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# DISSEMINATED INTRAVASCULAR COAGULATION

## SUMMARY

Disseminated intravascular coagulation (DIC) is a condition in which blood clots form throughout the small blood vessels of the body leading to deposition of intravascular thrombin and fibrin that ultimately leads to end-organ tissue damage (1,2). Paradoxically, due to utilization of the multiple factors of the clotting cascade as well as platelets, DIC can lead to further bleeding, both internally and externally. Specific patient populations are at higher risk of this disease, notably those with sepsis, surgery or trauma, cancer or obstetric complications of pregnancy and childbirth. Paramount to the treatment for this disease is addressing the underlying cause. In addition, one must control bleeding, often requiring administration of blood and clotting factors.

## RECOMMENDATIONS

- **Level 1**
  - **Treatment of trauma patients with DIC of the fibrinolytic phenotype in the first few hours of presentation with tranexamic acid may improve mortality**
  - **In sepsis-associated DIC, antithrombin can improve DIC scores and is not associated with increased bleeding**
- **Level 2**
  - **Goal-directed therapy with replacement of blood products via use of thromboelastography in DIC associated with trauma and bleeding leads to lower mortality**
- **Level 3**
  - **High suspicion of DIC in the critical care setting should prompt evaluation via a scoring system; this score should be periodically repeated.**

## INTRODUCTION

Several phenotypes of DIC have been described and these separate manifestations are directly related to their underlying cause. These types include a predominately coagulative organ failure type, which is associated with sepsis, a fibrinolytic type associated with bleeding, an asymptomatic type, which is a combination of fibrinolysis and coagulation type, and finally the extreme of each, the massive bleeding type in which both fibrinolysis and coagulation phenotypes are fully activated (2). Though there is debate about which type is most associated with bleeding in trauma, recent research suggests that DIC is a continuum and that different states of DIC may be a function of the time course of the disease process. Furthermore, it appears that acute trauma most closely matches DIC of the fibrinolytic phenotype (2,3). In the critical care setting, prompt identification of those with potential of DIC is prudent, particularly as those with bleeding

## EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

## LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

type DIC require rapid administration of blood products or they face a consequence of increased risk of mortality.

A recent attempt was made by the International Society of Thrombosis and Hemostasis (ISTH) to standardize the three separate international guidelines for DIC from Japan, Italy and Britain and concluded that diagnosis of DIC should be based upon a scoring system rather than a single diagnostic test (2,4). Furthermore, they state that a combination of tests taken over time provide the best means for diagnosis (4). For the purposes of trauma, the consensus shows that any of the three criteria can diagnose bleeding type DIC, and the Japanese Association of Acute Medicine (JAAM) criteria for DIC is thus included below (2,4,5).

**Fig 1: JAAM Scoring Criteria for DIC**

<b>SIRS criteria</b>	<b>Score</b>
≥3	1
0-2	0
<b>Platelet count</b>	
<80 or > 50% decrease within 24 hrs	3
≥ 90 and <120 or >30% decrease within 24hrs	1
≥ 120	0
<b>Prothrombin Time (PT/INR)</b>	
≥ 1.2	1
<1.2	0
<b>Fibrin/ fibrinogen Degradation products (mg/L)</b>	
≥ 25	3
≥ 10 and <25	1
<b>Diagnosis</b>	
≥ 4 points	<b>DIC</b>

## **LITERATURE REVIEW**

### ***Treatment of DIC***

The mainstay of treatment for DIC remains addressing the underlying condition whether that be sepsis, malignancy or bleeding. The bleeding type requires administration of blood products. In particular, low platelets and coagulation factors are keystones for treatment of fibrinolytic and bleeding type DIC. In those actively bleeding, platelets and FFP are recommended (3). Platelets are typically given for those with less than 50,000 cells/ microliter or active bleeding and FFP is given at doses of 15 ml/kg in initial dosing (3). With DIC, fibrinogen is also low, and thus purified fibrinogen or cryoprecipitate are also recommended (3).

### ***Goal directed therapy for DIC***

The use of goal directed therapy for addressing coagulopathy has been studied and shown to be valid. Schöchl investigated a strategy for management of trauma-induced coagulopathy using coagulation factor concentrates (6). They conducted a retrospective analysis of patients who received > 5 L of pRBCs within 24 hours. The management of coagulation was guided by thromboelastometry (ROTEM). In their protocol fibrinogen concentrate was given for hemostasis when max clot firmness (MCF) was <10mm. Prothrombin complex concentrate (PCC) was given in case of extrinsic activation test >1.5 normal. If lack of improvement was seen after fibrinogen was given, then platelet concentrate was given. They then compared observed mortality with that of predicted mortality by the trauma injury severity score (TRISS) and revised injury severity classification (RISC) score. Their observed mortality when traumatic brain injury was omitted was 14.4%, less than the TRISS of 27.8% (P=0.0018) and RISC mortality of 24.3% (P=0.014). They conclude that ROTEM guided therapy with fibrinogen and then PCC showed better survival (6).

Similar to the study above, Gonzales showed in a randomized control trial that thromboelastography (TEG) guided massive transfusion protocol improved survival compared to conventional coagulation assays (7).

In this study 111 patients were randomized to TEG versus conventional coagulation to guide therapy and the primary outcome of 28 day survival was analyzed. 34.6% mortality was seen with conventional methods and 19.6% for those with TEG guided therapy (7). Evidence for the use of TEG or ROTEM to guide therapy in massive transfusion and traumatic coagulopathy, with TEG as the primary means in the United States and ROTEM in Europe, is emerging as advantageous to overall survival.

Antifibrinolytic treatment, also known as tranexamic acid, is recommended in select cases of DIC, but as shown in the CRASH 2 trial, its efficacy is only seen within the first few hours after onset of bleeding (8). The pathophysiology of this reaction can be correlated with the activity of plasminogen activator inhibitor 1, which in the first hours of trauma has not yet begun to elevate (3).

### ***Defining DIC in Trauma***

Defining DIC in the trauma patient is not without some contention specifically whether DIC is a different entity than that seen with acute coagulopathy of trauma or shock (ACOTS). Johansson conducted an observational study that looked at 80 adult trauma patients in which arterial cannula allowed for blood draw (9). In these patients, plasma serum was tested for various biomarkers for tissue damage, coagulation activation, factor consumption, fibrinolysis, and inflammation. These various factors were used to stratify patients into DIC (based upon ISTH criteria) and ACOTS. None of their patients had DIC, whereas 15% met criteria for ACOTS all of whom had higher Injury Severity Score (ISS). Furthermore, they found that with those patients who did not meet ACOTS criteria, the higher the ISS the more they resembled ACOTS findings. They conclude that the trauma patients in their study may represent a “Continuum of coagulopathy” and that DIC is not part of the early trauma response (9).

Gando argues a different point, that the two emerging concepts of hemostatic changes in trauma, DIC with fibrinolytic phenotype and Coagulopathy of trauma and ACOTS are more a continuum (10). He argues that DIC has been presented as separate concepts: The first being DIC with fibrinolytic phenotype in which coagulation pathways are activated, there are insufficient anticoagulant mechanisms and increased fibrinolysis. The second being ACOTS in which increased activation of the thrombomodulin and protein C pathways leads to suppression of the coagulation and activation of fibrinolysis. Gando argues that this separation may be based on flawed studies which do not properly control for timing of blood samples, different properties of blood inside and outside vessels just to name a few (10). Gando further describes the continuum of DIC and argues that with traumatic coagulopathy, even though multifactorial, DIC with fibrinolytic phenotype is the predominant pathogenic pathway and the transition from a fibrinolytic phenotype as previously described to a thrombotic phenotype occurs at 24 to 48 hours when one begins to see high of plasminogen activator inhibitor-1 (11). Treatment in trauma therefore involves surgical repair, improvement of shock and rapid replacement of platelet, FFP and depleted coagulation factors, but also provides a physiologic paradigm for how administration of antifibrinolytic agent (tranexamic acid) may reduce the risk of death in bleeding trauma patients with DIC (11).

Finally, Oshiro further tests the assertion that DIC with fibrinolytic phenotype and ACOTS are a similar disease process (12) This study was conducted using retrospective data on 562 trauma patients, 338 of whom had data collected immediately upon admission. A diagnosis of DIC was then assigned based upon JAAM DIC scoring system and ACOTS defined as Prothrombin-time ratio of >1.2. They found that DIC with fibrinolytic phenotype had lower platelet counts and fibrinogen levels, increased PT time ratios, higher FDP and D-dimer levels, and lower antithrombin levels compared to Non DIC patients upon arrival to ED. Furthermore, almost all ACOTS patients met criteria for diagnosis of DIC. JAAM DIC score was found to be an independent predictor of massive transfusion and death due to trauma and correlated with amount of blood transfused. They conclude that those who develop DIC with fibrinolytic phenotype during trauma exhibit consumption coagulopathy associated with increased fibrinolysis and lower antithrombin (12).

### ***Is there a role for antithrombin in DIC***

Attempts to answer this question focus on the coagulopathic phenotype often associated with sepsis. In a randomized controlled multicenter study using the JAAM DIC criteria for diagnosis, administration of antithrombin incidence of minor bleeding and even major bleeding were not seen to increase and DIC scores actually improved (13). However, no change was seen in sequential organ failure assessment score (SOFA) or markers of coagulation. They concluded that moderate doses of antithrombin can increase

recovery from DIC without increasing risk of bleeding in the septic patient (13). These recommendations for antithrombin do not hold for active bleeding DIC (2,4).

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