Symmetrical peripheral gangrene in critical illness

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ABSTRACT
Symmetrical peripheral gangrene (SPG) is a disabling complication that affects a small proportion of patients who survive critical illness. Its pathogenesis reflects profoundly disturbed procoagulant-anticoagulant balance in susceptible tissue beds secondary to circulatory shock (cardiogenic, septic). There is a characteristic SPG triad: (a) shock (hypotension, lactic acidemia, normoblastemia, multiple organ dysfunction), (b) disseminated intravascular coagulation (DIC), and (c) natural anticoagulant depletion (protein C, antithrombin). In recent years, risk factors for natural anticoagulant depletion have been identified, most notably acute ischemic hepatitis (“shock liver”), which is seen in at least 90% of patients who develop SPG. Moreover, there is a characteristic time interval (2–5 days, median 3 days) between the onset of shock/shock liver and the beginning of ischemic injury secondary to peripheral microthrombosis (“limb ischemia with pulses”), reflecting the time required to develop severe depletion in hepatically-synthesized natural anticoagulants. Other risk factors for natural anticoagulant depletion include chronic liver disease (e.g., cirrhosis) and, possibly, transfusion of colloids (albumin, high-dose immunoglobulin) lacking coagulation factors. A causal role for vasopressor therapy is unproven and is unlikely; this is because critically ill patients who develop SPG do so usually after at least 36–48 hours of vasopressor therapy, implicating a time-dependent pathophysiological mechanism. The most plausible explanation is a progressive time-dependent decline in key natural anticoagulant factors, reflecting ongoing DIC (“consumption”), proximate liver disease whether acute or chronic (“impaired production”), and colloid administration (“hemodilution”). Given these evolving concepts of pathogenesis, a rationale approach to prevention/treatment of SPG can be developed.

1. Introduction
Tissue necrosis involving acral (distal) extremities is an infrequent complication of critical illness, yet one that represents an important cause of significant and permanent morbidity in affected patients who survive their intensive care unit (ICU) stay. This is particularly the case in those patients who sustain major tissue losses involving multiple limbs, e.g., bilateral lower-extremity amputations with or without loss of fingers on both hands. When necrosis is predominantly acral and bilateral, the term “symmetrical peripheral gangrene” (SPG) is often applied; when non-acral necrosis is also present, “purpura fulminans” (PF) is used to describe the clinical picture [1]. Our review will focus on the topic of SPG, as this entity is more frequently encountered in ICU patients than PF; however, both entities have considerable clinical and pathophysiological overlap.

This narrative review is aimed at summarizing current concepts in the pathogenesis of SPG, emphasizing the role of profoundly disturbed procoagulant-anticoagulant balance in patients with poor peripheral limb perfusion in the setting of hemodynamic (circulatory) shock. Moreover, we will discuss emerging issues in recognizing and potentially correcting severe depletion in natural anticoagulants, including the (theoretical) role of therapeutic plasma exchange (hereafter called “plasma exchange”). Our review addresses SPG from the emerging thesis that three features are generally observed in these patients: (a)
circulatory shock; (b) disseminated intravascular coagulation (DIC), and (c) profound natural anticoagulant depletion [1,2]. Although one or more of these factors is commonly seen in critically ill patients, it is the less common concurrence of all three factors, i.e., the “perfect storm” scenario, in which these three elements occur contemporaneously, and of a sufficiently severe degree, that ischemic limb injury occurs.

2. Illustrative case: two distinct phases of ischemic necrosis

Fig. 1 presents an illustrative case that highlights perplexing features of DIC-associated ischemic limb injury. This patient has two distinct episodes of DIC, the first relating to bacterial sepsis (retained placental products), and the second to post-cardiac surgery shock (cardiac tamponade). The first manifestation of ischemic limb injury consisted of three large areas of non-acral skin necrosis involving bilateral thighs and the right calf. In contrast, the second episode of ischemic limb injury presented as the more conventional picture of SPG (the focus of this paper). Moreover, the episode of SPG included the three characteristic features addressed in this paper, namely (a) circulatory shock; (b) DIC; and (c) natural anticoagulant depletion associated with proximate acute ischemic hepatitis (“shock liver”). Whereas this review addresses the concepts relating to the patient’s second episode of DIC, the pathophysiological basis for non-acral skin necrosis complicating the first DIC episode remains unexplained.

3. Historical perspectives

3.1. Symmetric peripheral gangrene and purpura fulminans

The first mention of “symmetrical gangrene of the extremities” is attributed to Hutchinson [3], a British surgeon who presented to his lecture audience a 37-year-old man with missing extreme tips of toes, borders of both ears, and mummified fingertips. The lecturer noted the remarkable symmetry of the lesions, and the patient’s recovery from an
unidentified prodromal illness (“an acute and unexpected illness ... confining him to bed for twenty weeks”).

The term “symmetric peripheral gangrene” was used in 1938 when Fishberg [4] noted two patients who developed this complication in the setting of “cardiac failure” which the author regarded as being “angio-spastic in origin.” No clinical details were provided. However, the next year, Perry and Davie [5]—citing Fishberg—revised the term “symmetrical peripheral gangrene” when they described a 64-year-old man who developed sharply demarcated limb gangrene involving distal legs/feet, without large artery occlusion, in the setting of terminal cardiac failure (presumed cardiogenic shock). Of note, post-mortem examination showed “cardiac cirrhosis”, an observation that has proven prescient given recent evidence implicating a high frequency of severe hepatic dysfunction, either acute or chronic, in helping to explain the majority of cases of SPG. Abrahams [6] reported a case of SPG complicating protracted fatal ventricular tachycardia, and Swan and Henderson [7] described two patients who developed SPG as a complication of myocardial infarction. The usual fatal outcomes in these cases suggest underlying cardiogenic shock. Although subsequent literature has emphasized sepsis as a common clinical setting for SPG, the early observations that SPG can complicate severe cardiac failure is noteworthy given the experience of one of the authors (T.E.W.), working in a cardiac surgery center, that cardiogenic shock is seen in at least 50% of patients with SPG [8].

The term “purpura fulminans” is even older, as Guelliot used the term “purpura infectieux foudroyant” (translated either as “overwhelming” or “fulminating” infectious purpura) [9]. Moreover, the term PF appears to be used in the context of complications of infection, especially acute septic (distributive) shock. There are two other much rarer forms of PF—post-infectious PF (often occurring after recovery from scarlet fever or varicella infection, and resulting from acquired autoimmune clearance of a natural anticoagulant protein, most often protein S) [10-12] and neonatal PF (occurring within days of birth, most often resulting from severe congenital deficiency of a natural anticoagulant protein, most often protein C) [13,14]; these two entities will not be discussed further in this review.

3.2. Shock and disseminated intravascular coagulation

The term “disseminated intravascular coagulation” (DIC) appears to have been used first by Schneider [15] in 1951 when describing three patients with fibrinogen depletion and “fibrin embolism” complicating placental abortion. The term gained increasing use during that same decade [16-18] with the growing recognition that various animal models of shock and sepsis resulted in reproducible situations of intravascular coagulation, as summarized by Hardaway in 1961 [19] when reporting on his investigations of this topic:

“Beginning in 1953, shock of several different origins was investigated, as summarised in the present paper, with emphasis being placed on the changes in the blood coagulation mechanism and evidence for an episode of blood coagulation. Evidence has been listed to indicate that the injection of incompatible blood, amniotic fluid, thrombin and endotoxin all not only cause shock but alter the coagulation mechanism in essentially the same manner, i.e., decrease in fibrinogen and prothrombin and activation of endogenous heparin and fibrinolysin. Pathologic changes, both gross and microscopic, were essentially similar. Micropic thrombi or capillary plagues were found in all cases. That these changes are not dependent on the injection of foreign substances into the blood stream is shown by the fact that similar changes are found in hemorrhagic shock.” [19].

Hardaway himself, along with his frequent coauthor, McKay, helped popularize the term “disseminated intravascular coagulation”, including use of the term in the title of two books, the first authored by McKay [20] (with a review by Ratnoff opining this book represented the “first time anyone has tried to assemble information about these important processes” [21]), and the second book by Hardaway [22], both books over 460 pages.

It became increasingly apparent that the pathophysiological consequences of animal models of shock and sepsis were also seen in critically ill humans who developed activation of hemostasis, characteristic laboratory abnormalities, and risk of intravascular thrombosis as well as bleeding as a consequence of “consumption” of platelets and hemostatic factors. Corrigan in 1968 summarized the laboratory changes seen in patients with sepsis [23]. Some representative reports of patients who developed SPG in the setting of what was now known as “DIC” include, for instance, a case by Stossel and Levy [24] when they described a patient who developed SPG during post-splenectomy sepsis, with DIC diagnosed by thrombocytopenia, elevated serum fibrin-split products, and fibrin microthrombi (skin biopsy); and by Chaudhuri and McKenzie [25], who described a child with infection-associated digital necrosis with underlying DIC indicated by severe thrombocytopenia. These latter authors concluded their paper with these words: “Disseminated intravascular coagulation or consumption coagulopathy, a relatively new terminology, is well documented in relation to virus diseases.”

3.3. Generalized Shwartzman reaction and microthrombosis

Gregory Shwartzman, a medical biologist working at Mount Sinai Hospital in New York City, reported in 1928 [26] the consequences of appropriately timed injections (first, intradermal; second, intravenous; 24-hr interval) of sterile culture filtrates from gram-negative bacteria into normal rabbits, which reproducibly resulted in a dermal reaction at the initial intradermal injection site (“localized Shwartzman reaction”) (for review [27,28]). These studies resembled those reported four years earlier by Sanarelli [29], who reported consequences of two sequential intravenous injections of bacterial culture filtrate (containing endotoxin), which resulted in characteristic systemic coagulopathic consequences that included multiple foci of microvascular thrombosis. Subsequent systematic studies were performed by Apitz [30], who gave two intravenous injections of E. coli culture filtrate (24 h interval), performing detailed histopathologic studies to show fibrin thrombus formation in numerous organ beds, especially bilateral renal cortical necrosis. Apitz termed this phenomenon the “generalized Shwartzman reaction”, a term that gained wide acceptance. As expressed by Robbins and Angell [31]: “disseminated intravascular coagulation is the human equivalent of the experimentally produced generalized Shwartzman reaction.” An SPG case reflecting this viewpoint was reported by Rappaport and colleagues [32]: the SPG complicated Pseudomonas septicaemia, with laboratory evidence of DIC (severe thrombocytopenia, abnormal global coagulation tests with reduced fibrinogen and coagulation factors) and post-mortem evidence of multiple microvascular thrombi including prominently within the glomeruli.

The modern concept of the generalized Shwartzman phenomenon is that it reflects the innate immune response. The sublethal first (“preparatory”) injection of endotoxin primes the immune response, with the second (“provocative”) endotoxin injection triggering the lethal systemic reaction. Interestingly, McKay and Shapiro showed over 60 years ago [33] that the first injection of toxin triggers an abrupt elevation in plasma fibrinogen levels, with the second injection leading to dramatic decrease in fibrinogen. This finding parallels the observation that only a single injection of endotoxin can cause lethality in pregnant rabbits (with high baseline fibrinogen levels). These intriguing findings have relevance to observations discussed later in this review of “high fibrinogen DIC” in which patients with prodromal illness (leading to hyperfibrinogenemia) can develop devastating multi-locm ischemic necrosis if the illness evolves into overt, decompensated DIC. Another implication of the studies of the Shwartzman phenomenon relates to studies of heparin anticoagulation; appropriately-timed heparin (prior to the second, provocative reaction) can reduce lethality [34].

The key role of DIC as the explanation for SPG is based on pathologic studies showing noninflammatory fibrinous deposits within small
vessels (fibrin microthrombi) [35]. It was in the early 1970s that this nexus between systemic hypercoagulability (i.e., DIC) and SPG became clear, as the foundational histopathology studies by Robboy et al. [36, 37] identified thrombosis within capillaries and venules (“small vessels of the skin”) in patients who had developed one or more of “purpura, purpura fulminans, gangrene, acrocyanosis, [and] hemorrhagic bullae.”

3.4. Emerging consensus regarding SPG pathogenesis: shock and DIC

In 1985, Molos and Hall [38] reported 3 cases of SPG complicating sepsis, and reviewed 68 previously reported patients in the English language literature. These authors identified DIC as “the most common underlying condition” associated with SPG, occurring in at least 90% of patients, with sepsis the most common underlying disorder, and with cardiac disorders explaining most of the remaining cases.

Knight and colleagues [39] performed another review of SPG in 2000. Their review noted that the two most common features are (a) sepsis and/or a low-flow state, and (b) the presence of DIC. They also considered SPG from the viewpoint of emerging literature implicating vasopressors, but were skeptical about a causal role of vasopressors in patients with septic shock, stating “vasopressor therapy may or may not be an aggravating factor in septic patients.” Their summary of the clinical problem provides a perspective on SPG at the beginning of the millennium:

Symmetrical peripheral gangrene is defined as symmetrical distal ischemic damage in two or more sites in the absence of major vascular occlusive disease. It occurs in patients who are septic and have disseminated intravascular coagulation and in nonseptic patients who have cardiogenic or hypovolemic shock. The syndrome is devastating and rare, and controlled studies of its etiology and management are lacking. [39]

Although Knight et al. did not overtly implicate DIC in non-septic patients with shock, it is our experience that patients who develop SPG in the setting of cardiogenic shock do indeed evince overt DIC [8, 40].

3.5. Natural anticoagulant depletion—The third entity of the trio

The review by Knight and colleagues speculated that there must be an unknown explanation, or explanations, for the vascular occlusions that occur in the low-flow state. The authors list “vasospasm”, “pre-existing pathology in the microcirculation”, “sludging of platelet or fibrin degradation products”, and “immunologic or molecular events not yet defined.” The last entity leads to the present time, with current emphasis on “immunothrombosis” as well as depletion of key molecular players, namely the proteins of the natural anticoagulant system. The scope of our review does not include the broad topic of “immunothrombosis”, as coined by Engelmann and Massberg [41] to indicate the role of the immune system—particularly, platelets, neutrophils, monocytes, and their respective prothrombotic host responses, such as formation of procoagulant platelet-derived microparticles [42], neutrophil extracellular traps (netosis) [43], and monocyte tissue factor expression [44]—in forming thrombi within blood vessels as part of an innate antimicrobial response. Indeed, as discussed in the remainder of this review, natural anticoagulant depletion is the third entity that together with the two other factors (shock, DIC) accounts for SPG pathogenesis.

3.6. Natural anticoagulant depletion in meningococccemia and Waterhouse-Friderichsen syndrome

Meningococcemia is a prominent trigger of SPG and PF, as meningococcal lipopolysaccharide is unusually potent in activating hemostasis, fibrinolysis, complement, kinin, and cytokine networks [45,46]. Tissue factor–bearing microparticles contribute to DIC pathogenesis [47]. Severely reduced protein C activity is associated with an increased extent of skin lesions (PF) [48,49]. Although protein C activity levels in meningococcemia were consistently lower than antithrombin activity levels (and antithrombin levels lower than protein S levels), antithrombin activity levels also were lower in patients with PF versus those without skin lesions [49]. Meningococcal sepsis is also associated with endothelial dysfunction, including ADAM-10-dependent cleavage of endothelial protein C receptor (EPCR), resulting in EPCR “shedding” [50,51]. A putative role for endothelial dysfunction in meningococcal sepsis is an important concept, as endothelial dysfunction will not be reversed by replacement of missing circulating coagulation factors. As we discuss later in this review (see section 5.2 Prodomal shock liver), acute liver dysfunction helps account for severe depletion of (hepatically-synthesized) natural anticoagulants in patients who develop SPG/PF; in our experience, meningococccemia patients who develop SPG/PF usually have severe shock liver.

Meningococcemia is also distinguished in the medical literature by its connection with the so-called Waterhouse-Friderichsen syndrome, defined by concurrence of bilateral adrenal hemorrhagic necrosis [52, 53]. However, shock can complicate meningococcal sepsis even in the absence of adrenal necrosis [54]. Although adrenal hemorrhages can be seen in any severe bacterial infection [55], just like the clinical picture of PF, it is apparent that both Waterhouse-Friderichsen syndrome and PF are more frequently seen in infection by Neisseria meningitidis than with other organisms. Paradoxically, the occurrence of hemorrhage seems to be a consequence of fibrin microthrombin within adrenal sinusoids [56].

3.7. Animal model of protein C and antithrombin knockout

Safdar and colleagues [57], in an animal model evaluating effects of silencing of hepatic antithrombin and protein C production, observed that when both—but not just one—genes were silenced, there resulted an acute coagulopathy featuring fibrin deposition with hind-leg necrosis. The authors concluded that there is synergism between the antithrombin and protein C anticoagulant systems. In our opinion, these findings are consistent with the role for acute or chronic liver dysfunction, resulting in dual anticoagulant depletion, in helping to explain SPG occurrence. It is worth noting here that the half-lives of protein C and antithrombin are quite different (approximately 8 h and 60 h, respectively [58]), and so the observed “delay” in onset of SPG/PF following development of shock and DIC in critically ill patients—usually at least 2 days—supports a key synergistic role for progressive antithrombin depletion, in addition to the more widely appreciated role of acute protein C depletion in such patients.

4. Current state of the art: Textbooks of critical care

We examined whether and how the topic of SPG is covered in critical care textbooks. We reviewed 4 representative books [59–62], with Table 1 summarizing key features. None used the term SPG but rather discussed the issue of limb-threatening necrosis in the context of PF. All 4 specifically mentioned that PF was characterized by “thrombosis”, with two specifically commenting on “microthrombosis.” All 4 books highlighted the frequent association between PF and meningococcemia. None indicated any contributory adverse role of vaspressors in the discussion of PF. Based on our review, it appears that the general critical care literature has not identified SPG per se as a consequence of DIC and natural anticoagulant depletion complicating shock. In contrast, however, when there is additional non-acral skin necrosis (i.e., PF), and especially when there is underlying meningococcal infection, the role of DIC and natural anticoagulant depletion is readily posited. Further, there is no mention of liver dysfunction as playing a crucial pathophysiologic role. Interestingly, two books mentioned plasma exchange as a potential treatment option for PF, which we will discuss in the last section of this review.

In contrast, the recent concepts of SPG pathogenesis are beginning to
Warfarin use has resulted in peripheral limb ischemic necrosis. "Gangrene" depletion is less established, for several reasons. First, natural anticoagulant well-established [38,39], the contributory role of natural anticoagulant depletion is (Table 2). Whereas the roles of circulatory shock and DIC are

5. Current paradigm: shock, DIC, and natural anticoagulant depletion (consumption, acute and chronic liver disease, colloid hemodilution)

The current paradigm of SPG we present focuses on the trio of (a) circulatory shock, (b) DIC, and (c) natural anticoagulant depletion [1,2,8,40] (Table 2). Whereas the roles of circulatory shock and DIC are well-established [38,39], the contributory role of natural anticoagulant depletion is less established, for several reasons. First, natural anticoagulant levels are usually not measured in patients with SPG. Second, the explanations for severe depletion in natural anticoagulants, beyond that of expected “consumption” in an underlying DIC state, have not been well-studied. However, an important role for natural anticoagulant depletion in microthrombosis disorders is suggested by the established role of natural anticoagulant depletion in other mimicking skin necrosis syndromes, in particular, so-called warfarin (coumarin)-induced necrosis syndromes, especially the variant known as “venous limb gangrene” [64-67]. Among the hypercoagulability disorders in which warfarin use has resulted in peripheral limb ischemic necrosis are: heparin-induced thrombocytopenia [68,69], cancer-associated hypercoagulability [70-74], antiphospholipid syndrome [67], infection/sepsis [75,76], cardiac failure/cardiogenic shock [77,78], and post-cardiac surgery DIC [79,80].

### Table 1

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<th>Symmetrical peripheral gangrene (SPG) and purpura fulminans (PF) discussion in critical care textbooks.</th>
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<tr>
<td><strong>SPG term used</strong></td>
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<td><strong>PF term used</strong></td>
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<tr>
<td><strong>Emphasis on meningococcus</strong></td>
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<td><strong>Acral limb necrosis</strong></td>
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<td><strong>Microvascular thrombosis pathogenesis</strong></td>
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<td><strong>Vasooppressors mentioned in PF pathogenesis?</strong></td>
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<td><strong>DIC pathogenesis</strong></td>
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<td><strong>Natural anticoagulant depletion</strong></td>
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<td><strong>Liver dysfunction role in natural anticoagulant depletion?</strong></td>
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<td><strong>Treatment options listed for PF</strong></td>
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<td><strong>Other comments</strong></td>
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<td><strong>Limb gangrene secondary to vasooppressors?</strong></td>
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Abbr.: DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; PF, purpura fulminans; SPG, symmetrical peripheral gangrene; tPA, tissue-plasminogen activator.

* Stated that PF occurs in 3% of meningococcal infections.

1 It was not clearly stated that losses of acral portions of extremities occurs.

3 Treatment option of replacing protein C concentrates and antithrombin concentrates indicated "if deficient".

4 "[Intense systemic vasoconstriction with organ dysfunction" [norepinephrine]; “can promote splanchnic and digital ischemia” (vasopressin)).

be recognized in the hemostasis and thrombosis literature. For example, in the fourth (2019) edition of Consultative Hemostasis and Thrombosis (Eds, Kitchens et al.), risk factors listed for “severe and/or progressive depletion of protein C” in the setting of DIC and its sequelae (“purpura fulminans”, “acral cyanosis with palpable pulses”) include: “acute hepatic failure ("shock liver") and “chronic severe liver failure” [63].

### Table 2

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<th>Clinical and laboratory features of symmetrical peripheral gangrene.</th>
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<td><strong>Three elements in SPG</strong></td>
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<td>Hemodynamic (circular) &quot;shock&quot;, most often cardiogenic and/or septic (distributive)</td>
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<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
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<tr>
<td>Natural anticoagulant depletion (usually profound)</td>
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</table>

Abbr.: PF, purpura fulminans; PT, prothrombin time; PTT, partial thromboplastin time; SPG, symmetrical peripheral gangrene.

* Although in our experience most patients with SPG have nadir antithrombin and protein C activity levels less than 40% and 20%, respectively, we have observed some exceptions.
5.1. Natural anticoagulant depletion and disturbed procoagulant-anticoagulant balance in warfarin-induced necrosis syndromes

There are two distinct, although overlapping, warfarin-induced microthrombosis syndromes: (a) “classic” warfarin-induced skin necrosis, and (b) warfarin-induced venous limb gangrene [64-66]. Whereas the former (“classic”) syndrome usually involves predominantly non-accrual tissue sites and is frequently associated with hereditary abnormalities in the protein C natural anticoagulant pathways (protein C deficiency [81–84], protein S deficiency [85,86], factor V Leiden [87,88], prothrombin gene mutation [89]), the latter disorder (“venous limb gangrene”) usually features a severe underlying DIC state such as HIT or metastatic adenocarcinoma [64,68-74]. A common misconception is that the microthrombosis reflects severe failure of the natural anticoagulant system per se; however, the key concept is that there is profoundly disturbed procoagulant-anticoagulant balance, as the depletion in vitamin K-dependent anticoagulants results in failure to control the greatly increased thrombin generation reflecting the underlying DIC state [64,68-71]. Indeed, protein C activity levels in patients with cancer-associated venous limb gangrene are actually higher than in bleeding patients with warfarin overdoses who have supratherapeutic INR values requiring urgent correction; the key difference is that markers of thrombin generation (e.g., thrombin-antithrombin complexes) are much higher in the patients with venous gangrene (reflecting DIC state), but essentially normal with warfarin overdoses [71]. Thus, the key is inadequate protein C (and, sometimes, protein S) to control the DIC state.

As we proposed elsewhere [2], warfarin-induced venous limb gangrene has several parallels with SPG (Table 3). Both occur in the setting of markedly increased thrombin generation. But, most crucially, it was the characteristic temporal profile of warfarin-induced venous limb gangrene, namely the onset of ischemic necrosis 2–5 days after starting warfarin, and the known role of a time-dependent decrease in heptatically-synthesized natural anticoagulants contributed to the pathogenesis of SPG (discussed subsequently).

5.2. Prodromal shock liver

In 2012, a case of SPG complicating postoperative cardiogenic shock was reported [58]. A notable feature was occurrence of shock liver that began 3 days before onset of SPG. (In the paper, we used the term “acute hepatic necrosis” rather than “acute ischemic hepatitis” or “shock liver”, although these terms can be considered synonymous in this clinical context.) It was proposed that time-dependent decrease in heptatically-synthesized natural anticoagulants contributed to the patient’s profoundly disturbed procoagulant-anticoagulant balance, including 100× to 200× increase in fibrin monomers, fibrin D-dimers, and thrombin-antithrombin complexes; marked reduction in natural anticoagulants protein C activity (~1%) and antithrombin activity (~20%).

To support this view, we measured 13 procoagulant and anticoagulant factors, and showed that the levels corresponded closely to the factor half-lives.

Prodromal shock liver is a very common finding in patients with SPG. In 2015, we reported aggregate data for 15 patients who developed SPG during critical illness [8]. All 15 patients had elevated liver enzymes (transaminases), with 14 (93%) of the 15 patients having a peak alanine aminotransferase level at least 10× the upper-limit of normal. Moreover, a characteristic temporal relationship was apparent: onset of limb ischemic necrosis began 2–5 days (median, 3 days) after onset of acute ischemic hepatitis. Fig. 2 summarizes the typical clinical, laboratory, and temporal clinical picture of patients who develop SPG in the setting of critical illness. Since the recognition of a role of proximate shock liver in helping to explain subsequent SPG [1,2,8,40], recent SPG papers by others [90,91] have commented on the occurrence of prodromal shock liver.

5.3. Chronic liver disease

There is a wide perception that chronic liver disease results in an acquired hemorrhagic disorder. However, as pointed out by Tripodi and Mannucci [92], chronic liver disease can also result in a prothrombotic diathesis in some settings. One such situation is acute DIC of critical illness. An example is a reported case of SPG complicating Klebsiella pneumoniae [93]. The noteworthy feature is that this patient had only a minor degree of acute transaminitis, but rather had chronic liver disease secondary to alcohol consumption. This patient developed severe depletion of natural anticoagulants (antithrombin, 24%; protein C, 20%) in the setting of severe DIC despite not meeting conventional criteria for shock liver. Interestingly, in a previous study reviewing 20 individual case reports of SPG [94], 4 (20%) were noted to have “cirrhosis” [95–98]. As mentioned earlier, one of the earliest cases of SPG (reported in 1939) occurred in a patient who at autopsy had “cardiac cirrhosis” [5].

5.4. Colloid transfusion

In theory, any treatment that contributes to reduction in natural anticoagulant levels could—in a susceptible patient—result in greater risk for triggering or exacerbating SPG. Recently, we reported on two patients who developed SPG in the setting of septic shock in whom there was no major role for proximate shock liver (Fig. 3) [99]. However, both patients received large amounts of colloid transfusion prior to development of SPG (patient 1, 6 units of albumin and 700 mL of high-dose intravenous immunoglobulin; patient 2, 3 units of albumin). Both patients had severely reduced levels of 3 natural anticoagulants (protein C, protein S, antithrombin), and we proposed a significant role for the colloid transfusions in predisposing to SPG pathogenesis in these particular cases. These observations also have implications for the type of replacement fluid in patients with critical illness who undergo plasma exchange (see section, 6. Treatment Implications).
5.5. Genetic predispositions

A case–control study showed that surviving 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% [14/233] to 21% [5/24]) in the risk of tissue necrosis associated with PF [100]. In theory, factor V Leiden could be a risk factor for SPG in critical illness, although to our knowledge this has neither been reported nor investigated.

5.6. Vasopressors

Arguments against vasopressor therapy playing a key causal role in SPG pathogenesis have been previously published [94]. One key point to emphasize here is summarized in Fig. 2—which highlights the characteristic 2–5 day gap in time between onset of circulatory shock (and initiation of vasopressor therapy) and onset of SPG. This argues for a time-dependent pathophysiological factor, most notably, progressive decrease in natural anticoagulant levels (e.g., exacerbated by proximate shock liver). If vasopressors caused SPG, one might expect limb ischemia to begin within just a few hours after their initiation, rather than beginning at least 36–48 hours later. This characteristic gap in time between onset of shock and initiation of vasopressors, and subsequent onset of SPG, which we have noted repeatedly in cases of SPG and PF, have analyzed [1, 2, 58, 99], has been observed also by others [101]. Skepticism regarding a causal vasopressor role is shared by other experts—factor V Leiden could be a risk factor for SPG in critical illness, although to our knowledge this has neither been reported nor investigated.

5.7. Other considerations

The three key elements involved in SPG pathogenesis—shock, DIC, natural anticoagulant depletion—are becoming clearer. Moreover, risk factors for natural anticoagulant depletion (acute and/or chronic hepatic dysfunction, colloid hemodilution) are becoming recognized. However, there likely are other poorly understood pathophysiological considerations, including for example the temporal interrelationships among these various pathophysiological factors. For example, we and others [103] have noted that following an initial period of shock, that SPG may be temporarily associated with a subsequent second episode (or exacerbation) of shock. For example, Fig. 4 illustrates a recent case of SPG recognized in our hospital. This case features the key trio of shock (cardiogenic, lactic acidemia, normoblastemia), DIC, and natural anticoagulant depletion (risk factors: shock liver, albumin transusions). The figure also depicts an asterisk (*) indicating a time when there was a secondary increase in lactate levels, as well as a further decline in platelet counts, corresponding to SPG onset. In our experience, many patients who develop SPG have such a secondary period of worsening of shock and/or DIC parameters. The overall concept is not unlike the “Shwartzman phenomenon”, the animal model where two appropriately timed injections of endotoxin trigger a syndrome of widespread microvascular thrombosis. In an analogous fashion, an initial trigger of shock, inflammation, and DIC (e.g., through rapid lipopolysaccharide-induced monocyte tissue factor expression [44], among other mediators) may help set the stage for subsequent SPG when a second period of hemostasis activation occurs 1–2 days later (per the Shwartzman phenomenon, a time interval of 24–48 hours between endotoxin injections is optimal in resulting in subsequent microthrombosis).

6. Treatment implications

The treatment of incipient SPG remains uncertain. Although certain treatments might seem beneficial in theory (e.g., antithrombin and/or protein C concentrates, heparin anticoagulation, frozen plasma transfusion), important practical and logistical problems exist. These include: lack of timely availability (factor concentrates), difficulties in achieving effective heparin anticoagulation (bleeding risk with heparin in profoundly thrombocytopenic and coagulopathic patients, misleading partial thromboplastin time (PTT) values, i.e., “PTT confounding” [104]), difficulties in volume administration (e.g., frozen plasma administration in oligo-anuric renal failure), or even pathophysiologial drawbacks (e.g., endothelial shedding of EPCR and thrombomodulin could obviate any benefits of protein C concentrates, as thiszymogen requires endotheial activation). Further, once the “perfect storm” conditions of evolving microthrombosis are present, irreversible multi-site microvascular thrombosis may occur quickly, and so it may be too late to intervene with therapeutic benefit. Accordingly, treatment approaches might be better directed to prevention of SPG, i.e., identifying the patient at risk

![Fig. 2. Typical clinical and laboratory picture of SPG.](image-url)
for this disorder (e.g., DIC, shock, acute or chronic liver dysfunction), and instituting therapies even when there is no clinical evidence of limb ischemia (Table 4) [105].

Two of the textbooks of critical care we reviewed listed plasma exchange as potential treatment for PF. Rationales include removal of toxins (e.g. endotoxin, harmful proinflammatory cytokines), and replacement of deficient coagulation factors. Rimmer and colleagues [106] reported on a systematic review and meta-analysis of plasma exchange for management of sepsis and septic shock. They identified only 4 relevant trials, studying total of 194 patients, for review. They found no difference in the primary endpoint, mortality (RR = 0.83; 95% CI, 0.45–1.52). Indeed, use of plasma exchange for the indication of

Fig. 3. SPG in two patients following colloid transfusions.

Panel A shows clinical and laboratory data for Patient 1, a 45-year-old woman who was admitted to the hospital with culture-negative septicemia and acute kidney injury. She met criteria for DIC with severe thrombocytopenia and coagulopathy (peak international normalized ratio [INR], 1.7; fibrin d-dimer, >20 mg/L). She had a minimally elevated level of alanine aminotransferase (peak, 69 U/mL). Soon after the onset of ischemic limb injury involving both hands and both feet, she had documented severe depletion of three natural anticoagulants (shown in red; reference ranges: antithrombin, 77–125%; protein S, 62–144%; and protein C, 70–180%). Ischemic limb injury occurred shortly after she had received 700 mL of high-dose intravenous immune globulin; she had also received 6 albumin infusions during the 36 h preceding the onset of limb injury. She ultimately recovered from the septicemia but underwent partial amputation of the thumb and three fingers of her right hand.

Panel B shows the data for Patient 2, a 38-year-old woman who was admitted to the hospital with influenza B–associated pneumonia that progressed to hemodynamic shock and respiratory and renal failure. She also met criteria for DIC with severe thrombocytopenia (peak INR, 2.4; fibrinogen, 13 mg/L). She had minimal elevation in the alanine aminotransferase level (peak, 44 U/mL). Soon after onset of ischemic limb injury, she had documented severe depletion of three natural anticoagulants (shown in red; reference values as indicated for Panel A). Ischemic limb injury involving both feet occurred after she had received three infusions of albumin during the 16 h preceding the onset of limb injury. She had multiple areas of toe necrosis at time of her death on day 21 after admission. NSQ denotes not sufficient quantity, SC BID subcutaneously twice daily, and UFH unfractionated heparin.

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Fig. 4. Ischemic limb necrosis complicating DIC: role of second episode of shock/lactic acidemia.

An elderly male with widely metastatic Merkel cell tumor receiving palliative treatment with a programmed death ligand-1 (PD-L1) inhibitor, avelumab, was admitted with right arm and leg weakness secondary to cervical spine metastases. There was a history of rheumatoid arthritis, giant cell arteritis, polymyalgia rheumatica, and of coronary artery disease with congestive heart failure (left ventricular ejection fraction, 30%). He underwent cervical spine decompression surgery that was complicated by lactic acidemia and hypofibrinogenemic DIC with bleeding requiring blood product replacement. On hospital day 9 the patient developed a recurrent episode of shock (see asterisk [*]) with elevated lactate level (2.6 mmol/L) and exacerbation of coagulopathy and thrombocytopenia. Progression to SPG coincided with this period of DIC exacerbation, in the setting of other risk factors (proximate shock liver, lactic acidemia, normoblastemia, albumin transfusion, and documented depletion of natural anticoagulants (protein C activity nadir, 0.29 U/mL [reference range, 0.70–1.80]; antithrombin activity nadir, 0.52 U/mL [reference range, 0.77–1.25]; however, free protein S levels were normal, nadir 0.91 U/mL [reference range, 0.78–1.61]).

Abbr.: ALT, alanine aminotransferase; AT3, antithrombin; Fbg, fibrinogen; FP, frozen plasma; HIT Abs, heparin-induced thrombocytopenia antibodies; INR, international normalized ratio; PC, protein C; Plt tnf, platelet transfusion; RBCs, red blood cells; RCC, red cell concentrate; RR, reference range; SPG, symmetrical peripheral gangrene; U, units.
None of these therapies should be considered proven or established for prevention of SPG, especially given the profound extent of shock, organ dysfunction, and disturbed procoagulant-anticoagulant balance in patients who develop SPG.

“sepsis with multiorgan failure” is classified as category III (“Optimum role of apheresis therapy is not established. Decision making should be individualized”) [107], based upon level of evidence classified as grade IIb (“weak recommendation, moderate-quality evidence”, in recognition of “RCTs with important limitations”). In our view, in theory, if future studies of plasma exchange for sepsis were to be designed, it would make sense to perform these in patients at risk for SPG, e.g., patients with ongoing hemodynamic shock, DIC, and risk factors for natural anticoagulant depletion (such as shock liver), and to institute plasma exchange within 48 h of onset of shock liver; moreover, the replacement fluid should be frozen plasma rather than albumin, to avoid worsening natural anticoagulant depletion. Moreover, SPG occurrence should be a clinically-relevant end point evaluated in such studies. Although SPG occurrence is too infrequent a complication to merit assessment as a secondary end point, it should be included as an important outcome measure to ascertain a primary end point in such trials, it should be included as an important secondary end point.

### Declaration of Competing Interest

Theodore E. Warkentin has received lecture honoraria from Alexion and Instrumentation Laboratory and royalties from Informa (Taylor & Francis); has provided consulting services to Aspen Global, Bayer, CSL Behring, Ergomed, and Octapharma; has received research funding from Instrumentation Laboratory; and has provided expert witness testimony relating to hirudin-induced thrombocytopenia (HIT) and non-HIT thrombocytopenic and coagulopathic disorders.

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The authors recently became aware of a study (Lerolle et al. 2013) providing evidence for significantly lower plasma levels of natural anticoagulants (protein C, protein S, antithrombin) in patients who developed purpura fulminans complicating sepsis versus two sepsis control groups (matched for age and sex) who did not develop purpura fulminans (control group #1: similar severity of organ dysfunction; control group #2: presence of overt DIC per International Society on Thrombosis and Haemostasis [ISTH] criteria). Lerrole N, Carlotti A, Melican K, et al. Assessment of the interplay between blood and skin vascular abnormalities in adult purpura fulminans. Am J Respir Crit Care Med 2013;188(6):684-692.

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