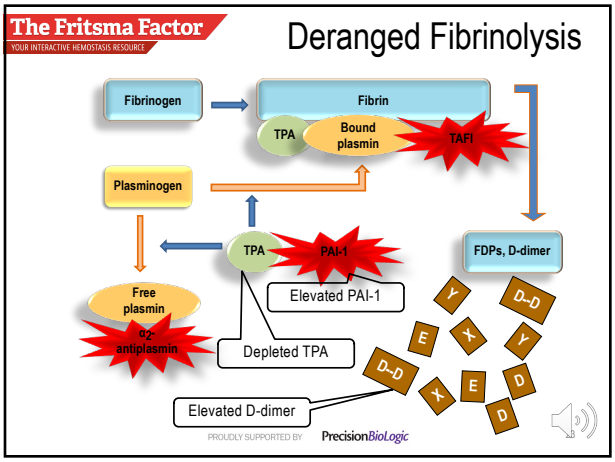

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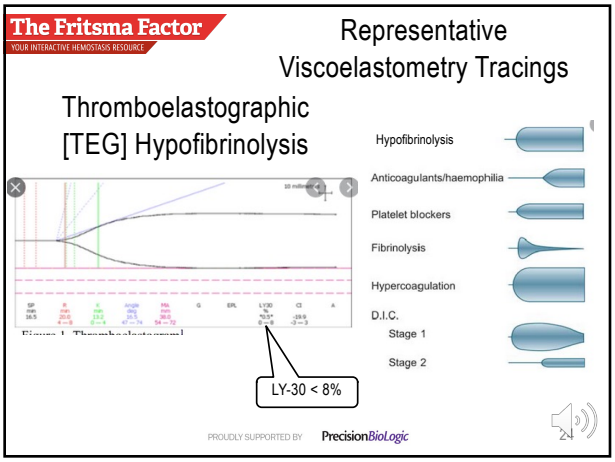

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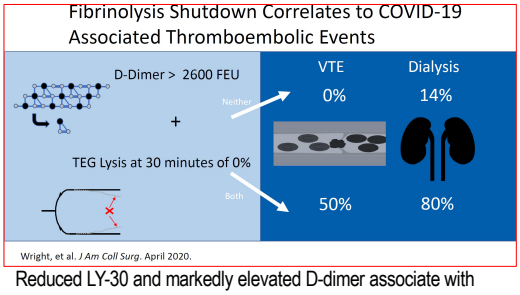
24 YO Biker: SARS-CoV-2 Tracing = Hypofibrinolysis



Courtesy of Andrew J. Goodwin, MD

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

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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

Courtesy of Dave McGlasson, DiaPharma Clot Club

- "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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32 YO Biker: Is it DIC?

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

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		

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

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32 YO Biker, 5 Days: Is it SIC?

- Tpenia: 90,000/uL
- PT prolonged—16.2s
- PTT unaffected
- Coag factors normal
- Thrombosis
- D-dimer 4300 ng/uL
- Is it sepsis?

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

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

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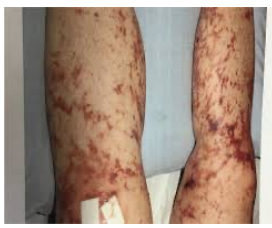
Sepsis: Infection Response



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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24 YO Biker, Sepsis Lab Assays

Courtesy of Dr. Susan LeClair and Dave McGlasson

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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Localized Inflammation--Lungs

- 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, pancreatic [diabetes], 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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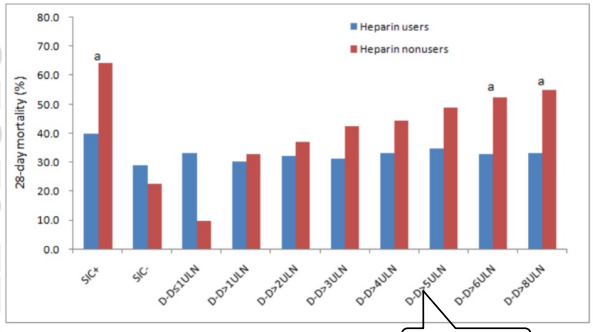
Heparin in SIC, DIC



D-dimer levels

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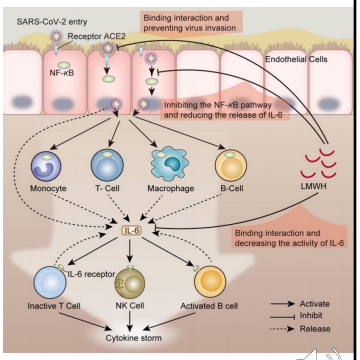
LMWH Anti-inflammatory

- 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



- Tang et al. J Thromb Haemost. 2020
- Mu et al. Respir Res. 2008
- Li et al. Zhonghua 2019.

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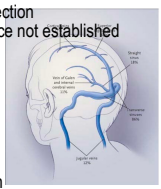
Vaccine Adverse Events

- CDC reporting site: VAERS accessed May 30
  - Self-reported or physician-reported adverse events
  - No attempt to establish causation, collect all data
- 4863 deaths/285 m doses, 1.7/100,000
  - causation not established
- Breakthrough Covid infection: 2/100,000 in 46 states, all vaccines
- Anaphylaxis 2–5/m; all vaccines, 30 m after injection
- Transient myo- or peri-carditis in teens, incidence not established
  - Pfizer
- Vaccine-induced thrombocytopenia with thrombosis [VITT]
  - Cerebral venous sinus thrombosis [CVST]
  - Abdominal splanchnic vein thrombosis
  - In US, only J&J vaccine
  - In Europe, AZ vaccine
- Thrombotic thrombocytopenic purpura: 1/million
  - Same incidence as unselected baseline



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Vaccine-Induced Thrombosis with Thrombocytopenia [VITT]

- Events documented after "replication-defective" adenovirus vector vaccines from J&J, AZ
- Adverse events documented 7–14 days after exposure
- Autoantibody with PF4-specificity resembles heparin-induced thrombocytopenia with thrombosis [HIT] Ab

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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J&J VITT

This is an official CDC HEALTH ALERT

- CDC: 10.2 m doses as of 5-24-21
  - 32 females got VITT, median age 37, report rate 3.7/million
    - 7–14 days after injection
  - Females VITT 50+ YO, report rate 1/million, no males
  - Risk factors: obese, OC, hypothyroid, hypertension
- CVST, DVT/PE, abdominal vein, acute myocardial infarction
- Strongly positive in EIA PF4/polyvinyl sulfonate fixed target, but not in functional HIT assays such as serotonin release
- Theoretic adverse response to heparin Rx as though it is HIT, use alternate such as argatroban, fondaparinux, DOACs

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

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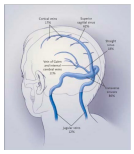
Astra-Zeneca VITT Incidence April 2021

- 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 TEet al. Thrombotic thrombocytopenia after CHAdOx1 nCoV19 vaccination [Germany. NEJM 2021; DOI 10.1056NEJMoa2104840.

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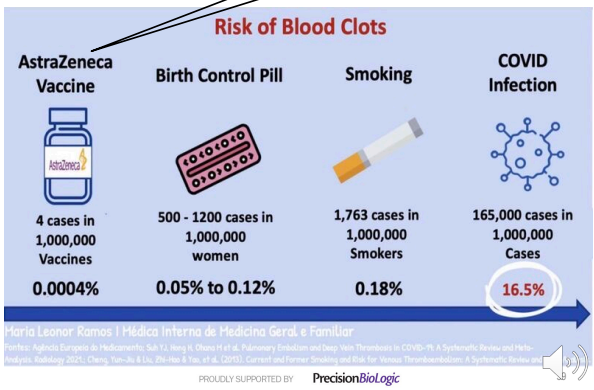
J&J: 3.7/million



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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
- IvIg 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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Ongoing COVID-Coag Challenges

- Is COVID-coagulopathy DIC? Is it SIC?
- Is it platelet-triggered thrombotic microangiopathy [TMA]?
- 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 VITT?
- Report adverse events to Vaccine Adverse Event Reporting System [VAERS] at vars.hhs.gov, 800-822-7967, info@vaers.org

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Bottom Line at the End [BLEAT]

Kept it Short and Simple [KISS—nope]

The participant…

- Proposed the pathophysiology and comorbidities associated with COVID.
- Applied relevant COVID progression laboratory assays results.
- Aligned COVID laboratory results and pathophysiology with disease progress.
- Discussed possible COVID vaccine adverse events.

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