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Original Articles

Purpura Fulminans: Mechanism and Management of Dysregulated Hemostasis



Meaghan E. Colling ^{a,b}, Pavan K. Bendapudi ^{b,c,d,*}

^a Department of Medicine, Massachusetts General Hospital, Boston, MA

^b Harvard Medical School, Boston, MA

^c Division of Hematology, Massachusetts General Hospital, Boston, MA

^d Blood Transfusion Service, Massachusetts General Hospital, Boston, MA

ARTICLE INFO

Available online 16 October 2017

Keywords:

Purpura fulminans
Disseminated intravascular coagulation
Acquired protein C deficiency
Sepsis

ABSTRACT

Purpura fulminans (PF) is a highly thrombotic subtype of disseminated intravascular coagulation that can accompany severe bacterial, and more rarely, viral infections. PF is associated with an extremely high mortality rate, and patients often die of overwhelming multisystemic thrombosis rather than septic shock. Survivors typically experience amputation of involved extremities and significant scarring in affected areas. Despite the devastating clinical course associated with this hemostatic complication of infection, the mechanism of PF remains poorly understood. Severe acquired deficiency of protein C and dysfunction of the protein C-thrombomodulin pathway as well as other systems that exert a negative regulatory effect on coagulation have been implicated. Management of PF involves treatment of the underlying infection, aggressive anticoagulation, and robust transfusion support aimed at correcting acquired deficiencies in natural anticoagulant proteins. In this review, we address the diagnosis and management of PF with a focus on a rational approach to this condition informed by the available data. Proposed mechanisms underlying the dysregulation of coagulation seen in PF are also covered, and implications for therapy are discussed.

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* Corresponding author at: Pavan K. Bendapudi, M.D., Massachusetts General Hospital, Division of Hematology, Yawkey 7B, 55 Fruit Street, Boston, MA 02114, USA.
E-mail address: pkbendapudi@partners.org (P.K. Bendapudi).

Purpura fulminans (PF) is a rare, life-threatening syndrome marked by disseminated intravascular coagulation (DIC) and endovascular thrombosis resulting in a characteristic pattern of cutaneous purpura [1–4]. Guelliot first described the condition in 1884 in children after bacterial and viral infections [5]. Although triggered by a number of clinical scenarios, PF most commonly occurs as a severe complication of infection and is characterized by aberrant activation of procoagulant pathways, dysfunction of anticoagulant pathways, and endothelial damage; patients often expire from thrombotic sequelae rather than the primary infection itself [4,6,7]. PF requires prompt recognition and initiation of treatment targeting the coagulation system in parallel with management of the underlying cause. This review aims to address the presentation and etiologies of infectious PF, describe our current understanding of its pathophysiology, and discuss current approaches to therapy.

Etiologies

PF is the clinical manifestation of a pathophysiology that can result from a range of triggering events (Table 1). PF occurs most often in children with a bimodal peak incidence that includes infants 1 to 3 years old and adolescents 16 to 18 years old [8]. The higher rate in adolescents is due primarily to the elevated incidence in this group of infection with *N. meningitidis*, an organism commonly associated with PF.

Sepsis

PF tends to occur as a result of infection by endotoxin-producing gram-negative bacteria but can also occur secondary to infections with gram positive and anaerobic organisms or viruses. Meningococcal disease is responsible for the largest number of cases due to a single infectious etiology [9]. Overall 15% to 25% of patients with meningococcal infection develop PF. The development of PF is poor prognostic sign associated with a mortality rate of 20% to 60% compared to ~15% mortality in uncomplicated cases of meningococcal disease [3]. In addition to *N. meningitidis*, many other infectious etiologies of PF have been identified, including *Streptococcus spp.*, *Haemophilus influenzae*, *Capnocytophaga canimorsus*, and *Staphylococcus aureus* (Table 1). Thrombotic complications can progress long after clearance of the inciting organism by antibiotics. Interestingly, while shock can be associated with infectious PF, many patients do not experience marked hypotension.

Inherited Deficiency

PF can be the presenting syndrome in neonates with severe inherited deficiencies of protein C (PC) (and rarely protein S (PS)) due to homozygous or compound heterozygous mutations in the *PROC* or

PROS1 genes, respectively [4]. Skin necrosis with subsequent gangrene typically develops on the lower limbs and male genitalia within a few hours or days of birth. Commonly, there is cerebral venous thrombosis resulting in significant neurologic symptoms. Treatment with PC concentrate can be life saving and prevent irreversible end-organ damage [10].

Post-Infectious

Post-infectious PF occurs 7 to 10 days after infection and is thought to be the result of acquired autoantibodies against PC or PS [11,12]. Cross-reacting IgG autoantibodies that increase PS clearance from the circulation are thought to trigger post-infectious PF [13] and patients tend to be lupus anticoagulant positive at the time of presentation [14]. The most common infections associated with this etiology are varicella and *Streptococcal* species, although other bacteria been implicated [15]. Lesions tend to occur in the thighs, lower legs, and buttocks as well as the scrotum and penis in men. There is usually distal extremity sparing without circulatory collapse, and this etiology is associated with a lower mortality rate (~15%) [3]. For patients who survive the acute phase of illness, many experience spontaneous resolution of the autoantibodies by three months [11].

Risk Factors

It is not clear why some patients develop PF while others are spared; however, some risk factors have been identified. Asplenic or immunosuppressed patients are more likely to develop PF in response to infection [4]. One study comparing patients who were heterozygous for factor V Leiden against patients with normal factor V found similar mortality between the two groups but a three-fold higher rate of PF (21% to 7%) in patients with factor V Leiden [16]. However, these results have been called into question since the prevalence of factor V Leiden and deficiencies of PS, PC, and AT in PF patients match those of the general population [17]. Patients with alcohol use disorder and abnormal complement levels also appear to be at increased risk (unpublished data), suggesting a role for the immune system.

Functions of Protein C

PF is thought to result from dysfunction of the body's natural anticoagulant mechanisms, particularly abnormalities in the function of PC and associated proteins. PC is a vitamin K-dependent serine protease that negatively regulates coagulation and has anti-inflammatory and cytoprotective properties [18].

Protein C in Coagulation

During thrombus formation, PC binds to the endothelial PC receptor (EPCR), forming a complex with thrombomodulin (TM)-bound thrombin, which activates PC by cleavage at Arg 506 (Fig 1A). This process is the so-called “thrombin switch” by which thrombin becomes anti- rather than procoagulant [19]. Once activated, PC cleaves and inactivates factors Va and VIIIa as well as plasminogen-activator inhibitor 1 (PAI-1), leading to potent anticoagulant and profibrinolytic effects and protection against excessive fibrin formation [20].

Protein C in Cytoprotection

In addition to its role in regulating coagulation, PC functions through a distinct but overlapping pathway to protect against vascular injury and cell death. Activated PC (APC) in the presence of EPCR cleaves protease-activated receptor-1 (PAR-1), initiating a signaling cascade that activates anti-inflammatory and anti-apoptotic genetic programs and strengthens the endothelial barrier (Fig 1B) [21]. This pathway also opposes the effects of thrombin-mediated cleavage of PAR-1,

Table 1
Etiologies of purpura fulminans

Infectious	Post-infectious/idiopathic
Bacterial:	Varicella
<i>Neisseria meningitidis</i>	<i>Streptococcus spp.</i>
<i>Capnocytophaga canimorsus</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i>	Rubella
<i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Leptospirosis</i>	Rubeola
<i>Enterococcus faecalis</i> <i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Rickettsia</i> <i>rickettsii</i>	
<i>Vibrio parahaemolyticus</i> , <i>Haemophilus aegyptius</i> , <i>Proteus mirabilis</i>	
Viral:	
Varicella	
Zoster	
Rubeola	
Protozoal:	
<i>Plasmodium falciparum</i>	

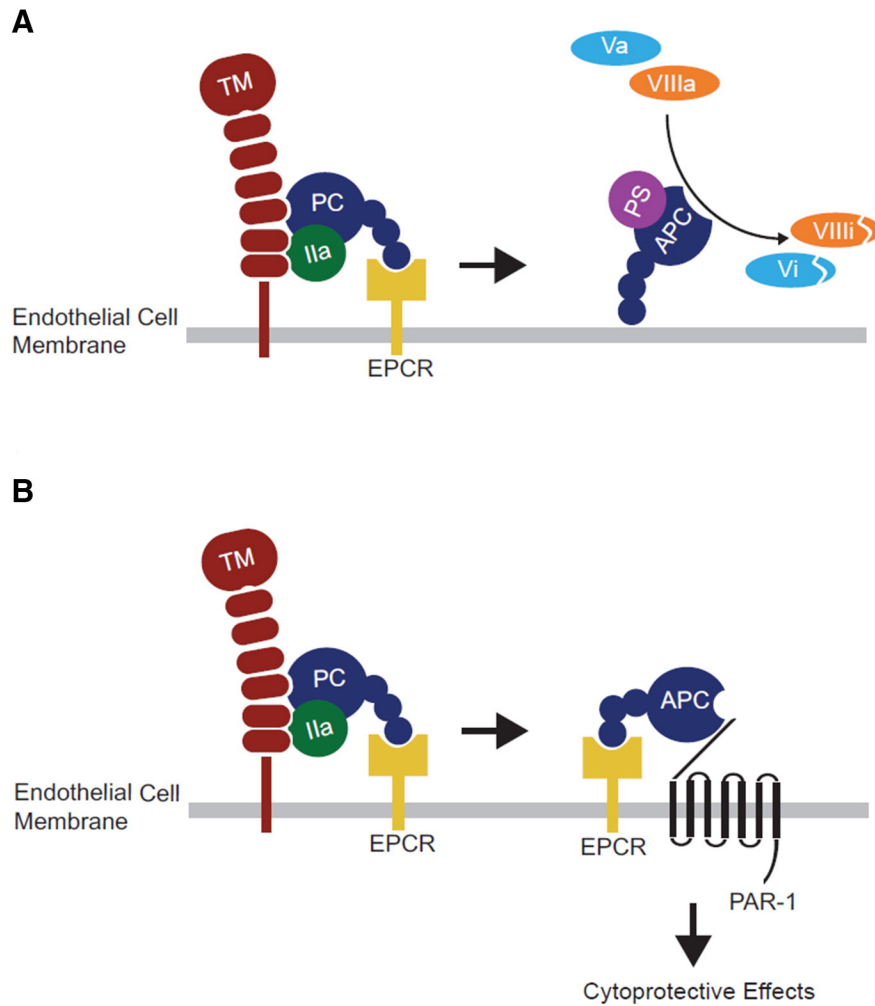


Fig 1. A, Anticoagulant activity: protein C (PC) binds endothelial protein C receptor (EPCR) on the endothelial cell membrane. PC is then activated by thrombomodulin (TM)-bound thrombin (IIa), which cleaves PC at arginine 506. Activated protein C (APC), with protein S (PS) as a cofactor, then inactivates factors Va and VIIIa, limiting progression of the coagulation cascade. B, Cytoprotective Activity: PC binds EPCR and is activated by the TM-thrombin (IIa) complex. APC then cleaves protease-activated receptor-1 (PAR-1) on the surface of endothelial cells. This cleavage initiates a signaling cascade that activates anti-inflammatory and anti-apoptotic transcriptional programs and strengthens the endothelial barrier.

which in contrast to APC, independently triggers pro-inflammatory pathways that exacerbate endothelial injury. In this way, PAR-1 can have opposing effects depending on its ligand, with APC acting as a biased agonist of PAR-1 [21,22]. The importance of the cytoprotective function of APC (as mediated by PAR-1) has been demonstrated in animal models of ischemic stroke, atherosclerosis, vascular disease, and sepsis [23–25]. *In vivo*, APC mutants that are capable of carrying out cytoprotective signaling with negligible anticoagulant effects demonstrated protection against endotoxin-induced death in mice, suggesting that APC-mediated cytoprotection is critical during sepsis [26–28].

Pathophysiology

Almost all patients with PF develop significant coagulopathy, consistent with PF being a highly thrombotic subtype of DIC [29]. Levels of the circulating anticoagulants PC, PS and antithrombin (AT) are invariably depleted in these patients. Under normal conditions, the endothelial surface has potent anticoagulant properties via the TM-PC system, endogenous heparans, and profibrinolytic mechanisms [30]. By contrast, damage to endothelial cells and concomitant dysfunction in the endothelial TM-PC system play a central role in the hypercoagulable state observed in PF.

In a seminal paper, Faust and colleagues studied pediatric patients with PF secondary to meningococcal sepsis and found severely decreased expression of endothelial thrombomodulin and EPCR associated

with increased plasma levels of soluble TM in PF patients compared to unaffected controls [6]. Plasma levels of PC, PS, and AT antigen were significantly lower in affected patients, all of whom had undetectable levels of APC between days 2 and 4. The authors concluded that an unknown property of the infecting organism led to cleavage and loss of endothelial TM with a subsequent inability to efficiently activate PC. This in turn resulted in unopposed activation of the coagulation system and overwhelming thrombosis.

A study by Lerolle et al, mirrored these findings by comparing levels of endothelial bound TM, plasma TM, PC and PS in three groups of patients: those with either sepsis alone, sepsis and DIC, or sepsis and PF [31]. Patients with sepsis and PF had significantly lower plasma levels of PS and AT than those in the other two groups.

Although abnormalities in the PC pathway seem fundamental to the development of thrombosis and consequently PF, they do not fully explain the development of PF, as sepsis without PF is often associated with depletion of PC and reduced PC activation. Endothelial damage and inflammation likely contributes to the necrosis and thrombosis observed in PF. Lerolle and colleagues found thrombi and maximal endothelial damage at sites where bacterial pathogens were present at the blood vessel wall. Additionally, when they compared skin biopsies of patients with PF against septic patients without PF, they found that PF patients had alterations in markers of endothelial integrity (CD31) as well as EPCR and TM. Comparisons with unaffected patients showed that these findings were specific to PF. These observations mirror

those in the localized Shwartzman reaction, a rabbit model that produces histopathologic changes in response to endotoxin that are similar to those observed in the lesions of patients with PF. Notably, endotoxin from *N. meningitidis* is five to ten times more effective at inducing this reaction than endotoxin from other gram-negative bacteria [32]. One hypothesis is that pathogen adherence to vessel walls results in up-regulation of cell adhesion molecules and recruitment of polymorphonuclear leukocytes (PMNs). Proteases elaborated by activated PMNs then cleave and disable endothelial TM, which in turn reduces activation of PC [6]. However, even in the context of impaired PC activation, it is still not known how thrombus formation is initiated in PF, nor are the relevant host-pathogen interactions fully understood.

Clinical Presentation

Classically, patients with PF first develop erythematous macules on both the trunk and extremities, which rapidly become indurated and nonblanching with thin, irregular, advancing borders. Early lesions can resemble a levido pattern and skin will appear mottled. Central areas of necrosis then develop and bullae may form if hemorrhage into the necrotic dermis occurs [3]. Within 24 to 48 hours, this pattern progresses to irreversible full-thickness necrosis of the skin, which is distinct from purpuric rashes seen in other conditions such as immune thrombocytopenic purpura (ITP) or thrombotic thrombocytopenia purpura (TTP) and can be susceptible to secondary infection (Fig 2A-C) [4,33]. The initial clinical findings correlate histologically with microthrombi of small dermal vessels (Fig 2D). It is not unusual for death to occur from end organ damage secondary to thrombosis of small and medium-sized vessels many days or even 1 to 2 weeks after successful clearance of the responsible organism. Therefore, treating clinicians must be vigilant with respect to the management of thrombotic complications in addition to the standard care of septic patients.

Diagnosis

PF remains a clinical diagnosis that requires a high index of suspicion early in the patient's presentation. The differential diagnosis includes warfarin-induced skin necrosis, cryoglobulinemic vasculitis, catastrophic anti-phospholipid syndrome, heparin-induced thrombocytopenia,

and Henoch-Schonlein purpura. Patients with PF have laboratory parameters consistent with DIC, including prolonged coagulation times, decreased fibrinogen, elevated d-dimers, and thrombocytopenia. These patients also often have elevated C-reactive protein (CRP) in the setting of an inappropriately low erythrocyte sedimentation rate (ESR). This "ESR-CRP disassociation" is due to relative or absolute hypofibrinogenemia in the setting of DIC, which leads to an artificially depressed ESR. Importantly, patients with PF usually have reduced levels of PC and PS [31,34–37]. Levels of PC below 40% are particularly suspicious for PF [38]. Clinical and laboratory features of PF are shown in Table 2.

Medical Management

PF is a life-threatening disease with a high mortality and significant long-term morbidity in survivors. It requires prompt recognition and immediate treatment of the underlying cause and of the ongoing hemostatic abnormalities to prevent permanent disability and death. Unfortunately, there is little evidence to guide clinical decision-making.

Activated Protein C Therapy in Sepsis

In the early 1990s, there was excitement about the potential therapeutic benefit of AT, PC or APC in patients with sepsis. A large proportion of septic patients have reduced levels of PC and declines in PC are associated with an increased risk of death [39]. Similarly, decreased AT levels are observed in most patients with sepsis, and decreased AT levels are a strong laboratory predictor of death in patients with septic shock [39]. Unsurprisingly, there is a linear correlation between AT and PC levels in these patients. It is important to note that a causative link between reductions in circulating PC and AT and worsened outcomes remains to be proven, and this phenomenon may be merely a marker of disease acuity. Nevertheless, motivated by these findings and by animal studies showing that AT and PC supplementation reduced the coagulopathic and lethal effects of *E. coli* infections in animal models [40,41], investigators began pursuing the possibility of using APC to treat patients with severe sepsis.

Early observational studies and a large randomized controlled trial demonstrated a mortality benefit of using APC in sepsis [33,42]. The

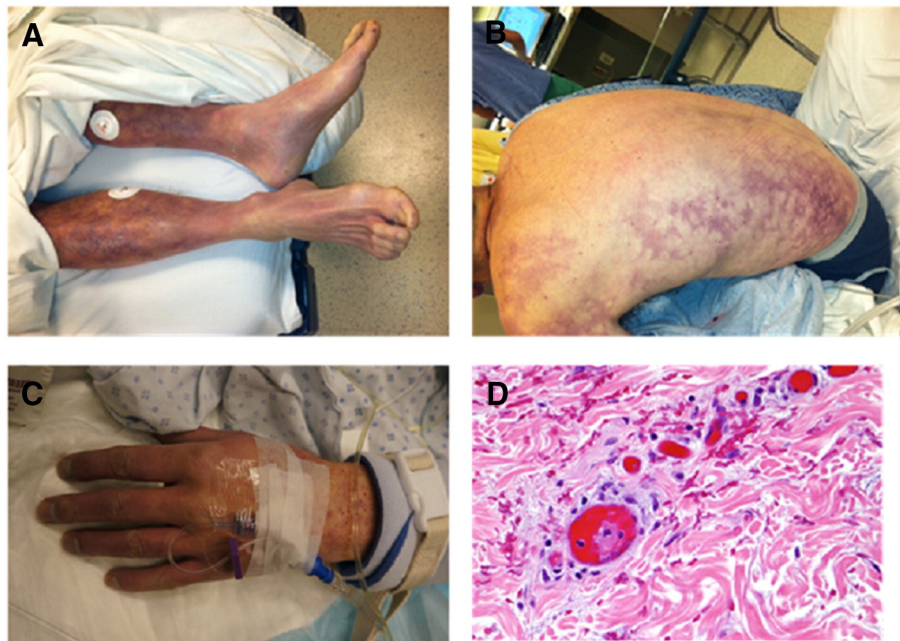


Fig 2. A-C, Images of a patient with purpura fulminans secondary to capnocytophaga canimorsus bacteremia on the day of presentation, with ecchymotic non-blanching lesions on the (A) bilateral legs, (B) back, and (C) left hand (D) H&E staining of a skin biopsy from this patient showing thrombosis in a small blood vessel with red blood cell extravasation.

Table 2
Clinical and laboratory features of PF

Clinical	Laboratory
Septic physiology +/- shock	Evidence of DIC (low platelets + fibrinogen; elevated PT, PTT, d-dimer)
Purpura or reticular rash/skin mottling (particularly over extremities)	Protein C activity \leq 40%
Meningeal signs	Elevated CRP
Immunocompromised state	Inappropriate low ESR

Prospective Recombinant Human Activated Protein C (rhAPC) World-wide Evaluation in Severe Sepsis (PROWESS) study randomly assigned patients with severe sepsis to receive rhAPC (drotrecogin alfa) or placebo and demonstrated a significant mortality benefit and nonsignificant trend towards increased risk of bleeding in those who received the study drug [42]. However, subsequent trials, which focused on characterizing the benefit of the drug in less severely ill patients, were unable to reproduce the mortality benefit [43–46]. This work culminated in the PROWESS-SHOCK trial, which tested drotrecogin alfa against placebo in a large population of patients with septic shock and failed to show a benefit in the treatment arm [38]. Following the negative results of this study, drotrecogin alfa was withdrawn from the market. Possible reasons given for the failure of APC treatment to show improved outcomes in these trials despite strongly supportive preclinical data include the use of insufficient dosing to obtain the cytoprotective effects of APC and the broad inclusion of patients with sepsis rather than only those with confirmed PF, who would be most likely to benefit from APC.

Treatment with Protein C Concentrate in PF

Some argue that patients with PF represent a unique patient population that might benefit from treatment with PC zymogen. Since the withdrawal of drotrecogin alfa, treatment with PC has been limited to PC concentrate, which is currently only available in the US as Ceprothin. The rationales for upfront use of these products are to rapidly replete PC and provide substrate to the remaining pool of endothelial TM. Several single-arm trials have assessed PC concentrate therapy for PF, and overall they suggest that treatment with PC can normalize PC levels and markers of DIC and possibly reduce morbidity and mortality (Table 3). Unfortunately, these studies are limited by their small size and weaknesses in design, including differing patient populations and medication dosing. Publication bias is also a concern as patients experiencing good outcomes after receiving PC concentrate may be preferentially reported in the literature compared to those who do poorly. Nevertheless, the logic of PC repletion in PF appears sound, and this approach warrants further investigation through well-designed trials.

Heparin and AT in PF

Prior to the approval of APC, heparin was commonly used to decrease the prothrombotic state in PF. Older trials of heparin in patients with severe meningococcal infection did not demonstrate a survival benefit [47–51]. Notably, these studies and case reports, performed primarily in pediatric patients, were limited by their small sample sizes, non-standardized inclusion criteria, delays in initiation of heparin, variable heparin dosing regimens, and limited monitoring of heparin levels. Other trials have suggested that heparin therapy may reduce the amount of skin necrosis and need for subsequent amputations in patients with infectious PF [48,50].

With the advent of APC therapy, many of the patients in the PF specific trials were treated with both APC and heparin. A recent retrospective, propensity matched cohort study suggested a reduced hazard ratio for death in patients with septic shock treated early with IV unfractionated heparin, without an increased risk of bleeding [52]. The subsequent randomized, double-blind, placebo controlled HETRASE

study looking at the use of systemic heparin in patients with septic shock did not reproduce these results, finding no difference in organ dysfunction, length of hospital stay, or all cause mortality with use of heparin. However, only 10% of patients in each group had septic shock and there was no significant difference between the median activated partial thromboplastin time (aPTT) between the treatment and control groups, calling into question the efficacy of the study intervention [53]. A recent meta-analysis of patients with sepsis, septic shock, and infection-associated DIC found that treatment with heparin as compared to placebo or usual care may reduce the relative rate of death by 12% [54]. Although the true effect of heparin on outcomes remains unknown, guidelines for the diagnosis and management of DIC recommend therapeutic doses of heparin in cases of DIC where thrombosis predominates (including PF) [55]. A recent review of ischemic limb gangrene with pulses also endorsed the use heparin in patients with PF [2]. It is important to note that prolonged baseline coagulation assay results in these patients is not a contraindication to heparin therapy, since these derangements are a marker of thrombosis, not bleeding tendency. Furthermore, the overwhelming inflammation present in PF can render these patients relatively resistant to heparin therapy due to circulating acute phase proteins that bind and inactivate heparin, e.g. vitronectin [56]. Therefore, heparin levels must be monitored closely with the anti-Xa assay and aggressive dose increases used in the event of sub-therapeutic results.

Plasma Exchange in Sepsis with Multiple Organ Dysfunction

Multi-organ system failure that persists beyond the initial trigger in sepsis is responsible for significant morbidity and mortality. Many studies and therapies have been designed to target ongoing cytokine release and activation of the complement system to improve outcomes in these patients. While studies of antibodies against cytokines [57–60], immunoglobulins [61], pentoxifyline [62] and high dose steroids [63,64] have been negative, therapeutic plasma exchange (TPE) with fresh frozen plasma replacement fluid or absorption have been supported in some small non-randomized and open randomized studies in patients with severe sepsis (with or without PF) [65–67]. Similarly, a number of case reports of TPE in PF have shown hemodynamic stabilization, improvement in skin lesions, and decreases in IL-6 and tumor necrosis factor- α [68–71]. However, there are no randomized studies of TPE in PF and published studies vary dramatically in inclusion criteria, therapeutic intervention, and outcome. Publication bias is also a significant concern when considering the literature surrounding TPE in sepsis and PF. Therefore, while theoretically this practice may offer a mechanism to rapidly replete protein C, we do not believe there is currently adequate evidence to support its routine use in PF.

Future Directions

A defining aspect of the clinical trials experience with drotrecogin alfa is the decision by investigators to minimize dosing of the study medication due to concern for potential bleeding complications with APC-based therapy. As a result, it remains unclear whether dosing in those trials was sufficient to provide optimal cytoprotective benefit from APC. Future APC-based therapies for sepsis and PF may include agents that harness the cytoprotective properties of APC without an increased risk of hemorrhage. Accordingly, preclinical and early stage clinical trials are ongoing of biased small molecule agonists of the PAR-1 receptor [22] as well as recombinant APC mutants that have minimal anticoagulant effect while retaining the cytoprotective function of the molecule [72].

Conclusions

Infectious PF is a rare but devastating disorder that manifests as a highly thrombotic form of DIC. Dysfunction of the body's natural anticoagulant

Table 3
Studies of protein C concentrate therapy in purpura fulminans

Author	Type of study	# and age of patients (years)	Clinical presentation	Protein C activity (%) unless stated otherwise	Primary Intervention	Concomitant Treatment	Outcome
de Kleijn et al. [73]	Randomized, double-blinded, placebo-controlled, dose study, phase 2	40, 1-18	Presumed meningococcal disease with petechial rash or PF + hypotension or evidence of end organ dysfunction	Median protein C level, placebo 0.15 U/mL, low dose 0.13, mid 0.21, high 0.18, normal range 0.7-1.2 U/mL	Protein C concentrate (low, middle, high dose) vs albumin		9/40 (22.5%) died (no sig difference) 5/40 (12.5%) required amputation (no sig difference) Increase APC in 27/28 treated pts. No adverse reactions to tx Faster normalization of d-dimer, ratio of thrombin: APC 3/36 died 4/33 survivors required amputations
White et al. [74]	Open-label prospective study	36, 3 months - 76	Meningococemia with septic shock and PF	Protein C level mean 18 IU/mL	Protein C concentrate	AT III (2/36) Heparin (26/36) CVVH (19/36) PD (2/36)	9/15 died Median increase in PC act. 21% (range -24 to +68%) Dose of PC supplementation should be at least 250 IU/kg loading dose and 200 IU/kg/day as maintenance therapy. 21/94 (22.3%) died 9/94 (9.6%) required skin graft 5/94 (5.3%) required amputation Non-survivors had lower PC plasma activity Higher PC activity by 1% at admission improved odds to survive by 1.06 (95% CI OR = 1.01 to 1.12, P = .03). 5/12 died 2/12 required amputations Rapid improvement in coagulopathy
Fourrier et al. [34]	Pharmacokinetic study	15, 1-47	Meningococemia and PF	Nonsurvivors 13 ± 14%, survivors 21 ± 3%	Protein C concentrate	AT III (15/15)	2/8 Died PC increased fibrinogen and decreased in d-dimer Surviving patients had no end organ or neurologic complications 0/12 died 2/12 required amputations (2/12), 1/12 chronic renal failure (1/12) PC increased fibrinogen + platelets, decreased d-dimer 1/8 died 2/4 required amputations PC level normalized w/ concomitant increase in fibrinogen, decrease in d-dimer, regression of lesions 0/6 died Normalization of PC activity, coagulopathy, d-dimer, plts Regression of majority of skin lesions
Veldman et al. [8]	Retrospective analysis of safety and outcomes	94, 1 month-18	Patients with PF who received non-activated PC concentrate in Germany from 2002 to 2005 (80% had N meningitidis)	Median 27% (range 1%-75%)	Protein C concentrate		2/8 Died PC increased fibrinogen and decreased in d-dimer Surviving patients had no end organ or neurologic complications 0/12 died 2/12 required amputations (2/12), 1/12 chronic renal failure (1/12) PC increased fibrinogen + platelets, decreased d-dimer 1/8 died 2/4 required amputations PC level normalized w/ concomitant increase in fibrinogen, decrease in d-dimer, regression of lesions 0/6 died Normalization of PC activity, coagulopathy, d-dimer, plts Regression of majority of skin lesions
Rintala et al. (2000) [75]	Case series	12, 17-68	PF and imminent peripheral necrosis	Median 26% (range 15-45%)	Protein C concentrate	AT III (12/12) Hemofiltration (10/12)	2/8 Died PC increased fibrinogen and decreased in d-dimer Surviving patients had no end organ or neurologic complications 0/12 died 2/12 required amputations (2/12), 1/12 chronic renal failure (1/12) PC increased fibrinogen + platelets, decreased d-dimer 1/8 died 2/4 required amputations PC level normalized w/ concomitant increase in fibrinogen, decrease in d-dimer, regression of lesions 0/6 died Normalization of PC activity, coagulopathy, d-dimer, plts Regression of majority of skin lesions
Schellongowski et al. [76]	Case series	8, 17-48	SIRS + skin lesions consistent with PF and/or signs of coagulopathy (plts <100 k, fibrinogen <150%)	Median 29% (range 19-56%)	Protein C concentrate	Heparin (8/8) AT III (3/8) Low dose rtPA (2/8)	2/8 Died PC increased fibrinogen and decreased in d-dimer Surviving patients had no end organ or neurologic complications 0/12 died 2/12 required amputations (2/12), 1/12 chronic renal failure (1/12) PC increased fibrinogen + platelets, decreased d-dimer 1/8 died 2/4 required amputations PC level normalized w/ concomitant increase in fibrinogen, decrease in d-dimer, regression of lesions 0/6 died Normalization of PC activity, coagulopathy, d-dimer, plts Regression of majority of skin lesions
Smith et al. [77]	Case series	12, 3 months - 27	Meningococemia and severe acquired protein C deficiency	Protein C level mean 0.2 IU/ml (range 0.13-0.3 IU/mL)	Protein C concentrate	Heparin (11/12) Hemodialysis (9/12) Peritoneal dialysis (1/12) AT III (4/8)	2/4 required amputations PC level normalized w/ concomitant increase in fibrinogen, decrease in d-dimer, regression of lesions 0/6 died Normalization of PC activity, coagulopathy, d-dimer, plts Regression of majority of skin lesions
Rintala et al. (1998) [78], Rivard et al. [79], Vaccarella et al. [80]	Case reports	8, 3 months - 49	Meningococemia with septic shock and PF	3 patients: 21, 20 and 50% 4 patients level mean 0.18 IU/mL (range <0.01-47, nl 0.7-1.2) mean 23% (range <5% - 33%)	Protein C concentrate	Hemofiltration (3/8) Hydrocortisone (1/8)	2/4 required amputations PC level normalized w/ concomitant increase in fibrinogen, decrease in d-dimer, regression of lesions 0/6 died Normalization of PC activity, coagulopathy, d-dimer, plts Regression of majority of skin lesions
Bachli et al. [81], Belloni et al. [82], Lokeshwar et al. [83], Wcisel et al. [84]	Case reports, Phase IIB open-label prospective study	7, 1-29	Meningococemia with septic shock and PF	mean 23% (range <5% - 33%)	Activated protein C	Heparin (2/4) CVVH (2/4)	0/6 died Normalization of PC activity, coagulopathy, d-dimer, plts Regression of majority of skin lesions
Lokeshwar et al. [83], Minhas et al. [85]	Case reports	2, 5 months +33	<i>Streptococcus pneumoniae</i> bacteremia and PF	29%, not recorded	Activated protein C	Hydrocortisone 50 mg q8hrs	0/2 died Resolution of skin findings Normalization of coagulation parameters Bilateral lower extremity graft w/ amputation of R toes On hospital day 3, pt. had decreasing d-dimer, normalization of PC, regression of skin lesions
Gerson et al. [86]	Case report	1, 13	Varicella and strep bacteremia with PF and cardiac arrest	0%	Protein C concentrate	Hemodialysis Heparin (bolus + gtt) IVIG	0/2 died Resolution of skin findings Normalization of coagulation parameters Bilateral lower extremity graft w/ amputation of R toes On hospital day 3, pt. had decreasing d-dimer, normalization of PC, regression of skin lesions

AT III = antithrombin III, rtPA = recombinant tissue plasminogen activator, IVIG = intravenous immunoglobulin, SIRS = systemic inflammatory response syndrome, plts = platelets, PC = protein C, PF = purpura fulminans, PD = peritoneal dialysis.

pathways likely plays a key role in the pathophysiology of PF but explains only part of the disease process. Despite advances in our understanding of the mechanisms underlying PF, clinical judgment is essential in identifying patients with this condition and prescribing treatment. Therapeutic options remain limited. Current treatment is focused on therapeutic anticoagulation and the prompt repletion of circulating antithrombotic proteins, while future therapies may harness the cytoprotective effects of the PC pathway in addition to current standard of care.

Conflict of Interest

None declared.

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