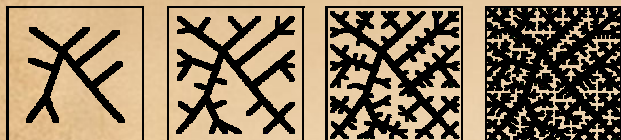


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COAGULOPATHIC ULCERS - CRITERIA & NOMENCLATURE

Original presentation May 15, 2006, Scottsdale, AZ
at the annual meeting of the Wound Healing Society

This is the original poster, reformatted for standard paper layout.
Additional annotations pending.

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COAGULOPATHIC ULCERS - CRITERIA & NOMENCLATURE

Marc E. Gottlieb, MD, FACS Phoenix, AZ

Presented at the Wound Healing Society Annual Meeting, Scottsdale, AZ, May, 2006

Abstract

The Problem. Hypercoagulopathies can cause microthrombotic soft tissue infarction and chronic ulceration. Recognized only for the past decade, awareness of this association remains limited among physicians, including those with a practice of wounds. Once one begins to recognize these disorders and their ulcers, many chronic ulcers that could not previously be assigned to a specific cause can be positively diagnosed. Most such ulcers respond quickly to warfarin or other anticoagulation, usually with complete rapid healing. This presentation defines clinical criteria (history, physical, lab) that permit positive diagnosis of hypercoagulopathic ulceration. Nomenclature (which has implications for therapy) begins with the causes of abnormal thrombosis and thrombotic syndromes:

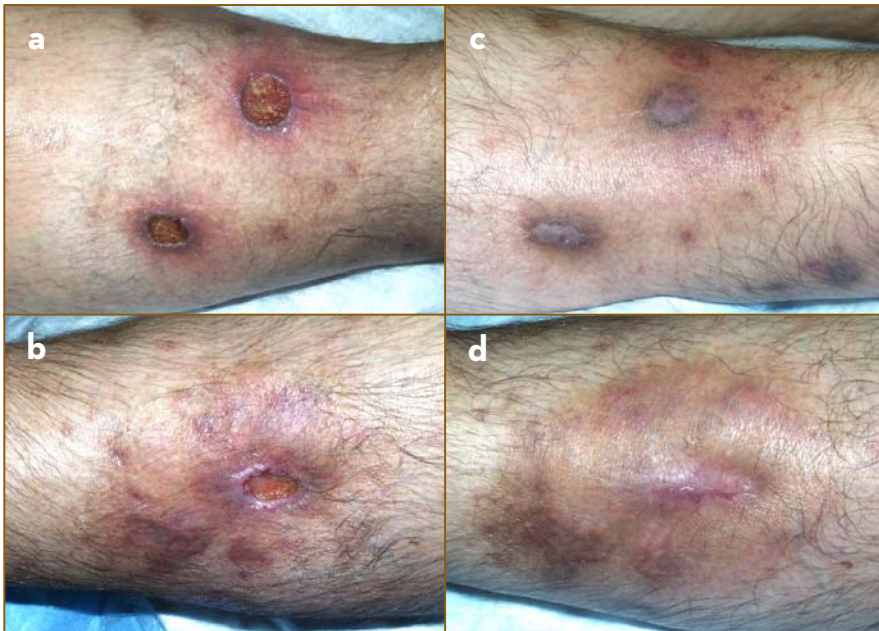
Nomenclature, micro-occlusive ulcers. **1-Hemodynamic disorders:** Blood, vessels, coagulation all normal. Thrombosis occurs as it is balanced to do, in response to abnormal hemodynamics (e.g. atrial fibrillation). **2-Endo-vasculopathies:** Blood and coagulation normal. Thrombosis is activated by abnormal blood vessels (intrinsic vascular diseases, e.g. atherosclerosis, allo-implants). **3-Exo-vasculopathies:** Same (extrinsic vessel disease, e.g. vasculitis, hyperparathyroid). **4-Non-hypercoagulable hemopathologies:** Disordered blood components cause stasis and trigger thrombosis. Coagulation is intrinsically normal (e.g. sickle, dysproteinemias). **5-The hypercoagulopathies:** Coagulation is inherently abnormal or unbalanced, causing mis-programmed primary thrombosis, even when blood and vessels are normal:

Nomenclature, hypercoagulopathic ulcers. **1-Intrinsic "pre-thrombotic" hypercoagulopathy:** Genetic: f.V Leiden, prothrombin mutation. Metabolic, dynamical: antithrombin-3, proteins C & S, fibrinogen, warfarin. **2-Extrinsic:** Triggered or unbalanced by other abnormalities: estrogens, pregnancy, cancer, homocysteinemia, inflammation, PNH, and any which affect the coagulation system. **3-Immune related:** Antiphospholipid antibodies (anticardiolipin, lupus anticoagulant), inflammatory conditions which trigger thrombosis. **4-Uncategorized:** As more disorders and lab tests are validated, diagnostic precision will increase. Non-exact but valid diagnoses can be established on sufficient clinical criteria.

Key features. Vascular occlusion and ischemia not overt; problems are subacute, chronic, recurring, perplexing, refractory. **History:** Overt thromboembolic events, especially in young or healthy people, multiple, or uncommon events (retinal artery occlusion, Budd-Chiari, Paget Schroeder); pathergy, soft tissue complications of trauma and surgery; miscarriage; non-healing ulcers. Other distinctive features: Similar family history, warfarin resistance. **Major disease associations:** Acute & chronic venous disease; connective tissue diseases.

Conclusion. The principles of recognizing and establishing these diagnoses, accurately, on positive criteria, will be presented. Treatment of these disorders and their wounds is contingent on anticoagulation, but the wounds often need additional judicious management.

INTRODUCTORY CASE STUDIES



Case 1. 29 year old man. Multiple leg ulcers for many years. Current set of ulcers unhealed for 2 years. Personal history otherwise negative. Family history of miscarriages. Laboratory: high anticardiolipins.

Dx: Antiphospholipid antibodies.

a, b. Right & left leg ulcers, prior to warfarin. **c, d.** Healed, 14 weeks after starting warfarin, 8 weeks after getting prothrombin time INR stable in therapeutic range (2.5 - 3.5).

Key points: Suspicious history. Family history. Otherwise young and healthy. Confirmatory blood tests. Healed with anticoagulation.



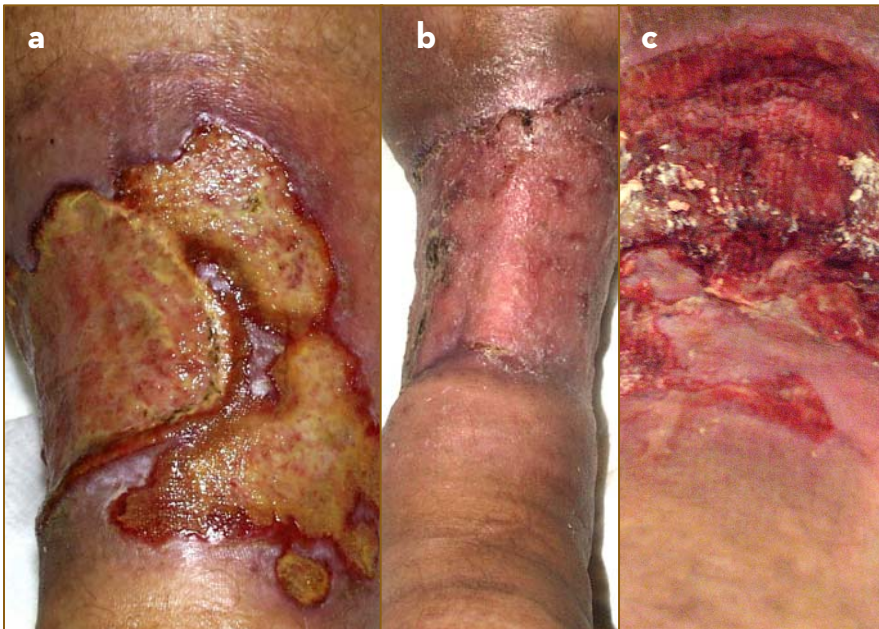
Case 2. 67 year old woman. Acute skin necrosis of legs. No overt risks or history. Good pulses in feet. Laboratory workup positive:

Dx: Anti-thrombin 3 deficiency.

a. Circumferential infarction of skin and subcutaneous fascias, legs and ankles. **b.** Close up of peri-infarct stasis and ischemic blistering. Note wrinkles and **lack** of pannicular and cutaneous edema, nor generalized peri-wound inflammation.

Key points: Pre-thrombotic events may have no prior history. Black infarcts. Severe ischemic pain. Lack of inflammatory signs. Good pulses.

INTRODUCTORY CASE STUDIES



Case 3. 43 woman. Refractory ulcers many years. History multiple DVT & PE. Low skin TcpO₂. No stigmata of “venous disease” (pigment, sclerosis, stasis dermatitis). Lab tests positive.
Dx: Proteins C & S deficiency.

a, Necrosis, active ulceration, stasis. **b.** Healed with high INR warfarin, skin recon with Integra. **c.** Re-ulceration after lapsed care and warfarin.

Key points: Many venous thrombo-embolism, ulcers long refractory to care, otherwise young and healthy. Characteristic wounds, no classic venous disease. Healed with warfarin. Re-ulceration after stopping warfarin.



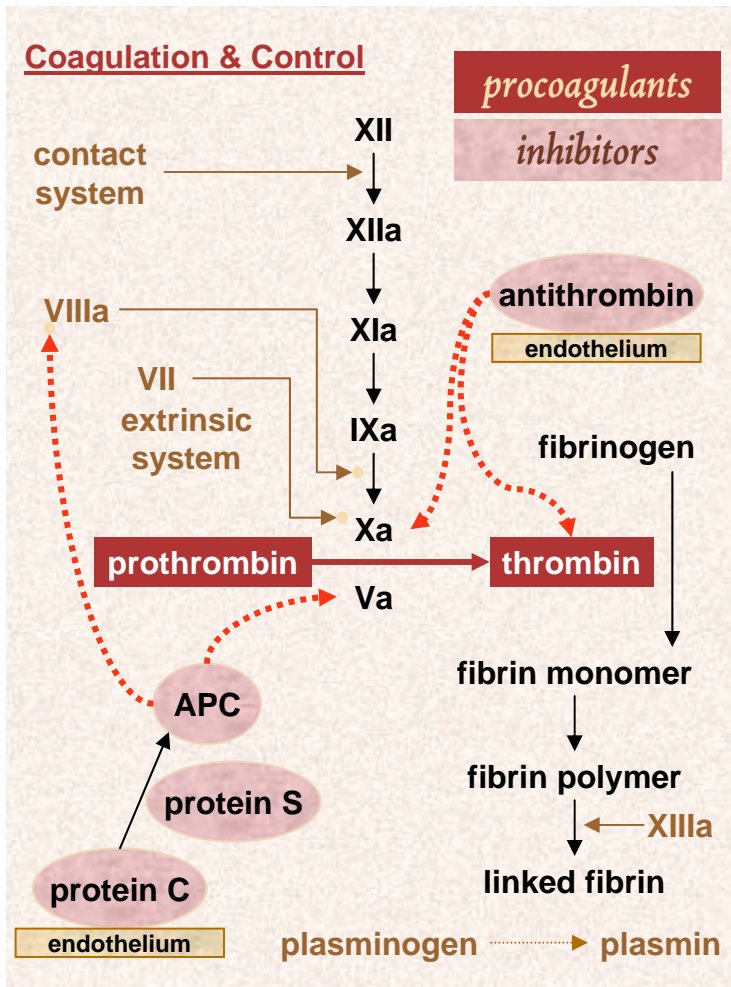
Case 4. 67 year old woman. Back wound necrosis following lumbar decompression. Strong family history leg ulcers and DVTs. Laboratory: Factor V Leiden, high protein C and plasminogen, very high fibrinogen.
Dx: Factor V Leiden.

a. Lumbar wound with necrosis of skin margins and wound surfaces, peri-wound vascular stasis.

Key points: Not an ordinary surgical complication (abscess, mechanical rupture, seroma) - outright necrosis. High risk history, confirmed by lab and clinical outcome. Healed with anticoagulation and further surgery.

Micro-occlusive disorders are a major cause of chronic ulceration, impaired wound healing, and complications of trauma and surgery. Little appreciated by most physicians, this subject requires broader awareness. Here is a conspectus of the subject, and a nomenclature of disease, focused on hypercoagulopathies.

PATHOLOGY OF HYPERCOAGULOPATHIES



1 - Basic coagulation. Thrombosis stops bleeding. It is a complex control system with a dozen main sequence proteins, and dozens of protein and other cofactors. It is normally activated by platelets or leukocytes. In principle, it is balanced so that blood never clots within an endothelial conduit, but it clots instantly for any other condition. Holding a complex multicontrol system to this narrow set point is a miracle of nature, but it can easily be perturbed or offset. Most clinicians are familiar with hypocoagulable conditions, but this subject is “new”. Hypercoagulopathies make blood clot where it shouldn’t - within blood vessels. They are a major cause of ulcers, problem wounds, and various other illnesses.

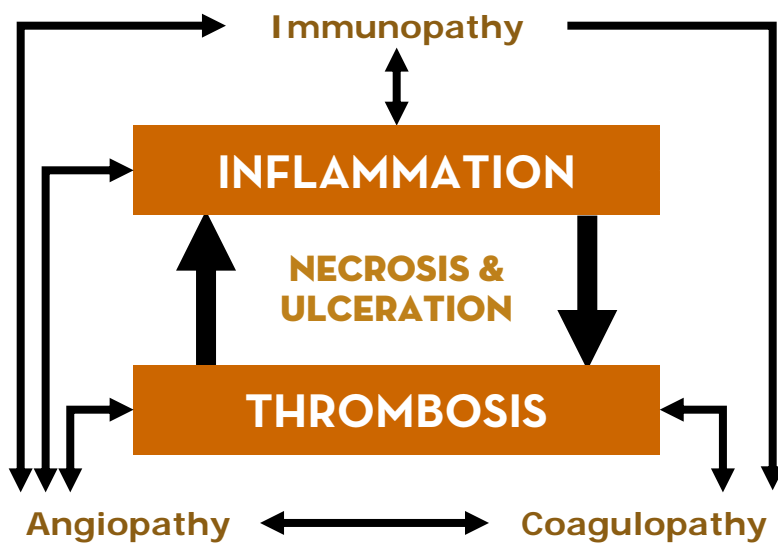
2 - Hypercoagulopathy. When hypercoagulopathic, blood is prone to clot within vessels. If the system is severely unbalanced, spontaneous untriggered intra-vascular thrombosis can occur. Usually though, the offset is subtle, making thrombosis more sensitive or overly responsive to a variety of customary triggers.

3 - Pathophysiology, clotting. Thrombosis occurs in vessels. For small vessel non-lethal events, blood flow is interrupted, causing severe hypoxia, vascular stasis, and infarction (later becoming ulcers). Secondary inflammation is triggered. Since stasis and inflammation are themselves normal triggers for thrombosis, a hypercoagulopathic event can be auto-amplifying, and self-perpetuating:

4 - Dynamical: As a complex non-linear system with multiple controls, feedback, and triggers, coagulation has chaotic dynamics. When healthy, it is in a stable well, barely variable, behaving properly. When it is unstable (orbiting), severe and unpredictable events can occur. There is no discrete time-domain solution for coagulation parameters. What this means is that patients can be normal then abnormal, healthy one day, sick the next, or year to year, without pattern or rationale, with or without obvious relationships to other factors or triggers. Hypercoagulable patients are not always hypercoagulable. This is a paradigm of “dynamical disease”. The auto-amplifying loop must be broken by appropriate treatment.

5 - Biochemical. The thrombosis chemicals can all be unbalanced or dysfunctional to promote clotting. To illustrate: *activated Factor 5* causes unregulated conversion of prothrombin. To slow it down, endothelial proteases *Proteins C & S* combine to make *Activated Protein C*, which inhibits F.Va. If C is deficient or defective, or if S is deficient so it cannot alter C, then F.Va stays unregulated, and the system is hypercoagulable. *Factor V Leiden* is a genetic mutation that makes it unresponsive to APC, with the same effect.

PATHOLOGY OF HYPERCOAGULOPATHIES



6 - Inflammation: Inflammation and coagulation have a crucial interrelationship. Inflammation triggers thrombosis. Thrombosis triggers inflammation. Injury of any sort can “push over the edge” in a susceptible occult hypercoagulopathy. The process can become self-sustaining in the injured area. Many hypercoagulopathies are related to immunopathic diseases. The antiphospholipid antibodies (anticardiolipin, etc.) are autoimmune. However, prethrombotic patients (clotting factor alterations and gene mutations) also often have elevated immune serologies, such as ANA, RF, and APLs. Chronic ongoing coagulation-triggered inflammation may induce autoimmune conditions.

Main clinical effects of hypercoagulopathic states:

Macrothrombosis: Acute large vessel events • overt • life-and-limb threatening • “old hat”.

Microthrombosis: Subacute, chronic, recurring • perplexing, refractory, non-obvious origin • vascular occlusion not overt, usually not life threatening (but there are some dramatic and lethal exceptions), recognized by secondary clinical events • young age, family history, special tip-offs (e.g. warfarin resistance) • long history of failed care (both non-specific wound care, or treatment for wrong diagnoses) • a new frontier of medical knowledge.

Defined clinical syndromes and sequelae of hypercoagulopathies

Recognized or well characterized

Macro / large vessel thromboembolism
(and derivative problems, e.g. MI, CVA)

Miscarriages (typically multiple)

Biochemical (warfarin use, estrogens)

Complications of trauma and surgery

Chronic ulcers and non-healing wounds

Other major suspects

Primary pulmonary thrombosis
(multiple diffuse PEs are not from DVT)

Small organ apoplexy (pituitary, adrenal)

Non-immune lupus nephritis (RPGN)

Digital ischemia of CTD / CVD

??? An open field for inquiring minds ???

PATHOLOGY OF COAGULOPATHIC ULCERS

Hypercoagulable ulcers are NOT diagnoses of exclusion.

These diagnoses can be made on specific criteria.

ONSET OF ILLNESS

acute micro-thrombosis & vascular stasis
severe local ischemia of skin and fascias
skin infarcts, progressing to ulceration
gross inflammation + / -, often absent
pseudo-inflammation from severe stasis

spontaneous -vs- triggered by an event
chronic or chronically recurring

common on lower extremities
can occur anywhere

LINK TO INFLAMMATION

strong tie, coagulation to inflammation:
1° thrombosis triggers 2° inflammation
1° inflammation triggers 2° thrombosis

some injuries purely coagulopathic
some mainly immune or inflammatory
some wounds inextricably mixed

strong association with CTD / CVD:
ongoing trigger from chronic 1° inflamm.
chronic 2° inflamm. induces autoimmunity
many patients with mixed lab profiles

FINDINGS

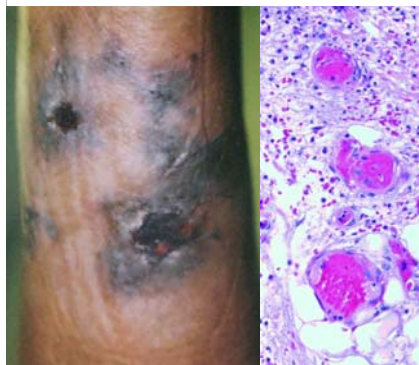
ischemic infarction: skin, fascias, wounds
periwound stasis, low TcpO₂, pain
active ulceration
edema & gross inflammation often absent
mixed wound module, non-healing

good pulses
no signs of other dx



Acute necrosis. Skin infarcts are usually small, scattered, isolated, but some-times large and life threatening.

35 yo woman, with acute lupus, Extensive skin infarcts (hips & thighs shown). Antiphospholipid antibodies. Low skin TcpO₂s.



Stasis and infarcts. Around the infarcts are zones of severe stasis which may die and ulcerate (or recover).

43 yo man, with very low proteins C and S (leg and ankle). Small vessel thrombosis and organization, with adjacent stasis, congestion, and hemorrhage.



Chronic active ulceration. Post-infarct eschar separates, leaving ulcers. The problem can be chronically active.

61 yo woman, protein S deficiency. Long history DVT, PE, and leg ulcers. Perpetual stasis, inflammation, active infarction and ulceration. Old recanalizing thrombus shown.



Trauma pathergy, morbidity.

Trauma and injury can trigger microthrombosis, with unexpected wound infarcts, dehiscence, failed repair.

53 yo woman, rheumatoid arthritis. Dogbite, forearm. Many complications of repeated surgery. Protein C&S deficient. Confirmatory histology.

PATHOLOGY OF COAGULOPATHIC ULCERS

Hypercoagulable ulcers are NOT diagnoses of exclusion.

These diagnoses can be made on specific criteria.

DYNAMICAL BEHAVIOR

refractory impaired wound behavior
characteristic of severe ischemia

recalcitrant and continuously pathological
persistent active necrosis and ulceration
can be self-perpetuating and amplifying

chaotic dynamics
net misbehavior over time
rapid evolution, but (very) slow resolution
variable state with each observation

COMPLICATIONS

necrosis, dehisce, ulcerate after biopsy
necrosis, dehisce, ulcerate after debride
necrosis, dehisce after trauma and surgery
necrosis, dehisce, failed repair or closure
graft loss, flap necrosis
potentially lethal severity and extent
intercurrent thrombotic events

THERAPIES & OUTCOMES

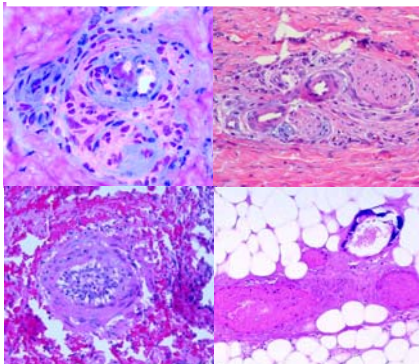
chronic, persistent, recurring
consistent failures of general wound care
multiple failed procedures
patient and provider frustration

chaotic dynamics of therapy
warfarin hard to regulate

REMEMBER:

you are not "thinning" normal blood,
you are restoring "sticky" blood to normal
high INRs required, 2.5 - 3.5 (some higher)

after adequate anticoagulation:
necrosis and pathology arrested
tissues revascularize as thrombosis stops
wound healing restored
success usually easy after anticoagulation



Surgical complications. For controlled injury, risks are the same. These patients need perioperative anticoagulation.

69 yo woman. Wound dehiscence and active ulceration after biopsy for minor skin lesion. Protein S deficient, and cryoglobulins. Histology shows thrombi, vessel and tissue necrosis.

Failed therapy. Ischemia and necrosis impair healing and impede success, for even the most mundane benign events.

72 yo woman, numerous problems healing a small wound of the leg. A skin graft donor site had similar problems: stasis and infarcts shown. High anticardiolipins and ANA.

Unexpected profiles. Think of hypercoagulopathies for young patients with peculiar ulcer histories and features.

39 yo man. Refractory leg ulcers since femur fracture, DVT at age 14. Factor V Leiden (most young men with venous ulcers have this mutant gene). Healed with 2 months of warfarin.

Histology. Debridement and biopsy can reveal: thrombi in various stages, stasis, vascular & tissue necrosis, ulceration, microangiopathy, 1° vasculitis, 2° chronic vasculitis, immune complexes, vessel fibrosis and stenosis, general wound histo.

4 patients with various diagnoses.

DIAGNOSIS AND MANAGEMENT

Hypercoagulable ulcers are NOT diagnoses of exclusion.

These diagnoses can be made on specific criteria.

1A. PERSONAL HISTORY

Any recurrent, unexpected, or inexplicable thromboembolism:

- arterial
- deep venous
- pulmonary
- common (mi, cva)
- peculiar or rare events (budd-chiari, padgett-schroeder)
- events triggered by illness, injury
- events in young healthy people
- events in spite of treatment

- absence of common risks
- peculiar profiles (e.g. retinal artery occlusion in a young healthy person)

Other diseases and events:

- miscarriages
- venous disease
- autoimmune, connective tissue
- liver disease
- angiopathies, blood disorders
- cancer (Trousseau), PNH
- estrogens, warfarin resistance
- absence of these or other risks

1B. FAMILY HISTORY

(important info to help establish diagnosis, especially when lab tests are negative)

- miscarriages
- thromboembolism
- any of above

1C. WOUND & TISSUE HISTORY

Wounds and ulcers:

- continuous pathological behavior
- absence of identifiable injury
- pain
- long history failed therapy

Other events:

- trauma-induced tissue pathergy (infarction, dehiscence, etc.)
- complicated or failed operations
- multiple such events
- identifiable event (eg warfarin rx)
- things that just don't add up

2A. EXAM - WOUND

Distinctive or consistent findings:

- impaired / non-healing wound
- necrosis
- progressive ulceration
- skin infarcts (as opposed to lysis)
- vascular stasis, periwound cyanosis
- pathergy / necrosis after debride
- absence of inflammation (or presence of inflammation)
- persistent pathological behavior
- characteristics of severe ischemia

Discrimination from other dx:

- infarction versus lysis
- inflammation, or not
- venous changes, or not
- pulses / macrovessels normal
- peculiar or non-specific locations
- not confined to tendons, synovium
- not in pressure / mechanical areas

DIAGNOSIS AND MANAGEMENT

Hypercoagulable ulcers are NOT diagnoses of exclusion.

These diagnoses can be made on specific criteria.

2B. EXAM - GENERAL

age (any age, including young)
vascular & skin exam
signs of previous ulcers or infarcts
rheumatoid & immunopathic signs

2C. EXAM - RESPONSE TO RX

Failures of general care:

resistance to most treatment
behaviors of severe ischemia
failed response to customary care
progressive infarction in spite of rx
failed therapy for other diagnoses
failed rx: steroids, anti-immune

Complications of specific care:

pathergy / necrosis after debride
necrosis, dehiscence after surgery
failure, complications of surgery

warfarin resistance
warfarin necrosis
difficulty regulating PT-INR

“things that just don’t add up”

3A. DIFFERENTIAL DX, R/O

pyoderma, immune dermatoses
immunopathies, CTD, CVD
vasculitis, angiopathies
hematological, micro-occlusive

3B. LAB

General:

CBC, platelets, PT, PTT, CMP

Hypercoagulable studies:

factor V Leiden (R506Q)
prothrombin mutation (20210G)
antithrombin III, protein C, protein S
fibrinogen (common pathway)
fsp, d-dimer, plasminogen
lupus anticoagulant, anticardiolipin
anti-beta-2-glycoprotein
cryoglobulins, cryofibrinogen
homocysteine
new and future tests

Screen CTD, CVD, vasculitis:

sedimentation rate, CRP
rheumatoid factor, ANA, anti-DNA
ANCA, anti-MPO
SPEP

3C. LAB 2

Vascular:

TcPO₂, laser doppler
(not useful: abi, pvr, ppg, doppler)

Biopsy and histology:

microthrombi
aggregates
tissue infarction
vessel infarction
minimum inflammation
microangiopathies
vascular fibrosis, stenosis
vasculitis

DIAGNOSIS AND MANAGEMENT

Without a correct diagnosis or treatment, hypercoagulable ulcers are prolonged, persistent, frustrating, refractory, and resistant to care.

Once a correct diagnosis is made and anticoagulants are started, they are usually easy to resolve, by anticoagulation alone, or with other necessary treatment.

4A. MANAGEMENT - GENERAL

Major thrombotic event, if true:

urgent management as required
thrombolysis, target specific
thrombolysis, optional general

Associated risks and diseases:

treat each accordingly
workup & treat immunopathies

After w/u, confirmed diagnosis:

initiate warfarin
optional heparins for short term
optional steroids for inflammation
regulate and monitor warfarin
infrequent: heparins, anti-platelet

4B. MANAGEMENT - WOUND, TISSUES

Basic wound care and control:

good wound hygiene
debridement
topicals (silvers, sulfas, etc.)
edema control

Problem specific management:

for associated or derived disorder:
arterial, venous, immunopathic

Management for closure:

topical care, natural contraction
repair, grafts, flaps as required
collagen-gag matrix: safe, effective
optional hyperbaric oxygen

4C. MANAGEMENT - LONG TERM

General:

manage underlying diagnoses
control associated risks & triggers

Wound support and prevention:

compression and edema control
general skin care
topical steroids for dermatoses

Anticoagulation:

until healed, plus 3-6 months
limited use for antiplatelet drugs
prophylaxis for procedures
long term or lifetime warfarin,
depending on diagnosis and risks

A NOMENCLATURE OF HYPERCOAGULOPATHIES

NOMENCLATURE

(Necrotizing & ulcerative thrombosis)

MICRO-OCCLUSIVE DISORDERS

1 - Hemodynamic disorders

Blood, vessels, & coagulation all normal.
Thrombotic balance normal.
Normal trigger from abnormal blood flow.

2 - Endo-vasculopathies

Blood and coagulation normal.
Vessels abnormal.
Normal trigger from abnormal vessels.

3 - Exo-vasculopathies

Blood and coagulation normal.
Vessels abnormal.
Normal trigger from abnormal vessels.

4 - Non-hypercoagulable hemopathology

Vessels and coagulation normal.
Disordered blood components & rheology.
Abnormal trigger from stasis.

5 - The hypercoagulopathies

Blood and vessels normal.
Coagulation abnormal or unbalanced.
Misfire / erroneous primary thrombosis.

SPECIFICS

(Illustrative, not exhaustive)

1 - Hemodynamics / macro-vasculopathies

Anatomic variations, compressive vasculopathies, (e.g. pelvic compression of pregnancy), interrupted flow, malformations & hamartomas.

2 - Endo-angiopathies

Intrinsic angiopathies, atherosclerosis, allo-implants.

3 - Exo-angiopathies

Extrinsic angiopathies, immunopathy, vasculitis, thromboangiitis, hyperparathyroid / calciphylaxis.

4 - Non-hypercoagulable hemopathology

Hemoglobinopathies: sickle, thalassemias, hemolytic anemias.

Dys- & cryoproteinemias: cryoglobulins, cryofibrinogens, macroglobulinemias, myeloma, gammopathy, myeloproliferative

Hematocytes & platelets: polycythemia rubra vera, spherocytosis, myeloproliferative disorders, thrombotic thrombocytopenic purpura, leukemias

5 - The hypercoagulopathies

aka "Thrombophilic" disorders. Detailed list below

A NOMENCLATURE OF HYPERCOAGULOPATHIES

NOMENCLATURE

(Necrotizing & ulcerative thrombosis)

HYPERCOAGULOPATHIC DISORDERS

1 - Intrinsic “pre-thrombotic” disorders

Defects, deficiencies, or altered levels of primary prethrombotic clotting factors and parathrombotic proteases.

Genetic: Specific gene mutations (severity dependent on homo- vs heterozygous).

Metabolic, dynamical: Acquired, episodic deficiencies or imbalances of factors.

2 - Extrinsic

Coagulation imbalances triggered by disease, injury, metabolism, drugs.

3 - Immune related

Autoimmune anticoagulants; association with connective tissue disorders; intimate association of clotting and inflammation; combined coagulopathic & immunopathic.

4 - Uncategorized

As more disorders are validated, diagnostic precision and available tests will increase.

Triggering conditions.

Coag balance offsets and hyper-reactivity.

1 - Trauma: Normal trigger for thrombosis

2 - Inflammation: Trigger for thrombosis

3 - Metabolic: Fluids, general metabolism

4 - Dysdynamia: Chaotic behavior of coag

5 - Disease association: Other serious dx

6 - Combinations: Effects & risks additive

SPECIFICS

(Illustrative, not exhaustive)

1 - Intrinsic “pre-thrombotic” disorders

Genetic: f.V Leiden (R506Q), prothrombin mutation (20210G), (incidental others not available in clinical labs).

Metabolic, dynamical: antithrombin-3, proteins C & S, fibrinogen, warfarin, many reactive or chaotic secondary changes.

2 - Extrinsic

Estrogens, pregnancy, warfarin, cancer, PNH, homocysteinemia, inflammation, anything affecting coagulation system.

3 - Immune related

Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, anti-beta-2-glycoprotein), inflammatory conditions (trigger thrombosis), autoimmune disease.

4 - Uncategorized

As disorders are validated, diagnostic precision and lab tests will increase.

Triggering conditions.

General types or categories:

1 - Trauma: Local, remote, trauma, surgery

2 - Inflammation: Immune, reactive, dermatoses

3 - Metabolic: Anything affecting blood or coag

4 - Dysdynamia: Effects of small perturbations

5 - Disease association: Immune, cancer, etc

6 - Combinations: system closer to triggering

All can cause necrosis and ulceration of skin and fascias, pathergy, impaired wound healing, and complications of trauma and surgery.

For most coagulopathic disorders and ulcers, a positive diagnosis can be made by even the limited number of tests available in clinical laboratories.

When positive lab identification cannot be made, non-exact but valid diagnoses are still made and treated on sufficient clinical criteria.

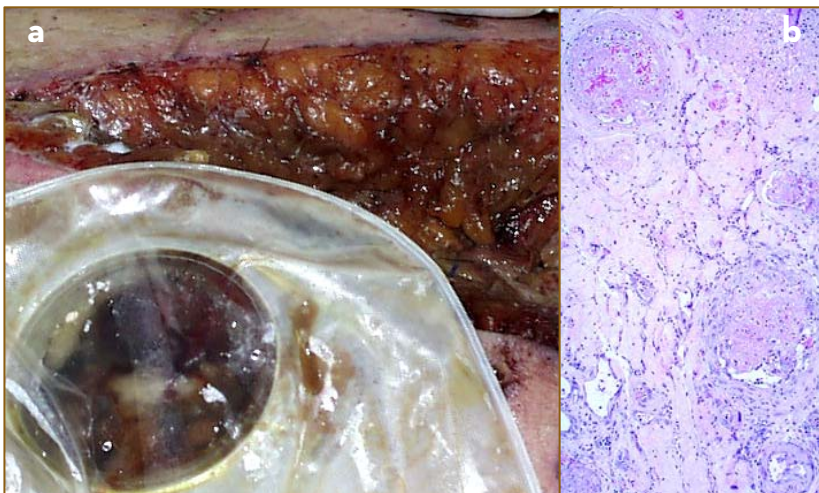
HYPERCOAGULOPATHIC ULCERS – CASE STUDIES



Case 5. 42m. Many years multiple DVT and recurring ulcers. Mother with same history.
Lab: V-Leiden heterozygote, low Protein C & AT-3, high anticardiolipins & homocysteine.
Dx: Multifactorial hypercoagulopathy.

a. Extensive ulcers and active necrosis. Different pattern than ordinary incompetent saphenous venous stasis. **b.** Healed with warfarin and compression.

Key points: Primary gene mutation, with many abnormalities (chaotic vs. compensatory vs. independent?). Family history. Warfarin cure.

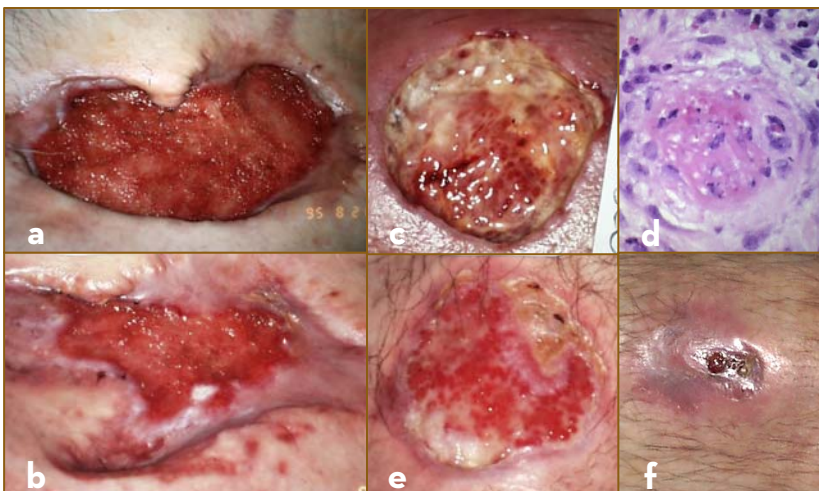


Case 6. 62m. History dvt/pe; history of finger necrosis from minor trauma. After surgery for colo-vesicle fistula, necrosis of abdominal wall and bowel (progressive with each operation). Died.

Lab / Dx: Activated protein C deficiency.

a. Necrotic ileostomy and abdominal fascias.
b. Microthrombi and infarcts of colon.

Key points: History of major thrombosis. History of post-trauma complications. Multiple infarcts and wound complications after each surgery. Problems affect more than just skin.



Case 7. 34m. Active lupus. Numerous injuries and operations complicated by necrosis, dehiscence, prolonged wound complications. (THA hip uncomplicated = routine anticoagulant use).
Lab / Dx: Antiphospholipid abx (cardiolipins).

a, b. Groin after minor surgery, improving with care. **c, d.** Pretibial ulcer 1 year after minor leg trauma; marginal microthrombi. **e, f.** Two and four weeks after starting warfarin.

Key points: Young. Multiple complications of trauma, and failed surgery. Associated with lupus, but wound behavior characteristic of coagulopathy. Rapid response to warfarin.

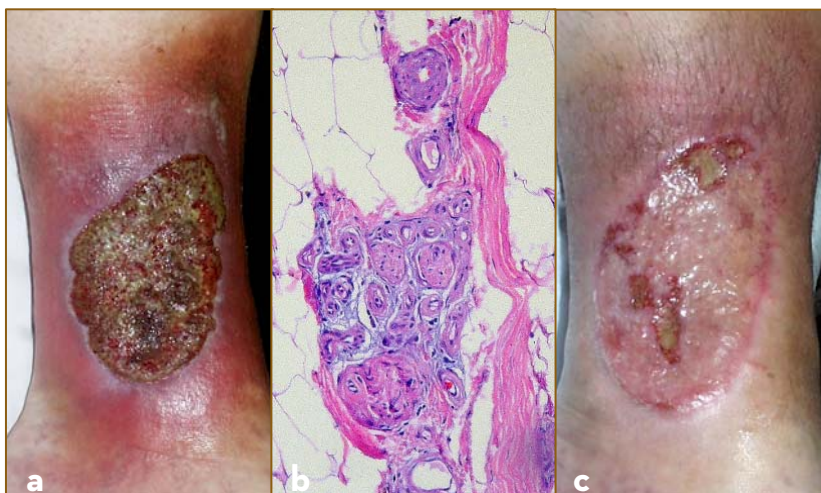
HYPERCOAGULOPATHIC ULCERS – CASE STUDIES



Case 8. 69f. Active rheumatoid. Miscarriages. Ankle ulcer after knee arthroplasty, persistent for months. TcpO₂ low, good pulses and ABIs.
Lab: V-Leiden heterozygote, low C & S, high homocysteine. Rheumatoid markers high.
Dx: Multifactorial hypercoagulopathy.

a. Lateral ankle, necrosis and inflammation.
b. Infarcts, progressive ulceration in spite of care. **c.** Healed with successful triad: warfarin, hyperbaric oxygen, Integra skin reconstruction.

Key points: Inflammatory wound features consistent with rheumatoid. Strong history and lab. Mixed immune-coagulopathic ulcer.



Case 9. 30f. Refractory progressive ulcers. Severe ischemic pain. History of miscarriage.
Lab: Protein C deficient. Lupus anticoagulant. Low skin TcpO₂ (with good pulses).
Dx: Prethrombotic coagulopathy, 2° species.

a. Leg ulcer, with infarcts and severe stasis.
b. Extensive microthrombosis. **c.** Toward end of skin reconstruction; stasis, infarction quiet.

Key points: Typical history. Confirmed by lab and histology. Extremely difficult to regulate and stabilize warfarin therapy. Dependable success with the “triad rx” - warfarin, short term hyperbaric oxygen, Integra skin reconstruct.



Case 10. 46m. Refractory progressive leg ulcers. History of multiple miscarriages.
Lab: Prothrombin mutation 20210 heterozyg., homocysteine extremely high, high p-anca and anti-mpo (myeloperoxidase antibodies).
Dx: 1° hypercoagulopathy. 2° immunopathy?

a. Infarcts, stasis, only mild inflammation.
b. Unchanged after 3 weeks non-specific care.

Key points: No response until proper therapy started. Prothrombin 20210 is a gene mutation - uncontestable evidence of coagulopathy. Example that immune state might be induced by chronic thrombosis-triggered inflammation.

Key Points and Summary

The hypercoagulopathies are a major class of ulcers, non-healing wounds, and complications of trauma and surgery.

Hypercoagulopathy lets blood clot where it should not - within normal blood vessels, creating ischemia, infarcts, and related clinical syndromes, including acute and chronic ulcers, wound healing problems, and complications of trauma and surgery.

For chronic wounds and unexplained wound and tissue complications, if the obvious diagnoses can be excluded (arterial, venous stasis, pressure, erythrocyte disorders, etc.), then much of what remains is immunopathic or coagulopathic. Hypercoagulopathic patients typically have frustrating histories, but they are easily managed once a diagnosis is made and anticoagulants are started.

Hypercoagulopathies are due to alterations in pre- and para-thrombotic proteins, or to increased trigger conditions.

Regarding tissue injury, these are a subset of micro-occlusive disorders, including angiopathies and hemopathologies. Hypercoagulopathies can be categorized as:

Intrinsic: alterations of the pre-thrombotic and para-thrombotic proteins, either genetic, acquired, or dynamical.

Extrinsic: perturbations of the clotting system from various metabolic, pharmacological, or pathological states.

Immune: associated with connective-tissue or collagen-vascular disorders (association of inflammation & thrombosis).

These disorders tend to alter the balance point of the coagulation system, making it more susceptible to thrombosis triggers. Spontaneous intravascular clotting can occur, and clots occur more readily from normal triggers (trauma, inflammation, disease).

Diagnosis of coagulopathies and coagulopathic wounds is made on specific criteria.

Typical histories of prolonged or recurrent problems and multiple failed procedures.

If a problem wound patient has even one of these criteria positive, probability is very high for a positive "hypercoag" blood test:

major thromboembolism (especially if young) • recurrent thromboembolism • young person with "venous stasis" • history of "inexplicable" trauma/surgery wound complications • miscarriages • family history of any of these.

Association with immunopathic diseases and inflammatory disorders or states is very important.

Physical exam also has characteristic features:

infarction and ulceration • often without significant inflammation • severe vascular stasis • normal macro-circulation • pathergy / necrosis with applied injury • persistent pathological behavior characteristic of severe ischemia • low T_{cpO_2} .

Lab confirmation usually possible. Absent positive lab studies, valid diagnoses can be made on clinical criteria. Histology useful.

Adequate care based on anticoagulation.

Warfarin is the cornerstone of effective care for active problems and for prophylaxis.

Heparins, antiplatelet drugs, and thrombolysis are used for acute or special circumstances.

Refractory problems, high morbidity, frustration, and expense - until diagnosis made - then easy to treat.

END