



# Prevention and treatment of trauma induced coagulopathy (TIC). An intended protocol from the Italian trauma update research group

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## Abstract

In recent years, a strong focus has been put on the need to assure early coagulation support in order to prevent and treat coagulopathy in patients with severe trauma, and to improve survival. Aggressive plasma administration with high plasma/red blood cells ratio is increasingly used worldwide. However, plasma transfusion is associated with increased risks of multiple organ dysfunction syndrome (MODS), adult respiratory distress syndrome (ARDS) and infection, which may prolong hospital stay and the need for artificial ventilation. Moreover, in the majority of European hospitals plasma cannot be immediately available and therefore it has been reported a significant delay in coagulation support. This has led to the proposal of using clotting factors as an alternative to plasma. However, strong evidence to define the best strategy is still missing, and the only published protocols are Institution-specific, thus depending on the local organization and the available resources. The Italian Trauma Centers Network (TUN) recently developed a treatment protocol aiming at shortening the interval before the onset of coagulation support and at reducing the use of plasma. We present this protocol-Early Coagulation Support (ECS) Protocol - and discuss its rationale. Its implications for the trauma-team workflow and hospital organization are also addressed. The ECS protocol must be considered as an integrated part of a comprehensive Damage Control Strategy. The impact of the ECS Protocol on blood products consumption, trauma mortality and morbidity as well as its financial aspects, will be strictly monitored by the TUN hospitals.

**Keywords:** Trauma, coagulopathy, transfusion, plasma, clotting factors, protocol, multicenter

## Background

Haemorrhage is the principal cause of death in the first few hours following severe injury. Coagulopathy is a frequent complication of haemorrhage and may occur in up to 25% of patients, even before hospital admission [1]. In recent years, international guidelines [2] that aim at preventing and treating trauma-induced coagulopathy (TIC), have been developed. However, due to the heterogeneous availability of haemocomponents and clotting factors in different countries and to the lack of sound data in the literature, there is not a widely agreed clinical strategy yet. Moreover, due to the aging population in western countries, elderly people with cardiovascular comorbidities and on antiplatelets agents or oral anticoagulants are increasingly represented. Therefore, a comprehensive protocol to treat the bleeding patients should also include strategies to quickly reverse the effect of these drugs.

Any strategy should rapidly tackle acute traumatic coagulopathy through the early replacement of clotting factors. Haemostasis is critically dependent on fibrinogen as a substrate

for clot formation. Fibrinogen is the single factor which is more and earlier affected in case of TIC. Many bleeding trauma patients with TIC present with a depletion of fibrinogen below levels currently recommended for therapeutic supplementation [2]. In a recent study, hypotension, increasing shock severity (as measured by the base deficit) and high degree of injury (ISS  $\geq 25$ ), were all associated with a reduction in fibrinogen levels [3]. Fibrinogen depletion is associated with poor outcomes and survival improves with the amounts of fibrinogen administered [4]. Plasma has traditionally been used as a source of fibrinogen. However, until few years ago plasma transfusion was not recommended in absence of a prolongation of PT or INR or fibrinogen decrease to less than 1.5 gr/L. More recently, retrospective evidence from both military [5] and civilian [6] practice suggested improved outcomes in patients with massive bleeding after the adoption of a massive-transfusion protocol (MTP), including the early administration of high-dose plasma therapy. Although the first reports based on the military experience suggested a 1:1 plasma/packed red

blood cells (PRBCs) ratio, more recent data, supported by thromboelastometry, have shown that a lower rate (*i.e.*, 1:2) may be preferable [7]. There are several limitations on the use of plasma to prevent and treat TIC. Both Fresh Frozen Plasma (FFP) and pathogen-inactivated plasma (industrial purified plasma) need to be group matched, thawed and warmed before administration. Therefore, unless pre-thawed plasma is available, plasma transfusion cannot be started at the same time as universal PRBCs. A delay of 93' has been reported, [8] possibly explaining why the targeted plasma/RBCs ratio is reached only a few hours after starting treatment. During this interval fibrinogen level is likely to be lower than desired.

Plasma transfusion has also been associated with an increased risk of post injury MODS, ARDS and infections. These complications increase with the volume of transfused plasma [9]. The risk of transfusion related acute lung injury (TRALI) has been greatly reduced by avoiding the use of the plasma of women with pregnancy history [10]. In Italy the recent introduction of pathogen-inactivated plasma enabled to further minimize the risks of TRALI and virtually eliminate the risks of transmission of infective diseases. Although these measures are effective in reducing some of the adverse effects of plasma transfusions, recent data [11] show that in patients who require less than 6 Units of PRBCs, the complications related to plasma transfusion may overcome the benefits.

The balance between a rapid intervention to treat or prevent TIC and the risk related to unnecessary transfusion of plasma, is difficult to achieve. The use of coagulation factor concentrates have been proposed as the strategy to reduce and even avoid plasma transfusion in patients with significant bleeding. In the Austrian guidelines [12] fibrinogen concentrate is the first-line treatment. Two retrospective studies comparing data from Austrian Trauma Centres with the German Trauma (TR-DGU) registry, reported a significant reduction in platelet transfusion and a limited decrease in blood transfusion for bleeding patients treated with fibrinogen concentrate and prothrombin complex concentrate (PCC) who did not receive FFP during initial resuscitation [13,14]. Early coagulation monitoring with ROTEM was used to guide the administration of coagulation factors, starting immediately after patient admission. However, these results have not been confirmed by prospective controlled studies.

Although very appealing, the "plasma-free" strategy proposed by Schöchel [13] may not be easily adopted by Italian Trauma Centres as it requires thromboelastometry monitoring to be started straight on patient's admission and only few Italian hospitals can adhere to this requirement at the moment. Moreover it may imply the use of a rather high amount of fibrinogen with considerable related costs. Fibrinogen availability might also turn out to be problematic as fibrinogen is not commercially available in Italy and hospitals are supplied with limited amount on the base of a national drugs agency (AIFA) authorization.

The Steering Committee of the Italian Trauma Update

Network has recently developed a comprehensive treating protocol (Early Coagulation Support – ECS) to improve and homogenize the early treatment of trauma patients with significant bleeding and at high risk of massive transfusion. Compatibility with the resources currently available in the average Italian Trauma Centre is a key point of its rationale. Besides supporting coagulation and shorten the "time-to-treat" to effectively reduce the bleeding, the other main objective of the protocol is to limit the use of plasma in patients who are not likely to need it, in order to reduce plasma-related adverse effects.

## Methods

The ECS protocol was developed by a multidisciplinary group of Anaesthetists, Haematologists, Surgeons and Intensive Care physicians involved in trauma care on daily basis. The Trauma Update Research Network (TUN) is an informal association of Italian Trauma Centres that jointly support and promote education and researches in Trauma Care sharing data and treatment strategies aimed to improve patients outcome. The ECS protocol is based on the available data from the current literature (as of August 2012). It is tailored on the current organization of the Italian Trauma Centres involved in the TUN, accounting for their limited financial and human resources. The TUN panel acknowledges the potential advantages of rapid (Point of Care) diagnostic tools to quickly identify coagulopathy and guide transfusion management as suggested by the European Guidelines [2]. However, the ECS protocol has been conceived to be feasible even when rapid diagnostic tools are not available, aiming to be a standard sustainable by all Institutions. The ECS protocol is presented in [Table 1](#) and [Table 2](#).

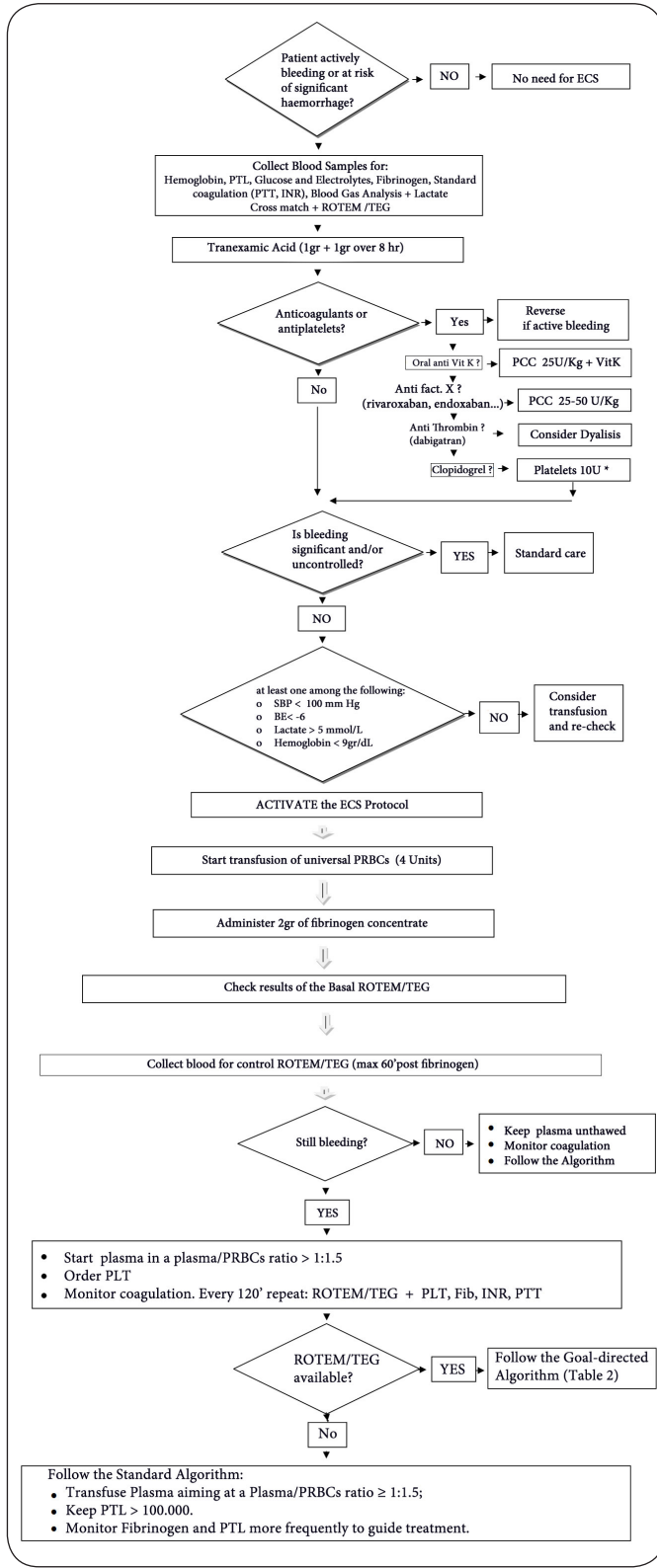
## Results and Discussion

Based on the results of the Crash 2 study [15], the early administration of Tranexamic Acid (TA) to all patients with ongoing bleeding or at risk of significant bleeding is now standard care for the Trauma Centres of the TUN. According to the protocol, TA must be initiated on patient's admission after the collection of a blood sample for laboratory tests, cross matching and basal clotting profile. TA must be initiated within the first 3 hours after trauma. If for any reason, a patient has not received TA within this deadline, TA administration is not recommended. Initial administration of TA complies with the Crash 2 study protocol: initial dose of 1gr, followed by a continuous infusion of the same dose of TA. If the viscoelastic monitoring allows to exclude ongoing fibrinolysis, further treatment may be avoided and the continuous TA infusion stopped.

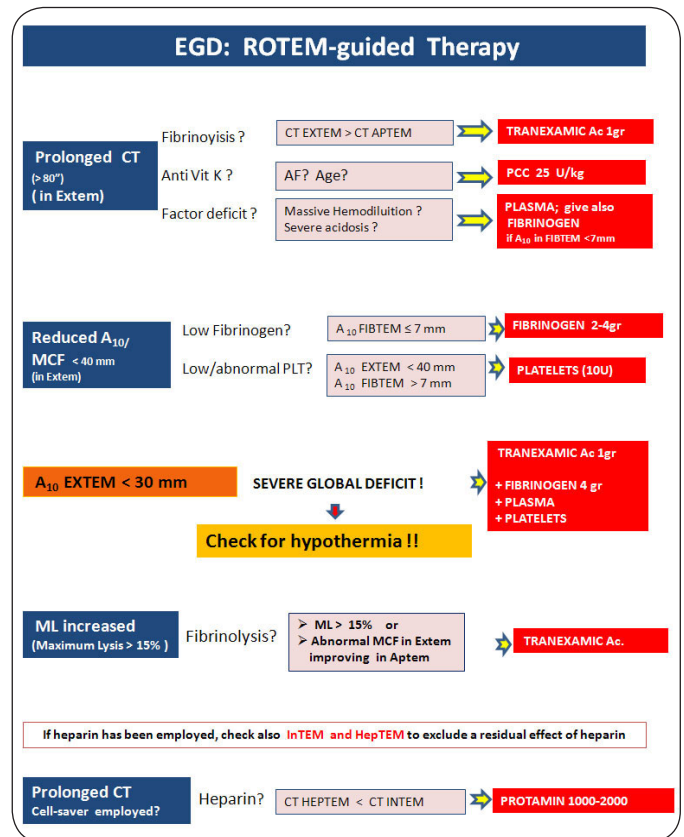
The number of patients on antiplatelet or anticoagulation therapies is increasing. A retrospective cohort study of Trauma Centres, that submitted data to the National Trauma Databank (NTDB) from 2002 to 2007, demonstrated an increase in vitamin K antagonists (VKA) use in the general trauma population

**Table 1. The Early Coagulation Support (ECS) Algorithm.**  
 \* 10 Units of PTL = 2 Units of single donor apheresis or 2 Units of buffy coats pool PTL.

\*\* 1 Plasma Unit = 250 mls of FFP or 200 mls of ; if Apheris plasma is used 1 Unit = 500 mls = 2 Units of FFP.



**Table 2. Early Goal Directed Therapy based on the results of thromboelastometry monitoring.**



from 2.3% in 2002 to 4% (p<0.001) in 2006. In patients older than 65 years the use of VKA increased from 7.3% to 12.8% in the same period (p<0.001). Pre-injury VKA use is age-related with a sharp increase between the age of 45 and 70 years. Head trauma patients on VKA have a higher risk of intracranial haemorrhage. The younger patients on anticoagulants have a 50% higher mortality [16]. Recent guidelines recommend emergency anticoagulation reversal with PCC and Vitamin K in trauma patients with major bleeding or cerebral haemorrhage who are on VKA treatment [17-19]. PCCs are classified into three-factor and four-factor products. Three-factor concentrates have therapeutically useful levels of FII, FIX and FX; four-factor PCCs contain FII, FVII, FIX, FX together with protein C and S. PCC is associated with a non negligible risk of thrombogenicity and disseminated intravascular coagulation (DIC) [20]. Eight retrospective studies have evaluated the outcomes associated with pre-injury anticoagulation therapy in patients admitted for traumatic head injury. In two of these studies the mortality was similar between the control and warfarin-treated patients; in the other six studies there was an increased mortality in the warfarin-treated group compare to the control group [21]. While mortality has been shown to increase in patients with traumatic brain injury on VKAs, data for trauma patients without brain injury are less

**Table 3. Anticoagulation reversal for bleeding patients on Vitamin K Antagonists (from FCSA recommendations [25], modified).**

INR not known (blind reversal)	→	PCC 25U/kg +VitK
INR 1.5-2,0	→	PCC 20U/kg +VitK
INR 2,1-3,9	→	PCC 30U/kg +VitK
INR 4,0-5,9	→	PCC 40U/kg +VitK
INR > 6,0	→	PCC 50U/kg +VitK

clear. "Time to correction of the INR" or "extent of correction of the INR" have been used as a surrogate outcome of clinical effectiveness rather than the cessation of clinical bleeding or mortality. Only one retrospective analysis could demonstrate that in trauma patients receiving warfarin, the addition of PCC treatment to FFP and vitamin K results in a quicker INR reversal. However, no outcome improvement was observed [22]. Notwithstanding the lack of strong evidence, the TUN experts agreed to introduce in the protocol the use of PCC for the emergency reversal of vitamin K dependent oral anticoagulation. Therefore, in patients with significant active bleeding known to be on VKAs, immediate administration of PCC (25 UI/Kg) is recommended even before INR results. PCC treatment will be subsequently adjusted according to INR results [23,24]. The F.C.S.A. recommendations [25] for the management of intracranial haemorrhage have been endorsed to guide treatment once INR is known (Table 3).

Recently several newer anticoagulants have been introduced in the clinical practice and a few more are under clinical development. Currently the oral thrombin inhibitor dabigatran etexilate (Pradaxa, Boehringer Ingelheim, Germany) is approved in the United States, Canada and Europe for the stroke prevention in atrial fibrillation and the oral factor Xa inhibitor rivaroxaban (Xarelto, Bayer AG, Germany) is approved for the prevention of venous thrombosis after orthopaedic surgery and for stroke prevention in atrial fibrillation.

These two drugs have a more balanced benefit/risk ratio and several advantages over warfarin: a rapid onset of action, a more predictable anticoagulant effect so that routine laboratory monitoring is not required, minor food and drugs interactions. Moreover they are expected to carry less hemorrhagic risks, particularly, less intracranial bleeding [26]. However a number of serious hemorrhages have been reported in the literature. On December 7, 2011, the FDA released a statement declaring that they were evaluating post-marketing reports of serious bleeding events in patients taking dabigatran, to determine if the rate of bleeding events was higher than what would be expected [27]. As novel agents, dabigatran and rivaroxaban, are relative unknown to the practicing community and there is little or no evidence to guide practical management when patients present with

acute bleeding. Because of the short half-life of the newer agents observation and supportive care with immediate anticoagulant withdrawal is the preferred strategy in patients with minor or mechanically controlled bleeding. However when a life-threatening haemorrhage occurs, intervention with reversal agents might be warranted. Unfortunately neither plasma nor cryoprecipitate, are effective in reversing the anticoagulant effect of the new drugs [28]. A few studies have investigated reversal agents; all of these have used animal model or healthy human subjects to evaluate the role of different reversal drugs. The human studies focused on the effect of four-factor PCC on coagulation tests [29,30] and demonstrated that high doses of 3-factors or 4-factors PCC are probably effective for the reversal of rivaroxaban, but not for dabigatran [31]. Dabigatran can be dialyzed, with the removal of about 60% of the drug over 2 to 3 hours, but data supporting this approach are limited and the potential use of dialysis in the context of severe trauma related bleeding is questionable [32]. The Italian Federation of Thrombosis Centres (FCSA) recently produced a consensus document suggesting the administration of 4-factors PCC for the reversal of rivaroxaban in the one shot dose of 50 UI/Kg [33].

Antiplatelet drugs - mostly aspirin and P2Y-thienopyridine antagonists (clopidogrel, prasugrel, ticlopidine) - are prescribed for prophylaxis and treatment in patients with cardiovascular or cerebrovascular diseases. These drugs are associated with an increased risk of intracranial haemorrhage. Drugs of both classes irreversibly inhibit platelets function making their short half-lives clinically irrelevant. For each day after the interruption of these medications, the 10-14% of normal platelet function is restored; so it takes 7 to 10 days for the entire platelet pool to be refurbished.

There is little evidence to guide platelet transfusion in major trauma patients on antiplatelet medications. A recent meta-analysis of six studies failed to demonstrate any clear benefit of platelet transfusions in patients with either spontaneous or traumatic intracranial haemorrhage [34]. In a retrospective analysis of a cohort of 113 patients with traumatic intracerebral haemorrhage (TICH) on antiplatelet medications, Washington [35] *et al.*, couldn't find any statistically significant difference in outcome between patients treated with platelets and those who were not transfused. Similar data were reported by Downey in a retrospective study involving two level 1 Trauma Centres over a 4 years period [36]. Ivascu [37] and Fortuna [38] in two separate studies observed a non significant trend towards higher mortality in patients with traumatic brain injury treated with platelets transfusion, but patients transfused were older and presented a lower GCS and higher ISS [35]. All of these studies though, have some weakness: they are retrospective, relative small and the indication and timing for platelet transfusion were not standardized. The timing of transfusion might play a key role as the haematoma may set up very early after trauma [39].

Despite the lack of evidence supporting the use of platelets,

**Table 4. The TASH-score (from Yücel N et al. J Trauma 2006).**

Variable	Value	Simplified score points
Hemoglobin (mg/dL)	< 7	8
	< 9	6
	< 10	4
	< 11	3
	< 12	2
Intra abdominal free fluid	+ve FAST	3
Orthopedic fractures	Clinically unstable pelvic fracture	6
	Femur fracture (open/dislocated)	3
Base excess	< - 10	4
	< - 6	3
	< - 2	1
Systolic blood pressure (mm Hg)	< 100	4
	< 120	1
Heart rate (beat/min)	≥ 120	2
Sex	Male	1

many Institutions have implemented protocols for the reversal of platelet medications in the presence of TICH. According to a multidisciplinary Institutional protocol published by Campbell, [40] 5 Units of platelets concentrate should be transfused right on admission to the patients on ASA who present with a small TICH. Patients on clopidogrel or with large TICH should receive 10 Units of platelets together with 0,3mcg/Kg of desmopressin. As patients with major trauma and critical bleeding often require surgical or intravascular procedures that may be significantly affected by platelet dysfunction, many Authors recommend the use of platelet concentrates even in the absence of brain injury [41]. The ECS protocol endorses this strategy, recommending platelets for patients on antiplatelet drugs with critical bleeding and/or intracranial haemorrhage and/or undergoing emergency surgery. In patients with TICH on ASA therapy, we suggest the administration of 1 apheresis platelet concentrate (single donor) or 1 pool platelet concentrate (from pooling of 4-6 buffy coats). In patients with TICH or significant extracranial bleeding who are on ticlopidin, clopidogrel or dual antiplatelet drugs, we suggest the administration of 2 apheresis platelet concentrates or 2 pool platelet concentrates [42-44]. We also suggest to guide platelet transfusions with platelet function tests whereas available, if platelet dysfunction is documented [45].

Bleeding patients who are not on anticoagulants or antiplatelet drugs as well as those with ongoing bleeding in spite of a correct drug reversal, may need early coagulation support. Immediate identification of these cases is of paramount importance. Unfortunately clinical criteria as well as predictive scores have a lower than desirable predictive ability for massive transfusion. Predictive models of massive

transfusion upon admission have been developed for this purpose. The Trauma Associated Severe Haemorrhage (TASH) score has been reported to have a high predictive value [46] and is widely used in Germany and other European countries. The TASH-score (Table 4) is based on a point-system taking into consideration clinical and laboratory data as well as the severity of injuries (orthopaedic fractures and intra-abdominal fluid). In a multicenter study based on the data of the German Trauma Registry, Borgman [47] divided the population of trauma victims according to their TASH score. A TASH-score ≥ 15 was associated with a 40% risk to receive a massive transfusion. Patients with a TASH-score ≥ 15, had a high ISS (42±15,4), and a mortality rate of 39.5%. Patients of these groups who received a high plasma: PRBCs ratio had a significantly lower mortality than those who received a lower ratio, although the two groups were not different for other confounders. Patients with a TASH-score < 15 had a lower mortality (19.1%) which was not further reduced by the aggressive administration of plasma. With all the limitations of a retrospective study, these data suggest that trauma patients who carry at least a 40% risk of massive transfusion according to the TASH-score, may benefit from an aggressive treatment with a high plasma:PRBCs ratio. However, the timely identification of patients who need aggressive haemostatic resuscitation remains challenging. In recent papers, Maegele [48] and Brockamp [49] used the German Trauma Society database to evaluate the predictive values for massive transfusion (MT) of six different scoring algorithms. Although the weighted and more complex systems such as the TASH score had the highest overall accuracy, more simple score as the one proposed by Vandromme [50], performed nearly as well. The Vandromme-score is based on 5 parameters four of which immediately available by clinical examination or by the generally available point of care devices: blood lactate ≥ 5 mmol/L, heart rate > 105 bpm, INR > 1.5, haemoglobin ≤ 11g/l and systolic blood pressure < 110 mm hg. Its predictive value for the need of massive transfusion increases with the number of positive parameters and the model with ≥ 3 positive criteria showed a sensitivity of 53% and a specificity of 98%. A major limitation of all models is their retrospective nature and the lack of prospective validation. It has been therefore suggested that individual triggers should be considered in order to improve the accuracy of the models [49]. An unpublished analysis of about 1700 major-trauma cases from the Italian Trauma Registry (RIT) showed that hypotension (SBP ≤ 90) on hospital admission is associated with a mortality rate as high as 50% mainly due to uncontrolled haemorrhage. However many hypotensive patients do not meet the MT criteria as they do not survive enough time to receive 10 Units of PRBCs. On the base of the analysis of the literature and of the data of the TUN trauma registries, the panel of experts suggested to activate the ECS protocol whenever a significant uncontrolled bleeding is associated with one or more of the following criteria: SBP

< 100, BE < -6, Lactate > 5mmol/L, Haemoglobin < 9gr/dL or a INR > 1,5. The last criterion may be relevant in the case of patients referred from other hospitals with laboratory data showing an impaired coagulation. All these patients are expected to be transfused with universal blood soon after admission. Four Units of universal PRBCs is the standard package for emergency transfusion immediately available in the trauma bay of the TUN trauma centres.

The utility of the standard coagulation tests (*eg.*, prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT], platelets count and fibrinogen [Claus method]) to guide the acute haemostatic treatment in trauma patients with significant bleeding is limited. First, their results are inevitably delayed. In addition, because they are not performed on whole blood but on plasma, they cannot analyze the entire process of coagulation as it occurs *in vivo*. Moreover hyperfibrinolysis cannot be detected [51]. Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) offer a quicker and more complete monitoring and allow a goal directed therapy. ROTEM, better than TEG, can also quickly detect fibrinolysis. Although the clear evidence of a positive impact on patients outcome is still missing, viscoelastic tests allow to distinguish the different haemostatic disorders following trauma, facilitating the proper management. The early use of thromboelastometry to guide treatment is recommended by the Austrian Guidelines [12]. As ROTEM or TEG are not always available at the moment in many Italian hospitals, the ECS protocol has been conceived without the obligatory guide of viscoelastic monitoring. However the panel acknowledges that viscoelastic monitoring may significantly improve the efficacy of the ECS protocol.

Brohi *et al.*, recently observed that as many as 41% of the hypotensive trauma patients have fibrinogen level below 1.5g/L on hospital admission and its reduction is associated with the increasing base deficit [3]. A high percentage of the patients who meet the ECS criteria are therefore expected to have a low fibrinogen. According to the ECS protocol as soon as these patients start the transfusion with universal PRBCs they should receive an initial dose of 2 gr of fibrinogen concentrate. In the Brohi's study patients who did not receive any source of fibrinogen had a reduction in fibrinogen level to 1.2g/L (1.0-1.8) as an average after the first 4 Units of PRBCs. The standard dose of 2 gr of fibrinogen concentrate therefore aims to immediately provide the needed amount of fibrinogen to prevent its expected decrease following the first 4 Units of PRBCs [3]. Two grams of fibrinogen is approximately equal to the content of 4 plasma (250ml) Units. In a recent multicenter study in cardiac surgery Görlinger [53] demonstrated that a goal-directed therapy with fibrinogen concentrate and Point-of-Care viscoelastic monitoring, was associated with a threefold reduction of intraoperative massive transfusion and a 90% reduction in the use of plasma. Although massive bleeding in trauma patients may have different underlying mechanisms

than intra-operative bleeding, reducing the time to achieve effective coagulation support should be equally important. Fibrinogen plays a key role in clot formation and clot firmness because it is the final substrate of coagulation and the ligand of the platelet GPIIb/IIIa receptors. Restoring or increasing fibrinogen levels may significantly contribute to improve the clotting process, control the bleeding and reduce the amount of transfused blood and plasma. In his retrospective study Schöchl showed that ROTEM guided haemostatic therapy with fibrinogen concentrate, was associated with a significant reduction in the number of patients requiring platelet transfusion and RBC transfusion, as compared with conventional treatment with plasma. However patients in both group required only 6 PRBCs Units as an average, thus the majority of them did not meet the MT definition. In truth Schöchl demonstrated that early coagulation support may effectively reduce the exposure of the bleeding trauma patients to allogeneic blood products, which is one of the goals of the ECS protocol.

In the daily practice of the TUN Trauma Centres a significant number of patients who eventually require less than 6 Units of PRBCs, receive plasma transfusion. Plasma is ordered in a fixed 1:1 ratio with PRBCs, immediately on arrival at the Emergency Room and immediately thawed in order to shorten the time-to-treat. Fibrinogen concentrate may allow a little delay in the decision to thaw the plasma possibly reducing the waste of thawed plasma or inappropriate transfusion. Transfusion of plasma and platelets is independently associated with the development of multiple organ failure in critically injured patients. In a retrospective study on a large number of transfused patients requiring less than 10 Units of PRBC within 12 hours of admission, Inaba [9] observed a higher rate of complication in the patients receiving plasma. Patients receiving more than 6 Units of plasma had a 12-fold increase in ARDS, 6-fold increase in MODS and 4-fold increase in pneumonia and sepsis with non significant improvement in survival. Johnson [11] confirmed these findings, but demonstrated that the deleterious effect associated with plasma transfusion outweighed the survival benefits of plasma only among patients receiving fewer than 6 Units of blood (PRBC). Therefore avoiding plasma transfusion in trauma patients who will not require at least 6 Units of PRBCs might be beneficial.

However fibrinogen concentrate does not provide volume expansion, hence higher amounts of crystalloids and/or colloids need to be infused to replace volume if a "plasma free" strategy is adopted. Crystalloids and more importantly, colloids significantly impair the clotting process, either by diluting clotting factors or directly impairing the clot strength. The potentially greater fluid infusion when concentrates are employed instead of plasma, may hamper the efficacy of this treatment strategy. This may explain the reason why, even in Schöchl series, a percentage of the bleeding patients still receive plasma. As no proper study have compared yet the

“factor based” strategy with the “plasma based” approach this issue hasn’t been settled. The rationale of the TUN protocol strategy is to provide a rapid support to the clotting process by the early administration of fibrinogen concentrate, with the aim to reduce plasma transfusion at least in patients who eventually will not need massive transfusion. These patients are the ones expected to get more harm than benefits from plasma.

Patients who continue to present significant a bleeding not withstanding early coagulation support and damage control surgery, will usually require more than 10 Units of PRBCs and meet the definition of massive transfusion (MT). Although data in the literature consistently show that early and aggressive plasma transfusion improve the survival of these patients, the optimal FFP/PRBC and PLT/PRBC ratio is controversial because of the possible survival bias flawing most studies [54,55]. A recent multicenter prospective study on a large population of patients undergoing MT showed that high FFP/PRBC and PLT/PRBC ratios are associated with a survival benefit also when time-dependency is accounted for [56].

The TUN expert committee feels there are still no enough evidence in the literature to adopt a “plasma free” strategy for the patients who require massive transfusion, for the following reasons: The pathophysiology of TIC is not yet [57] fully understood. Early coagulopathy (EC) occurring before hospital admission is caused mainly by tissue hypoperfusion and severe tissue injury. EC might have different causes than coagulopathy associated with haemodilution, acidosis and hypothermia. Patients with tissue hypoperfusion and severe tissue damage have a strong activation of the protein C pathway that seems to be associated with a depletion in PC levels and protein C stores. This brings to increased levels of plasminogen activator inhibitor-1, favouring fibrinolysis. Activated protein C also inactivates factor Va and factor VIIIa [58] bringing to a significant consumption of factor V and VIII. Coagulopathy caused by hypoperfusion is therefore characterized by an acquired deficit in coagulation factor V (and by a less extent, VIII,VII,II,IX,X and XI [59]) together with a hyperfibrinolytic condition. Acidosis as a consequence of massive haemorrhage has a detrimental effect on the coagulation cascade; a low pH strongly affects the activity of factor VII and to a lesser extent factor X and factor V [60]. Moreover massive bleeding may cause also an acquired deficit of factor XIII which has an important role in clot stabilization and clot firmness. It has been suggested that a decreased factor V activity as well as a deficit in factor XIII concentration might play a role in the pathogenesis of the early onset acute traumatic coagulopathy [61,62]. Unfortunately factor XIII is available in some European country, but not in Italy. Some concern therefore has been raised about the potential risk of a “plasma free” strategy, as administration of plasma might play a role in restoring factor XIII levels and factor V activity in the coagulopathic patients with severe hypoperfusion. It has been remarked that a level of factor V as low as 5% still

allows an effective coagulation in patients with hematologic diseases; however bleeding trauma patients might require higher levels.

In case of massive bleeding the restriction of plasma implies higher quantities of crystalloids and colloids for volume replacement. High volume of crystalloids may affect the haemostatic process through factors dilution and hypercloremic acidosis. The use of colloids has also been recently challenged as they cause fibrinogen dysfunction reducing the clot stability. In a recent randomized controlled study comparing saline with HES 130/0.4 for trauma resuscitation, patients in the HES group required significantly more blood and blood products [63]. Moreover it has been shown that the use of HES for fluid resuscitation is associated with a significantly higher complication rate if compared with normal saline [64]. Therefore volume replacement with colloids should probably be limited if not abandoned.

The panel agreed that additional data from controlled trials are needed before a pure “plasma free strategy” can be endorsed in the ECS protocol even for the patients requiring MT. If a viscoelastic monitoring is available, the ECS protocol recommend to treat the patients who need MT with the administration of plasma with the addition of factors, following the goal-directed algorithm presented in **Table 2**. Treatment goals has been adapted from the AUVA Protocol [65] which is based on rotational thromboelastometry (ROTEM). Thromboelastography (TEG) might provide the same information. A treatment algorithm for TEG guided treatment has been proposed by Johansson *et al.*, [66]. If ROTEM and TEG are not available, the ECS protocol recommends a standardized approach aimed to transfuse blood and plasma keeping the plasma/PRBCs ratio  $\geq 1.5$  and to maintain platelets over 100.000.

The economic impact of the ECS protocol has been one of the main concerns addressed by the panellists. Data from the Surgical and Trauma Intensive Care Units of the Innsbruck University show that a goal directed coagulation management based on Point of Care monitoring and the use of factors brought to a sharp reduction in plasma transfusions (-88%) and PRBCs requirement over a 5 years period [53]. The overall cost of blood products decreased by 200.000 Euro per year in spite of a significant increase in the cost of fibrinogen. However these results are referred to the general population of patients requiring transfusions, including patients undergoing elective cardiac surgery, therefore they might not be applicable to major bleeding in trauma victims. Fibrinogen concentrate is imported in Italy in limited amount provided authorization by the National Agency AIFA. One gram of fibrinogen costs around 400 Euro, thus the first step of the ECS protocol is associated with an estimated cost for fibrinogen concentrate of 800 Euros. The equivalent cost if plasma was used as the source of fibrinogen is difficult to calculate, because the cost of blood collection from blood donors cannot be easily quantified. However one Unit (200 mls) of industrial purified plasma, costs around 75 Euro. Therefore the estimated cost

of 1000 mls of commercial plasma, with a content of 2 g of fibrinogen, is 375 Euro. The additional cost of the TUN protocol strategy to reduce plasma transfusion in patients who eventually will not need massive transfusion have therefore been estimated in 425 Euro per patient. These patients are the ones expected to get more harm than benefits from plasma and the additional treatment cost should be balanced by the expected reduction in plasma related complications, ICU and hospital length of stay. The impact of the ECS protocol on the global treatment cost in case of massive transfusion, is even more complex to estimate also because an earlier support to the clotting process may reduce transfusion requirements as shown by Görlinger [53]. The TUN trauma centers that adopt the protocol will therefore carefully monitor financial aspects.

## Conclusion

To meet the need of standardized the treatment of trauma patients with critical bleeding, the Italian trauma centers of the TUN network have developed a common therapeutic protocol called ECS. The protocol aims to avoid the use of plasma in the patients who will need a limited number of PRBCs, reduce the plasma related complications, and improve coagulation support in patients requiring massive transfusion through the early restoration of fibrinogen blood concentration. The ECS protocol has been developed assuming to have a point of care monitoring of coagulation, but can also be applied if a viscoelastic monitoring is not available. The ECS will be adopted by the TUN trauma centers with strict monitoring of economic impact and clinical results.

## Competing interests

Before joining the panel all the panelists agreed to interrupt any professional relationships with organization that might held commercial interests in the topics. Neither the panel meetings nor the manuscript preparation have received financial or technical support. None of the Authors holds any stocks or shares in organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future. Here enclosed are listed all the potential competing interest related to the last five years :

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