Patients with Stevens - Johnson syndrome and Toxic Epidermal Necrolysis Develop Coagulopathies Similar to Those Seen in Burn Patients: A Pilot Study

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Abstract
Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are a continuum of a life-threatening skin loss condition due to an immune or hypersensitivity reaction. Patients are frequently treated in burn centers.

Objective: This study was undertaken to determine if patients with SJS and TEN have a coagulopathy with comparable hemostatic perturbations to those seen in patients with burn injury.

Materials & Methods: Blood plasma parameters studied were factors of coagulation, fibrinolysis, Interleukin-6 (IL-6) and Endothelin-1. Results were compared to historical hemostatic and cytokine data from burn patients treated at the same center.

Results: Sixteen patients with SJS-TEN (6 males/10 females) with ≥20% total body surface area (TBSA) sloughed skin were studied. The majority had received phenytoin or an antibiotic as the precipitating medication for the SJS-TEN. There was a significant increase in Thrombin-Antithrombin Complex (TAT) p<0.0004, tissue Plasminogen Activator (tPA), p<0.02, Plasminogen Activator Inhibitor-1 (PAI-1), p<0.02, and D-dimer p<0.007 plasma levels on admission. Antithrombin (AT), p<0.04 and plasminogen (PLG) p<0.02 plasma levels were significantly decreased. Conventional global coagulation tests (prothrombin and partial thromboplastin times) were not abnormal in patients with ≤7 days duration of the rash on admission. Patients with delayed admission at >7 days after the start of the rash had a significantly increased chance of demise, p<0.01. These patients also had a significantly decreased AT levels (p<0.01) compared to normal controls and to patients admitted at ≤7 days of the disease process, (p<0.01). The pattern of hemostatic aberrations of TAT, tPA, PAI-1, D-dimer, Interleukin -6, AT, and PLG was similar to that seen in burn patients during the acute phase of injury and resuscitation. The mortality rate was 37.5%.

Conclusions: Patients with ≥20% TBSA SJS-TEN had hemostatic perturbations consistent with those observed in ≥20% TBSA burn injuries coagulopathies.

Keywords: Stevens -Johnson Syndrome, Burns, Toxic Epidermal Necrolysis, Coagulopathy, Hemostasis, Coagulation Activation, Fibrinolysis, Endothelin-1, IL-6, Disseminated Intravascular Coagulation (DIC)

Introduction
Stevens -Johnson syndrome (SJS) was first described in 1922 as “fever with stomatitis and ophthalmia” [1]. In 1956, Dr. Lyell considered toxic epidermal necrolysis (TEN) to be a severe, life-threatening mucocutaneous disorder of extensive epidermal detachment, erythema and necrosis [2]. The 1995 Roujeau et al estimates of SJS incidence at 1 to 6 cases/million person-years, and of TEN at 0.4 to 1.2 cases/million person-years have not changed dramatically today [3]. A more recent case-control study determined that, of the medications that precipitated SJS and TEN, the antibacterial sulfonamides had an excess risk of 4.5 cases/million exposed people per week [3]. These two conditions are the severe form of the spectrum of rashes characterized as erythema multiforme major (EMM), and skin involvement of SJS (<10%), SJS-TEN overlap (10-30%), and TEN (>30%) [4,5]. Most frequent drug culprits have been anticonvulsants such as phenytoin, carbamazepine, antibiotics such as co-trimoxazole, and anti-inflammatory agents [6].
There have also been populations identified, which have a genetic proclivity to develop these conditions on exposure to carbamazepine, allopurinol, and co-trimoxazole [7].

With the loss of the epidermis through bullae and sloughing of skin, this rash is clinically equivalent to a second degree or partial thickness thermal injury. Burn and SJS-TEN patients are immunosuppressed and at risk for infection, with severity depending on the extent of total body surface and other mucocutaneous membrane involvement. The difference is that in SJS-TEN patients, the blistering and skin slough progress over the course of several days rather than being at highest severity at the initial impact of the burn trauma.

Kvasnička et al were the first to report the presence of disseminated intravascular coagulation (DIC) in eight TEN patients on the basis of tests such as prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), with increased fibrinogen and fibrin degradation products [8]. Clinical and subclinical DIC are a known consequence of the Systemic Inflammatory Response Syndrome (SIRS) even before infection sets in [9-11]. Burn injury has been documented to initiate subclinical and clinical DIC varying in severity according to the extent of % total body surface involvement (%TBSA) [12-15]. This study was undertaken to determine whether SJS-TEN patients develop coagulopathies similar to those seen in burn patients, and the impact of this complication on survival. The hypothesis was that SJS-TEN patients have skin damage and a coagulopathy akin to a partial thickness burn injury, even though SJS-TEN is an immune reaction compared to burn which is a mechanical traumatic injury. To our knowledge, there have been no recent studies on hemostatic disorders in SJS-TEN patients.

Materials & Methods

Sample Population

Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis (SJS-TEN) This was a retrospective study of the coagulopathy and cytokine laboratory results of sixteen patients with biopsy proven SJS-TEN admitted to the Burn Unit during a 5 year period. The patients arrived in various stages of the disease, most frequently at the point of skin rash or sloughing (Nikolsky sign), the phase past the crescendo defined by a period of rash and blisters. There were no patients with thrombosis or hemorrhage in this study. The majority (75%) had received some form of steroid therapy. The rash usually appeared with fever and flu-like symptoms approximately 2-3 weeks after the new medication had been started. SJS-TEN patients meeting the following criteria were eligible for study enrollment: 1) admission to the Burn Center within 15 days of rash onset; 2) age between one and 90 years; 3) informed consent. The study consisted of three blood collections for determining plasma levels of hemostatic and cytokine parameters on days 1-3, 4-7 and 8-12 after hospital admission. All the plasma hemostatic markers, endothelin-1, and IL-6 were analyzed within 3 months of acquisition. This study was approved by the Institutional Review Board. There was no further opportunity to study additional SJS-TEN patients after this investigation. The results of coagulation testing in these SJS-TEN patients were compared to historical burn patients whose coagulation and cytokine parameters were studied and published in the same time period in the same laboratory, and by the same investigators.

Historical Burn Population for Comparison of Hemostatic Factors

All eligible patients admitted to the burn unit during a 4-year period, >12 years old, with second-degree or third degree burns between 8% and 95% TBSA consented for participation within 24 hours of injury. This study was approved by the Institutional Review Board, and patients gave written informed consent. The results of this study were published previously [12].

SJS-TEN Care

Patients underwent sharp debridement and washing of all wounds with half strength Hibiclens soap. Silver nitrate impregnated gauze dressings were used for wound coverage and changed twice daily. Fluid resuscitation according to the Parkland formula was performed as needed, depending on the percent skin slough at the time of arrival at the hospital. As the wounds healed, the dressings were changed to Xeroform (Sherwood Medical, St. Louis, MO.), antimicrobial ointments, or aloe vera. The patients had early enteral feeding, meticulous eye care, ophthalmologic consultation, as well as aggressive physical and occupational therapy, and respiratory support if needed. No steroids were administered; if the patients were on steroids at admission, the medications were tapered and discontinued. Unlike burn patients, the majority of the SJS-TEN patients had received treatment at another institution for a variable number of days. The Burn Unit treatment protocol has been previously reported in detail [16]. The clinical history, general hematology and laboratory test results were obtained from patient medical charts.

Laboratory Analyses

Blood Collection

Venous blood samples were obtained by venipuncture or central venous access catheters within 24 hours of admission to the Burn Unit. A maximum of 3 samples per patient were collected up to a maximum of 12 days post-onset of rash. Samples are designated as days 1-3, 4-7, and 8-12 (dependent on the day post admission; day 1 was the day of admission). Blood was collected in 3.8% sodium citrate Vacutainer tubes (Becton Dickinson, Irvine, CA). Tubes were centrifuged at 40 C for 20 minutes at 3000g and the plasma was aliquoted and stored at -700 C until the assays were performed according to manufacturer’s instructions. All laboratory assays on the patients were performed within three months of entry into the study. None of the participating patients received anticoagulant therapy. Ten normal controls were assayed with the patient samples.

Assays

Antithrombin (AT), and plasminogen (PLG), plasma levels were determined using chromogenic substrate assays (Instrumentation Laboratory/Lexington, MA) on the ACL300 Plus (Instrumentation Laboratory/Coulter, Miami, FL). Thrombin-antithrombin complex (TAT) plasma levels were determined using an ELISA from Organon Teknika (Durham, NC). Tissue plasminogen activator (tPA), D-dimer, plasminogen activator inhibitor-1 (PAI-1) plasma levels were determined using ELISAs from Diagnostica Stago (Asnieres, France). Endothelin-1 (ET-1) plasma levels were determined using an RIA from Amersham (Arlington Heights, IL). Interleukin-6 (IL-6) plasma levels were determined using ELISAs from Genzyme (Cambridge, MA). All the studies were performed by the Hemostasis and Thrombosis Research Laboratory. All samples were analyzed in runs containing samples from clinical trial subjects and laboratory controls for the SJS-TEN patients. Historical Burn Patient Samples were processed in the same manner by the same laboratory personnel.
Table 1: Comparison of SJS-TEN Patient Characteristics Classified by Duration of Symptoms at the Time of Admission

| Days after Onset of Symptoms | 1-3 | 4-7 | 8-12 |
|------------------------------|-----|-----|------|
| No.                          | 10  | 4   | 2    |
| Age (years)                  | 56.3±19.3 (57) | 31.4±24.3 (35.5) | 36.0±1.4 (36) |
| Sex                          | 5M/5F | 1M/3F | 0M/2F |
| Race                         | 4C/6 AA | 3C/1AA | 2C/0AA |
| %TBSA                        | 38.1±23.6 (34) | 77.0±32.6 (89) | 100±0 (100) |
| Duration of Symptoms (days)  | 2.7±0.5 (3) | 5.3±1.5 (5) | 10.5±2.0 (7.5) |
| LOS (days)                   | 22.2±23.8 (12.5) | 26.5±21.4 (19) | 8.0±4.2 (8) |
| Mortality (%)                | 30  | 25  | 100  |
| Seizures (%)                 | 50  | 25  | --   |
| Phenytoin Cause (%)          | 50  | 50  | --   |
| Antibiotic Cause (%)         | 40  | 25  | 50   |

M=male; F= female; C= Caucasian; AA= African-American; TBSA=total body surface area; LOS=length of stay Results are given as mean±SD with median values given in parentheses.

Table 2 shows the hemostatic and cytokine parameters at the time of admission categorized by the duration of their symptoms prior to hospital admission. Although the values were elevated (compared to controls) representing an upregulation of inflammation, IL-6 and ET-1 had high coefficients of variation and were not statistically significant. Compared to control levels, TAT levels were significantly increased at the time of admission in all patients demonstrating coagulation activation. Patients admitted to hospital 1-3 days, 4-7 days, and 8-12 days after the start of the SJS-TEN symptoms had a median TAT level of 16.3 ng/ml (p<0.0004), 20 ng/ml (p<0.0004) and 4.6 ng/ml (p<0.02) respectively, Figure 1. Compared to normal levels, AT was significantly decreased encompassing consumption, dilution, and loss in individuals admitted on days 1-3 and days 8-12 of symptom duration, (median plasma levels of 36.0 % and 53.7 %), p<0.04. Similarly, PLG was decreased in individuals admitted on days 1-3 (p<0.007), days 4-7 (p<0.02), and days 8-12 of symptom duration (median plasma levels of 54.5%, 82.0 %, and 29.5 %) respectively. Significant elevations for tPA (p<0.02), PAI-1 (p<0.02) and D-dimer (p<0.003) levels were found in all patient groups indicating a strong activation of fibrinolysis. Fibrinogen plasma levels remained in the normal range in all cohorts, Figure 1.

When SJS-TEN patients were categorized by duration of symptoms as being in either the early (≤ 7days) or late (>7 days) period of the disease, i.e., after the development of the rash and bullae, only AT levels revealed a significant alteration. Patients admitted at >7 days after the start of the rash had a significantly increased chance of demise, p<0.01; these patients also had a significantly decreased AT compared to normal and to patients admitted at ≤ 7 days of the disease process, p<0.01.
Table 2: SJS-TEN Hemostatic and Cytokine Parameters Categorized by Duration of Symptoms on Admission

| Parameters  | Control          | 1-3 Days       | 4-7 days       | 8-12 days       |
|------------|-----------------|----------------|----------------|-----------------|
| AT (%)     | 115±35          | 52.0±33.9 (36.0) | 71.2±29.1 (65.0) | 54.4±17.2 (33.7) |
| TAT (ng/ml) | 3±2             | 26.4±33.6 (16.3) | 40.3±38.9 (20.0) | 5.1±0.95 (4.6)  |
| tPA (ng/ml) | 3±1             | 39.0±25.6 (38.7) | 21.1±10.0 (17.8) | 68.2±56.6 (67.6) |
| PAI-1 (ng/ml) | ≤48            | 80.6±40.6 (83.9) | 63.5±67.5 (42.5) | 91.5±55.96 (101.0) |
| PLG (%)    | 97.3±6.8        | 51.5±33.1 (54.5) | 67.7±29.3 (82.0) | 48.8±50.9 (29.5) |
| D-dimer (ng/ml) | 163±54         | 1718.2±443.4 (1659) | 1104.3±155.8 (1094.5) | 1543.0±424.3 (1543.0) |
| Fibrinogen (mg/dl) | 275±125        | 471.2±221.2 (375) | 214.8±72.8 (208) | 359.0±147.1 (359) |
| ET-1 (pg/ml) | 304.5±43       | 384.1±200.8 (362.3) | 437.2±178.3 (423.6) | 336.4±33.0 (324.0) |
| IL-6 (pg/ml) | 90±6            | 701.6±692.8 (530) | 420.9±366.5 (308.2) | 367.5±296.1 (257) |

P values reflect a comparison to laboratory normal controls. Results are given as mean±sd; median values are in parentheses. AT= antithrombin; TAT= thrombin-antithrombin; tPA= tissue plasminogen activation; PAI-1= plasminogen activator inhibitor-1; PLG= plasminogen; ET-1 = Endothelin-1; IL-6= Interleukin-6

Figure 1: Coagulopathy in SJS-TEN patients by Duration of Symptoms on Admission

Survivors versus Non-Survivors Regardless of Duration of Symptoms on Admission
Table 3 shows a demographic comparison between the SJS-TEN survivors and non-survivors. Both groups had a similar median age (51.5 versus 47 years), and duration of symptoms on admission (3 versus 3.5 days). The median length of stay (19 versus 7.5 days) was shorter for the non-survivors. The non-survivors had a greater %TBSA involvement on admission (median of 35% in the survivors versus 70% in the non-survivors) Figure 2.

Table 3. Characteristics of Survivor and Non-Survivor SJS-TEN Patients

| Parameter           | Survivor | Non-Survivor |
|---------------------|----------|--------------|
| No.                 | 10       | 6            |
| Age (years)         | 46±14 (51.5) | 51±33 (47)   |
| Sex                 | 4M/6F    | 2M/4F        |
| Race                | 6C/4AA   | 3C/3 AA      |
| %TBSA               | 48.1±32.7 (35) | 68.0±34.5 (70) |
| Duration of Symptoms (days) | 3.5±1.7 (3.0) | 5.7±3.9 (3.5) |
| LOS (days)          | 25±22 (19) | 16±21 (7.5)  |
| Seizures (%)        | 30       | 50           |
Table 4 shows that the conventional clinical coagulation and hematology tests of PT, APTT, hemoglobin, and hematocrit did not differ significantly between the survivor and non-survivor groups. The white cell count was higher in the non-survivors versus survivors; the platelets were significantly decreased in the non-survivors versus survivors. Table 5 shows the hemostatic and cytokine parameters of the SJS-TEN patients at the time of admission compared to normal controls without reference to % TBSA or duration of symptoms. In most cases, the hemostatic and cytokines aberrations were increased in severity in the non-survivors when compared to the survivors. AT and PLG were significantly decreased in the non-survivors. All SJS-TEN patients had significant increases in TAT, tPA, PAI-1, and D-dimer, indicating a significant activation of coagulation and fibrinolysis, Figure 2,3,4. Although IL-6 was increased in both groups, it was only significantly increased in the non-survivors compared to normal controls.

Table 4: Comparison of Laboratory Values in SJS-TEN Survivors and Non-Survivors at the Time of Admission

| Parameter | Control | Survivors | Non-Survivors |
|-----------|---------|-----------|---------------|
| PT (seconds) | 11.5±13.5 | 14.1±13.2 (13.7) | 13.9±1.13 (16.5) |
| APTT (seconds) | 23-31 | 27.2±6.1 (24.4) | 28.6±0.85 (28.6) |
| WBC (K/cu mm) | 3.1-9.4 | 6.97±3.8 (6.9) | 10.5±11.9 (10.5) |
| Hemoglobin (gm%) | 11.9-15.7 | 10.8±2.0 (10.7) | 10.00±2.8 (10.0) |
| Hematocrit (%) | 35.7-46.0 | 31.3±7.3 (30.0) | 29.0±8.3 (29.0) |
| Platelets (K/uL) | 150-400 | 191.0±110.0 (199) | 57.0±33.9 (57.0) |

Results are given as mean±SD or Percentage, median values given in parentheses. PT= Prothrombin Time; APTT= activated partial thromboplastin time. It is not known if patients received transfusions at institutions from which they were admitted to the burn unit. If there were any transfusions, the SJS-TEN patients admitted with symptom duration of 8-12 days were most likely at risk.

Table 5: Comparison of Hemostatic and Cytokine Parameters in SJS-TEN Survivors and Non-Survivors at the Time of Admission

| Parameter | Control | Survivors | Non-Survivors |
|-----------|---------|-----------|---------------|
| AT (%) | 115±35 | 79.4±30.5 (78.0) | 0.46 | 34.4±15.8 (34.8) | 0.004 |
| TAT (ng/ml) | 3±2 | 25.6±33.9 (16.3) | 0.0002 | 16.1±11.9 (15.1) | 0.001 |
| tPA (ng/ml) | 3±1 | 40.5±23.9 (38.9) | 0.0014 | 22.8±15.9 (17.2) | 0.01 |
| PAI-1 (ng/ml) | <48 | 72.5±45.6 (69.1) | 0.0002 | 59.5±27.7 (55.9) | 0.001 |
| PLG (%) | 97±7 | 82.0±4.1 (82.0) | 0.006 | 21.3±9.4 (20.5) | 0.006 |
| D-dimer (ng/ml) | 163±54 | 1260.0±303.3 (1202.0) | 0.003 | 1848.0±542.1 (1880.0) | 0.01 |
| ET-1 (pg/ml) | 304.5±43 | 479.2±195.3 (423.6) | 0.01 | 274.0±121.3 (317.8) | 0.87 |
| IL-6 (pg/ml) | 90±2 | 548.9±677.7 (237) | 0.24 | 584.1±461.5 (565.7) | 0.03 |

Results are given as mean±sd; median values are in parentheses. P values reflect a comparison to laboratory normal controls. AT= antithrombin; TAT= thrombin-antithrombin; tPA= tissue plasminogen activation; PAI-1= plasminogen activator inhibitor-1; PLG= plasminogen; ET-1 = Endothelin-1; IL-6= Interleukin-6

It is not known if patients received transfusions at institutions from which they were admitted to the burn unit. If there were any transfusions, the SJS-TEN patients admitted with symptoms of 8-12 days were most likely at risk.

Figure 2: Coagulopathy in SJS-TEN survivors and non-survivors on admission
Table 6 illustrates the hemostatic parameters in patients with thermal injury previously reported for comparison [12]. These values can be directly compared to the hemostatic parameter alterations in SJS-TEN patients, since all studies were performed by the same laboratory. The equivalent burn values correspond as follows: Burn Day 1 corresponds to SJS-TEN duration of symptoms Days 1-3; Burn Day 5-7 corresponds to SJS-TEN duration of symptoms Days 4-7. The findings based on %TBSA severity of burn patients on Day 1 of admission and on Days 5-7 indicated coagulation and fibrinolysis activation the patients encountered once exposed to the traumatic injury and the start of SIRS. The smaller the burn or fewer days of the rash reflected less severe hemostatic aberrations when compared to larger burns or longer periods of rash and sloughing without treatment. In subsequent studies, the level of AT was used as an effective monitor of the status of the burn patients [17,18]. When compared to normal control values, the patient data of Tables 2 (SJS-TEN) and 6 (Burn) demonstrates similar coagulation, fibrinolytic, and cytokine abnormalities, Figure 3 and 4.

Table 6: Comparison of Hemostatic and Cytokine Parameters in Burn Patients by Severity of Injury

| Parameter | Normal Control N=20 | 20-40% TBSA N=18 | >40% TBSA N=20 |
|-----------|---------------------|------------------|----------------|
| Day 1     |                     |                  |                |
| AT (%)    | 106.95±10.8 (106.5) | 86.1±20.1 (84.0) | 95.7±17.3 (99.0) | 48.2±20.2 (46.0) | 75.5±24.6 (82) |
| TAT (ng/ml) | 5.47±13.8 (2.25)   | 16.0±6.9 (15.1)  | 6.5±4.1 (5.0)   | 20.4±12.87 (16.2) | 9.8±9.6 (5.3) |
| tPA (ng/ml) | 5.33±2.0 (5.3)      | 7.33±3.98 (6.9)  | 6.06±3.6 (6.4)  | 15.96±10.9 (11.2) | 8.78±6.9 (5.3) |
| PAI-1 (ng/ml) | 2.99±1.6 (2.45)    | 4.0±3.96 (3.2)   | 4.6±4.8 (3.7)   | 10.3±5.95 (11.0)  | 9.2±6.1 (7.1) |
| PLG (%)  | 96.7±7.3 (95)       | 81.2±17.7 (80.5) | 111.4±24.5 (109) | 46±21.7 (49.5) | 90±45.5 (88) |
| D-dimer (ng/ml) | 144.4±131.5 (111.5) | 933.5±678.1 (760.5) | 1307.6±887.7 (1322.5) | 1116.2±775.7 (844.5) | 1262.6±810.6 (1450.0) |
Discussion

This study demonstrates that SJS-TEN patients have a coagulopathy similar to that of burn patients, which can progress to intravascular disseminated activation of coagulation and fibrinolysis (DIC). This conclusion is supported by the significant increases in plasma levels of TAT, tPA, PAI-1, D-dimer, and a decrease in AT and PLG in these patients [12,14,15]. On admission in the acute phase of the disease, patients were able to maintain a homeostatic equilibrium, which resulted in normal PT, APTT, platelets, and fibrinogen levels. Those presenting late in the disease process (8-12 day subset in our study) were most at risk for clinical DIC due to continual coagulative and fibrinolytic activation if not appropriately treated for that time period prior to admission. Patients admitted after 7 days of disease symptomatology had significantly increased coagulopathy and mortality when compared to those admitted earlier. There is an active literature debate as to whether burn injury patients develop DIC or trauma-induced coagulopathy (TIC), as seen in trauma patients. Although SJS-TEN and Burn injury coagulation activation and fibrinolytic parameter aberrations are similar to those seen in trauma-induced coagulopathy, other factors distinguish these conditions.

DIC vs Trauma-Induced Coagulopathy (TIC)

In patients with trauma, burn, and SJS-TEN, injury initiates the Systemic Inflammatory Response Syndrome which triggers the activation of systemic coagulation, fibrinolysis, and platelets. As a result, all hemostatic factors such as Protein C, and natural anticoagulants such as AT are consumed and depleted contributing to the coagulopathy. A comparison study of coagulopathy in burn and trauma patients indicated higher TAT complexes, and endothelin-1 plasma levels in trauma patients compared to burn patients on admission in the first five hospital days [19]. There were elevated levels of IL-6, tPA and PAI-1 plasma levels compared to control levels in both groups [19]. The physiologic response was similar although the degree and consequences of injury, and circumstances in these two groups were not [19].

Clinical DIC has been documented in SJS-TEN and burn patients [8,12]. Unless they also have traumatic injuries, they usually do not have a disruption of their vascular system resulting in hemorrhage. On admission, commensurate with the severity of injury (extensive % TBSA involved), SJS-TEN patient hemostatic systems become deranged through factor and natural anticoagulant consumption, hemodilution, and loss, as seen in burn patients. Trauma patients frequently hemorrhage and have massive transfusion requirements on admission due to trauma-induced bleeding [20,21]. They may also be more likely than burn or SJS-TEN patients to have major infections within days of admission, requiring early antibiotic therapy. TIC has been reported as Coagulopathy of Trauma/Acute Coagulopathy of Trauma Syndrome (COT/ACOTS) and has been mainly defined in terms of the Activated Protein C hemostatic pathway, fibrinolysis, and strength and elasticity of clot formation [20,22]. There is much controversy about the actual definition of trauma-induced-coagulopathy. Explanations have been published as to how to differentiate DIC with fibrinolytic phenotype from coagulopathy of trauma and acute coagulopathy of trauma-shock (COT/ACOTS) [23]. Currently, a position paper was published on Remote Damage Control Resuscitation Trauma Hemostasis and Oxygenation Research (THOR) Network which is attempting to standardize and gain a consensus this area of trauma research [22].

The majority of burn literature considers DIC as a more likely derangement than TIC because of the systemic seeding and breakdown of microthrombi in the microvasculature in the acute phase, which is not the case in trauma patients, who are diagnosed as having TIC [24-26]. A recent study, evaluating the hematologic parameters of 102 burn patients (15-100% TBSA) on admission, was not able to categorize them as TIC because they presented with a normal hematologic profile, not suggestive of TIC [27].

This is the first, albeit small, study of the complex hemostatic and fibrinolytic status of SJS-TEN patients to date. Our study confirms the report of Kvasnička et al that SJS-TEN patients develop subclinical and clinical DIC, which must be addressed medically [8]. Similar to burn patients, these individuals are also at risk for hypercoagulability, because of the continued fibrinolysis resulting in fibrin monomers and debris clogging the capillaries, arteriole, and small vessels if they are not adequately resuscitated with fluid [28]. There have been recent literature reports of thrombosis in SJS-TEN patients [29,30]. If the hemostatic derangements are not corrected by appropriate treatments, increased morbidity and mortality may ensue.

The identified hemostatic aberrations in our study indicate that there is a subclinical DIC in SJS-TEN patients similar to that seen in thermal injury. These patients have been compared to second degree (partial thickness) burn patients in respect to the destruction of the epidermis and blister formation [31]. Although the agent of skin destruction may be different, the skin loss and systemic impact are similar [32].

The only other literature comparison between TEN and burn injury patients was that of tissue necrosis factor-α (TNF-α) and IL-6 in the blisters and in the serum of TEN and burn patients [31]. There did not appear to be a significant difference in the presence of IL-6; however, there was a significantly increased amount of the associated receptors, TNF-R1 and TNF-R2, in TEN and burn blisters compared to plasma levels [31]. This may be contributing to the increase of the cytotoxic effect of TNF-α in the blisters [31]. There is indication of a certain degree of endothelial damage with the higher levels of ET-1 in some patients [33]. Once the fibrinolytic system is activated, feedback loops in the hemostatic system stimulate the coagulation system and thrombin generation causing clot formation, consumption, fibrinolysis, and platelet activation with the loss of the natural anticoagulants such as AT [33]. In addition to the supportive care as standard for burn patients which permits the autologous regeneration of the skin in SJS-TEN patients, AT concentrate therapy has been shown to provide a positive clinical impact and reduced
mortality in the burn patient population [17,18,25,26]. Tagami et al showed that severely burned AT-treated patients had significantly decreased 28-day mortality and increased ventilator free days compared to controls [34]. A recent report found AT plasma levels decreased in TEN patients [35]. The authors found that treatment with AT and cyclosporine reduced mortality in SJS-TEN patients with low plasma levels of AT on admission [35].

The limitations of this study were the small number and unequal distribution of SJS-TEN patients in each of the symptom duration groups on admission. This unequal number of patients, especially in the duration of symptoms for 8-12 days at the time of admission made statistical analysis difficult. There was also the challenge to determine the start of the rash from the patient histories and therefore, the exact number of days (hours) of symptom duration. Also, the interpretation of the hemostatic parameters was complicated by the treatment the patients received prior to the study admission date. The majority had received steroids, which may have impacted the plasma levels of the hemostatic factors, and cytokines. In addition, the presence of infection on admission or during the hospital stay may have affected the coagulation and fibrinolytic factors. Comorbidities such as diabetes, hypertension and cancer with the attendant radiation and chemotherapy may have contributed to patient response to treatment and outcome. While we were able to demonstrate that coagulation and fibrinolytic plasma levels were “time of presentation” and “TEN-SJS % TBSA severity” dependent, we were not able to evaluate whether they were also affected by the culprit drug or patient gender.

Conclusion
Patients who develop SJS-TEN have a similar response to the initial impact of a rash, skin loss and mucocutaneous disorder, as do patients with a traumatic second degree (partial thickness) thermal injury. Depending on the severity and extent of their injury, they undergo a SIRS reaction to their homeostasis with activation of coagulation, fibrinolysis, and cytokine production developing a coagulopathy which may evolve into a clinical DIC if not resuscitated appropriately. Although the mechanism of injury is different from that of burn injury (immune versus traumatic mechanical), rapid withdrawal of the offending agent or mechanism of injury and supportive treatment is paramount to the healing process. Further studies of the coagulation, fibrinolytic, and cytokine systems in SJS-TEN patients are warranted. Although this study still has many unanswered questions, it is hoped that it will stimulate not only discussion but further investigations.

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