Objectives

- To recognize the diverse etiologies of hypercoagulability
- To review the basic biochemistry of hypercoagulability
- To understand the laboratory indications that hypercoagulability exists and needs treatment
- To identify hypercoagulable states by history, physical and laboratory examinations
- How to treat hypercoagulability in chronically ill patients
- To understand the clinical ramifications for those chronically ill patients whose treatment plans have not addressed hypercoagulability
Clinical case study

• 12 y/o female, ill since age 2 ½, first seen October 2014
  – Lyme diagnosed 2013 with positive Bb serology & high SED
  – Poor response when treated with antibiotics by LLMD
• *Babesia* FISH positive; antibodies to *Borrelia, Babesia duncani, Bartonella, EBV, HHV-6* (IgG 38.49)
• Mold illness with ongoing exposure (*home and school*)
  – HLA 13-6-52A; 1-5
  – TGFB-1 & MMP-9 elevated (*for years, sometimes >12,000*)
• Hypercoagulable
  – Factor II 112, alpha-2 antiplasmin 126, protein S 107, protein C 199, anti-thrombin 108
• Vaccine stress (*fully immunized/yearly flu shot, no HPV*)
Clinical case study

• Chronically inflamed for years, living with 3-8/10 pain, but accomplished academically, ongoing participation in varied extracurricular activities, including aerobic sport.

• November 2019 – “downhill” after significant mold exposure on vacation and Herxheimer to treatment
  – Fatigue (5-6/10), trouble falling asleep, myalgias, joint pain, morning stiffness, sensitive teeth, sore throat, worsening of aerobic tolerance with longer recovery time, slower cognition
  – Eating standard American diet
  – Stopped her entire protocol “weeks ago”
Clinical case study

- November 2019 protocol:
  - Clean, gluten/dairy free, organic diet, PLEASE!!
  - Cytokine/hypercoagulability labs; urinary mycotoxins
  - IMN-CALM 10 drops BID
  - MC-REA 5 drops BID
  - Nattokinase 100mg soft gels 2 BID
  - Serrapeptase 1 BID
  - Plant enzyme digestive formula 2 BID
  - Cytoquel 3 BID
  - Glutathione 1 tsp QD
Clinical case study

- December 2019 labs drawn:
  - TGFB-1 7274; MMP-9 1074; C4a 897.6; VEGF 412
  - Fibrinogen 352; Thrombin/antithrombin complex 4.3
  - Prothrombin fragment 1&2 129; D-dimer 0.27;
  - Alpha-2 antiplasmin 161; Factor II activity 131
  - Protein C 168; Anti-thrombin 131; Protein S 101
  - Lipoprotein(a) 44.8
  - Homocysteine 11.5
  - PAI-1 <4
  - Activated Protein C Resistance 2.9
Review of 1001 cases between 2001-2005:

- 87.3% demonstrated low level activation of coagulation (ISAC)
- 89.7% had ≥ 1 hereditary defects (HTRP)
  - Four-fold increase over normal incidence
- Only 1.9% had normal results
What is hypercoagulability?

• The body maintains a very delicate balance of proteins to encourage or discourage blood clotting via a very complex and redundant system.

• After injury, we must be immediately able to stop bleeding by plugging holes in our blood vessel walls and we must also be ready to thin the blood and contain blood clot formation to avoid blocking life-giving blood flow to organs and tissues.

• A hypercoagulable (HC) state results when there is an abundance of molecules encouraging blood clotting over blood thinning.
What is soluble fibrin?

- The coagulation cascade is a series of enzymatic reactions that result in the production of soluble fibrin (SF) molecules.

- Fibrin can be soluble as monomers, polymers, or protofibrils. Only with a burst of thrombin do these link together in interlocking bonds to form insoluble cross-linked fibrin or blood clot.

- Generally, in the absence a blood vessel wall tear, there are insufficient bursts of thrombin to create insoluble fibrin or clot. In the majority of hypercoagulable patients, only SF is produced.

- If SF formation outpaces fibrinolysis, fibrin accumulates on endothelial linings as a sludge-like layer, trapping toxins, infections, and biologically active molecules, such as thrombin.
Hypercoagulability precipitated by

- Anything that increases inflammation:
  - Natural aging process
  - Pregnancy
  - Genetic factors in 20-30% \((\text{most chronically ill patients have } \geq 1)\)
  - Infectious agents \((\text{acute and chronic})\)
  - Cancer
  - Exogenous toxins and chemicals \((\text{mold toxins, heavy metals})\)
  - Allergens
  - Physical trauma
  - Vaccinations
  - Biologically incompatible frequencies \((\text{man-made EMR})\)
  - Biological warfare agents \((\text{trichothecenes})\)
Hypercoagulability exacerbated by

- Acute/chronic infections
  - Especially febrile illnesses
- Acute trauma
- Chronic inflammation and chronic infections
  - Gut dysbiosis, dental cavitations, vasculitis, toxic loads
- Cytokine flares from
  - Herxheimer reactions, mold exposure
- Detoxification protocols
  - Mold toxins, heavy metals
- Glyphosate-induced sulfate deficiency (Seneff)
  - Deficiency of heparan sulfates on endothelial membrane
Coagulation

• Depends on platelet activation and fibrin production
• Controlled by three different systems:
  – Platelet behavior
    • Acute or low level activation of aggregation, adhesion, secretion contributes to clot formation
  – Fibrin formation or thrombophilia
    • Low level activation of coagulation results in excess soluble fibrin deposition
  – Fibrin degradation or fibrinolysis
    • Hypofibrinolysis – genetic tendencies create weaknesses in breaking down fibrin
Platelet activation/aggregation

- Platelets aggregate and stick in response to
  - Trauma to blood vessels to stop blood loss
  - Immune system activation by toxins and infections
    - Pro-inflammatory cytokines from WBCs cause platelets to aggregate around toxic or infectious foci
    - Activation can be sign of viral infection
  - Junk food and sedentary lifestyle
- Platelets supply clotting factors to produce fibrin
- Chronic low level activation of platelet aggregation is one inducer of cardiovascular disease
# Fibrin formation/degradation

<table>
<thead>
<tr>
<th><strong>Fibrin formation</strong></th>
<th><strong>Physiological balance</strong></th>
<th><strong>Fibrin degradation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombophilia</strong></td>
<td></td>
<td><strong>Fibrinolysis</strong></td>
</tr>
<tr>
<td><strong>Pro-coagulant:</strong></td>
<td>←</td>
<td>now→</td>
</tr>
<tr>
<td>Thrombin (Factor IIa)</td>
<td></td>
<td>Anti-coagulant:</td>
</tr>
<tr>
<td>Tissue Factor</td>
<td></td>
<td>Anti-thrombin</td>
</tr>
<tr>
<td>Platelet factors</td>
<td></td>
<td>Protein S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protein C</td>
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<tr>
<td></td>
<td></td>
<td>Heparans; GAGs</td>
</tr>
<tr>
<td><strong>Anti-fibrinolytic:</strong></td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>PAI-1</td>
<td></td>
<td>Fibrinolysis:</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td></td>
<td>Plasmin</td>
</tr>
<tr>
<td>α-2 antiplasmin</td>
<td></td>
<td>uPA, tPA</td>
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<tr>
<td>TAF-1</td>
<td></td>
<td>Streptokinase</td>
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<tr>
<td></td>
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<td>Lumbrokinase</td>
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<td></td>
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<td>Nattokinase</td>
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</tbody>
</table>
Fibrin formation

• Determined by:
  – Thrombin level and rate of thrombin formation
• Each step has both activators and inhibitors:
  – Activators: tissue factor, platelet factors
  – Inhibitors: Anti-thrombin, Protein C & S (heparans, GAGs)
• Fibrinogen level elevation seen in:
  – Acute or chronic inflammatory disorders, cancer, estrogen therapy, normal pregnancy
• A pro-coagulant environment is a self-perpetuating positive feedback cycle
  – Can result from direct infection of endothelial cells
HEMOSTASIS

CLOT FORMATION

ProTime (PT) Pathway

TF/VIIa

X

Xa

Prothrombin (II)

Vα

F1+2

Thrombin (IIa)

Fibrinogen

Clot

Extrinsic Pathway
HEMOSTASIS

Intrinsic Pathway

aPTT Pathway

IXa

XIIa

Xa

Fibrinogen

Clot

TF/VIIa

Prothrombin (II)

Thrombin (IIa)

F1+2

VIIIa

X

XIIa

IXa

Prothrombin (II)
HEMOSTASIS

Intrinsic Pathway (Minutes)

Extrinsic Pathway (30Secs)

TF/VIIa

Prothrombin (II)

Thrombin (IIa)

Fibrinogen

PC Activation (APC) (4 minutes)

TAFI (Blocks Fibrinolysis)

AT → T/AT (Heparin)

Fibrinogen

SFM

X-Linked Fibrin Stable Clot

TFPI

IXa

VIIIa

Xa

APC + PS

Va

IXa

XIIIa

XIII

Xa

TF/VIIa

Prothrombin (II)

AT

–>

T/AT

(Heparin)

TFPI

F1+2

XIIa Burst

Stable Clot

March 27, 2020

Ann F. Corson, MD

Az Coag 2011

March 27, 2020
ANTITHROMBIN

Intrinsic Pathway (Minutes)

TF/VIIa → X → Xa → IXa → AT / Hep

Prothrombin (II) → Thrombin (IIa) → F1+2 → CLOT

AT → T/AT (Heparin)

VIIIa → X → Xa

Fibrinogen
PROTEINS C & S

Intrinsic Pathway

IXa

APC + PS

Xla

TF/VIIa

CoFactors

Prothrombin (II)

Thrombin (IIa)

Fibrinogen

Clot

F1+2

March 27, 2020
Ann F. Corson, MD
Fibrin degradation and inhibition

Plasminogen

Annexin II

Exogenous kinases

A2-Antiplasmin

SFM

D-dimer

Fibrin degradation and inhibition

Plasmogen

Lp(a)

Plasma

tPA

PAI-1

Endothelial cell

Adapted from Az Coag 2011
Consequences of excess fibrin

One micron of soluble fibrin reduces oxygen diffusion across endothelium by about 500%!!!


Adapted from Az Coag 2011
Consequences of excess fibrin

• Congestion of intra-vascular and extra-vascular spaces results in organ and tissue compromise
  – Nutrients, hormones, tissue factors cannot exit
  – Metabolic wastes and toxins cannot enter
• Loss of vasodilation and vasoconstriction creates rigid vessel walls
  – Results in altered autonomic responses and blood pressure control
Consequences of excess fibrin

Fibrin deposition in response to pathogens/toxins

Blood Flow

Tight soluble fibrin formation

Pathogens/toxins

Inflammation

Endothelial Cells

T: thrombin trapped in fibrin is physiologically active when uncovered!

Increased systemic inflammation with cytokine release: TNFα, IL6, IL1, etc.

Adapted from Az Coag 2011
# Coagulation testing

<table>
<thead>
<tr>
<th><strong>Pro-coagulant</strong></th>
<th><strong>Anti-coagulant</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin fragments 1&amp;2</td>
<td>Antithrombin III</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Protein S activity</td>
</tr>
<tr>
<td>Factor II activity</td>
<td>Protein C activity</td>
</tr>
<tr>
<td>T/AT complexes</td>
<td></td>
</tr>
<tr>
<td>Activated protein C resistance</td>
<td></td>
</tr>
<tr>
<td>Homocysteine</td>
<td></td>
</tr>
<tr>
<td>PT/PTT</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Anti-fibrinolytic</strong></th>
<th><strong>Fibrinolysis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PAI 1</td>
<td>D-dimer</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td></td>
</tr>
<tr>
<td>Alpha-2 antiplasmin</td>
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</tbody>
</table>
724. Does Borreliosis (Lyme Disease) Activate the Coagulation System and Is a Coagulation Regulatory Protein Defect Predispositional? C E CRIST¹, D E BERG ² and H H HARRISON ²,³. ¹Springfield, MO, ²HEMEX Laboratories, Phoenix, AZ, ³Univ AZ Coll Med, Phoenix, AZ

- **Fibrinogen**: increased in 68.7%; decreased in 1.1%
- **Prothrombin fragments 1+2**: increased in 67.0%
- **T/ATs**: increased in 40.0%; decreased in 3.3%
- **Factor II Activity**: increased in 49%; decreased in 2% (on coumadin)
- **Lipoprotein(a)**: increased in 32%
- **Homocysteine**: increased in 29.4%; decreased in 5.2%
- **PAI-1**: increased in 16.6%
- **Antiphospholipid antibodies**: positive in 7.7%

March 27, 2020

Ann F. Corson, MD

Coagulation testing

• Immune System Activation of Coagulation (ISAC)
  – Fibrinogen activity
    • Elevated in acute and/or chronic inflammation, with infection, cancer, pregnancy, and ongoing clotting
  – Prothrombin Fragment 1+2
    • Elevated with increased thrombin formation and cancer
  – T/ATs Thrombin/Antithrombin Complexes
    • Elevated with increased thrombin breakdown
Coagulation testing

- **PT/PTT**
  - *Shortness of either can indicate hypercoagulable state*
  - *Prolongation occurs with treatment*

- **D-dimer**
  - *Elevation is evidence of fibrin breakdown*

- **SED rate**
  - *Very low (<5) indicates hypercoagulable state*

- **Lipid panel**
  - *Cholesterol and LDL often elevated with inflammation*

- **Antiphospholipid antibody testing**
  - *Indicates auto-immune activity, endothelial dysfunction that predisposes to HC, blood clots and miscarriage*
Confirmation of:
Thrombin formation & fibrin deposition

- F1&2 – Prothrombin fragments 1&2
- T/ATs – Thrombin/anti-thrombin complexes
- Fibrinogen activity
## Interpretation of: Prothrombin fragment 1&2 and Thrombin/anti-thrombin complexes

<table>
<thead>
<tr>
<th>F1+2</th>
<th>80 - 315</th>
<th>514</th>
<th>628</th>
<th>1053</th>
<th>192</th>
<th>351</th>
<th>139</th>
<th>190</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/ATs</td>
<td>1.0 - 4.1</td>
<td>30.5</td>
<td>32.1</td>
<td>3.7</td>
<td>3.7</td>
<td>2.1</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Nor</td>
<td>Nor</td>
<td>ABN</td>
<td>NOR</td>
<td>ABN</td>
<td>ABN</td>
<td>ABN</td>
<td>ABN</td>
</tr>
</tbody>
</table>

- T/ATs should be elevated when the F1+2 is elevated. This is a normal physiological adaptation to hypercoagulation stress.

- When the F1+2 is elevated and the T/ATs are normal or F1+2 is normal and the T/ATs are low that indicates a lack of fibrinolysis and fibrin deposition.

Adapted from Az Coag 2011
Coagulation testing

• Hereditary Thrombosis Risk Panel (HTRP)
  – Activated Protein C Resistance
    • A measure of the failure of activated Protein C to have an anticoagulant effect
    • Most often caused by Factor V mutation or Factor V Leiden
  – Factor II Activity (Prothrombin)
    • If elevated, making too much thrombin causing HC state
    • In TBD patients, values over 120% may indicate mild consumption of prothrombin
  – Lipoprotein(a)
    • Elevated with inflammation or genetic weakness
Coagulation testing

• Hereditary Thrombosis Risk Panel (HTRP), cont.
  – Alpha-2 Antiplasmin
    • Protects fibrin by blocking fibrinolysis
    • Occurs as acute phase reactant to trauma or infection, in chronic inflammation, or is a genetic weakness
  – Plasminogen Activator Inhibitor-1 (PAI-1)
    • Blocks fibrinolysis
    • Occurs in acute and/or chronic inflammation or genetic weakness (4G/4G worst)
  – Homocysteine \(\text{best between 6-9}\)
    • Too high (>9) indicates toxic effect on endothelial cells, platelet activation, LDL oxidation
    • Too low (<5) indicates a hypercoagulable state
Coagulation testing

• Hereditary Thrombosis Risk Panel (HTRP), cont.
  – Anti-thrombin activity
  – Protein C activity
  – Protein S activity
  • 1:1:1 balance is normal
  • An upset balance indicates
    – Stress – acute and/or chronic inflammation, trauma
    – Genetic weakness – multiple
    – Physiologic adaptation to hypercoagulable state
      » Low protein S can be an indicator of a chronic hypercoagulable state
Interpretation of:
Anti-thrombin, Protein C, and Protein S

- **Case I** – pt. in flare
  - Anti-thrombin 131
  - Protein C 168
  - Protein S 101

- **Case II** – new pt.
  - Anti-thrombin 144
  - Protein C 181
  - Protein S 65

- **Case III** – new pt.
  - Anti-thrombin 124
  - Protein C 138
  - Protein S 78

- **Case IV** – pt. improving
  - Anti-thrombin 107
  - Protein C 150
  - Protein S 103

- **Case V** – new pt.
  - Anti-thrombin 128
  - Protein C 114
  - Protein S 78

- **Case VI** – pt. improving
  - Anti-thrombin 105
  - Protein C 111
  - Protein S 62
Genetic variations

• Approximately 30% of the population has some genetic abnormalities of the coagulation cascade
  – Roughly 7% are under-coagulators or bleeders
    • About 5% have abnormal factor VIII or Von Willebrand’s disease (hemophilia)
  – 20-25% are hyper-coagulators - 1 in 5 hypercoagulable due to low level activation of coagulation
    • Hyper-coagulators are more likely to develop chronic disease
    • Up to 95% of chronically ill patients are hypercoagulable
Common genetic variants

- Excess thrombin formation
  - Factor V Leiden
    - *Elevated prothrombin (Factor II) and APC Resistance*
- Weak fibrinolysis or hypofibrinolysis
  - Protein S (several hereditary defects)
  - Protein C (several hereditary defects)
    - *In hypercoagulable states, PS and PC can either be high, low or not in the normal ratio (1:1:1) with each other either as a physiologic adaptation or as a result of genetic weakness.*
    - *Important to repeat testing once patient is well to determine if abnormality was physiologic adaptation to stressful stimulus or represents a genetic weakness.*
Common genetic variants

- Decreased fibrinolysis
  - Elevated lipoprotein(a)
  - Elevated alpha 2 antiplasmin
  - Elevated plasminogen activator inhibitor 1 (PAI-1)
    - 4G/4G mutation is the worst
  - Elevated homocysteine
    - Check for MTHFR variants C677T or A1298C

- Most chronically ill patients have genetic issue:
  - Protein S, Protein C, or Antithrombin III deficiency
  - Elevated lipoprotein (a), alpha-2 AP, or PAI-1
  - Factor V Leiden
# Normal versus reference range

<table>
<thead>
<tr>
<th>TEST</th>
<th>NORMAL *</th>
<th>REFERENCE RANGE **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II Activity:</td>
<td>90 – 110 %</td>
<td>75 – 135 %</td>
</tr>
<tr>
<td>APC Resistance:</td>
<td>Same as RR</td>
<td>2.2 – 4.0 ratio</td>
</tr>
<tr>
<td>Antithrombin:</td>
<td>80 – 120 %</td>
<td>75 – 125 %</td>
</tr>
<tr>
<td>Protein C Activity:</td>
<td>80 – 120 %</td>
<td>55 – 140 %</td>
</tr>
<tr>
<td>Protein S Activity:</td>
<td>80 – 120 %</td>
<td>63 – 140 %</td>
</tr>
<tr>
<td>Homocysteine:</td>
<td>6.0 – 10.0</td>
<td>5.0 – 15.0 umol/L</td>
</tr>
</tbody>
</table>

* Desirable Normal Range
** Esoterix, Inc. Reference Ranges
# Normal versus reference range

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<tr>
<th>TEST</th>
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<th>REFERENCE RANGE **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen Activity:</td>
<td>200 – 325</td>
<td>160 – 420 mg/dL</td>
</tr>
<tr>
<td>Fragment 1+2:</td>
<td>90 – 300</td>
<td>80 – 315 pmol/L</td>
</tr>
<tr>
<td>T/AT Complexes:</td>
<td>2.0 – 4.1</td>
<td>1.0 – 4.1 ug/L</td>
</tr>
<tr>
<td>Alpha-2-Antiplasmin:</td>
<td>80 – 110</td>
<td>75 – 125 %</td>
</tr>
<tr>
<td>PAI-1 Activity:</td>
<td>Same as RR</td>
<td>&lt; 31.1 IU/mL</td>
</tr>
<tr>
<td>Lipoprotein (a):</td>
<td>Same as RR</td>
<td>&lt; 31 mg/dL</td>
</tr>
</tbody>
</table>

* Desirable Normal Range  
** Esoterix, Inc. Reference Ranges
Clinical case study

- December 2019 labs drawn:
  - TGFB-1 7274; MMP-9 1074; C4a 897.6; VEGF 412
  - Fibrinogen 352; Thrombin/antithrombin complex 4.3
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  - Lipoprotein(a) 44.8
  - Homocysteine 11.5
  - PAI-1 <4
  - Activated Protein C Resistance 2.9
Clinical case study

December 2019 labs interpretation:

- Significant systemic inflammation – mold/infections
  - TGFB-1 7274; MMP-9 1074; C4a 897.6; VEGF 412
- Excess thrombin driving fibrin production
  - Factor II activity 131; fibrinogen 352; T/AT complex 4.3
- Strong physiologic response to hypercoagulable state
  - Protein C 168; anti-thrombin 131; protein S 101
- Hypofibrinolysis – worsening HC state
  - Alpha-2 antiplasmin 161; lipoprotein(a) 44.8
- Possible genetic weakness predisposing to HC state
  - Alpha-2 antiplasmin 161; lipoprotein(a) 44.8; homocysteine 11.5; Protein S 101
Clinical case study

- PC/OV January 14, 2020
  - “Improved significantly” on November protocol
  - Cleaned up diet!
  - Never did mold urinary testing
  - URI Dec. 31st
    - Sore throat for 4 days (strep neg), congestion that developed into sinusitis requiring antibiotics
    - Crashed back to November levels
- Suspected viral-induced platelet activation and worsening of HC state
Clinical case study

• January 2020 protocol:
  – Increased dose of MC-REA 10 drops BID
  – IMN-CALM 10 drops BID
  – Added Boluoke 2 TID; increased nattokinase 2 TID; and serrapeptase 1 TID (stopped PEDF)
  – Cytoquel 3 BID
  – Fish oil 4 mgs daily
  – Added Dan Shen Supreme 2 caps BID
  – Added Houttuynia 5 drops increasing to 20 BID
  – Activated Charcoal 1 at bedtime three nights a week
Hypercoagulability symptoms

- Generalized pain that can be debilitating
  - Limbs “fall asleep easily, painful numbness
  - Deep achy +/- sharp stabbing shooting pains
  - Neuralgic type pain
- Brain fog – significant encephalopathy, generalized irritability, anxiety/panic, labile affect
- Insomnia, with/without restless leg syndrome
- Motor restlessness (day or night)
Hypercoagulability symptoms

• Stiffness and pain upon awakening or after being sedentary
• Nausea upon awakening +/- poor am appetite
• Painful teeth or sensation of teeth being loose
• Aerobic exercise intolerance
  – Post exertional fatigue
  – SOB with exercise
  – Exacerbation of pain with exercise
Hypercoagulability signs

- Encephalopathic with cognitive compromise
- CNS irritability, emotionally labile
- Mottled skin
- Cold +/- clammy distal extremities with prolonged capillary refill (warm centrally)
- Pale swollen tongue with scalloping edges and full sublingual veins
- Doughy abdomen with peri-umbilical tenderness
Hypercoagulability signs

- Soft tissue congestion
- Head and neck becomes ruddy when supine
- Feet may get deep purple with dependency, dependent rubor
- Poor capillary refill (normal < 2 sec)
  - Check abdominal skin as well as digits
Hypercoagulability treatment

• Reduce systemic inflammation
  – Normalize omega 3:6 ratio (1:1 to 1:4)
  – Optimize liver detoxification pathways
  – Fix gut dysbiosis
  – Clean up the extracellular matrix with drainage medicines
  – Treat acute, chronic and stealth infections
  – Adequate hydration
  – Clean diet with adequate antioxidants, supplement as needed
  – Appropriate physical exercise
  – Reduce stress

• Reduce insulin resistance
  – Diet and exercise
  – Mineral supplementation (Mg, Cr, Va), B vitamins
  – Herbal remedies
Hypercoagulability treatment

• Decrease platelet activation
  – Traditional allopathic medicine
    • Aspirin 81 mg daily
    • Plavix and other platelet inhibitors
  – Integrative medicine
    • Omega 3 EFAs (EPA and DHA) > 1500 mg daily
    • Vitamin E
    • Ginkgo, other herbs
    • Anti-inflammatory and antioxidant nutrients
    • Treat/remove underlying triggers such as viral infections and toxins
Hypercoagulability treatment

• Dissolve excess soluble fibrin
  – SQ Heparin/Lovenox
  – Fibrinolytic and/or proteolytic enzyme combinations
    • Dosages must start low and gradually increase as the debris, toxins and infective agents that are released as soluble fibrin is dissolved can easily overwhelm the body’s abilities to detoxify

• Herbs, nutraceuticals, homeopathic immune modulators
  – Help control both the coagulation cascade and platelet activity as well as to contribute blood vessel wall, tissue, and organ healing
Hypercoagulability treatment

• Eliminate root causes of hypercoagulability
  – Infections
  – Toxins
    • Mold, heavy metals, glyphosate, other pesticides, petroleum byproducts, and other environmental toxins

• Buffer genetic weaknesses
  – PAI-1, alpha-2 antiplasmin, lipoprotein(a), protein C, protein S, factor V Leiden
    • May need fibrinolytics whenever stressed for whatever reason or for life
Fibrinolytics: nattokinase

- Enzyme derived from natto – soybean fermented with *Bacillus subtilis*
  - It closely resembles plasmin and can dissolve soluble fibrin and existing clot or thrombus directly
  - It enhances the body’s endogenous production of plasmin and other clot-dissolving agents such as urokinase
  - Decreases plasma levels of fibrinogen, factor VII, factor VIII in humans
Fibrinolytics: nattokinase

- Orally administered
- Prolonged action – 8 to 12 hours
- Lowers blood pressure
  - Acts as ACE inhibitor (human and animal studies)
- Clinically helps patients with:
  - Abnormal platelet aggregation
  - CVD, PVD, HTN, DM, dementia
Fibrinolytics: lumbrokinase

- Lumbrokinase consists of 6 proteolytic enzymes from the earthworm *Lumbricus rubellus*
  - Potent fibrin-dissolving properties
  - Decrease fibrinogen
  - Lower blood viscosity
  - Markedly reduce platelet aggregation

- Orally administered
  - One study showed only 10% of the full-sized enzyme could pass through intestinal endothelium intact into the blood stream Fan et al., *Biochem Biophys Acta.* 2001 Jun 15;1526(3):286-92.
Fibrinolytics: lumbrokinase

• Is active ONLY in the presence of fibrin (unlike streptokinase and urokinase)
• It is very specific to fibrin and doesn’t affect other blood proteins
• Therefore, it has a very low risk of causing hemorrhage due to excessive fibrinolysis
Fibrinolytics: lumbrokinase

- A 2000 study of 51 stroke patients found lumbrokinase to be beneficial for ischemic stroke and it did not appear to increase the risk of excessive bleeding
  

- A larger 2013 multicenter study found treating post ischemic stroke patients with lumbrokinase for one year reduced fibrinogen levels and decreased plaques and carotid artery intima-media thickness
  
Treatment during pregnancy

- Fibrinolytics and proteolytic enzymes
- Heparin/Lovenox
- Treatment reduces complications of:
  - Maternal HTN, pre-eclampsia and eclampsia
  - Placental insufficiency
  - Prematurity, fetal hypoxia, distress/demise
  - Miscarriage
Treatment caveats

- The body’s endothelial cells generate thrombolytic enzymes routinely but this activity declines with age
- All chronic diseases of the capillaries worsen hypercoagulability
- People with uncontrolled infections will continue to be hypercoagulable
- Adequate treatment of infections/chelation of toxins results in resolution of many HC issues
Treatment caveats

• Movement of heavy metals and mold toxins worsen hypercoagulability and its symptoms exponentially

• Herxheimer reactions result from both increased cytokines and soluble fibrin production
  – Reaction can be significantly reduced with the addition of sufficient doses of fibrinolytic enzymes, inflammatory cytokine blockade, and appropriate tissue and organ drainage remedies
Treatment caveats

• When weaning patients off coumadin:
  – Follow Prothrombin fragment 1&2
  – Use fibrinolytic enzymes
  – Decrease platelet aggregation
    • High dose fish oil
    • Vitamin E
    • Herbs
Treatment caveats

• Rarely, fibrinolytics can result in paradoxical worsening
  – Initial testing:
    • Fibrinogen - 348
    • Prothrombin fragment 1&2 - 335
  – Three months into fibrinolytic therapy:
    • Fibrinogen - 480
    • Prothrombin fragment 1&2 - 456

• Thrombin trapped in the fibrin sludge layer was uncovered, became active again, stimulating more fibrin production. Treat by:
  – Increasing fibrinolytic enzyme doses significantly
  – In severe cases, add heparin SQ/IV
Extra credit clinical case

• 37 y/o dentist exposed to mercury in practice
  – Seropositive *Borrelia* and *Babesia duncani*
  – Living in mold, positive urinary mycotoxins (ochra A, aflatoxin)
  – Initial labs:
    
    | Test                      | Value       |
    |---------------------------|-------------|
    | MMP-9                     | 643         |
    | Anti-thrombin             | 144         |
    | C4a                       | 10,252      |
    | Protein C                 | 181         |
    | Homocysteine              | 6.5         |
    | Protein S                 | 65          |
    | Lipoprotein(a)            | 112.8       |
    | T/ATs                     | 3.0         |
    | D-dimer                   | 0.30        |
    | Prothrombin fragment 1&2 | 165         |
    | Fibrinogen act.           | 318         |
    | Alpha-2 Antiplasmin       | 116         |
    | APC Resistance            | 2.7         |
    | Factor II activity        | 124         |
    | PAI-1                     | <4          |
Extra credit clinical case

• What is the coagulation issue?

• What are all possible differential diagnoses and why?

• How would you approach this patient?

• How would you initiate treatment?
References for learning more

• Role of Hypercoagulation & Biofilms in Chronic Illness

• Decoding the Mystery of Chronic Illness

• ARG’s Focus Newsletter
  – January 2003: Hypercoagulation Linked to Chronic Fatigue, Fibromyalgia, MS, Infertility, Chronic Illness
  – November 2008: Nattokinase: Clinical Updates from Doctors Support its Safety and Efficacy
  – March 2009: New Enzyme Complex Isolated From Earthworms is Potent Fibrinolytic Lumbrokinase has Anti-Platelet, Anti-Thrombotic Activity
Hopefully, now you understand What’s the Fuss About Fibrin! Thank you!