REVIEW ARTICLE

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Ischemic Limb Gangrene with Pulses

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THERE IS A COMMON MISCONCEPTION THAT ISCHEMIC LIMB NECROSIS results only from thrombosis or thromboembolism involving limb arteries, with loss of arterial pulses. Yet ischemic limb gangrene can also result from thrombosis involving the microcirculation, including small venules. In this situation, arterial pulses are palpable or identifiable with the use of Doppler signals. This review focuses on limb gangrene caused by microthrombosis that results from disseminated intravascular coagulation and the loss of natural anticoagulant mechanisms.

SYNDROMES OF MICROTHROMBOSIS-ASSOCIATED LIMB ISCHEMIA

There are two distinct syndromes of microthrombosis-associated ischemic limb injury (Table 1). Venous limb gangrene can complicate thrombocytopenic disorders that are strongly associated with deep-vein thrombosis (e.g., cancer-associated disseminated intravascular coagulation[1] and heparin-induced thrombocytopenia[2]). In these conditions, microthrombosis occurs in the same limb with acute large-vein thrombosis, resulting in acral (distal-extremity) ischemic necrosis. Usually, only one limb is affected. The potentially reversible, prodromal state of limb-threatening ischemia is phlegmasia cerulea dolens, indicating the respective features of a swollen, blue (ischemic), and painful limb (Fig. 1A).

In contrast, two and sometimes all four limbs are affected in symmetric peripheral gangrene, also featuring acral limb ischemic necrosis but usually without deep-vein thrombosis[3,4] (Fig. 1B). The limb necrosis is often strikingly symmetric; lower limbs are most often affected, with additional involvement of fingers or hands in approximately one third of patients. When there is additional or predominant nonacral tissue necrosis, the term purpura fulminans is applicable. Patients are usually critically ill, with cardiogenic or septic shock. In 1904, Barraud[5] discussed limb gangrene as a complication of acute infection, a complication that continues to occur today. The two syndromes have common pathophysiological features of microthrombosis associated with a disturbed procoagulant–anticoagulant balance (Fig. 1C).

DISSEMINATED INTRAVASCULAR COAGULATION AND NATURAL ANTICOAGULANT FAILURE

Disseminated intravascular coagulation is characterized by systemic activation of hemostasis (pathologic thrombin generation), impaired fibrinolysis, and intravascular formation and deposition of fibrin, with a potential for thrombotic occlusion of the microvasculature.[6] Depending on the inciting disorder, mediators include tissue factor expressed on endothelium and monocytes, enhanced leukocyte–endothelial interactions, proinflammatory cytokines (e.g., tumor necrosis factor α, interleukin-1β, and interleukin-6),[7] and cytokine-mediated endothelial down-regulation of thrombomodulin.[8] Triggering or potentiating factors include the presence of bacterial endotoxin, shock, acidemia, tissue injury, and platelet- or tumor-derived procoagulant microparticles.[9,10]

Table 1. Two Syndromes of Ischemic Limb Gangrene with Pulses.

Variable	Venous Limb Gangrene*	Symmetric Peripheral Gangrene†
Underlying disseminated intravascular coagulation	Heparin-induced thrombocytopenia, metastatic adenocarcinoma, antiphospholipid syndrome	Septic shock (e.g., meningococcemia), cardiogenic shock
Deep-vein thrombosis in ischemic limb‡	Yes	Usually not
Number of limbs affected	Usually 1 limb with deep-vein thrombosis	Usually 2 or 4 limbs (symmetric)
Warfarin implicated	Often	Usually not
Congenital hypercoagulability state	Usually not	Usually not
Thrombocytopenia	Yes	Yes
Peak international normalized ratio	Typically >4.0, especially if associated with coumarin§	Typically >2.0
Fibrin-specific marker (fibrin D-dimer, fibrin monomer)	Greatly elevated	Greatly elevated
Thrombin–antithrombin complexes	Greatly elevated	Greatly elevated
Protein C <10%	Yes, especially if associated with coumarin	Yes
Acute liver dysfunction or failure	Usually not	May be common

* The prodromal state of venous limb gangrene is called phlegmasia cerulea dolens, indicating the features of a swollen, blue, and painful limb.
† Symmetric peripheral gangrene can present with or without purpura fulminans (nonacral skin necrosis).
‡ Iliofemoral deep-vein thrombosis (i.e., thrombosis of the iliac vein or common femoral vein) can also be associated with phlegmasia cerulea dolens in the absence of disseminated intravascular coagulation. Risk factors include hypercoagulable disorders (e.g., cancer), a postoperative or post-traumatic state, pregnancy or postpartum state, vena cava filter insertion, and the May–Thurner syndrome (an anatomical variant in which the right common iliac artery overlies the left common iliac vein and compresses it against the lumbar spine).
§ Coumarin derivatives include oral vitamin K antagonists, such as warfarin, acenocoumarol, and phenprocoumon.

Venous limb gangrene and symmetric peripheral gangrene (with or without purpura fulminans) are cutaneous manifestations of disseminated intravascular coagulation that are modified and aggravated by interacting clinical factors such as warfarin therapy, deep-vein thrombosis, hypotension, and vasopressor therapy.[1-4] Associated failure of the natural anticoagulant systems, both the protein C system (crucial for down-regulating thrombin generation in the microvasculature[11]) and the antithrombin system (catalyzed by circulating pharmacologic heparin and endogenous endothelial-bound heparan sulfate), helps to explain why risk factors for microthrombosis include the use of warfarin (a vitamin K antagonist) and hepatic dysfunction or failure, since the liver synthesizes protein C (a vitamin K–dependent anticoagulant) and antithrombin (Fig. 1C).

VENOUS LIMB GANGRENE

Venous limb gangrene indicates acral ischemic necrosis in a limb with deep-vein thrombosis. Early investigators described virtually complete occlusion of the proximal venous limb vasculature, including collateral vessels, often in patients in the postpartum or postoperative period or in those with cancer. Limb ischemic necrosis was explained by sufficiently increased venous and interstitial pressures that collapsed small arteries or arterioles when closing pressure was exceeded.[12,13] However, in recent years, patients with venous gangrene have often been reported with underlying acquired hypercoagulability states, such as cancer-associated consumptive coagulopathy,[1,14] heparin-induced thrombocytopenia,[2,15] and the antiphospholipid syndrome,[16,17] with associated macrovascular and microvascular thrombosis that is frequently exacerbated by protein C depletion associated with the administration of warfarin or other coumarin derivatives.[1,2,14-16] The characteristic laboratory picture includes thrombocytopenia and an international normalized ratio (INR) that typically exceeds 4.0; a supratherapeutic INR is a proxy for a severely reduced protein C level.[1,2,14]

CANCER-ASSOCIATED VENOUS LIMB GANGRENE

At least 50% of patients with venous gangrene have underlying cancer,[13] together with disseminated intravascular coagulation. In a recent series,[1] a characteristic clinical picture was described in which patients with apparent idiopathic deep-vein thrombosis were found to have phlegmasia or venous limb gangrene soon after completing

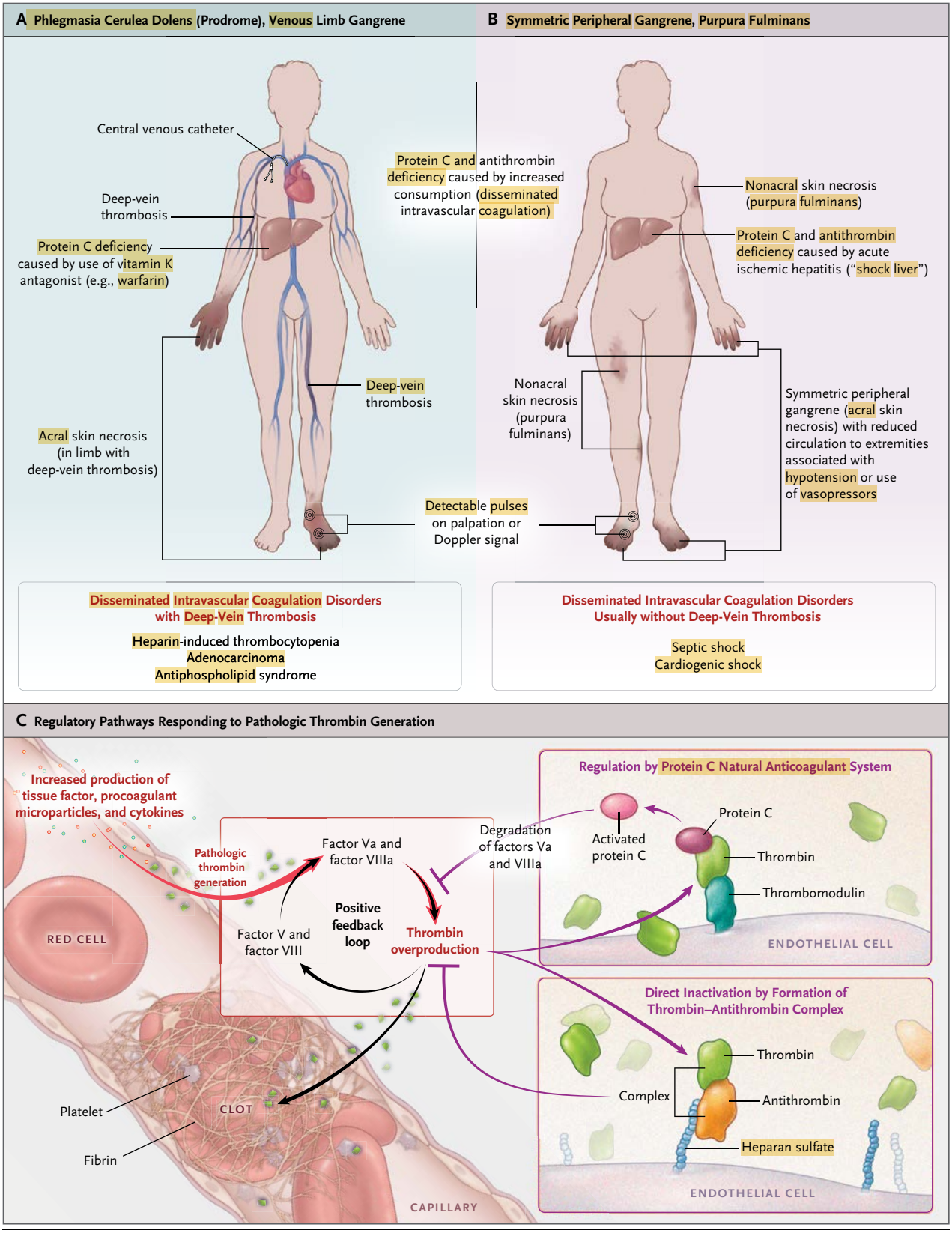


Figure 1 (facing page). Clinical Profile of Venous Limb Gangrene and Symmetric Peripheral Gangrene.

Both venous limb gangrene (Panel A) and symmetric peripheral gangrene (Panel B) feature ischemic limb gangrene with pulses, underlying microvascular thrombosis, and a high frequency of disseminated intravascular coagulation with the failure of one or both natural anticoagulant systems (protein C and antithrombin) (Panel C). Venous limb gangrene is characterized by acral necrosis in a distal limb with deep-vein thrombosis. A reversible prodrome of this condition is phlegmasia cerulea dolens. Underlying disorders include heparin-induced thrombocytopenia, cancer (especially metastatic adenocarcinoma), and the antiphospholipid syndrome (especially the catastrophic antiphospholipid syndrome). Upper-limb venous thrombosis and limb ischemic necrosis may be associated with the use of a central venous catheter. Symmetric peripheral gangrene typically occurs in critically ill patients with cardiogenic or septic shock who have hypotension and are receiving vasopressor therapy, with acral limb necrosis that usually occurs in the absence of deep-vein thrombosis. When there is additional or predominant nonacral skin necrosis, the condition is called purpura fulminans. Pathologic thrombin generation, which can be triggered or exacerbated by tissue factor, procoagulant microparticles, and proinflammatory or prothrombotic cytokines (among other factors), requires regulatory control (Panel C). This control occurs through two major systems. In the protein C natural anticoagulant system, thrombin that is bound to endothelial thrombomodulin converts protein C to activated protein C, which degrades activated factors V and VIII (Va and VIIIa, respectively), thereby down-regulating thrombin generation. In the antithrombin system, thrombin is inactivated by the formation of covalently linked thrombin–antithrombin complexes, a process that is catalyzed by endothelial heparan sulfate (a proteoglycan that binds to a variety of protein ligands and regulates a wide variety of biologic activities) or circulating pharmacologic heparin.

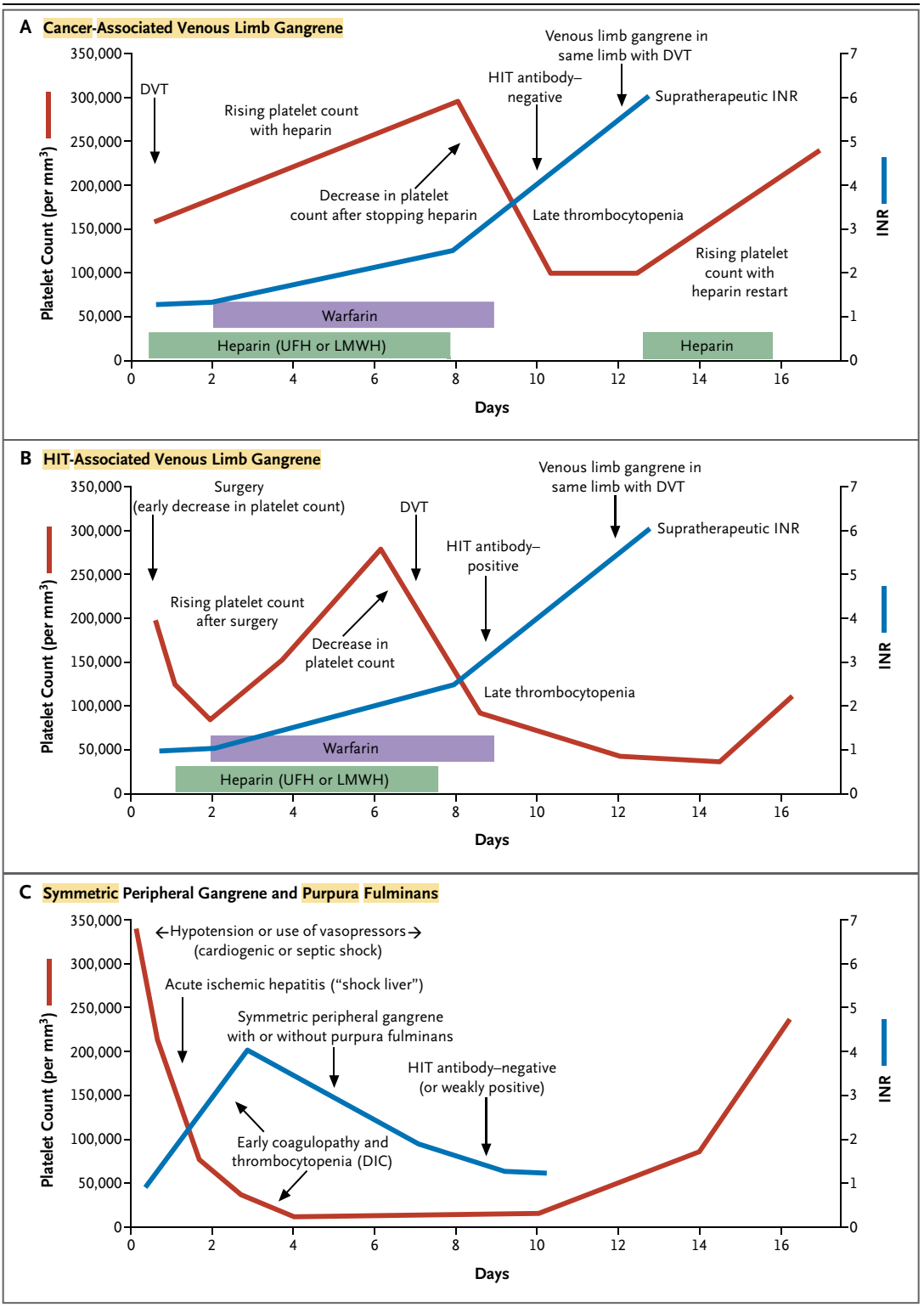
the heparin phase of heparin–warfarin overlap (Fig. 2A). The patients had a rising platelet count during the initial phase of heparin treatment (with either unfractionated or low-molecular-weight formulations), consistent with heparin control of cancer-associated hypercoagulability,[18] with a rapid decrease in the platelet count after heparin was stopped. Progression to ischemic limb necrosis occurred in association with an abrupt increase in the INR to supratherapeutic levels (usually, >4.0). Unlike patients with heparin-induced thrombocytopenia, patients with this syndrome test negative for heparin-dependent, platelet-activating antibodies, and the platelet count increases if heparin is restarted.[1] Metastatic cancer, usually adenocarcinoma, is characteristic.

Laboratory studies support a model of profoundly disturbed procoagulant–anticoagulant balance in patients with cancer in whom venous gangrene develops during warfarin anticoagulation. Uncontrolled thrombin generation is shown by greatly elevated thrombin–antithrombin complexes (a marker of in vivo thrombin generation) together with greatly reduced levels of protein C activity — in other words, the ratio of thrombin–antithrombin complex to protein C is elevated as compared with that in controls.[1,14] In essence, warfarin does not inhibit cancer-associated hypercoagulability while at the same time it predisposes the patient to microthrombosis by depleting protein C activity (often to <10% of normal levels).

VENOUS LIMB GANGRENE AND HEPARIN-INDUCED THROMBOCYTOPENIA

In patients with heparin-induced thrombocytopenia, the decrease in the platelet count usually begins 5 to 10 days after the immunizing exposure to heparin, often caused by the intraoperative use of heparin (e.g., in cardiac or vascular surgery) or during the early postoperative period (for thromboprophylaxis) (Fig. 2B).[19] Sometimes, thrombocytopenia begins while the patient is still receiving heparin (called typical onset), although often the decrease in the platelet count begins — or worsens — after heparin is discontinued (called delayed onset).[20] Ischemic limb injury develops in up to 5% of patients with heparin-induced thrombocytopenia,[21] either because of arterial occlusion by a platelet-rich thrombus (a so-called white clot) or because of venous limb gangrene.

Warfarin therapy is implicated in the majority of patients with heparin-induced thrombocytopenia in whom venous limb gangrene develops. Again, a characteristic feature is a supratherapeutic INR.[2,15] In such patients, a markedly elevated ratio of thrombin–antithrombin complex to protein C[2] supports a model of profoundly disturbed procoagulant–anticoagulant balance. In the minority of patients with heparin-induced thrombocytopenia in whom venous gangrene develops in the absence of warfarin administration, unusually severe thrombocytopenia (platelet count, <20,000 per cubic millimeter) and laboratory evidence of decompensated disseminated intravascular coagulation (e.g., elevated INR, hypofibrinogenemia, and circulating nucleated red cells) is found.[22]



SUPRATHERAPEUTIC INR

Analysis of the vitamin K–dependent coagulation factors that influence the INR — factors II (prothrombin), VII, and X — explains the basis for the supratherapeutic INR that is characteristic of warfarin-associated venous limb gangrene.[1,2,14] The elevated INR correlates closely with reduced factor VII levels, with factor VII showing a strong

Figure 2 (facing page). Changes in Platelet Count and INR in Three Clinical Scenarios Associated with Ischemic Limb Gangrene with Pulses.

Panel A shows the characteristic clinical picture and associated changes in platelet counts and international normalized ratios (INRs) in patients with cancer (which is diagnosed in at least 50% of patients with venous gangrene) and disseminated intravascular coagulation. Venous limb gangrene develops in the limb affected by deep-vein thrombosis (DVT) soon after the completion of the heparin phase of heparin–warfarin overlap following a rising platelet count during the initial phase of heparin treatment (with either unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) and a rapid decrease in the platelet count after heparin is stopped. Progression to ischemic limb necrosis occurs in association with an abrupt increase in the INR to supratherapeutic levels. Patients with this syndrome test negative for heparin-dependent, platelet-activating antibodies. Panel B shows a scenario for patients with heparin-induced thrombocytopenia (HIT) who receive heparin during cardiac surgery with routine heparin–warfarin overlap (e.g., mechanical valve replacement). Patients with HIT test positive for platelet-activating antibodies. An alternative scenario would be later initiation of warfarin at the time that DVT occurs or during argatroban–warfarin overlap for the treatment of heparin-induced thrombocytopenia. Panel C shows the characteristic interval of a few days between the onset of acute ischemic hepatitis ("shock liver") and the development of ischemic limb injury in a critically ill patient with cardiogenic or septic shock. This syndrome is evidence of the role of impaired hepatic synthesis of protein C and antithrombin in exacerbating a disturbed procoagulant–anticoagulant balance during disseminated intravascular coagulation (DIC).

colinear relationship with protein C. In essence, the supratherapeutic INR is a surrogate marker for severely reduced protein C (<10% activity levels) caused by a parallel severe reduction in the factor VII level. This close correlation between procoagulant factor VII and anticoagulant protein C is interesting, given that both factors have short half-lives (5 hours and 9 hours, respectively) and low (nanomolar) plasma concentrations (10 nM and 65 nM, respectively), values much lower than those of the major procoagulant factor, prothrombin (60 hours and 1400 nM, respectively).[23] These characteristics help to explain the unique susceptibility to depletion of factor VII and protein C in consumptive coagulopathic states with compromised factor synthesis associated with the use of warfarin. Ironically, despite the high INR, thrombin generation persists and microthrombosis occurs.[1,2,14]

VENOUS LIMB GANGRENE VS. WARFARIN-INDUCED SKIN NECROSIS

Warfarin-associated venous limb gangrene differs from classic warfarin-induced skin necrosis in that for the latter disorder, necrosis is usually localized to skin or subdermal tissues, predominantly in nonacral locations (e.g., breast, abdomen, thigh, and calf),[24,25] whereas venous gangrene affects acral skin and underlying tissues (e.g., bone).[1,2,14,15] In the two disorders, the onset of tissue necrosis begins approximately 2 to 6 days after the initiation of warfarin therapy.[24,25] This characteristic delay probably reflects the time needed for a critical reduction in protein C levels. Congenital abnormalities in the protein C anticoagulant system (e.g., protein C deficiency and factor V Leiden) are often implicated in patients with classic warfarin-induced necrosis but are usually not found in patients with venous limb gangrene. These observations suggest that the profound consumptive coagulopathy associated with heparin-induced thrombocytopenia or cancer, combined with deep-vein thrombosis, are sufficient to cause the conditions for warfarin-induced microthrombosis that is manifested as venous gangrene without the additional need for an underlying heritable defect.

PREVENTION AND TREATMENT OF VENOUS LIMB GANGRENE

Venous limb gangrene can be prevented if warfarin therapy is avoided (or reversed in a timely manner with vitamin K) in a patient with acute deep-vein thrombosis in whom the presence of associated thrombocytopenia or coagulopathy indicates a potential diagnosis of cancer-associated coagulopathy or heparin-induced thrombocytopenia.[1,2] Consensus conference guidelines recommend the avoidance of warfarin during the acute (thrombocytopenic) phase of heparin-induced thrombocytopenia.[21,26] Furthermore, low-molecular-weight heparin is superior to warfarin in patients with cancer-associated deep-vein thrombosis.[27] Also, the use of inferior vena cava filters should be avoided in patients with hypercoagulable states, such as cancer or heparin-induced thrombocytopenia, since their use can predispose the patient to venous gangrene.[28]

In a patient who is recognized to have phlegmasia or venous limb gangrene, treatment is based on two principles. The first — for a patient with a prolonged INR that is caused by treatment with a vitamin K antagonist — is the administration of vitamin K (at least 10 mg by slow intra-

venous infusion, with 5 to 10 mg repeated 12 to 24 hours later if the prolongation in the INR persists or recurs). The second is therapeutic-dose anticoagulation. These measures can be limb-saving in a patient with phlegmasia.[2,29]

However, the use of anticoagulation in a patient with an underlying coagulopathy is inherently problematic if an agent that is monitored by the activated partial thromboplastin time (APTT) is used. This is because the systematic administration of an inappropriately reduced dose of anticoagulant therapy, called APTT confounding, can result when a standard APTT-adjusted treatment nomogram is applied to a patient whose baseline (pretreatment) APTT is already elevated.[30] Such an effect can occur if unfractionated heparin is used to treat cancer-associated hypercoagulability or if argatroban is given for thrombosis complicating severe heparin-induced thrombocytopenia with associated disseminated intravascular coagulation.[30,31] Warfarin also prolongs the APTT, further contributing to less effective administration of heparin or argatroban.[30,32] This problem can be avoided by the use of low-molecular-weight heparin or monitoring of unfractionated heparin by measuring levels of anti–factor Xa (for treating cancer-associated hypercoagulability) or the use of an anticoagulant that does not require APTT monitoring (e.g., danaparoid or fondaparinux for treating heparin-induced thrombocytopenia).[30]

Adjunctive surgical considerations include fasciotomies (to reduce compartment pressures, if elevated)[33] and thrombectomy,[34] but prolonged wound healing, risk of infection, and a delay in or interruption of anticoagulation are drawbacks. Local pharmacomechanical thrombolysis is another option,[35] but the choice of the most effective agent, dose, and adjunctive anticoagulation is uncertain, and risks in patients with thrombocytopenia are increased.

SYMMETRIC PERIPHERAL GANGRENE AND PURPURA FULMINANS

Symmetric peripheral gangrene and purpura fulminans are two syndromes typically associated with thrombocytopenia and coagulopathy in patients who are critically ill (Fig. 2C). Symmetric peripheral gangrene indicates predominantly acral necrosis, which affects the distal limbs (with more frequent and extensive involvement of the feet than the fingers or hands) but sometimes also the nose, lips, ears, scalp, and genitalia.[3,4] The term purpura fulminans is used when there is extensive, multicentric, nonacral skin necrosis, although patients usually have acral limb necrosis as well. Septicemia and cardiac failure are the most common underlying disorders, and patients usually have metabolic (lactic) acidosis.[22,36] Although underlying infection may suggest septic embolization, the presence of pulses and findings on histopathological analyses show the role of microthrombosis associated with disseminated intravascular coagulation.[37] Most patients with symmetric peripheral gangrene have shock, but this complication can occasionally also occur in a normotensive patient with a severe systemic inflammatory state and in the absence of overt disseminated intravascular coagulation (Fig. 3A through 3F).

Septic shock that is caused by meningococcemia is a well-recognized underlying disorder with considerable evidence for failure of the protein C natural-anticoagulant pathway. More recently, acute ischemic hepatitis ("shock liver") has been identified as a potential risk factor for symmetric peripheral gangrene or purpura fulminans.[22,30]

CLINICAL PICTURE

Patients with septicemia-associated disseminated intravascular coagulation that is complicated by dermal manifestations usually present with fever, hypotension, and a petechial rash that evolves to more extensive confluent nonacral and acral purpuric areas of evolving ischemic necrosis. Early signs of ischemic limb injury include marked coldness, pallor, and distal limb pain. Bullae (often hemorrhagic) indicate tissue necrosis, as does nonblanching acral cyanosis. The dermal abnormalities are often sharply demarcated and strikingly symmetric, with initial gray, blue, or purple discoloration that progresses to black as the skin tissues die. Autoamputation of digital tips can occur, although more extensive necrosis usually requires surgical débridement, with or without amputation. Limb ischemic necrosis typically involves lower limbs before upper limbs; approximately one quarter of patients require four-limb amputations.[38] Mortality exceeds 50%.

PATHOLOGICAL FEATURES

The histopathological features of symmetric peripheral gangrene and purpura fulminans are dermal microthrombosis involving venules and

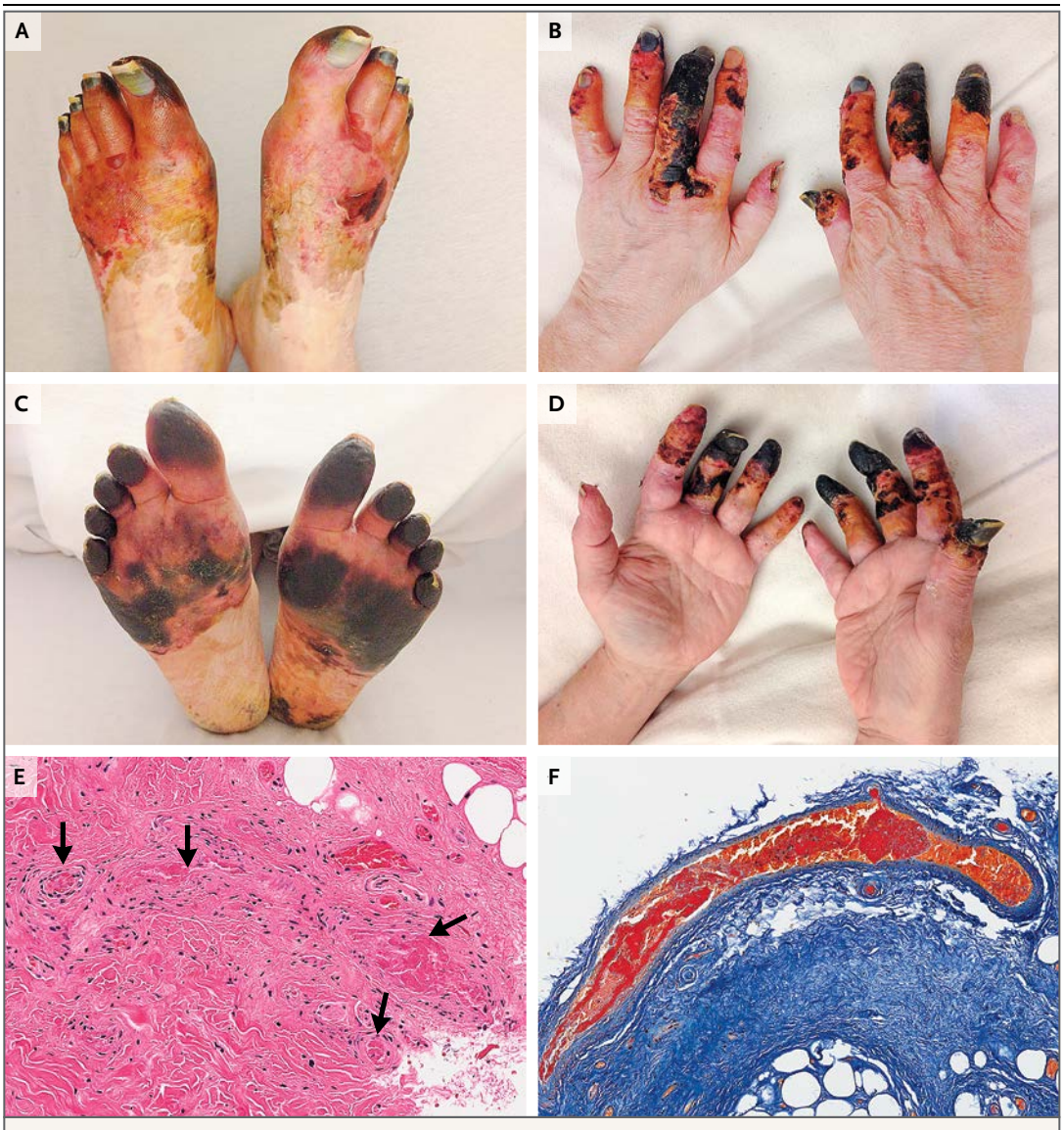


Figure 3. Symmetric Peripheral Gangrene.

In a 62-year-old man with severe, uncontrolled ulcerative colitis that was resistant to infliximab therapy, an acute onset of swollen, discolored, and painful feet was followed 2 days later by pain and cyanosis in the fingers, with progression to ischemic necrosis of both forefeet (Panels A and C) and hands (Panels B and D) over the next several days. No evidence of bacterial endocarditis or macrovascular aortic disease was found. Laboratory evidence of inflammation included elevated C-reactive protein levels, along with hyperfibrinogenemia, hyperferritinemia, thrombocytosis, and anemia of inflammation. Testing for autoimmune markers and antiphospholipid antibodies was negative. Laboratory studies performed at the time of admission did not strongly support a diagnosis of decompensated disseminated intravascular coagulation, with the following values: platelet count, 472,000 per cubic millimeter; international normalized ratio (INR), 1.1; activated partial thromboplastin time, 39 seconds; fibrinogen, 650 mg per deciliter (reference range, 160 to 420); and fibrin D-dimer, 1390 μg per milliliter of fibrinogen equivalent units (reference value, <500). Skin biopsy of the left hallux showed multiple fibrin thrombi within small vessels, as seen on hematoxylin and eosin staining (Panel E, with arrows indicating the vessel–lumen interface) and Martius scarlet blue staining, in which fibrin is colored red (Panel F). The patient's proinflammatory process improved after treatment with high-dose glucocorticoids and unfractionated heparin. (Courtesy of Dr. Ahmed Barefah, Department of Medicine [Panels A through D], and Dr. Linda Kocovski, Department of Pathology [Panels E and F], both at McMaster University.)

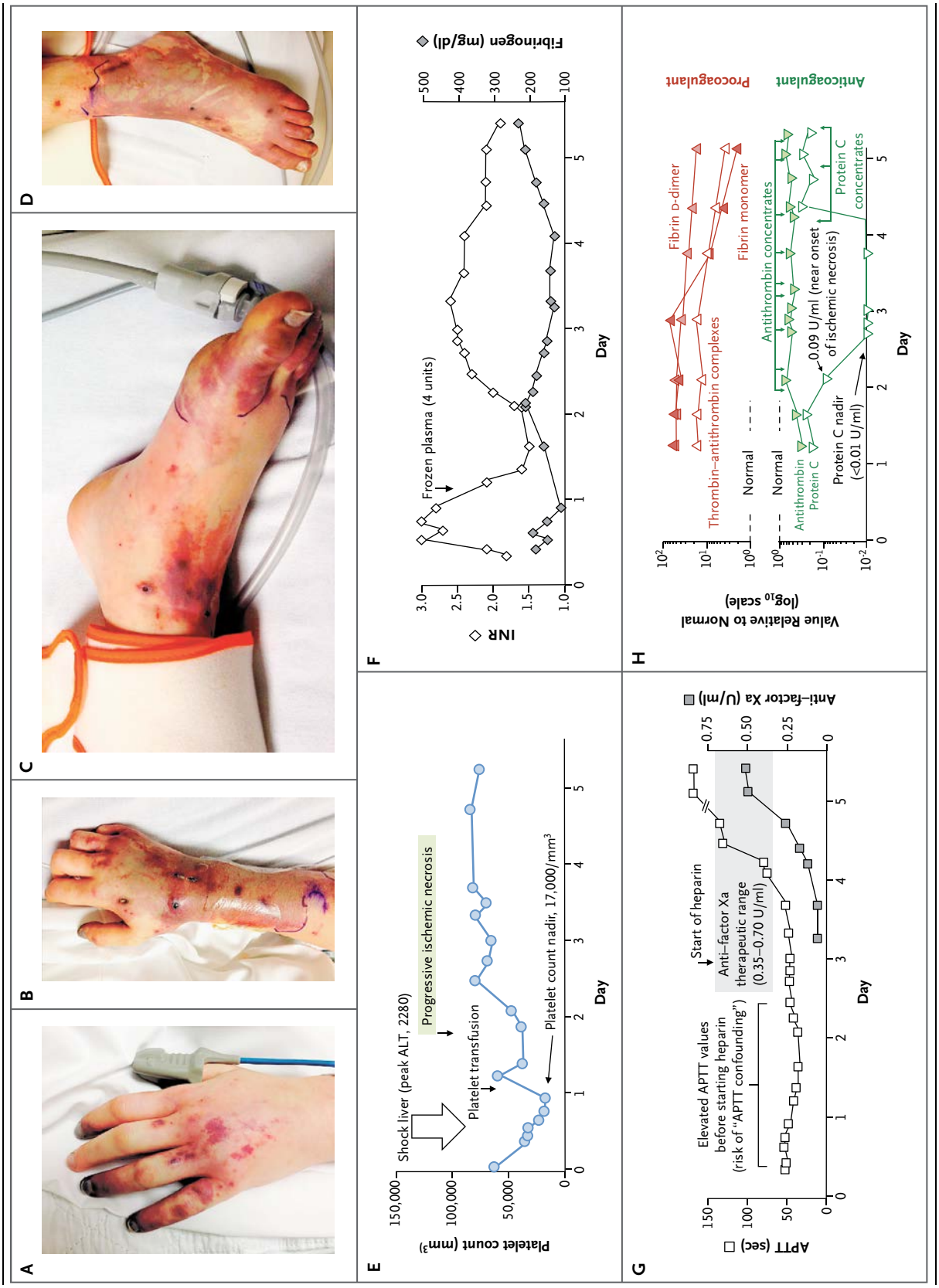


Figure 4 (facing page). Clinical and Laboratory Picture of Purpura Fulminans.

Shown are photographs and laboratory results for a 23-year-old woman with endocarditis caused by *Staphylococcus aureus* that resulted in combined septic and cardiogenic shock. The patient's condition was complicated by acute ischemic hepatitis ("shock liver") along with respiratory and renal failure. The patient had both acral and nonacral necrosis affecting the left and right hands (Panels A and B) and the right and left feet (Panels C and D). Severe thrombocytopenia and an acute elevation in the alanine aminotransferase (ALT) level indicate that disseminated intravascular coagulation and shock liver had developed (Panel E). Approximately 2 days later, acral and nonacral ischemic necrosis (purpura fulminans) developed. Coagulation changes that were consistent with decompensated disseminated intravascular coagulation included an increase in the international normalized ratio (INR) and a decrease in fibrinogen (nadir, 110 mg per deciliter; reference range, 160 to 420) (Panel F). Computed tomography of the brain showed cerebral septic emboli, so the use of heparin was initially deemed to be contraindicated. However, because of progressive limb ischemic necrosis, heparin was started in low doses on day 3, with monitoring of anti–factor Xa (target level, 0.35 to 0.70 U per milliliter) and gradual dose increases, which resulted in a therapeutic anti–factor Xa level approximately 2 days later (Panel G). The elevated activated partial thromboplastin time (APTT) of 51 seconds (reference range, 22 to 35) at baseline indicated the risk of "APTT confounding" if anticoagulant monitoring had been performed by means of an APTT nomogram. Indeed, supratherapeutic APTT levels were shown on day 5, when therapeutic anti–factor Xa levels were noted. A laboratory profile of profoundly disturbed procoagulant–anticoagulant balance was indicated by markedly elevated thrombin–antithrombin complexes and levels of fibrin D-dimer and fibrin monomer (approximately 20 to 70 times the upper limit of the normal range), with a severe antithrombin deficiency (nadir, 0.32 U per milliliter; reference range, 0.77 to 1.25), values that improved after the administration of antithrombin concentrates (Panel H). The patient also had severely reduced protein C activity levels, which initially measured 0.20 U per milliliter (reference range, 0.70 to 1.80) and then fell to 0.09 U per milliliter at the time of the onset of ischemic necrosis and reached profoundly depressed levels (0.01 U per milliliter) during progressive ischemic necrosis, before levels began to rise after the administration of protein C concentrates. Other laboratory abnormalities included lactic acidosis (peak lactate, 15.0 mmol per liter on day 1; reference range, 0.5 to 2.2) and elevated conjugated bilirubin (peak, 3.0 mg per deciliter on day 3; reference value, <0.5 [51 μmol per liter; reference value, <9]). Despite the achievement of a target therapeutic heparin level (0.54 U per milliliter), partial platelet count recovery (to 141,000 per cubic millimeter), and only a mildly prolonged INR (1.4), the patient died from an intracerebral hemorrhage on day 9. (Photographs courtesy of Dr. Craig D. Ainsworth, Department of Medicine, McMaster University.)

capillaries.[39] Edematous endothelial cells, capillary dilatation, and red-cell extravasation contribute to the petechial appearance of early lesions, which over time can coalesce into confluent areas of ischemic necrosis with associated hemorrhagic bullae. Although nonacral necrosis typically is localized to dermal and subdermal tissues, when extensive acral necrosis develops, underlying tissues, including bone, can become involved; bone scans can be used to judge the extent of tissue injury.[40]

Concomitant multiple organ failure (e.g., respiratory, renal, and hepatic) is common. Postmortem studies can show microthrombi in kidneys (cortical necrosis), lungs, liver, spleen, adrenal glands, heart, brain, pancreas, and gastrointestinal tract.[41,42] When bilateral adrenal hemorrhage occurs in children (most often, associated with meningococcemia), the term Waterhouse–Friderichsen syndrome applies, with evidence of fibrin microthrombi within adrenal sinusoids.[43]

IMPLICATED MICROORGANISMS

Purpura fulminans in young children and adolescents is usually associated with meningococcemia (caused by *Neisseria meningitidis*), whereas in adults *Streptococcus pneumoniae* (pneumococcus) is most often implicated.[3,4,38,44] Encapsulated bacteria (meningococcus, *Haemophilus influenzae*, or pneumococcus) are usually found when purpura fulminans occurs in a patient who has undergone splenectomy or who has functional asplenia.[45] Numerous other bacteria, both gram-positive (e.g., *Strep. pyogenes* and staphylococcus species) and gram-negative (e.g., *Escherichia coli*), have been implicated, as well as rickettsia,[46] malaria,[47] disseminated tuberculosis,[48] and viral infections (e.g., rubeola[49] and varicella[3]). Infection with capnocytophaga species associated with a dog bite or human saliva has a high risk of purpura fulminans.[50]

MENINGOCOCCEMIA

Meningococcemia represents the quintessential disease in which bacterial endotoxin (lipopolysaccharide), in a dose-dependent fashion, activates the hemostatic cascades (both procoagulant and anticoagulant), fibrinolysis, and complement, kinin, and cytokine networks.[51] Tissue factor–bearing microparticles contribute to the pathogenesis of disseminated intravascular coagulation.[52] Severely reduced protein C activity is

associated with an increased extent of skin lesions and rate of death in children with meningococcemia.[53] A case–control study showed that patients with meningococcemia who also had factor V Leiden — a mutation that impairs factor V proteolysis by activated protein C — had a rate of death that was similar to that of controls but had a tripling (from 7% to 21%) in the risk of tissue necrosis associated with purpura fulminans.[54]

ACUTE ISCHEMIC HEPATITIS

Recently, the prodrome of acute ischemic hepatitis (shock liver) has been reported in patients without meningococcemia who have acute disseminated intravascular coagulation along with symmetric peripheral gangrene or purpura fulminans.[22,30,55] Figure 4 illustrates a representative case in which a 23-year-old woman was treated for cardiogenic and septic shock associated with *Staphylococcus aureus* endocarditis with severe aortic regurgitation. Combined acral and nonacral skin necrosis (i.e., purpura fulminans) developed (Fig. 4A through 4D). Before the onset of ischemic limb necrosis, the patient was found to have acute ischemic hepatitis (peak alanine aminotransferase level, 2280 U per liter; reference level, <28) and acute, severe thrombocytopenia (Fig. 4E). Disseminated intravascular coagulation was shown by an elevated INR (peak, 3.0), hypofibrinogenemia (fibrinogen nadir, 110 mg per deciliter [reference range, 160 to 420]) (Fig. 4F), elevated APTT (Fig. 4G), and greatly elevated fibrin-specific markers (Fig. 4H). At the onset of necrosis, the protein C activity level was markedly reduced (0.09 units per milliliter [reference range, 0.70 to 1.80]) (Fig. 4H). Within 2 days, protein C levels were severely reduced (0.01 units per milliliter), and irreversible tissue necrosis was evident. Marked thrombin generation and fibrin formation continued, as shown by greatly elevated thrombin–antithrombin complexes and fibrin D-dimer levels, respectively (Fig. 4H). Treatment with unfractionated heparin to a therapeutic level (according to anti–factor Xa levels) was accompanied by APTT levels of more than 150 seconds (illustrating that a subtherapeutic heparin dose would have resulted if an APTT-based nomogram had been used).

Preceding shock liver is a common finding that is observed in approximately 90% of critically ill patients with disseminated intravascular coagulation in whom acral ischemic necrosis develops.[22,30] Furthermore, the onset of ischemic limb necrosis usually begins 2 to 5 days after the initial elevation in liver enzymes. This time frame evokes the scenario of warfarin-induced skin necrosis, in which there is a similar time frame of skin necrosis after the initiation of warfarin therapy.[24,25] This characteristic time period presumably reflects the time that is required for the development of critically low levels of protein C when its synthesis is impaired by acute liver dysfunction or warfarin therapy. Further systematic studies evaluating the role of preceding shock liver in the pathogenesis of ischemic limb injury are warranted.

Some case reports have implicated hypotension requiring vasopressor therapy (e.g., with dopamine,[56] noradrenaline,[57] or phenylephrine[58]) in the pathogenesis of symmetric peripheral gangrene. In parallel with the role of deep-vein thrombosis in predisposing the patient to warfarin-associated microthrombosis in the same limb with large-vein thrombosis, it seems plausible that hypotension and vasopressor therapy, by reducing blood flow into the distal extremities, could predispose the patient with disseminated intravascular coagulation to acral microthrombosis.

DIFFERENTIAL DIAGNOSIS

Sometimes, symmetric peripheral gangrene can occur in the absence of definite disseminated intravascular coagulation.[59,60] Representative disorders include frostbite, ergotism,[61] vasospasm (idiopathic or scleroderma-associated Raynaud's phenomenon),[60] calciphylaxis,[62] postoperative thrombotic thrombocytopenic purpura,[63] myeloproliferative or lymphoproliferative disorders (including monoclonal gammopathies), vasculitis,[64] certain rheumatologic or immunologic disorders (e.g., adult-onset Still's disease[65] and the antiphospholipid syndrome[66]), and uncontrolled proinflammatory disorders such as ulcerative colitis (Fig. 3).[67]

TREATMENT

Venous limb gangrene and symmetric peripheral gangrene are observed in a small minority (<1%) of patients with disseminated intravascular coagulation, so treatment considerations are based primarily on theoretical considerations and case-based observations, rather than on results of clinical trials. Theoretical considerations include pharmacologic interruption of thrombin genera-

tion (e.g., heparin anticoagulation), coagulation-factor replacement aimed at correcting depletion of natural anticoagulants such as protein C and antithrombin (given either as frozen plasma or specific factor concentrates), and efforts to minimize risk factors for decreased limb perfusion (e.g., correction of hypotension and reduction or avoidance of vasopressors). However, since ischemic limb injury that is associated with profoundly disturbed procoagulant–anticoagulant balance can occur quickly when the "perfect storm" conditions are met, initiating anticoagulation even at the first signs of ischemic limb injury may already be too late. Some experts advise early protein C replacement therapy in patients with severe meningococcemia.[68,69] However, in order to become activated, protein C requires the presence of thrombomodulin on the surface of endothelial cells (Fig. 1C). Since injured endothelial cells down-regulate and shed thrombomodulin, current experimental approaches include the infusion of recombinant human soluble thrombomodulin.[70]

In choosing an anticoagulant, many practitioners favor heparin,[30,71] since its anticoagulant effect can be monitored directly (by measuring anti–factor Xa levels), thus avoiding the potential for systematic underadministration in a patient with an elevated APTT at baseline (Fig. 4G). Also, heparin clearance remains normal even with liver and renal failure, and heparin has antiinflammatory properties independent of its role as an anticoagulant.[72] Moreover, drug regimens that involve prophylactic and therapeutic doses are available, depending on the clinical situation. However, heparin requires its cofactor, antithrombin, and antithrombin levels can be reduced in patients with consumptive coagulopathies, particularly with concomitant liver dysfunction.

A recent meta-analysis suggested that the use of heparin (as compared with placebo or usual care) in patients with sepsis, septic shock, and infection-associated disseminated intravascular coagulation may be associated with a relative decrease of 12% in the rate of death.[72] Whether there is any potential benefit for the use of heparin in the prevention of microthrombosis and ischemic limb injury is unknown. Recombinant activated protein C, although theoretically attractive, was withdrawn from the market after a large, randomized trial did not show improved survival in septic shock.[73] High-dose antithrombin concentrates did not improve mortality in a trial involving patients with severe sepsis,[74] although the rate of death appeared to be lower in the antithrombin-treated subgroup with disseminated intravascular coagulation who did not receive heparin.[75]

SURGICAL CONSIDERATIONS

Some surgeons advocate the use of fasciotomy in patients in whom compartment syndromes related to tissue edema can compromise flow into a limb.[38,45] However, fasciotomy disrupts the skin barrier and usually results in the interruption or postponement of anticoagulant therapy and so is not without risk. Early amputation should be avoided, whenever possible, since it can be difficult to distinguish viable tissue from nonviable tissue. Indeed, patience to the point of autoamputation in some cases can minimize ultimate tissue losses. A multidisciplinary team that involves plastic surgery or wound care, medicine or infectious diseases, and podiatry, with management in a burn unit, can be helpful.

NEONATAL PURPURA FULMINANS

Although purpura fulminans is most commonly associated with bacterial infection, in neonates it can be caused by a congenital deficiency in protein C or protein S. Such disorders may require lifelong treatment with frozen plasma or protein C concentrates or possibly liver transplantation.[76]

IDIOPATHIC AND POSTVIRAL PURPURA FULMINANS

Idiopathic purpura fulminans is a rare disorder characterized by onset without any known trigger (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) or that occurs a few weeks after an otherwise unremarkable varicella infection. In the latter disorder, transient autoantibodies that inhibit protein S have been implicated.[77]

CONCLUSIONS

The concept that venous limb gangrene and symmetric peripheral gangrene are usually associated with microvascular thrombosis with underlying disseminated intravascular coagulation provides a framework for a rational approach to diagnosing and treating these diverse and potentially devastating disorders. Prevention and treatment

of venous gangrene requires correction of abnormalities associated with the use of vitamin K antagonists and aggressive anticoagulation, whereas treatment of symmetric peripheral gangrene (with or without purpura fulminans) theoretically involves heparin-based anticoagulation and the substitution of natural anticoagulants.

Dr. Warkentin reports receiving fees for serving on an advisory board from Instrumentation Laboratory, consulting fees from W.L. Gore, lecture fees from Instrumentation Laboratory and Pfizer Canada, and fees for providing expert testimony in cases regarding thrombocytopenia, coagulopathy, or ischemic limb losses. He also reports that his institution has received fees from W.L. Gore to provide laboratory testing for a randomized, controlled trial of heparin-coated versus non–heparin-coated hemodialysis grafts. No other potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Warkentin TE, Cook RJ, Sarode R, Sloane DA, Crowther MA. Warfarin-induced venous limb ischemia/gangrene complicating cancer: a novel and clinically distinct syndrome. Blood 2015;126:486-93.
2. Warkentin TE, Elavathil LJ, Hayward CPM, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. Ann Intern Med 1997;127:804-12.
3. Molos MA, Hall JC. Symmetrical peripheral gangrene and disseminated intravascular coagulation. Arch Dermatol 1985;121:1057-61.
4. Ghosh SK, Bandyopadhyay D, Ghosh A. Symmetrical peripheral gangrene: a prospective study of 14 consecutive cases in a tertiary-care hospital in eastern India. J Eur Acad Dermatol Venereol 2010;24:214-8.
5. Barraud S. Über Extremitätengangrän im jugendlichen Alter nach Infektionskrankheiten. Dtsch Z Chir 1904;74:237-97.
6. Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341:586-92.
7. Gando S. Microvascular thrombosis and multiple organ dysfunction syndrome. Crit Care Med 2010;38:Suppl:S35-S42.
8. Levi M, Van Der Poll T. Thrombomodulin in sepsis. Minerva Anestesiol 2013;79:294-8.
9. Warkentin TE, Hayward CPM, Boshkov LK, et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. Blood 1994;84:3691-9.
10. Geddings JE, Mackman N. Tumor-derived tissue factor-positive microparticles and venous thrombosis in cancer patients. Blood 2013;122:1873-80.
11. Esmon CT. The protein C pathway. Chest 2003;124:Suppl:26S-32S.
12. Haimovici H. The ischemic forms of venous thrombosis. 1. Phlegmasia cerulea dolens. 2. Venous gangrene. J Cardiovasc Surg (Torino) 1965;5:Suppl:164-73.
13. Perkins JMT, Magee TR, Galland RB. Phlegmasia caerulea dolens and venous gangrene. Br J Surg 1996;83:19-23.
14. Warkentin TE. Venous limb gangrene during warfarin treatment of cancer-associated deep venous thrombosis. Ann Intern Med 2001;135:589-93.
15. Srinivasan AF, Rice L, Bartholomew JR, et al. Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. Arch Intern Med 2004;164:66-70.
16. Grim Hostetler S, Sopkovich J, Dean S, Zirwas M. Warfarin-induced venous limb gangrene. J Clin Aesthet Dermatol 2012;5:38-42.
17. Padjas A, Brzezinska-Kolarz B, Undas A, Musial J. Phlegmasia cerulea dolens as a complication of deep vein thrombosis in a man with primary antiphospholipid syndrome. Blood Coagul Fibrinolysis 2005;16:567-9.
18. Bell WR, Starksen NF, Tong S, Porterfield JK. Trousseau's syndrome: devastating coagulopathy in the absence of heparin. Am J Med 1985;79:423-30.
19. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 2001;344:1286-92.
20. Warkentin TE. Agents for the treatment of heparin-induced thrombocytopenia. Hematol Oncol Clin North Am 2010;24:755-75.
21. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:6 Suppl:340S-380S.
22. Warkentin TE. Heparin-induced thrombocytopenia in critically ill patients. Semin Thromb Hemost 2015;41:49-60.
23. Vadivel K, Schmidt AE, Marder VJ, Krishnaswamy S, Bajaj SP. Structure and function of vitamin K-dependent coagulant and anticoagulant proteins. In: Marder VJ, Aird WC, Bennett JS, Schulman S, White GC, eds. Hemostasis and thrombosis: basic principles and clinical practice. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2013:208-32.
24. Cole MS, Minifee PK, Wolma FJ. Coumarin necrosis — a review of the literature. Surgery 1988;103:271-7.
25. Warkentin TE. Coumarin-induced skin necrosis and venous limb gangrene. In: Marder VJ, Aird WC, Bennett JS, Schulman S, White GC, eds. Hemostasis and thrombosis: basic principles and clinical practice. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2013:1308-17.
26. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:Suppl 2:e495S-e530S.
27. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53.
28. Rice L. A clinician's perspective on heparin-induced thrombocytopenia: paradoxes, myths, and continuing challenges. In: Warkentin TE, Greinacher A, eds. Heparin-induced thrombocytopenia. 5th ed. Boca Raton, FL: CRC Press, 2013:608-17.
29. Weaver FA, Meacham PW, Adkins RB, Dean RH. Phlegmasia cerulea dolens: therapeutic considerations. South Med J 1988;81:306-12.
30. Warkentin TE. Anticoagulant failure in coagulopathic patients: PTT confounding and other pitfalls. Expert Opin Drug Saf 2014;13:25-43.
31. Greinacher A. Heparin-induced thrombocytopenia. N Engl J Med 2015;373:252-61.
32. Smythe MA, Warkentin TE, Stephens JL, Zakalik D, Mattson JC. Venous limb gangrene during overlapping therapy with warfarin and a direct thrombin inhibitor for immune heparin-induced thrombocytopenia. Am J Hematol 2002;71:50-2.
33. Qvarfordt P, Eklöf B, Ohlin P. Intramuscular pressure in the lower leg in deep vein thrombosis and phlegmasia cerulae dolens. Ann Surg 1983;197:450-3.
34. Meissner MH. Rationale and indications for aggressive early thrombus removal. Phlebology 2012;27:Suppl 1:78-84.
35. Erdoes LS, Ezell JB, Myers SI, Hogan MB, LeSar CJ, Sprouse LR II. Pharmaco-

mechanical thrombolysis for phlegmasia cerulea dolens. Am Surg 2011;77:1606-12.
36. Knight TT Jr, Gordon SV, Canady J, Rush DS, Browder W. Symmetrical peripheral gangrene: a new presentation of an old disease. Am Surg 2000;66:196-9.
37. Reinstein L, Govindan S. Extremity amputation: disseminated intravascular coagulation syndrome. Arch Phys Med Rehabil 1980;61:97-102.
38. Warner PM, Kagan RJ, Yakuboff KP, et al. Current management of purpura fulminans: a multicenter study. J Burn Care Rehabil 2003;24:119-26.
39. Robboy SJ, Mihm MC, Colman RW, Minna JD. The skin in disseminated intravascular coagulation: prospective analysis of thirty-six cases. Br J Dermatol 1973;88:221-9.
40. Hamdy RC, Babyn PS, Krajbich JI. Use of bone scan in management of patients with peripheral gangrene due to fulminant meningococcemia. J Pediatr Orthop 1993;13:447-51.
41. Watanabe T, Imamura T, Nakagaki K, Tanaka K. Disseminated intravascular coagulation in autopsy cases: its incidence and clinicopathologic significance. Pathol Res Pract 1979;165:311-22.
42. Shimamura K, Oka K, Nakazawa M, Kojima M. Distribution patterns of microthrombi in disseminated intravascular coagulation. Arch Pathol Lab Med 1983;107:543-7.
43. Fox B. Disseminated intravascular coagulation and the Waterhouse-Friderichsen syndrome. Arch Dis Child 1971;46:680-5.
44. Betrosian AP, Berlet T, Agarwal B. Purpura fulminans in sepsis. Am J Med Sci 2006;332:339-45.
45. Childers BJ, Cobanov B. Acute infectious purpura fulminans: a 15-year retrospective review of 28 consecutive cases. Am Surg 2003;69:86-90.
46. Kirkland KB, Marcom PK, Sexton DJ, Dumler JS, Walker DH. Rocky Mountain spotted fever complicated by gangrene: report of six cases and review. Clin Infect Dis 1993;16:629-34.
47. Kato Y, Ohnishi K, Sawada Y, Suenaga M. Purpura fulminans: an unusual manifestation of severe falciparum malaria. Trans R Soc Trop Med Hyg 2007;101:1045-7.
48. Chen CF, Wang JL, Wei YF. Symmetrical peripheral gangrene, an uncommon complication of tuberculosis. QJM 2012;105:279-80.
49. Wynne JM, Williams GL, Ellman BA. Gangrene of the extremities in measles. S Afr Med J 1977;52:117-21.
50. Christiansen CB, Berg RM, Plovsing RR, Møller K. Two cases of infectious purpura fulminans and septic shock caused by *Capnocytophaga canimorsus* transmitted from dogs. Scand J Infect Dis 2012;44:635-9.
51. Brandtzaeg P, Sandset PM, Joø GB, Ovstebø R, Abildgaard U, Kierulf P. The quantitative association of plasma endotoxin, antithrombin, protein C, extrinsic pathway inhibitor and fibrinopeptide A in systemic meningococcal disease. Thromb Res 1989;55:459-70.
52. Hellum M, Øvstebø R, Brusletto BS, Berg JP, Brandtzaeg P, Henriksson CE. Microparticle-associated tissue factor activity correlates with plasma levels of bacterial lipopolysaccharides in meningococcal septic shock. Thromb Res 2014;133:507-14.
53. Fijnvandraat K, Derkx B, Peters M, et al. Coagulation activation and tissue necrosis in meningococcal septic shock: severely reduced protein C levels predict a high mortality. Thromb Haemost 1995;73:15-20.
54. Kondaveeti S, Hibberd ML, Booy R, Nadel S, Levin M. Effect of the Factor V Leiden mutation on the severity of meningococcal disease. Pediatr Infect Dis J 1999;18:893-6.
55. Siegal DM, Cook RJ, Warkentin TE. Acute hepatic necrosis and ischemic limb necrosis. N Engl J Med 2012;367:879-81.
56. Colak T, Erdogan O, Yerebakan O, Arici C, Gurkan A. Symmetrical peripheral gangrene and dopamine. Ulus Travma Acil Cerrahi Derg 2003;9:222-4.
57. Hayes MA, Yau EHS, Hinds CJ, Watson JD. Symmetrical peripheral gangrene: association with noradrenaline administration. Intensive Care Med 1992;18:433-6.
58. Kalajian AH, Turpen KB, Donovan KO, Malone JC, Callen JP. Phenylephrine-induced microvascular occlusion syndrome in a patient with a heterozygous factor V Leiden mutation. Arch Dermatol 2007;143:1314-7.
59. Sharma BD, Kabra SR, Gupta B. Symmetrical peripheral gangrene. Trop Doct 2004;34:2-4.
60. Hotchkiss R, Marks T. Management of acute and chronic vascular conditions of the hand. Curr Rev Musculoskelet Med 2014;747-52.
61. Wollina U, Hansel G, Gruner M, Schönlebe J, Heinig B, Köstler E. Painful ANA-positive scleroderma-like disease with acral ulcerations: a case of chronic gangrenous ergotism. Int J Low Extrem Wounds 2007;6:148-52.
62. Hammadah M, Chaturvedi S, Jue J, et al. Acral gangrene as a presentation of non-uremic calciphylaxis. Avicenna J Med 2013;3:109-11.
63. Chang JC, Ikhlaque N. Peripheral digit ischemic syndrome can be a manifestation of postoperative thrombotic thrombocytopenic purpura. Ther Apher Dial 2004;8:413-8.
64. Sharif M, Hameed S, Akin I, Natarajan U. HIV diagnosis in a patient presenting with vasculitis. Int J STD AIDS 2015.
65. Ames PRJ, Walker E, Aw D, Marshall D, de Villiers F, Staber M. Multi-organ failure in adult onset Still's disease: a septic disguise. Clin Rheumatol 2009;28:Suppl 1:S3-S6.
66. Grob JJ, Bonerandi JJ. Thrombotic skin disease as a marker of the anticardiolipin syndrome: livedo vasculitis and distal gangrene associated with abnormal serum antiphospholipid activity. J Am Acad Dermatol 1989;20:1063-9.
67. Bhoola PH, Shtofmakher G, Bahri A, Patel AA, Barlizo SR, Trepal M. Pedal gangrenous changes in the digits of an adolescent with ulcerative colitis: a case report. J Foot Ankle Surg 2014.
68. Smith OP, White B. Infectious purpura fulminans: diagnosis and treatment. Br J Haematol 1999;104:202-7.
69. Piccin A, O'Marcaigh A, McMahon C, et al. Non-activated plasma-derived PC improves amputation rate of children undergoing sepsis. Thromb Res 2014;134:63-7.
70. Vincent JL, Ramesh MK, Ernest D, et al. A randomized, double-blind, placebo-controlled, phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med 2013;41:2069-79.
71. Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. J Thromb Haemost 2013;11:761-7.
72. Zarychanski R, Abou-Setta AM, Kanji S, et al. The efficacy and safety of heparin in patients with sepsis: a systematic review and metaanalysis. Crit Care Med 2015;43:511-8.
73. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012;366:2055-64.
74. Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient: high-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286:1869-78.
75. Kienast J, Juers M, Wiedermann CJ, et al. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. J Thromb Haemost 2006;4:90-7.
76. Price VE, Ledingham DL, Krümpel A, Chan AK. Diagnosis and management of neonatal purpura fulminans. Semin Fetal Neonatal Med 2011;16:318-22.
77. Josephson C, Nuss R, Jacobson L, et al. The varicella-autoantibody syndrome. Pediatr Res 2001;50:345-52.