Review Article

BURN-INDUCED COAGULOPATHIES: A COMPREHENSIVE REVIEW

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ABSTRACT—Burn-induced coagulopathy is not well understood, and consensus on diagnosis, prevention, and treatments
are lacking. In this review, literature on burn-induced (and associated) coagulopathy is presented along with the current
understanding of the effects of burn injury on the interactions among coagulation, fibrinolysis, and inflammation in the acute
resuscitative phase and reconstructive phase of care. The role of conventional tests of coagulopathy and functional assays
like thromboelastography or thromboelastometry will also be discussed. Finally, reported methods for the prevention and
treatment of complications related to burn-induced coagulopathy will be reviewed.

KEYWORDS—Clot dysfunction, coagulopathy, hemostasis, thermal injury, thrombosis

The development of coagulopathy, (i.e., dysfunctional hemostasis resulting in either hemorrhagic or thrombotic events) after burn injury complicates the already intricate level of care required for this patient population. An experienced multidisciplinary team is essential to meet the needs of a severely-burned individual. The typical course of a patient who has survived a critical thermal injury is represented in Figure 1. The dynamic process of recovery is highlighted as patients transition from aggressive interventions immediately after injury and in the phase of acute burn shock to the period of chronic recovery that begins during hospitalization and continues after discharge.

At each of these phases, internal and external forces impact coagulation homeostasis. The inflammatory mechanism initiated by the injury itself has profound effects that impact clot formation and can lead to burn induced coagulopathy (BIC). During transport and initial hospital care, patients are subjected to lifesaving measures including large volume resuscitation and surgical interventions that further influence coagulation. After stabilization, hemostasis is altered by care that may include blood product transfusion, extensive excision and grafting, and other surgical interventions.

The coagulation status of patients who survive the acute phase is impacted during recovery by a battery of forces. The development of infection or sepsis remains a leading cause of

mortality for severely-burned patients, and the physiologic stress of this event can precipitate coagulopathy. After discharge, patients may encounter events that could trigger coagulopathy, such as incomplete wound healing, surgical reconstructions, and impaired mobility.

Underlying these external forces, patient-specific characteristics must be continually recognized. Age, gender, race, pre-existing conditions, and concomitant injuries may play a role in the physiologic response to thermal injury, and must be considered when treating BIC.

In the past few decades, impressive advances have been made in the understanding of coagulopathy following blunt and penetrating trauma resulting in promising clinical interventions to diagnose, prevent, and treat trauma induced coagulopathy (TIC) (1–5). While the extent of research in the burn population has lagged in comparison with other types of trauma, a growing body of knowledge elucidates many unique characteristics of BIC.

In this review, we examine the history of BIC research, and discuss the current understanding of potential biochemical mechanisms underlying BIC in the contexts of the initial response to injury, the acute care provided during large-volume resuscitation, the recovery during a prolonged hospital stay, and long after discharge. The tools that allow clinicians to recognize BIC and initiate clinical interventions are also be discussed. This review will synthesize basic science and clinical studies by connecting the pathophysiologic mechanisms of BIC with clinical manifestations, and identify areas that merit further investigation.

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HISTORY OF BURN-INDUCED COAGULOPATHY RESEARCH

On review of the literature, the first mention of coagulopathy in thermally-injured patients appeared in the Polish journal, *Polski Tygodnik Lekarski*, by Blonska and Kamienski in 1957
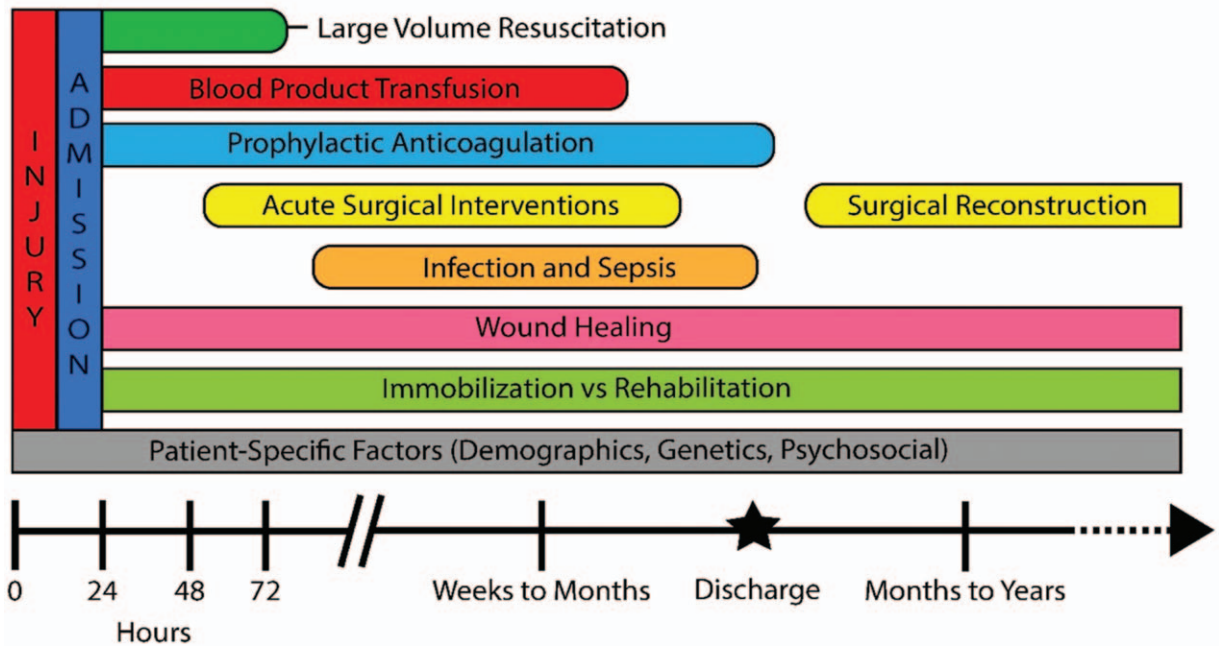
Fig. 1. **A simplified schematic illustrating a patient's hospital course after burn injury.**

(6). Hemostasis following scald injuries in children and adults was investigated. By measuring clotting time, a hypercoagulable state following scald injury was observed, and this was more pronounced and prolonged in children. A transition to a hypocoagulable state was noted in patients with severe scalds at 3 weeks postinjury. The authors postulated the increased bleeding tendency was a result of liver damage induced by bacterial toxins.

Longitudinal studies of BIC by the French military in the early 1960s examined clot formation and platelet function (7, 8). Thrombocytopenia was described in the initial 24 to 48 h after injury with a rebound thrombocytosis and slow return to normal platelet levels over 2 to 4 months. Thromboelastography (TEG), a viscoelastic hemostatic assay that was first introduced in 1948 in Germany by Hartert (9), which measures the global viscoelastic properties of whole blood clot formation under low shear stress, was performed to supplement platelet counts. Despite initial thrombocytopenia, TEG conducted at 2 days demonstrated hypercoagulability and was attributed to high levels of fibrinogen and thromboplastin due to tissue lysis. The investigators also demonstrated a reduction of this hypercoagulability observed using TEG with the administration of heparin and proposed the use of thromboembolic prophylaxis with heparin in burn patients.

The earliest available English-language publication focusing on coagulopathy in burn patients appeared in *Surgery* in 1963 (10). Holder et al. (10) noted evidence of thromboembolic events on autopsy of severely-burned patients. They further examined coagulopathy after thermal injury in a mouse model using clotting time measurements and evaluated the effects of heparin and thromboplastin on BIC. A novel method of extracting thromboplastin from burned skin was developed. Subsequently injecting this extract into mice resulted in significant procoagulant states or death (10). Ultimately, the authors concluded that thermal injury induced a hypercoagulable state and hypothesized that thromboplastic material in the injured tissue may be partially responsible.

Investigation of BIC continued in the 1970s with animal models again focusing on platelet function and clot dynamics. In 1974, using a scald-burned rat model, Eurenius and Rothenberg (11) observed an initial period of markedly depressed platelet function in burned animals using ADP-induced platelet aggregation tests. The initial depression was followed by increased platelet aggregation by 24 and 48 h, which the authors presented as a possible mechanism behind the clinically observed hypercoagulability noted in human burn and trauma patients.

In 1975, using a similar scald-burned rat model, Curreri et al. (12) studied the effects of heparin and protamine sulfate on coagulation dynamics. In this study, an initial low-normal platelet level was followed by thrombocytosis after 48 h, echoing the findings of Eurenius and Rothenberg. When fibrin split product concentration was measured after administering heparin to burned rats at 24 h postinjury, no significant effect was observed relative to controls (12). The authors conclude by strongly advocating against prophylactic anticoagulation with heparin, contrary to current practices in many burn institutions. Debate continues on the role of prophylactic anticoagulation in burn care and will be discussed, but it is important to note that here, the effects of heparin were measured at 24 h postinjury.

A more longitudinal and thorough case series on BIC in human patients was published by Bartlett et al.(13) . Numerous coagulation tests were serially conducted on 11 patients with large burns (total body surface area (TBSA) range 30%–68%) with data collected up to 5 weeks postinjury. In addition to tests of platelet counts and function, coagulation function was assessed by activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT), as well as individual clotting factors (fibrinogen, Factor (F) V, and FVII).

Again, an initial decrease in platelet function and clotting factors was observed in the first 48 h before returning toward baseline, and platelet function remained depressed even after initial resuscitation (up until 3 or 4 days postinjury) (13). The authors used these findings to propose changes in care plans of their patients that included avoiding surgical interventions until the fourth or fifth day after injury. However, the conclusions of this series must be viewed in the context of the institution-specific treatment protocols and standard practices of the time. Colloid-only resuscitation with albumin was used and average time to excision and grafting was 21 days (13). This is in stark contrast to crystalloid-based resuscitation (14) and early excision and grafting that is the practice of most burn institutions today (15, 16).

More recently, Sherren et al. (17) defined the effects of clotting alterations caused by thermal injury in their retrospective review of acute BIC. Their analyses demonstrated that 39.3% of severely-burned patients met their established criteria for coagulopathy on admission based on elevations of PT (>14.6 s), aPTT (>45 s), or international normalized ratio (INR, >1.2) on admission labs. They found a significant correlation between PT elevation and burn severity and acute BIC was an independent predictor of 28-day mortality.

In contrast to Sherren et al. (17), in another retrospective study from the same year, Lu et al. (18) concluded that major burn injury was not associated with acute coagulopathy. Acute coagulopathy was defined as an INR of 1.3 or greater, an aPTT of 1.5 or greater times normal, and normal platelet count. Thermally-injured patients needed to meet all three criteria to be classified as having coagulopathy. Of the 102 patients included, none met criteria on admission. Lu et al. highlighted the difference of this 0% frequency with a previously established 20% frequency in blunt and penetrating trauma to assert that TIC is unique to non-burn trauma.

Perceptions regarding existence and relevance of BIC are clearly varied. The difference between time of injury and admission sampling in the retrospective studies above could explain the divergent conclusions. For example, Sherren et al. (17) reported a mean time from burn to hospital arrival of approximately 6 h, while Lu et al. presented a median time of only 2.5 h. Review of the longitudinal data presented by Lu et al. reveals increases in INR to levels above 1.3 in the days following injury for several patients. Furthermore, 68% of the patients in the Lu et al. study suffered burns between 15% and 30% TBSA, whereas all 117 patients included in the Sherren et al. review had burns of at least 30% TBSA. The extent of burn injury has been shown to correlate with development of coagulopathy (19, 20). The relatively small number of patients with burns greater than 30% TBSA in the Lu et al. study weakens their assertion that BIC does not exist.

In 2016, Glas et al. (21) summarized current understanding of BIC, presented outcomes, and highlighted the need for better management strategies for this disease process. The review aimed to clarify definitions to arrive at consensus. Here, acute BIC was defined as abnormal INR (>1.5) and aPTT (>60s) with early onset BIC defined as presence of these abnormalities in the first 24 h after injury (21). Severe burns are defined as greater than 30% TBSA and are associated with a greater

coagulopathy with earlier onset. It is noted that early detection of coagulopathy is a challenge and routine tests of coagulation (PT, aPTT, INR) have limited diagnostic value, while the presence of coagulopathy is associated with increased mortality. The pathophysiology of BIC was characterized over time with a discussion of relevant clinical influences and the response of systemic markers of coagulation and inflammatory cytokines. Ultimately, the authors conclude that further work is needed to optimize the diagnosis and subsequent treatment of BIC.

The lack of consensus for monitoring BIC was highlighted in a reported survey of burn care providers conducted by Lavrentieva et al. (22) in 2016. Of the 55 respondents who completed the questionnaire, 46 burn specialists (70.8%) indicated that they only use PT, aPTT, fibrinogen, and platelets as tests to detect BIC. The remaining providers noted the use of measurements of antithrombin (AT), protein C (PC), and D-dimer levels, as well as viscoelastic methods like TEG to supplement traditional measurements. Furthermore, 41 respondents (74.5%) revealed that no specific coagulopathy scoring system was used at their institutions.

Conventional tests of coagulopathy, such as PT, INR, and aPTT, do not reliably detect the presence of coagulopathy in burn patients, and global assay methods (i.e., viscoelastic and thrombin generation assays [TGA]) are more informative. Viscoelastic testing of whole-blood clotting uses technology that has been in existence since it was introduced by Hartert (9) in 1948. Viscoelastic testing is conducted using TEG or rotational thromboelastometry (ROTEM). TGAs are plasma-based assays that can identify phenotypic differences in thrombin generation that can contribute to altered hemostatic states and coagulopathy (23–26) and provide more information beyond the clotting end point. Wiegele et al. (27) showed a procoagulant state in burn patients in the first 2 weeks following injury reflected by TGA and ROTEM, while conventional assays including PT, aPTT, and platelet count remained within reference ranges. The authors concluded that further studies correlating TGA and ROTEM results and clinical outcomes are needed to potentially develop patient-specific clinical interventions. A recent review in 2019 suggests that the use of viscoelastography during intraoperative blood product resuscitation in burn surgery is associated with decreased transfusion requirements (28).

The greater availability and array of laboratory and point of care testing has led to a deeper understanding of BIC. In turn, greater understanding of BIC informs the selection of diagnostic tests. In recent years user-friendly point-of-care viscoelastic devices have enabled the development of treatment algorithms aimed at identifying and managing coagulopathy (2, 28–31). Nonetheless, there is no consensus on how best to diagnose BIC, potentially related to an incomplete understanding of the pathophysiology.

MECHANISMS CONTROLLING HEMOSTATIC BALANCE: INTERACTIONS BETWEEN COAGULATION, FIBRINOLYSIS, AND INFLAMMATION

There are two fundamental mechanisms for triggering a coagulation, the exposure of blood to functional tissue factor
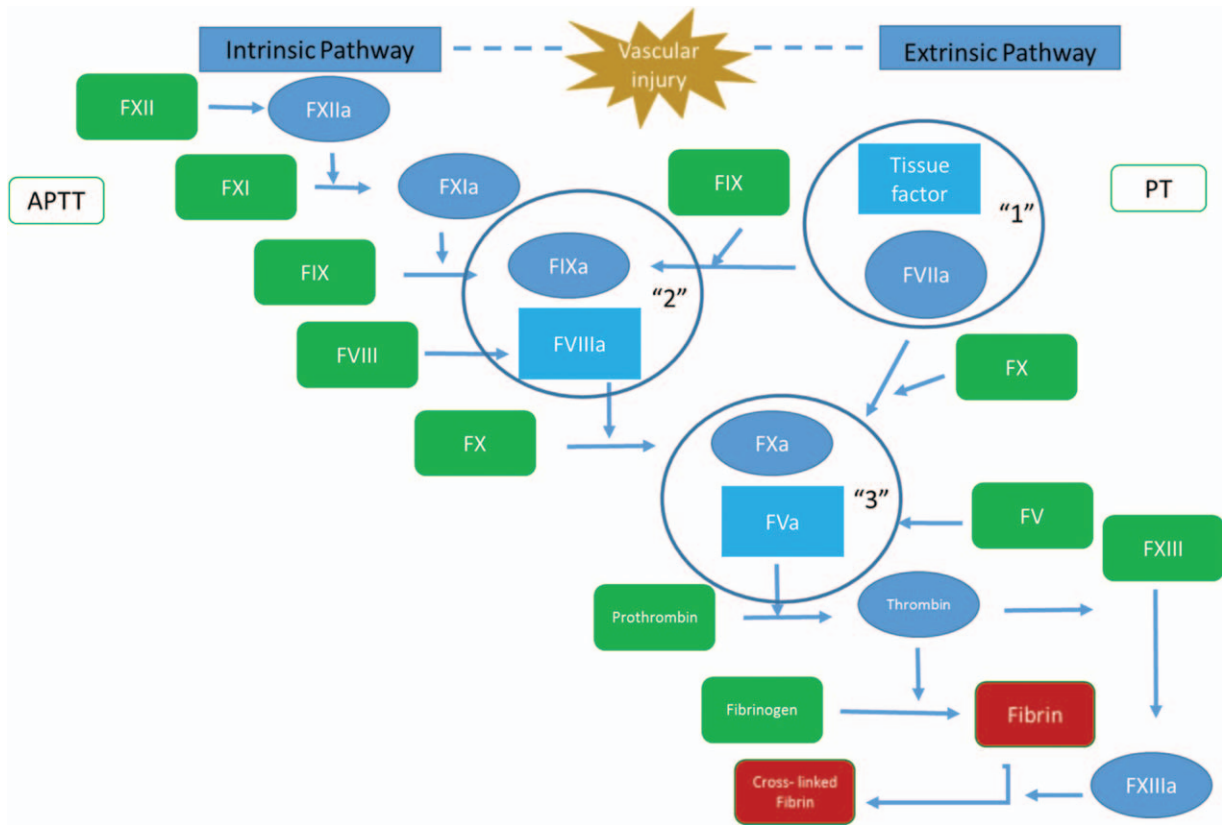
Fig. 2. **Pathways to thrombin generation:** *Extrinsic pathway:* **Extravascular TF, exposed as a result of vascular injury, forms a complex with circulating FVIIa forming the extrinsic tenase ("1") which activates FIX and FX.** Direct activation of prothrombin by FXa results in trace amounts of thrombin which: rapidly activates the procofacors FVIII and FV to their functional forms, FVIIIa and FVa; and activates platelets Activated platelets provide separate binding sites for the intrinsic tenase ("2") and the prothrombinase complex ("3"). The intrinsic tenase provides the majority of FXa used to assemble the prothrombinase complex while the prothrombinase complex is the primary source of thrombin needed to propagate the clotting reaction. The PT assay relies on the use of very high concentrations of TF, thus eliminating the need for the intrinsic tenase production of FXa. *Intrinsic pathway:* Initiation of the intrinsic pathway to thrombin formation requires the exposure of blood to materials capable of supporting FXII autoactivation. FXIIa then activates FXI; FXIa is an extremely efficient activator of FIX. FIXa directly activates FX to FXa which then directly activates prothrombin as described above leading to the formation of both the intrinsic and prothrombinase complexes. Both the PT (utilizing the extrinsic pathway) and the aPTT, (utilizing the intrinsic pathway) assays are ideal for detecting gross coagulation defects. However, as the endpoint of these assays is the fibrin clot, these assays exclude over 95% of the thrombin generated in the complete reaction.

(TF) (extrinsic pathway) and the exposure of blood to materials capable of supporting FXII autoactivation (intrinsic/contact pathway). Functional TF interactions with blood arise through two primary routes: exposure of blood to extravascular cells such as smooth muscle cells and fibroblasts (which constitutively express TF on their surfaces); and intravascular display of functional TF on the surface of white cells (monocytes) and/or endothelial cells which occurs in response to agonists (i.e., inflammatory cytokines). In the first scenario, TF exposure is coincident with the exposure of extracellular matrix proteins that support the adhesion/activation of platelets thus localizing platelets and TF at the injury site. With respect to a coagulant response dependent on FXII activation, the mechanisms include the release into the blood of bacterial products (sepsis) and the presence of intracellular material such as DNA-histone complexes due to physical disruption of cells or the induction of apoptosis. Extravascular TF functions to initiate a localized coagulant response upon vessel injury with the goal of forming and maintaining a physical barrier (fibrin/platelet clot) that restores the separation between the circulatory system and the extravascular space. In contrast, the presence of initiators of coagulation in circulating blood, whether molecules triggering FXII activation or intravascular cells expressing TF, is often a part of a secondary consequence of injury or is associated with disease states.

The enzyme thrombin is the critical product of this response to vascular injury, displaying procoagulant, anticoagulant, antifibrinolytic, and cellular effects (32, 33). Figure 2 summarizes the series of enzymatic events for each of the pathways leading to thrombin generation. Key roles of thrombin in the initial phase of the response to vascular injury include: formation of fibrin from fibrinogen; activation of platelets; activation of FXIII which crosslinks fibrin subunits improving the mechanical stability of the fibrin matrix; and activation of thrombin activatable fibrinolysis inhibitor (TAFI), a carboxypeptidase that modifies fibrin making it more resistant to lysis.

Negative regulation of the coagulant response is primarily accomplished by the activities of tissue factor pathway inhibitor (TFPI), AT, protein S (PS), and the PC pathway (Fig. 3). In combination, these inhibitory processes provide a threshold-limited reaction system in which a stimulus of sufficient magnitude must be provided if the reaction is to proceed. TFPI
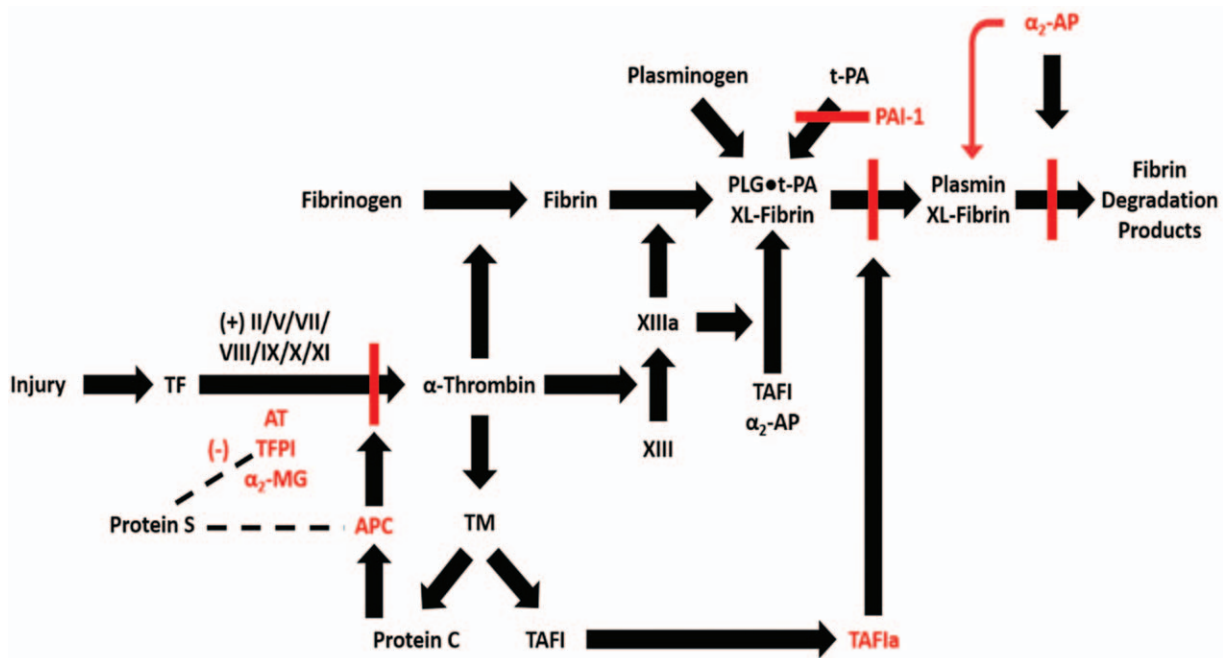
Fig. 3. **Pathways linking fibrin formation and fibrinolysis.** Key proteins and pathways linking the onset of coagulation at an injury site to thrombin formation, the formation of a crosslinked fibrin matrix and the process of fibrin lysis are shown. Key inhibitors and their targeted pathways are shown in red. α2-AP indicates α2-antiplasmin; α2-MG, α2-macroglobulin; PLG, plasminogen; XL-Fibrin, cross-linked fibrin.

is a multivalent Kunitz type plasma proteinase inhibitor functioning as the principal inhibitor of the FVIIa-TF complex. TFPI inhibits the FVIIa-TF complex in a FXa-dependent manner and is a primary regulator of the initiation phase of thrombin generation. AT is an abundant member of the serpin proteinase inhibitory family and forms irreversible 1:1 complexes with most of the proteinases participating in the coagulant response including thrombin, FXa, FIXa, TF-FVIIa, and FXIa. AT appears to be the primary inhibitor of thrombin and deficiency is associated with increased thromboembolic events. PS functions as an inhibitory cofactor, improving the efficiency of TFPI inhibition of FVIIa-TF complex and activated PC (APC) inactivation of FVa and FVIIIa. The PC pathway is responsible primarily for limiting the conversion of prothrombin to thrombin. Consistent with these activities, PS and PC deficiency is associated with increased risk of thrombosis (34). Key components of the PC pathway include two proteins expressed on the luminal surface of endothelial cells: thrombomodulin (TM), which binds thrombin to form the PCase complex, an efficient catalyst of PC conversion to APC, and the endothelial cell PC receptor, which delivers PC to the thrombin–TM complex. APC has been shown to proteolytically inactivate FV/FVa, FVIII/FVIIIa. The formation of APC via the PC pathway is the central dynamic anticoagulant mechanism limiting clot formation to the injury site.

The presence of fibrin triggers a complementary pathway, the fibrinolytic system, which plays an important role in down regulating the physical extension of the clot and in the ultimate restoration of vessel structure and integrity (Fig. 3). Key components of the fibrinolytic pathway include: plasminogen, the zymogen precursor of the enzyme plasmin which degrades fibrin, t-PA (tissue plasminogen activator), which catalyzes the conversion of plasminogen to plasmin, PAI-1, (plasminogen activator inhibitor 1), the primary plasma inhibitor of t-PA; alpha-2-antiplasmin (AP), the primary plasma inhibitor of plasmin; and TAFI, which in its activated form works to suppress plasminogen activation on the fibrin surface. The fibrin component of the blood clot acts as a cofactor for the activation of plasminogen by t-PA, leading to efficient production of plasmin only at the site of fibrin deposition.

The complex interplay of inflammation with coagulation through an induced expression of TF has been described (35). Interleukin-6 (IL-6) and interleukin-8 (IL-8) have been shown to increase monocyte TF expression *in vitro* while other inflammatory cytokines such as IL-1 and tumor necrosis factor-α (TNF-α) have been shown to induce the tethering of TF-bearing micro-particles from monocytes at the endothelial surface (36). This would augment the pre-existing pro-coagulant effects of TF in the blood. A study of endotoxemia in humans reported that TF mRNA expression increased 100-fold following lipopolysaccharide injection (37). A rise in thrombin–antithrombin complex (TAT) and prothrombin fragment 1.2 (F1.2) closely followed the elevation in TF mRNA indicating a resulting increase in thrombin activity (37).

Inflammation also increases coagulation through the inhibition of fibrinolysis (35). PAI-1 is stimulated by IL-6 and TNF-α, contributing to the inhibition of fibrinolysis (38). Furthermore, the down regulation of TM and PC by IL-1 and TNF-α can promote the spread of coagulation beyond directly injured tissue (38).

In subsequent sections, we will examine a more global picture of burn injury to include studies that investigate procoagulant, anticoagulant, fibrinolytic, and inflammatory changes during the acute phase in the first 48 h and beyond.

THE FIRST 48 HOURS: BURN SHOCK AND ACUTE RESUSCITATION PHASE

The first 48 h of care for burn patients differ markedly from that of other trauma patients due to myriad of factors including fluid resuscitation, inhalation injury, and dysfunctional integument (Fig. 1). Derangements in coagulation and fibrinolysis can manifest rapidly after injury, Figure 3 graphically depicts the relationships between many of these factors. Given the acute hyperinflammatory state of individuals with severe burns, the inflammatory cascade likely contributes to coagulopathy.

Procoagulant factors

In the setting of thermal injury, the most commonly studied components used to assess the level of hemostatic dysfunction are platelets, fibrinogen, and two markers of *in vivo* thrombin generation, the TAT complex and prothrombin activation fragment 1.2, a noncatalytic peptide released during the conversion of prothombin to thrombin (Table 1). More recently thrombin generation potential has been measured using direct (TGA), and indirect (TEG/ROTEM) measurements, as well as mechanism based computational modeling (27, 39).

Overwhelmingly, platelet levels are found to be unchanged by acute thermal injury (40–47). There are a few studies that suggest platelet counts are elevated as early as admission in thermally injured patients (47–49), which may reflect variability in time to measurement following injury. Lawrence and Atac (50) concluded that intravascular hemolysis and fragmentation of erythrocytes can result in pseudothrombocytosis, which may occur during the early resuscitation period. Thrombocytopenia on admission may reflect early disseminated intravascular coagulation (DIC) (47). Growing use of viscoelastic measurements has suggested that in the setting of normal platelet counts, platelet function is diminished (27, 43, 45).

Fibrinogen levels increase in the first 48 h after burn injury (40, 41, 48, 49), and in the preoperative period before excision and grafting (43, 46, 51), although one study notes normal or decreased levels in burn patients exhibiting severe coagulopathy and DIC (47). Levin and Egorihina (49) reported an association between increasing fibrinogen levels in burn patients and a decrease in the degree and velocity of platelet aggregation, which would clearly impact clot formation.

TAT levels increase immediately post burn and peak within 48 h (44, 52–59). The time frame of the onset of this change has been more consistent than for other markers, occurring within the first 24 h (53, 56). Interestingly, TAT levels correlate with burn severity. Two separate studies reported elevated TAT levels in all patients, with significantly higher levels among nonsurvivors (54, 58). Consistent with data for TAT, several studies have found F1.2 levels to be elevated within the first 24 h, often in proportion to TBSA. Burn patients who developed DIC exhibited even higher elevations (45, 47, 58, 59).

Increased F1.2 and TAT levels in the first 48 h post-burn, suggest ongoing systemic thrombin generation. However, the increased free thrombin levels do not appear sufficient to affect the elevated level of fibrinogen. Independent of fibrinogen, thrombin has numerous roles in coagulation homeostasis, inflammation, and in cellular functions such as growth, migration, and regulation of protein synthesis and secretion (60). Thrombin generation assays (27) and computational thrombin modeling (39) have demonstrated a shift toward increased thrombin generation potential following burn injury. This is consistent with the data for the *in vivo* thrombin generation surrogates F1.2 and TAT. If viewed in context with other hemostatic markers, measuring F1.2 and TAT may help to paint a more comprehensive picture of the progression of coagulopathy in burns.

Several studies have investigated factors within the coagulation cascade in the first 48 h after burn injury, including FV, FVII, and FVIII. FV levels are normal within the first 48 h of injury (40). This suggests that the observed increase in thrombin generation is not substantial enough to deplete FV levels. Additionally, it may point to an underlying difference in the mechanisms underlying hemorrhage risk in thermal versus mechanical trauma. In TIC, reductions in the levels of FV due to APC-mediated proteolysis have been advanced as an important contributor to bleeding risk (61–63).

FVIIa activity appears elevated in the first 48 h after thermal injury (54, 55). FVIIa may have use as a prognostic indicator. Garcia-Avello et al. (54) found FVIIa levels to be higher in nonsurvivors compared with survivors and controls within 24 h after burn (post-burn day 1, PBD 1). The activity of FVIIa is elevated in burn patients when compared with healthy controls, indicating a hypercoagulable state (55). Increasing levels of FVIIa correspond to the severity of injury in the acute phase (54). Increased levels of FVII activating protease have been reported in trauma patients, thus providing a potential mechanism for the observed higher levels of FVIIa (64).

Lastly, FVIII rapidly increases in the first 48 h and remains elevated above normal values up to 40 days postinjury (40, 45, 48). The extent of FVIII elevation in the acute phase correlates with TBSA (45). FVIII is stored along with von-Willebrand Factor (vWF) within endothelial cell Wiebel-Palade Bodies (WPB) (65). The exocytosis of vWF from WPB into the vascular lumen is an important initiator of primary hemostasis in response to vascular endothelial injury (66). Elevated FVIII levels may be a result of endothelial damage in burned tissue and subsequent WPB exocytosis. In an environment of hemostatic activation, as in burn injury, increasing concentrations of FVIII may work to accelerate production of FXa and thrombin (Fig. 2).

Anticoagulant system

Endogenous anticoagulants have been better characterized in burn injury relative to procoagulants. Factors such as AT, PC, and PS, TM, and TFPI inhibit coagulation by attenuating or

TABLE 1. **Effects of burn injury on procoagulants**

	48 h	>48 h
Platelets	↔(38–45)	↑(39, 40, 42, 46, 91)
Fibrinogen	↑(38, 39, 46, 47)	↑(41, 44)
Thrombin−antithrombin complex	↑(42, 50−57)	↑(52, 53)
Prothrombin fragment 1.2	↑(43, 45, 56, 57)	↑(45)
Factor V	↔(38)	
Factor VIIa	↑(52, 53)	↑(52, 53)
Factor VIII	↑(38, 43, 46)	↑(83)

Table 2. **Effects of burn injury on anticoagulants**

	48 h	>48 h
Antithrombin	↓(41−43, 45, 46, 50−53, 56, 57, 65, 66)	↓(51, 56)
Protein C/S	↓(43, 52, 53, 56, 57, 67)	↓(43, 52, 53, 83)
Thrombomodulin (soluble)	↑(51)	↑(51)
Tissue factor pathway inhibitor	↔(75)	↔↑(83)

suppressing the effects of procoagulant factors (Fig. 3). In burns, three of these factors (AT, PC, and PS) have been shown to decrease during the first 48 h after injury, while the other two (TM and TFPI) increase or remain at normal levels (Table 2).

AT is the primary inhibitor of key coagulation enzymes including thrombin and FXa. Thus, decreased AT levels reflect reduced capacity to suppress coagulation. Within 48 h of burn injury, there is a marked decrease in AT levels (43–45, 47, 48, 52–55, 58, 59, 67, 68). Consistent with F1.2 and TAT level increases after burn injury, the extent of AT level decrease following burn injury is correlated with severity (52, 55). From a prognostic side, survivors return to near normal levels while non-survivors exhibit persistently depressed levels (55).

PC and PS are key components of the anticoagulant response. The concentrations of PC and PS decrease immediately after thermal injury (45, 54, 55, 58, 59, 69). Loss of both PC and PS following burn injury results in a simultaneous reduction in the capacity to suppress coagulation, with potentially increased thrombotic risk (55), and decreased inhibition of inflammation (35). Levels of PC and PS have been investigated as prognostic indicators; significant lower PC and PS levels are found in non-survivors and with larger burns, as compared with healthy controls (54, 58, 69, 70).

TM is a transmembrane glycoprotein expressed on the luminal surface of endothelial cells (71). It functions as a high affinity receptor for thrombin and the resulting complex is the primary physiologic activator of PC. Assessment of TM following injury generally depends on the measurement of fragments released by the proteolysis of the TM extracellular domain (72), measured as soluble TM. In a rabbit burn model, thermal injury was found to produce shedding of TM from the endothelium (71), effectively removing it from its anticoagulant role in the activation of PC. In human patients, Aoki et al. (53) found TM plasma levels to increase by 48 h after injury. Taken together, these findings suggest endothelial activation or damage following burn, results in shedding of TM from the endothelium and an increase in plasma soluble TM. Burned integument and progression of the zone of stasis may initially contribute to a hypercoagulable state through proteolysis of TM. Elevated levels of soluble TM have also been associated with TIC (61, 73).

TFPI, an inhibitor of the initiation phase of TF-mediated thrombin generation, is present on endothelial cell surfaces and circulates through plasma bound to lipoproteins. Association of TFPI with the endothelial glycocalyx provides localized control to thrombin generation, which may have implications for thrombotic complications in microvasculature adjacent to burns (74). It has been shown in non-burn trauma that despite markedly increased levels of thrombin 24 h after injury, there are no compensatory increases in TFPI levels (75). One of the few studies investigating TFPI levels in burns by Ravindranath

et al. (76) found TFPI levels in rats with 30% TBSA wounds to be decreased significantly at 24 h after burn. In contrast, Kowal-Vern et al. (77) found in humans that TFPI levels remain normal during the acute and restorative phases after large burn injury, consistent with observations in non-burn trauma patients. The available data suggests TFPI is not significantly altered by thermal injury in humans. A decrease in TFPI would be cause for concern as it would add to a hypercoagulable state.

Fibrinolysis

After burn injury, pro-fibrinolytic enzymes increase in activity and concentration. The most frequently studied are t-PA and plasminogen. t-PA concentration increases during the acute phase of burn injury. When comparing survivors and non-survivors, both Garcia-Avello et al. and Lavrentieva et al. found t-PA levels to be elevated in both groups, with non-survivors having higher levels immediately after burn injury (54, 58). It is important to note that increased t-PA levels alone are not indicative of increased fibrinolytic potential. Plasminogen levels decrease immediately after burn, proportionately to the severity of the injury (41, 54, 55). While there is a rapid increase in pro-fibrinolytic activity following burn injury, increases in anti-fibrinolytic factors are also observed. PAI-1 and AP are the most widely studied fibrinolytic inhibitors while plasmin-α2-antiplasmin complex (PAP) is measured to infer the amount of plasmin inhibition (Table 3). PAI-1 binds with t-PA and urokinase plasminogen activator (u-PA) to prevent the activation of plasminogen to plasmin. PAI-1 levels increase and peak immediately after burn injury, then proceed to decrease in concentration toward normal or near normal levels (53–55, 58, 59, 77). This trend is similarly exhibited by t-PA levels, several studies have noted that both the fibrinolytic activator (t-PA) and inhibitor (PAI-1) elevate in tandem correlating with burn size and mortality (54, 55, 58). Aoki et al. (53) studied 15 patients in a detailed analysis of PAI-1. An increase in free PAI-1 was observed earlier and of greater magnitude (40 times healthy control) than the elevation in t-PA. The authors suggested the greater increase in PAI-1 compared with t-PA immediately after

Table 3. **Effects of burn injury on fibrinolysis**

	48 h	>48 h
Tissue plasminogen activator	↑(52, 56)	↑↔(51−53)
Plasminogen	↓(39, 52, 53)	↓↔(52)
Plasminogen activator inhibitor	↑(51−53, 56, 57, 75)	↔(56)
α2-Antiplasmin	↓(52, 75)	
Plasmin- α2-antiplasmin complex	↔(56, 57)	↔(56, 57)
D-Dimer	↑(41−43, 45, 52−57, 75, 82)	↑(56)

burn injury may be explained by the behavior of PAI-1 as an acute-phase reactant. The authors go on to speculate that immediate post-burn suppression of fibrinolysis may be necessary to preserve coagulation homeostasis after thermal injury, but that secondary activation of the fibrinolytic system in response to fibrin deposition may lead to a paradoxical state of hypofibrinolysis coexisting with targeted fibrinolysis (53). Several phenotypes of fibrinolysis have been described following traumatic injury. While the hyperfibrinolytic phenotype is associated with a doubling of mortality, the subset of non-burn trauma patients presenting with fibrinolytic shutdown also experience poor outcomes (78, 79). These fibrinolytic phenotypes are less well studied in the burn population.

AP is the primary inhibitor of activated plasmin; unlike PAI-1, it is observed to decrease after burn injury (54, 77). From a prognostic standpoint, various authors have found AP levels to be low immediately post-burn, with non-survivors having lower levels compared with survivors. However, AP levels eventually normalized in both groups (54, 77). Interestingly, plasminogen levels follow a similar trend to AP, in that both factors are decreased within the first 48 h after injury (44, 54). This could be explained by a progression of rapid conversion of plasminogen to plasmin resulting in lowered levels of plasminogen. As plasminogen is converted to plasmin, AP quickly complexes and is consumed, resulting in depressed AP levels. This hypothetical progression is further supported by evidence in other studies that PAP complex levels increase immediately post burn (53). However, PAP levels remained within normal physiologic range for both survival and non-survival burn patients, despite a marked increase in PAI and moderate increase in t-PA after injury (58, 59). The lack of PAP increase in this more recent data can be explained by a number of scenarios. Either AP and activated plasmin are not complexing efficiently, AP production is inhibited or depressed, or the higher increase of PAI-1 relative to t-PA is preventing excessive activation of plasmin (80). Another alternative could simply be technical; the rapid degradation or clearance of PAP after complex formation could result in the lack of change observed within this data.

The last metric used to measure fibrinolytic activity is the presence of fibrin degradation products (FDP), the most notable being D-dimer (81, 82). D-Dimer is a marker that reflects activation of coagulation and fibrinolysis, it is a sensitive but not specific marker, with elevated levels found in a myriad of disease states (83). Although various studies report that burn patient's D-dimer levels are elevated upon admission (43–45, 47, 54–59, 77, 84), further investigation is needed to determine its clinical utility. Given local tissue damage and the resulting hyperinflammatory state following burn injury, elevated D-dimer levels are not surprising. As stated earlier, there seems to be a greater increase of PAI-1 relative to t-PA during the acute phase of injury suggesting an initial systemic hypofibrinolytic state (53). In one study, eight of 36 patients showed no clot lysis after 24 h when assessed using the euglobulin clot lysis time assay and had a significantly lower plasma ratio of PAI-1/t-PA complex to free PAI-1 (53). Elevated D-dimer may therefore be due to an excessive amount of fibrin clot formation; the local fibrin degradation at the site of burn injury raising the level of FDPs (53, 54, 85).

INFLAMMATORY FACTORS

Burn injury causes both a local inflammatory response to coagulative necrosis as well as a systemic inflammatory state secondary to circulating cytokines (86). Many pro-inflammatory molecules are elevated in the acute phase in response to burn injury (85, 87, 88). IL-1, IL-6, IL-12, and TNF-α are elevated by 24 h and levels are significantly higher in burn patients who die of their injuries at 48 h (85). Burn injury is associated with a systemic inflammatory response that is associated with injury severity and precedes a hypermetabolic state (89). Cytokine derangements are more severe in adult patients when compared with children and this heightened immunoinflammatory response has been suggested as a contributor to the increased morbidity and mortality observed in adults (87). Matsuura et al. examined a cytokine network including monocyte chemoattractant protein-1 (MCP-1), IL-6, IL-8, and IL-10 and showed that cytokine derangements in burn patients with > 20% TBSA compared with healthy controls were correlated with burn injury severity and prognosis (90). When compared with non-burn trauma patients, patients with severe burns were found to have higher levels of IL-6 and IL-8 as early as 24 h after injury (91). The inflammatory state, specifically IL-6, IL-8, TNF-α, among other cytokines have been shown to shift the hemostatic balance towards coagulation (35). However, the interplay between the inflammatory response to burn injury and its effects on BIC has not been well studied.

Summary

Overall, in the first 48 h thermally-injured patients appear to exhibit a net increase in pro-coagulant potential. Studies of the components of the fibrinolytic cascade provide evidence of both hyper- and hypofibrinolysis. Whether these changes are part of a larger phenomenon unique to burn injury or rather, are part of a general response to trauma is uncertain.

Caution must be taken when trying to define the first 48 h after burn injury, as a hyper- or hypocoagulable state based solely on the levels of individual markers. Indeed, studies have demonstrated induction of both states following burn injury. Global coagulation assays have the potential to better characterize individual differences in the dynamics of clot formation and lysis among patients. In a study on TEG measurements of 65 patients with > 15% TBSA injuries, Huzar et al. (92) found 60% of patients to be hypercoagulable on admission while 24% were hypocoagulable. Identifying potential factors that predispose patients to hyper- or hypocoagulability, such as severity of injury, pre-existing conditions, or demographics, must be further explored in future research.

FORTY-EIGHT HOURS AND BEYOND: POST BURN SHOCK RESUSCITATION

Once a patient survives the acute phase of burn injury, he or she moves into a period wherein infections, protracted hypermetabolism, and hospital convalescence impact outcomes. During this period, excision and grafting is initiated to mitigate the impact of sustained exposure to thermally damaged tissue

(93, 94). During these surgeries burned and devitalized tissue is excised and replaced with auto-, allo-, or xenografts to gain temporary or permanent skin resurfacing. The ability to make and sustain a clot plays a pivotal role in the ability to perform safe operations. Of note, while levels of a few of the components of coagulation discussed in the first 48 h of injury change in this time frame, most remain abnormally elevated or depressed. Longitudinal data studying BIC are limited.

Procoagulant

After 48 h, many studies identify an increase in platelet levels (41, 42, 44, 48, 95). In the presence of infection, Housinger et al. (96) determined falling platelet counts to be an independent predictor of sepsis in severely burned pediatric patients. Cowan et al. (40) noted mean platelet counts were significantly lower in adult burn patients who developed sepsis, and that development of dysfunctional platelet aggregation was more reliably correlated with sepsis than lower count. Burn patients generally present with normal platelet counts and develop a thrombocytosis following the acute phase (Table 1). Dysfunctional platelets at any point after burn injury correlate with poor outcomes. TAT and FVII activity remain elevated in the week following burn injury, suggesting hypercoagulability (54, 55). While overall TAT values in burn patients return toward normal over time, average levels are higher in larger TBSA injury (56) and in non-survivors (54, 58). FVIII activity is elevated in the days following burn injury during excision and grafting while the activities of FII and FX are depressed (43). The differential activity of FVIII has been rationalized by its function as an acute phase reactant. Factor activities were shown to decrease perioperatively reflecting a consumptive process secondary to intraoperative blood loss (42, 43). FVIII activity is higher in non-survivors and FII functional activity is lower with larger burns (85). F1.2 remains elevated for 5 to 7 days but is not significantly higher than on admission (47) or by mortality (58). At 1 to 2 weeks following burn injury, the potential to generate thrombin appears to increase (27). Fibrinogen levels peak within the first week following burn injury and remain elevated (27, 41). Consistent with factor activity, fibrinogen levels fall in the perioperative period with blood loss (42, 43).

Anticoagulant

AT activity is depressed after thermal injury (53, 58). The depression of AT activity tends to be more severe with increasing TBSA (45, 77). Decreased AT activity correlated with poor outcomes including increased length of stay and mortality (67). The perioperative period further exacerbates AT activity depression (43). Kowal-Vern et al. have published case reports on systemic infusion of AT concentrate to reduce microvascular thrombosis associated with burn wound progression (44, 68). PC and PS levels tend to be decreased in the days after burn injury (45, 54, 55, 85) (Table 2). PC and PS normalization following burn injury has been associated with survival. All patients had reductions in PC and PS on admission; survivors' PC levels were normalized by day 5 and PS by day 7, while PC/PS remained low in non-survivors (58). As discussed, normalization of AT, PC, and PS after 48 h has been associated with survival.

Soluble TM is typically elevated by 48 h and continues to be elevated as far out as 7 days from injury (53). In addition, soluble TM levels in humans have been shown to closely parallel TNF-α increases after burn injury, suggesting TNF-α stimulates TM production (97). Plasma TM levels were found to be significantly higher in non-survivors, as well as those who developed sepsis (97), perhaps reflecting an ongoing state of endothelial activation or damage. TFPI levels are generally within normal range following burns, however, TFPI levels are elevated at later timepoints in non-survivors, and this increase was shown to be significant at hour 60 (85). Again, this clinical finding differs from TFPI activity described in a rat model of sepsis following burn injury. TFPI activity levels were decreased in animals subjected to either burn injury or sepsis alone, with even lower activity when combinatory insults occurred, this decrease was most pronounced at 24 h with a rebound to near normal TFPI activity at 72 h (76). In humans, TFPI levels are found to be increased in several disease states, including sepsis (98, 99). However, interpretation of TFPI levels as a biomarker of coagulopathy can be misleading, given its various isoforms and distribution within the body, and varied methods of measurement (100).

Fibrinolysis

Most studies describe an acute rise in tPA levels within 24 h of burn injury that normalizes within the first week (53–55). Mortality may influence tPA levels, in one study survivors were within normal range and non-survivors had persistently elevated levels (58). This survivor – non-survivor difference was also observed for PAI-1, though not for PAP, which remained normal throughout, or D-Dimer, which remained elevated (58). It has been reported that plasminogen levels gradually increase to normal or near normal physiologic levels by post-burn day 5. When compared by mortality, the drop and subsequent return to normal levels for plasminogen was comparable (54). When plasminogen levels are compared by burn severity, larger burns experienced a sharper decrease and the return to normal levels was slower (55). Overall, it seems plasminogen levels are sensitive to burn severity but are not indicative of mortality (Table 3).

The relationship between plasminogen levels and burn severity may be illustrating a "dose-dependent" activation of fibrinolytic activity: greater severity burns result in more fibrinolysis and drop in plasminogen. If evaluated in tandem with observed t-PA activity, there is evidence that profibrinolytic factors increase their activity, as t-PA levels increase, plasminogen levels fall. Circulating PAI-1 effectively inhibits tPA. tPA is released locally in response to burned tissue as microvasculature thrombosis develops. Relatively greater disturbances in this homeostasis are observed in non-surviving patients (53). It is possible that ineffective fibrinolysis contributes to burn wound progression or organ system dysfunction.

INFLAMMATORY FACTORS

The inflammatory and hypermetabolic state that develops after burn injury persists following the acute phase (90, 101). Nonsurvivors have significantly higher plasma levels of IL-1,

IL-6, IL-10, IL-12, and TNF-α at 1 week from burn injury when compared with survivors (85). Septic complications are devastating sources of morbidity and mortality in burn patients. Burn injury alone causes an inflammatory state, infection, and sepsis compound this inflammatory response (102). Lantos et al. (103) observed an acute and sustained elevation in both pro- and anti-inflammatory cytokines in response to burn injury, consistent with other studies. Furthermore, IL-10 which suppresses immune function and predisposes patients to infection was found to be significantly higher at admission and perimortem in nonsurvivors (103). Sepsis has been associated with patterns of gene expression such as increased concentrations of mRNA for IL-10 and TNF-α (104). In pediatric patients, IL-8 levels were correlated with injury severity, infection, and mortality and were suggested as a sensitive and specific prognostic biomarker (105). Sepsis can be associated with DIC characterized by alterations in fibrinolysis that result in microvascular thrombotic complications (106). Burn injury and subsequent injury-specific complications such as infection and sepsis are independently associated with the inflammatory state. Following the acute phase of injury, the complex interplay between these factors and their impact on coagulation homeostasis are not well characterized.

Summary

Based on current studies, the period following acute burn injury is characterized by either maintenance of admission levels of coagulation factors or recovery to normal range values of said factors. In general, a hypercoagulable state persists for days to weeks. Derangements in biomarkers of coagulation are often correlated with size of burn (TBSA), as well as mortality. Excision and grafting impacts factor function, causing a consumptive coagulopathy, which may underlie bleeding complications. Sepsis, a common complication of major burn injury, further impacts coagulation causing platelet dysfunction as well as increases in the release of the endogenous anticoagulant TFPI. The hyperinflammatory state caused by burn injury persists over time, and infection and sepsis further exacerbate inflammation and may impact coagulation. Normalization of fibrinolytic factors seems to be associated with survival, though that data still needs to be explored. The paucity of longitudinal data characterizing BIC outside of the acute phase underscores the need for further research.

CLINICAL COMPLICATIONS OF BURN-INDUCED COAGULOPATHY

The advances in the general understanding of BIC in the last half-century have led to improvements in outcomes for burn patients through targeted thrombotic prophylaxis and hemorrhage control. Applications of the understanding of BIC and future directions that will be discussed in the following sections arose from the foundations built by these pioneers in coagulopathy research and burn care.

Venous thromboembolism

Given the recognized hypercoagulable state and potential for hypofibrinolysis after thermal injury, the development of deep vein thrombosis (DVT) and venous thromboembolism (VTE) in burn patients is a concern. Burn patients often meet all criteria of Virchow's triad for the pathogenesis of VTE—endothelial injury, venous stasis, and hypercoagulability (107). The actual incidence and significance of DVT and VTE after burn injury, however, remains unclear.

In 2015, Meizoso et al. (108) published a comprehensive review of VTE in burn patients. Through their review of over 50 studies, the authors discovered reported incidence of VTE from 0.2% to 25%. The wide range can be explained by varying methodology among studies. Higher incidence is found in those studies with autopsy or with sonographic screening of all patients. Lower incidence is reported when investigating only symptomatic patients. The incidence of potentially fatal consequences of DVT like pulmonary embolism (PE) has been reported to be as low as 0.001%, but this figure was derived from a study that also included patients with minor injuries (109). Others have reported rates of PE as high as 3.3% (110).

Given the wide range of reported incidence of thrombotic events, it is not surprising to find disparate views on the use of chemoprophylaxis for DVT and VTE in burn patients. In a retrospective analysis of a burn registry data, Sikora and Papp (111) determined that although burn severity was associated with VTE complications, chemoprophylaxis did not prevent VTEs. Other authors have proposed that bleeding risks associated with chemoprophylaxis, especially heparin, outweigh the potential benefits (112).

In contrast, Ahuja et al. (113) published a randomized, controlled trial in 2016 of 100 patients with 30% to 60% TBSA burns that examined DVT risk factors and the use of chemoprophylaxis. In the control group of 50 patients that did not receive chemoprophylaxis, four patients (8%) had sonographic evidence of DVT, compared with none of the patients on chemoprophylaxis. One patient in the treatment group developed epistaxis; no other complications associated with treatment were noted. The authors concluded that the benefit of DVT prevention outweighed bleeding risk in burn patients. These findings should be validated in future studies to develop consensus on chemoprophylaxis among providers.

Even when providers opt for chemoprophylaxis, studies have shown that dosing may be inadequate given burn pathophysiology. By monitoring anti-FXa levels, Lin et al. (114) found that standard dosing of enoxaparin in burn patients failed to achieve target anticoagulation. Thus, conflicting evidence on incidence, clinical significance, and prevention of VTE in burn patients obfuscates guidelines on chemoprophylaxis.

Disseminated intravascular coagulation (DIC)

DIC is a consumptive coagulopathy in which excessive, systemic activation of coagulation results in depletion of platelets and coagulation factors (115). Subsequently, diffuse bleeding can occur and lead to poor outcomes. In a 2010 review, Lippi et al. (116) examined the development of DIC in burn patients. As with VTE, there was variability in reported prevalence and recognition of DIC in this population.

The rarity of DIC in burn injury was argued by Barrett and Gomez in a retrospective review of 3,331 consecutive burn patients admitted over 9 years (117). Of all patients, 454

patients (13.6%) sustained burns greater than 20% TBSA. Only three patients were diagnosed with DIC—0.09% of all study patients and 0.66% of patients with TBSA > 20%. The authors used discharge diagnoses of DIC and reviewed clinical/autopsy data to identify other potential patients with DIC.

In contrast to these findings, Lavrentieva et al. (58) reported that in patients with greater than 25% TBSA, the prevalence of a DIC phenotype was 91%. Here, the authors used a scoring system developed by the International Society of Thrombosis and Hemostasis to identify patients with DIC that is based on markers such as platelet count, fibrin split products, prolonged PT, and decreased fibrinogen (118). The wide range of DIC reported in the burn population highlights the need for uniform definitions and large population studies.

INTRAOPERATIVE BLOOD LOSS

Intraoperative blood loss is a challenge in burn surgery and coagulopathy with transfusion requirement is associated with poor outcomes. Niemi et al. (43) studied perioperative hemostatic parameters in burn patients and identified an intraoperative depletion of factors, fibrinogen, and platelets with resulting coagulopathy consistent with a consumptive process. Several studies have described a similar phenomenon, where burn patients typically show preoperative factor, platelet, and fibrinogen levels above reference ranges that fall predictably during excision and grafting (42, 95).

In a recent review, Welling et al. (28) concluded that coagulopathy in burn patients is a heterogenous disease process with a described hypercoagulable state following injury, but that intraoperative hemorrhage, hypothermia, and hemodilution can lead to significant hemorrhage. On review of the data, they suggested that a more protocolized use of viscoelastic assays such as TEG and goal-directed blood product resuscitation can reduce transfusion requirements and improve outcomes (28). In a prospective study randomizing 30 severely burned patients undergoing excision and grafting into a TEG-based resuscitation algorithm versus standard of care, cumulative blood product use was reduced by more than half (46). In this study, the treatment algorithm was based on recommendations for TIC, highlighting the need for burn-specific protocols.

BURN WOUND CONVERSION

The zones of burn wounds were first described by Jackson in 1953. The central zone of coagulation is surrounded by a zone of stasis, and an outermost zone of hyperemia (119). Burn wound conversion is a significant source of morbidity with further tissue loss over time within the zone of stasis, which is characterized by coagulation, inflammation, and resulting ischemia. Investigations into the use of anticoagulant and anti-inflammatory agents to prevent burn wound progression have been undertaken in animal models with varied results (120). One study investigated the administration of t-PA to prevent burn wound progression in a rat model. They found significantly greater percentages of interspace viability (87.8% vs. 31.8%) at 1 week in the t-PA treatment group (121). In a

similar rat burn model, Meyerholz et al. (122) studied the utility of APC, and found that it increased burn depth severity, local inflammation, and tissue damage.

Kowal-Vern et al. conducted a prospective trial on administration of human AT concentrate to burn patients with injuries greater than 20% TBSA. AT plasma levels were reduced on admission for all burn patients, treatment with AT was initiated within 24 h of burn injury, and plasma levels improved over the course of treatment in the first 4 days following injury. The treatment group showed shorter time to graft healing in all body regions, and this difference reached significance for the hands. The authors concluded that human AT concentrate infusion is safe and suggested clinical trials to confirm the potential to improve clinical outcomes (77). More recent reviews on the topic of AT therapy in burn care reaffirm that AT has been shown in small human studies and animal models to be safe with a positive effect on wound healing in burns; however, well-designed prospective clinical trials are required to establish its role as clinical adjunct in burn care (123, 124).

CONCLUSIONS AND FUTURE DIRECTIONS

Overall, current understanding of BIC proposes that alterations in the components of the coagulation, fibrinolytic, and inflammatory systems yield functional changes in clot dynamics after burn injury. These alterations differ from those seen in TIC. However, focusing only on changes in the levels of these markers may lead to erroneous conclusions about an individual's clotting dynamics and thus may lead to missed opportunities for identifying (and preventing or treating) thrombotic or hemorrhagic states. Attempts to capture these changes with conventional assays of coagulation (PT, aPTT, platelet counts) have proven to be generally insufficient in the characterization of BIC. Assays that incorporate and combine more information regarding a patient's blood clotting phenotype into a single profile will be more useful.

Many methods of identifying potential BIC have been developed and continue to be optimized. Global and dynamic assays of coagulation such as the viscoelastic assays (TEG/ROTEM) and TGA provide more comprehensive and clinically relevant assessments of coagulation homeostasis (27). The availability of TEG/ROTEM parallels utilization at the point-of-care, TGA, and computational thrombin modeling show promise in characterizing procoagulant potential in burn patients and may experience increased use with increasing availability (27, 39). Research and development of new technologies to advance trauma and critical care is ongoing. Application of these developments to burn patients is promising in regards to diagnosis of BIC and clinical decision-making, such as the management of resuscitation (92). In addition to these laboratory tests, a consensus on an appropriate BIC diagnostic scoring system will clarify the prevalence of this phenomenon across institutions.

The clinical significance and approaches to prevention and treatment of BIC continue to be debated. While this review focused on coagulopathy after thermal injury, burn teams treat injuries from a variety of mechanisms, including chemical and

electrical. BIC studies often exclude these groups or include them within the larger thermal injury population without regard for potential disparities. Further studies should investigate potential manifestations of coagulopathy unique to these subgroups.

Severely-burned patients face innumerable challenges on their journey to recovery. After the initial management and resuscitation, these patients face prolonged hospital stays, multiple surgeries, increased risk of infection and sepsis, and a host of psychosocial obstacles. The addition of a progressive or unrecognized coagulopathy can further complicate this journey and lead to devastating consequences. By anticipating and better understanding BIC, providers will be able to optimize the care of their patients with reliable triage and targeted interventions.

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