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How I Treat

How I diagnose and treat acute infection–associated purpura fulminans

Pavan K. Bendapudi[1-4] and Julie-Aurore Losman[4-6]

[1]Division of Hematology and Blood Transfusion Service, Massachusetts General Hospital, Boston, MA; [2]Division of Hemostasis and Thrombosis, Beth Israel Deaconess Medical Center, Boston, MA; [3]Center for the Development of Therapeutics, The Broad Institute of MIT and Harvard, Cambridge, MA; [4]Harvard Medical School, Boston, MA; [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; and [6]Division of Hematology, Brigham and Women's Hospital, Boston, MA

Purpura fulminans (PF) is a rare but devastating complication of sepsis characterized by a highly thrombotic subtype of disseminated intravascular coagulation (DIC). A medical emergency, PF often requires the involvement of consultant hematologists to assist with diagnosis and management of patients who are in a highly dynamic and deteriorating clinical situation. Patients who survive past the first 24 to 72 hours often die from complications of unchecked thrombosis rather than shock, and survivors are usually left with severe scarring and tissue loss. Despite these challenging features, PF is a pathophysiologically distinct, homogeneous, and highly predictable form of sepsis-associated DIC for which poor outcomes are not a foregone conclusion. The fundamental pathologic lesion in PF is a failure of the anticoagulant protein C pathway, which leads to uncontrolled microvascular clotting and inadequate protein C–mediated cytoprotective effects, which are vital for survival in sepsis. Herein, we review the clinical features and diagnosis of PF. Drawing from existing clinical literature and recent advances in our understanding of the pathophysiology of PF, we describe rationally designed treatment approaches for this disorder, including repletion of natural circulating anticoagulants, use of therapeutic anticoagulation, and ways to optimize transfusion support, and we outline specific interventions that we would recommend avoiding.

Introduction

Purpura fulminans (PF) is a life-threatening hematologic emergency characterized by a highly thrombotic subtype of disseminated intravascular coagulation (DIC) and rapidly progressive purpura. There are 3 forms of PF: neonatal, idiopathic, and infection-associated. Neonatal PF occurs in ~1 in 1 million live births and is caused by homozygous or compound heterozygous loss of the gene encoding protein C (*PROC*) or, less frequently, the gene encoding protein S (*PROS1*).[1,2] Neonatal PF typically presents hours after birth with overwhelming microvascular thrombosis of the skin and other organs, and treatment involves repletion with plasma-derived protein C concentrate.[3] Idiopathic PF is an exceedingly rare condition that is thought to result from the development of autoantibodies to protein S.[4] Idiopathic PF has also been reported in patients receiving anticancer immunotherapy, presumably triggered by therapy-related immune dysregulation and hyperinflammation.[5,6] PF associated with acute infection (hereinafter referred to as "PF") is the third and most common form of PF and is the focus of this review. PF is typically triggered by bacterial infections with encapsulated microorganisms such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Capnocytophaga canimorsus* and has been reported to occur in up to 25% of patients with invasive meningococcal disease.[7,8] Less common triggers include bacterial pathogens such as *Vibrio* and *Rickettsia* species and viruses such as varicella-zoster virus and measles virus. PF has an overall mortality rate of ~60%, and survivors are often left with extensive scarring and tissue loss, including amputations.[7] Although devastating, the clinical course of PF is highly predictable, and clinicians should bear in mind that rationally designed therapies can help minimize morbidity and mortality.

Pathophysiology of acute infection–associated PF

Over 30 years ago, Powars et al first noted the striking similarity between neonatal PF caused by homozygous or compound heterozygous *PROC* loss-of-function mutations and the prothrombotic DIC and tissue damage seen in meningococcemia. This observation led them to hypothesize that the central pathophysiologic event in PF is failure of the protein C system.[9,10] Under physiologic conditions, protein C zymogen binds to endothelial protein C receptor (Figure 1A). Activation and binding of thrombin to thrombomodulin, a type-I transmembrane protein expressed on endothelial cells, results in cleavage and activation of protein C zymogen. Thereafter, activated protein C participates in 2 key physiologic processes:

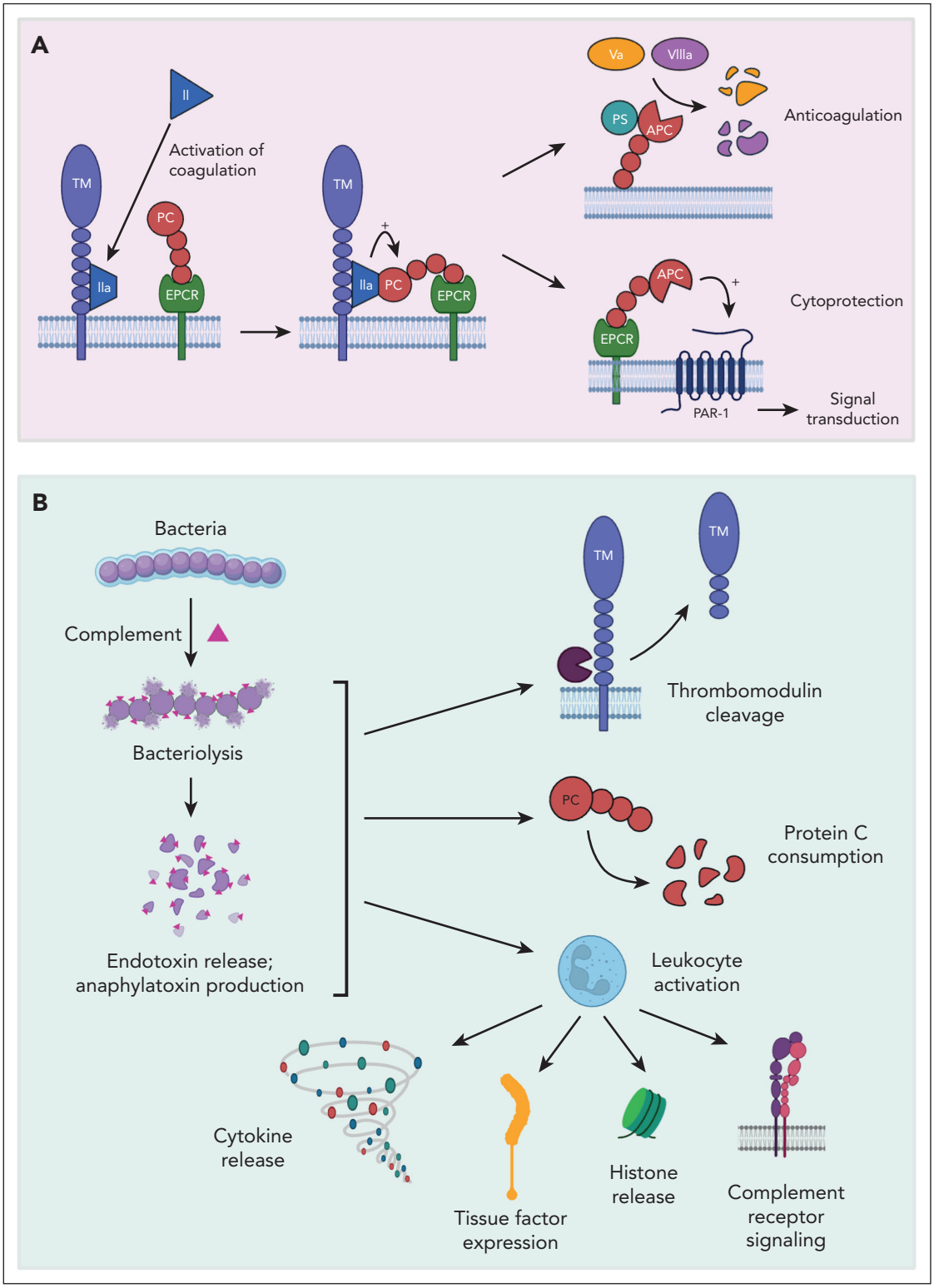

Figure 1. The role of protein C in PF. (A) Protein C (PC) is an inactive (zymogen) serine protease that both circulates in plasma and is tethered to the endothelial cell surface via binding to endothelial PC receptor (EPCR). Upon activation of the coagulation cascade, prothrombin (II) is converted to thrombin (IIa) and binds thrombomodulin (TM) on the endothelial cell surface. TM-bound IIa becomes an anticoagulant molecule (the so-called "thrombin switch"), capable of converting EPCR-bound PC into activated PC (APC) via cleavage of PC at Arg^{169}. Lipid-associated APC binds its cofactor protein S (PS) and cleaves and inactivates factors Va and VIIIa to negatively regulate coagulation (top); and EPCR-associated APC cleaves protease-activated receptor 1 (PAR-1) on the endothelial cell surface to activate a cytoprotective signal transduction program (bottom). (B) Complement activation in response to severe bacterial infection results in significant bacteriolysis, which triggers the release of endotoxin and production of the anaphylatoxin complement fragments C3a, C4a, and C5a, which in turn triggers systemic inflammation and activation of coagulation. Leukocyte hyperactivation results in the release of proinflammatory cytokines, widespread expression of TF, release of TF-rich procoagulant microparticles, and release of histones and nonhistone nuclear proteins. Hyperactivation of coagulation results in impaired PC function. A number of different mechanisms impair the function of the PC system in PF. These include proteolytic cleavage of TM from the endothelial cell surface and depletion of PC as a consequence of excessive thrombin generation. The overall result is severe maladaptive thromboinflammation. PAR-1, protease-activated receptor 1.

(1) downregulation of coagulation via proteolytic inactivation of factors Va and VIIIa; and (2) endothelial cytoprotection via noncanonical activation of protease-activated receptor 1. PF is characterized by a severe acquired deficiency in protein C, which causes both of these functions to fail.

Patients with PF invariably lose endothelial cell surface expression of thrombomodulin due to cleavage and release of thrombomodulin into the circulation,[11] and soluble thrombomodulin is not able to localize proteolytic reactions to the vascular surface. Several observations suggest that thrombomodulin detachment itself is not the inciting cause of PF but rather an ancillary event that contributes to disease progression.[11,12] First, we have demonstrated that severe protein C deficiency precedes detachment of thrombomodulin in at least some patients with PF.[13] Second, administration of protein C concentrate leads to the generation of activated protein C in vivo even after the onset of PF, with a corresponding decline in coagulation markers such as D-dimer and thrombin-antithrombin complex levels.[14] Third, although loss of thrombomodulin would be expected to impair activation of protein C, it should not cause the profound depletion of circulating protein C that is seen in PF. Of note, soluble thrombomodulin released from the endothelium does retain measurable cofactor activity.[15,16] Although its contribution to the activation of protein C in sepsis is not clear, recombinant human soluble thrombomodulin has been approved in Japan for the treatment of sepsis-associated DIC.[17,18]

The pathogenesis of PF is likely a maladaptive hyperinflammatory response to infection (Figure 1B). Patients with PF exhibit extraordinarily high plasma levels of proinflammatory cytokines, including tumor necrosis factor α and interleukin-1 (IL-1).[19,20] Together with bacterial endotoxin–mediated activation of toll-like receptor 4, these cytokines downregulate the expression of endogenous anticoagulant molecules on the endothelial surface, promote tissue factor (TF) expression by multiple cell types, and stimulate release of TF-rich procoagulant microparticles by activated endothelium, monocytes, and macrophages.[21,22] High concentrations of circulating TF result in unchecked thrombin generation, intravascular thrombosis, and ischemic tissue damage. Simultaneously, endogenous anticoagulants such as protein C, protein S, and antithrombin are rapidly consumed in response to overwhelming thrombin generation. Release of histones and nonhistone nuclear proteins such as platelet-derived high mobility group box-1 during severe sepsis may also reduce protein C activation by impairing the expression and function of thrombomodulin.[23-25] The combined effect of these processes is to trigger diffuse, uncontrolled intravascular thrombosis and consumptive coagulopathy. Buttressing the hypothesis that dysregulated inflammation is the proximal cause of coagulopathy in PF, investigators have recently reported cases of "sterile PF" in patients experiencing severe cytokine release syndrome from immune checkpoint inhibitor therapy.[5,6]

Although hyperinflammation is very likely the driver of DIC in severe sepsis, it is not clear why some patients mount a well-balanced response to infection, whereas others develop overwhelming thromboinflammation. Interestingly, despite experiencing recurrent infections by encapsulated microbes such as *N meningitidis* and *S pneumoniae*, patients born with complete loss of terminal complement components rarely develop severe sepsis or PF.[26] This observation suggests that complement plays a critical role in the pathogenesis of sepsis-associated hyperinflammation. Complement activation promotes inflammation in at least 2 ways: the generation of anaphylatoxins C3a and C5a,[27,28] and the release of endotoxin as a consequence of complement-mediated microbial lysis.[29,30] Indeed, high levels of complement activation and endotoxemia are correlated with disease severity in meningococcemia.[26,31] Consistent with this model, we recently reported that heterozygous loss-of-function mutations in humoral complement system genes are significantly enriched in patients with PF. We hypothesize that partial loss of humoral complement function results in suboptimal killing of bacteria while still allowing for significant complement-mediated thromboinflammation to occur. In the same study, we found that mutations in genes encoding opsonophagocytic complement system components are also enriched in patients with PF. These mutations impair the function of the anti-inflammatory complement receptor CR3 and enhance the activity of the proinflammatory complement receptor CR4, further supporting the concept that dysregulated complement function and, more specifically, complement-dependent signaling, play a critical role in PF.[32]

Clinical features and diagnosis of PF

The diagnosis of PF requires a high index of suspicion early in the patient's presentation. We have adapted the clinical tetrad for symmetric peripheral (limb) gangrene developed by Theodore Warkentin to provide a useful rubric for approaching suspected cases of PF.[33] The key features of PF are as follows: (1) very rapid onset of thrombotic DIC; (2) profound depletion of endogenous anticoagulants (especially protein C); (3) a triggering infectious event; and (4) characteristic skin findings. The sine qua non of PF is a purpuric rash that typically begins on acral surfaces, including the nose, knees, and feet (Figure 2A-D). Skin findings initially present as livedo racemosa (reddish-blue mottling of the skin in an irregular, reticular pattern) before progressing to retiform purpura (branching purpuric lesions) and full-thickness skin necrosis. The retiform pattern stems from the highly ordered net-like structure of venous drainage from the skin and suggests that these superficial vessels become occluded early in the disease process. These skin findings correspond histologically to the accumulation of bland fibrin-rich thrombi throughout the small vessels of the dermis (Figure 2E). PF-associated skin changes are thus markedly different from those seen in other purpuric conditions such as thrombotic thrombocytopenic purpura (platelet-rich microvascular thrombi) and immune thrombocytopenic purpura (perivascular hemorrhage). In cases in which the diagnosis of PF is not clear-cut, a skin biopsy can help to confirm the diagnosis by demonstrating pathognomonic histologic findings, including diffuse, fibrin-rich microvascular thrombosis. However, it is critically important, given the rapidly progressive nature of PF, that empiric treatment is not delayed awaiting biopsy results.

Laboratory findings in PF are similarly distinctive. Patients exhibit profound depletion of circulating protein C levels (typically <40% and often <20%) as well as low protein S and antithrombin levels (typically <50%). Laboratory findings are consistent with severe DIC, including thrombocytopenia,

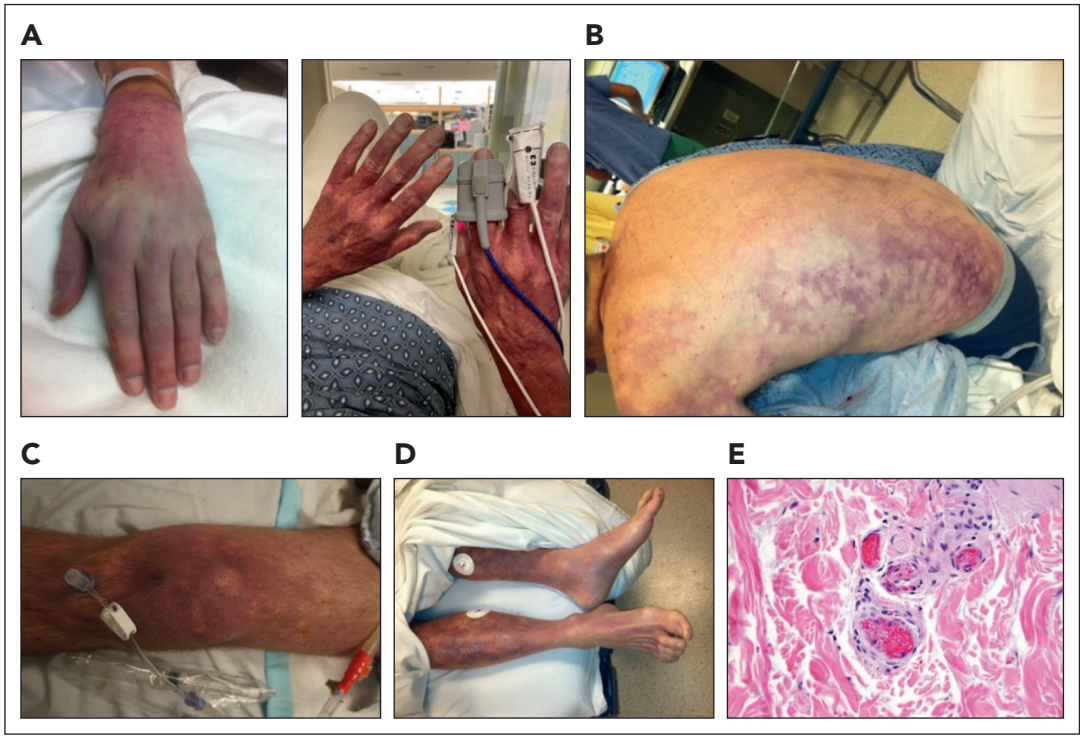

Figure 2. Early skin findings in acute infection–associated PF. (A-D) Shown are the skin mottling and livedo racemosa that are characteristic of PF during the first 24 hours after presentation, as seen on the (A) hands, (B) trunk, (C) knees, and (D) lower extremities. These findings eventually progress to retiform purpura and full-thickness necrosis of the skin. (E) Pathology specimen showing fibrin-rich thrombi in the small vessels of the dermis in a patient with PF (hematoxylin and eosin; magnification ×400). Adapted, in part, from Bendapudi et al.[13]

prolonged coagulation times, elevated D-dimer, and low or pseudonormal fibrinogen (Table 1). Patients frequently have a markedly elevated plasma C-reactive protein (CRP) level and inappropriately low erythrocyte sedimentation rate (ESR) (often <5 mm/h, or even undetectable). This "ESR–CRP decoupling" is caused by the extremely rapid turnover of fibrinogen, which artifactually decreases the ESR. Finally, a microbial culture growing an encapsulated organism from a sterile site, particularly *N meningitidis*, *S pneumoniae*, or *C canimorsus*, can greatly facilitate diagnosis.

It should be noted that, although patients with PF frequently present with some degree of hemodynamic instability and with elevated serum lactate levels, the severity of their lactic acidosis (>10 mmol/L) tends to be out of proportion to their degree of shock, reflecting the dominant role of microvascular thrombosis rather than hypotension in causing tissue ischemia. Clinicians should also be aware of the risk for hemorrhagic adrenal necrosis (Waterhouse-Friderichsen syndrome), which may contribute to shock and require additional endocrine-directed therapy. This complication is classically most associated with invasive meningococcal disease but can be caused by a range of bacterial pathogens.[34]

Hematology-directed treatment of PF

Data to support specific interventions for PF are limited, and we note at the outset that much of the guidance contained herein is expert opinion. Wherever possible, we will attempt to make clear the evidence underlying our recommendations. Our approach to treating PF (outlined in Figure 3) focuses on interventions to mitigate coagulopathy, ideally before skin findings have progressed beyond livedo racemosa. Given the extremely rapid clinical progression of PF, this almost invariably

Table 1. Common features of purpura fulminans

Suggested diagnostic criteria for acute infectious PF
Clinical picture
Critically ill patient with rapid-onset consumptive coagulopathy
New skin findings of mottling, livedo racemosa, and/or purpura
Initial laboratory findings
aPTT ≥45 s and/or INR ≥1.5
Platelets <100 × 10^9/L
D-dimer >3000 ng/mL
Elevated lactate
Protein C activity <40%
Additional suggestive features
Lactic acidosis out of proportion to degree of shock
Low or pseudonormal fibrinogen
Elevated CRP with low ESR ("ESR-CRP decoupling")
Sterile-site culture positive for an encapsulated organism, an encapsulated organism, especially *N meningitidis*, *S pneumoniae*, or *C canimorsus*

The presence of these features considerably increases the probability of PF. However, PF ultimately remains a clinical diagnosis requiring the judgment of individual providers.

aPTT, activated partial thromboplastin time; INR, international normalized ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

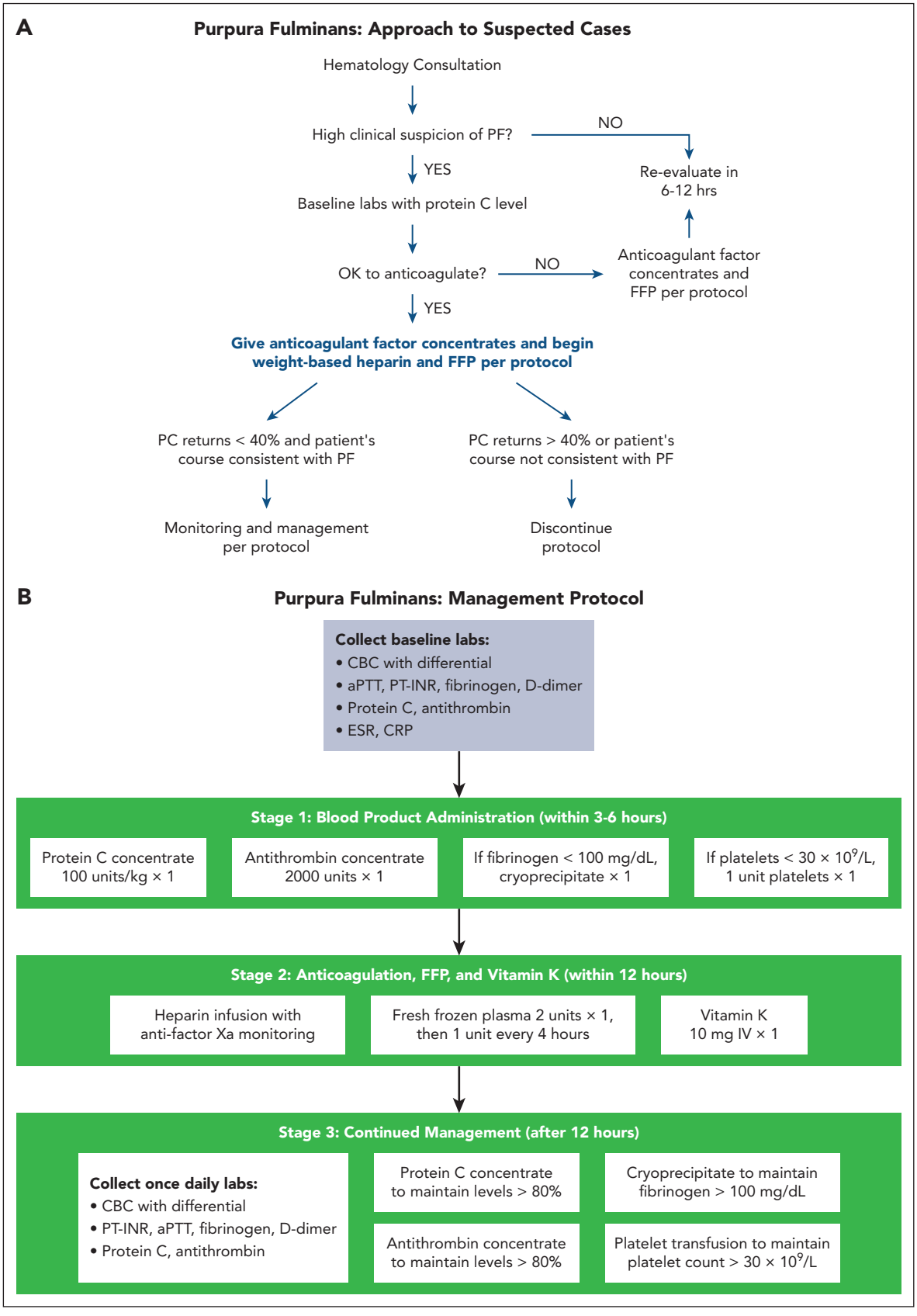

Figure 3. Suggested algorithm for the diagnosis and management of acute infection–associated PF. (A) PF is a medical emergency that usually requires the initiation of empiric therapy before the availability of comprehensive diagnostic laboratory data. Our approach to suspected cases of PF involves establishing a provisional clinical diagnosis and initiating therapy while awaiting the results of plasma PC testing. A baseline PC level >40% renders the diagnosis of PF unlikely. (B) Once a presumptive diagnosis of PF has been established and bleeding risk has been assessed, protocol-directed therapy should be initiated within no more than 6 hours and ideally within 3

requires initiating empiric therapy emergently, within the first few hours after presentation.

Repletion of protein C

Observational data suggest that the use of protein C concentrate can reduce the extent of tissue damage and improve mortality in PF.[13,35-39] We typically administer protein C concentrate as an initial IV bolus dose of 100 to 150 IU/kg in patients with suspected PF. Protein C concentrate can then be given once daily to maintain levels >80%. Our suggested dosing is based on prior data showing that 100 IU/kg of protein C concentrate provides optimal pharmacokinetic exposure in patients with PF[14,35] and the observation that plasma thrombin-antithrombin complex concentrations reach a nadir when protein C levels exceed 80% in patients with neonatal PF.[40] Others have reasonably recommended more aggressive regimens, including every 6-hour dosing of protein C concentrate at 100 IU/kg[14,38] and administration of protein C by IV bolus, followed by continuous IV infusion.[37] The specific protein C dose should be chosen based on clinical judgment and resource availability (please note that this is a recommendation for off-label use of protein C concentrate). After the initial dose of protein C concentrate, we continue repletion until patients are able to maintain their endogenous protein C levels at >80%, which typically occurs in 4 to 7 days. We also give IV vitamin K to support endogenous production of proteins C and S. If protein C concentrate is not available, plasma exchange may be considered to rapidly and euvolemically replete protein C. We would recommend performing a high-volume exchange (1.5-2.0 blood volumes) using fresh frozen plasma (FFP) as the replacement fluid. Citrate toxicity is a concern in patients with significant liver and kidney dysfunction, and ionized calcium levels should be monitored closely during and immediately after plasma exchange. Importantly, simple transfusion of FFP alone is not sufficient to replete protein C and cannot reliably be used for this purpose.

Given that protein C is an endogenous anticoagulant, it is reasonable to consider the safety of administering protein C to patients who are profoundly coagulopathic. Reassuringly, to our knowledge, the largest clinical trial to date of protein C concentrate in PF found no increased risk of bleeding,[14] presumably because protein C activation is tightly regulated by thrombomodulin and other components of the protein C system. Of note, recombinant activated protein C (drotrecogin alfa), which was associated with increased bleeding in patients with severe sepsis,[41,42] is no longer available, and experience with this agent in PF is limited.[43,44]

Repletion of antithrombin and protein S

Patients with PF invariably present with low plasma antithrombin and protein S levels, although both tend to be less severely depleted than protein C. Evidence to support antithrombin repletion in severe sepsis is poor[45]; however, the studies that have been done did not evaluate patients with PF and included many participants who did not have low antithrombin levels. We recommend an initial fixed dose of 2000 IU of antithrombin concentrate IV if the antithrombin level is not known, and we administer subsequent doses once daily to maintain levels >80%. This target antithrombin level lacks supporting clinical data and is based on the rationale that achieving a normal antithrombin level will promote the proper functioning of heparin. We advise greater caution with empiric antithrombin dosing than with protein C dosing because high antithrombin levels can enhance the anticoagulant effects of heparin (see below). With respect to protein S, no specific factor concentrate is available, and we typically do not attempt repletion beyond providing FFP. We find that patients generally recover their protein S levels after the thrombotic process has been controlled through other interventions. A combined protein C and protein S concentrate may become available in the future.[46]

Therapeutic anticoagulation

Despite the strongly prothrombotic nature of PF, the decision to therapeutically anticoagulate patients with severe coagulopathy can be fraught. Anticoagulation with IV unfractionated heparin is of uncertain benefit in the broader population of individuals with sepsis-associated DIC,[47,48] and bleeding is a well-founded concern. Our rationale for using heparin in the treatment of PF is that PF is a uniquely prothrombotic state in which clinical harm is driven largely by uncontrolled coagulation. However, we recommend exercising caution in patients with advanced age, frailty, a history of bleeding, or other risk factors for hemorrhage. In patients who are deemed to be at relatively low risk of bleeding, we typically start with a weight-based IV heparin bolus of 80 U/kg, followed by a continuous infusion at 18 U/kg per hour, with close monitoring to achieve an anti-Xa level of 0.3 to 0.7 U/mL (please note that the baseline activated partial thromboplastin time is almost always prolonged in PF and is not a reliable means of monitoring heparin dosing). Reduced-intensity regimens (eg, no bolus) may also be used when clinically indicated. It is important to keep in mind that many patients with PF will exhibit moderate-to-severe heparin resistance due to low circulating antithrombin levels and high levels of systemic inflammation. In such instances, frequent dose adjustments may be needed, including the use of additional boluses. On balance, we err toward more aggressive heparin administration in patients without clear contraindications to anticoagulation given the rapidly progressive, life-threatening, and irreversible nature of PF-associated tissue damage. We typically continue heparin until the D-dimer declines and stabilizes (please note that the D-dimer will not completely normalize during the index hospitalization for most patients). Once the D-dimer level has decreased and plateaued, we slowly wean heparin while continuing to monitor the D-dimer level. Anticoagulation is discontinued once the patient is able to maintain a steady D-dimer level off of heparin. We do not recommend long-term anticoagulation after recovery because the coagulopathy of PF is situational and transient; there is no known long-term thrombotic risk in patients with PF that justifies indefinite anticoagulation. We also do not recommend the use of low molecular weight heparin products in patients with PF due to the prominent renal failure experienced by most patients and the lack of pharmacokinetic validation of low molecular weight heparin under these conditions.

Figure 3 (continued) hours of presentation. The backbone of this strategy is rapid judicious repletion of the natural anticoagulants, PC and antithrombin. aPTT, activated partial thromboplastin time; CBC, complete blood count; CRP, C-reactive protein; PT-INR, prothrombin time-international normalized ratio.

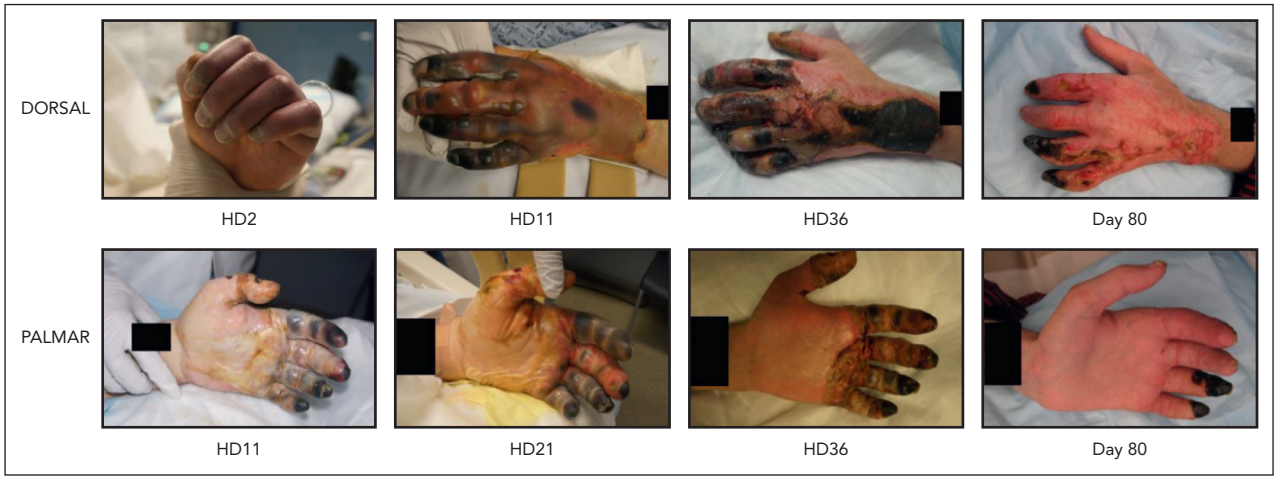

Figure 4. Evolution of cutaneous findings on the hand of a patient with PF. Areas of necrosis can require a significant period of time to demarcate, and viable tissue may underlie necrotic-appearing areas. Absent wet gangrene, we favor a conservative approach to surgical amputation, up to and including allowing digits to autoamputate. Adapted, in part, from Bendapudi et al.[13]

Other types of transfusion support

Additional transfusion support required by most patients with PF includes cryoprecipitate, platelet concentrate, packed red blood cells (pRBCs), and FFP. We transfuse cryoprecipitate to maintain plasma fibrinogen at >100 mg/dL but would recommend against excessive use of this product because it contains several procoagulant factors. There are limited data regarding the optimal platelet count for patients with severe sepsis. Our practice is to maintain a platelet count of > 30 x 10^9/L, particularly if patients are being anticoagulated. Patients with PF typically normalize their fibrinogen levels within 5 to 7 days of presentation, and it is common for plasma fibrinogen and platelet counts to rise far above the upper limit of normal once consumption of these factors ceases and their roles as acute phase reactants become evident. We recommend that pRBCs be administered to maintain a hemoglobin level >7 g/dL, and pRBC transfusions may be required for days or even weeks after the resolution of critical illness due to the shortened life span of damaged red blood cells and inflammation-associated suppression of erythropoiesis. We also supplement anticoagulant factor concentrates with FFP because FFP provides balanced repletion of coagulation factors and may reduce the need for concentrates. If the patient can tolerate the volume load, we give 2 units of FFP immediately, followed by 1 unit every 4 hours, with gradual tapering over the first 7 days. Finally, during the first 7 days, we use FFP in place of crystalloid or other colloid preparations for volume expansion whenever possible.

Surgical intervention

Decisions regarding surgical debridement can be very challenging. Absent wet gangrene, we recommend against early amputation because there may be substantial viable tissue underlying areas that appear necrotic, and the demarcation of dead and viable regions is often unclear until late in the disease course (Figure 4).[49] The absence of pulses alone does not indicate that distal territories cannot be salvaged. Fasciotomies should be avoided if possible because they require interrupting anticoagulation and can cause further injury to poorly perfused and inflamed tissues. Based on our experience, we favor a conservative approach for most patients, up to and including allowing autoamputation of necrotic tissue.

Interventions to be avoided

DTIs We do not use direct thrombin inhibitors (DTIs) such as argatroban in lieu of unfractionated heparin. Thrombin exerts a crucial negative feedback effect on coagulation via its activation of protein C as part of the thrombin-thrombomodulin complex (Figure 1).[50] Perhaps for this reason, clinical trials have shown that oral DTIs are associated with a paradoxically increased risk of myocardial infarction.[51-53] Given the theoretical possibility that DTIs can interfere with protein C activation, we recommend against the use of these agents in patients with PF.

Single-component colloid preparations Colloid preparations lacking coagulation factors, such as intravenous immunoglobulin (IVIG) and albumin, are often given in high volume to patients with sepsis. We try to mimize the use of these preparations, as they may exacerbate thrombosis in PF by diluting already low concentrations of circulating anticoagulants while failing to substantially affect the function of procoagulant factors.[54] We reserve IVIG for situations in which there is high clinical suspicion for toxic shock syndrome or other specific indications.

CASE 1

A previously healthy 39-year-old man presents to the emergency department after experiencing 12 hours of sore throat, malaise, and a rapidly expanding purpuric rash on his face, as well as new discoloration of his distal extremities (Figure 5A-B).[13] Physical examination is notable for normal blood pressure, tachycardia (heart rate, 125 [sinus rhythm]), hypothermia (temperature, 95.4°F), mask-like facial retiform purpura with periorbital sparing, purpura overlying his knees, and dusking of his hands and feet. He reports having sustained a dog bite 3 days prior. Initial laboratory studies are consistent with severe consumptive coagulopathy and end-organ ischemia (Table 2). Review of his peripheral blood smear shows neutrophils containing toxic

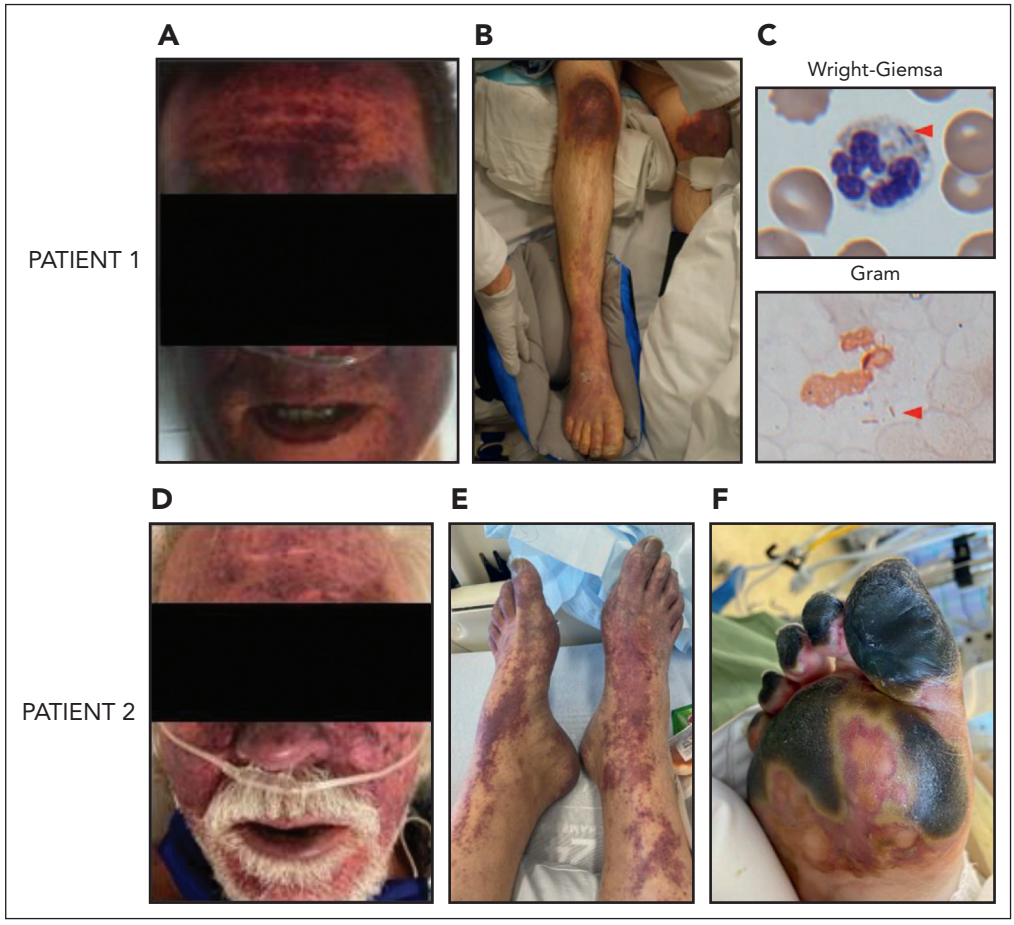

Figure 5. Presentation of patients 1 and 2. (A-F) Both patients experienced a mask-like facial rash within 12 to 24 hours of development of symptoms (A,D), as well as mottling and retiform purpura of the lower extremities (B,E-F). In particular, Patient 1 displayed retiform purpura of the knees (B) early in his course, a classic finding in PF. At presentation, the peripheral blood smear of patient 1 also revealed numerous basophilic inclusions in his neutrophils (C; top, arrowhead), which were later determined to be gram-negative rods (C; bottom, arrowhead) consistent with his eventual diagnosis of *C canimorsus* bacteremia. Adapted, in part, from Bendapudi et al.[13]

granulations, Döhle bodies, prominent vacuoles, and frequent rod-like basophilic inclusions (Figure 5C) that are later identified as gram-negative bacteria. Four hours after presentation, he develops shock and experiences cardiac arrest requiring 10 minutes of cardiopulmonary resuscitation. After return of spontaneous circulation and within 6 hours of his initial presentation, he receives protein C and antithrombin concentrates, IV unfractionated heparin, cryoprecipitate, and FFP, and he is started on renal replacement therapy. The next day, his admission laboratory tests return with a protein C activity of 12% (normal range, 66%-140%), a protein S activity of 30% (normal range, 70%-134%), and an antithrombin activity of 37% (normal range, 69%-127%). He continues to receive protocol-driven treatment (Figure 3), including daily protein C and antithrombin supplementation as well as therapeutic unfractionated heparin. During the first 5 days of hospitalization, shock resolves, and most of his coagulation parameters normalize. Renal replacement therapy is later discontinued. Limb ischemia improves and progresses to necrosis in only limited regions. With meticulous wound care and minimal bedside debridement, the patient requires amputation of the fourth and fifth distal phalanges of the left hand and 9 of 10 phalanges of both feet. He is discharged to an inpatient physical rehabilitation center on hospital day 58 and eventually returns to work as a graphic designer. Although blood cultures remain negative throughout his hospitalization, the diagnosis of *C canimorsus* septicemia is confirmed by whole-blood polymerase chain reaction.

CASE 2

A 70-year-old man with a history of immune thrombocytopenic purpura, status post splenectomy, and successfully treated hepatitis C infection presents after ~24 hours of nausea, vomiting, diarrhea, and back pain. On initial examination, he is normotensive and in sinus rhythm (heart rate 88). While awaiting evaluation in the emergency department, he develops a retiform rash over his face, hands, and feet (Figure 5D-E) and experiences acute worsening of fatigue and nausea. Laboratory data are consistent with severe consumptive coagulopathy and lactic acidosis (Table 2). His blood cultures later grow *S pneumoniae*. Because protein C concentrate is not immediately available, he receives 50 U/kg of KCentra (Confidex or Beriplex in Europe), a 4-factor prothrombin complex concentrate with a high protein C content.[55] He is also started on IV unfractionated heparin within 24 hours of presentation. He continues to receive KCentra daily until hospital day 3, when repletion is switched to protein C concentrate. Protein C concentrate is then administered daily to maintain levels at >80%. Unfractionated heparin is titrated to a therapeutic anti-Xa level and eventually discontinued after decline and stabilization of his D-dimer. Renal

Table 2. Presenting laboratory findings of patients 1 and 2

Variable	Reference range (adults)	Patient 1	Patient 2
Creatinine, mg/dL	0.5-1.2	5.10	2.3
Total bilirubin, mg/dL	0-1.0	3.9	2.6
Lactate dehydrogenase, U/L	135-225	4080	961
Lactic acid, mmol/L	0.5-2.2	13.1	5.0
ALT, U/L	10-50	2067	65
AST, U/L	10-50	2776	151
Alkaline phosphatase, U/L	35-130	108	92
Creatine kinase, U/L	39-308	2919	1397
Troponin T, ng/mL	0.0-0.0	0.03	<0.01
White cell count, × 10^3/μL	4-10	6180	7300
Differential count, %			
Neutrophils	48-76	52	76
Lymphocytes	18-41	4	6
Monocytes	4.0-11.0	0	2
Eosinophils	0-5	0	0
Basophils	0-1.5	1	0
Bands	0-3	34	16
Metamyelocytes	0	8	0
Myelocytes	0	1	0
Hemoglobin, g/dL	13.5-18.0	14.2	12.9
Platelet count, × 10^9/L	150-450	6	28
International normalized ratio	0.9-1.1	8.9	3.0
Activated partial thromboplastin time, s	23.8-36.6	>150	150
D-dimer, ng/mL	<500	>4000	>21 600
Fibrinogen, mg/dL	200-450	<60	35
Protein C activity, %	70-170	12	<10
Protein S activity, %	50-150	30	48
Antithrombin activity, %	69-127	37	54

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

replacement therapy is initiated in the intensive care unit and is required for a total of 50 days. A conservative approach to wound management results in the eventual loss of part of his right toe and tissue from the plantar surfaces of his feet bilaterally (Figure 5F) as well as the distal tips of 3 right and 2 left fingers. He ultimately returns home, where he maintains a high degree of functionality but struggles with chronic pain in his feet bilaterally.

COMMENTS ON THE CASES

Both of these patients experienced an extremely rapid clinical decline, as is typical of PF. Nevertheless, their cases highlight the potential benefits of hematology-directed interventions when initiated rapidly after presentation. Notable points include the following:

1. Risk factors for PF include splenectomy (as illustrated by patient 2), alcohol use disorder, and recent dog or cat exposure.

2. In PF, some presenting features can appear inconsistent or misleading. For example, both patients presented with a normal leukocyte count and patient 1 exhibited hypothermia rather than fever, which is a poor prognostic marker in

sepsis.[56] Clinicians should have a high index of suspicion and remain focused on the clinical tetrad of PF when approaching suspected cases.

3. Correlative studies performed on tissue samples from patient 1 demonstrated that endothelial thrombomodulin remained detectable at 24 hours after presentation but was significantly decreased at 72 hours.[13] This suggests that there is a limited time window during which exogenous protein C can be converted to activated protein C.

4. The need for renal replacement therapy should not be interpreted as an indicator of irreversible kidney damage. In survivors, dependence on renal replacement therapy generally resolves even in the most severe cases, although this can take months.

Conclusions and future directions

Due to the prominent coagulopathy and often dramatic presentation of PF, hematologists are frequently tasked with assessing and developing treatment plans for rapidly deteriorating patients. The lack of high-quality data to guide clinical decision-making makes management of PF very challenging. There is no question that large, well-designed clinical trials in PF are urgently needed. However, until such studies are completed, recent advances in our understanding of the pathophysiology of PF, as well as knowledge gained from personal experience and small studies, can be used to formulate rationally designed treatment strategies. A key unmet need remains the lack of therapeutic agents that target the interface between inflammation, innate immunity, and coagulation. It is currently unknown whether inhibitors of complement function or of inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor α would change the disease course of PF; however, given the key roles these mediators play in the pathogenesis of PF, such therapeutic strategies deserve further study. The future may also see patients preventatively risk stratified via germ line genetics[32] and treated with specialized recombinant forms of protein C designed to maximize cytoprotection.[57] Such approaches could ultimately be used individually or in combination to manage this devastating hematologic emergency.

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ORCID profiles: P.K.B., 0000-0002-0754-7688; J.-A.L., 0000-0002-3790-2660.

Correspondence: Pavan K. Bendapudi, Center for Life Sciences, Room 906, 3 Blackfan Circle, Boston, MA 02115; email: pbendapudi@mgb.org; and Julie-Aurore Losman, Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Mayer 422, Boston, MA 02215; email: julieaurore_losman@dfci.harvard.edu.

Footnote

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