

# MONITORING AND TREATMENT OF COAGULATION ABNORMALITIES IN BURN PATIENTS. AN INTERNATIONAL SURVEY ON CURRENT PRACTICES

## MONITORAGE ET TRAITEMENT DES TROUBLES DE LA COAGULATION CHEZ LE PATIENT BRÛLÉ. ÉTUDE INTERNATIONALE DES PRATIQUES ACTUELLES

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**SUMMARY.** The magnitude of coagulation abnormalities, and the definition and treatment of coagulopathy in burn patients are inadequately understood and continue to be discussed in the literature. We aimed to analyse physicians' views on monitoring and treating coagulation abnormalities in burn patients. A total of 350 questionnaires were distributed electronically to burn ICU physicians. Participation was voluntary and anonymous. Responses were analysed electronically and comparisons were made according to the region of the ICU or the specialty of the physician. Of the 350 questionnaires distributed, 55 (15.7%) were returned. The majority of burn specialists consider sepsis-induced coagulopathy to be the most frequent coagulopathy in burn patients, and 74.5% declare that they do not use any specific definition/scoring system in their department to detect coagulopathy. The majority of specialists (70.8%) use standard coagulation tests. The most frequent indications for plasma transfusion are massive bleeding (32.8%) and Disseminated Intravascular Coagulation syndrome treatment (20%). The main specific factors reported in our study are cryoprecipitate (23.2%) and fibrinogen concentrate (18.9%). 21.1% of respondents state that they do not use any specific coagulation factor substitution in burn patients. Specific coagulation factor substitution is not a routine practice. The low response rate precludes the generalization of our results.

**Keywords:** burn, blood coagulation, monitoring, treatment

**RÉSUMÉ.** La définition, l'importance et le traitement des anomalies de la coagulation chez les patients brûlés sont mal connues et font régulièrement l'objet de controverse dans la littérature. Nous avons analysé le point de vue des praticiens sur le monitoring et le traitement de ces anomalies. Trois cent cinquante questionnaires ont été envoyés par voie électronique à des médecins travaillant en USI pour brûlés. La participation était volontaire et anonyme. Les réponses ont été comparées en tenant compte de la géographie et de la spécialité du répondant. Cinquante cinq (15,7%) ont été remplis. La majorité des praticiens considèrent que le sepsis est la cause la plus fréquente de coagulopathie chez les brûlés. Les ¾ n'utilisent pas de définition ni de score spécifiques, 70,8% utilisant les tests standard. Les indications les plus fréquentes de transfusion plasmatique (32,8%) sont le saignement massif et la CIVD (20%). Les facteurs spécifiques le plus souvent utilisés sont les cryoprécipités (23,2%) et le fibrinogène (18,9%), et 21,1% des sondés n'utilisent jamais de tels dérivés du sang. L'utilisation en routine de facteurs de coagulation est donc rare chez les brûlologues. Le faible taux de réponse ne permet pas d'inférer ces résultats à la population brûlologique générale.

**Mots-clés:** brûlés, coagulation, monitoring, traitement

### Introduction

Burn injury is traditionally referred to as a common triggering cause of acute coagulopathy, ranging from subclinical activation of coagulation to fulminant overt Disseminated Intravascular Coagulation (DIC). Coagulopathy associated with burn injury was well recognized as early as the 1970s.<sup>1,2</sup> Coagulopathy in burn patients is considered to be driven by an endothelial injury, release of tissue factor and inflammatory cytokines.<sup>3</sup> Blood loss, hypovolaemia or excessive volume expansion, hypothermia and acidosis further aggravate the situation.<sup>4,6</sup> Coagulation system activation is characterized initially

by thrombin generation, hypercoagulability and hyperfibrinolysis.<sup>7</sup> Activation of both thrombosis and fibrinolysis and increased consumption of coagulation factors leads thereafter to the development of consumption coagulopathy.<sup>3,6-8</sup> The coagulation system abnormalities may be further enhanced by surgery; wound excision may be associated with extensive blood loss, dilution and consumption of coagulation factors which may have an additional negative impact on the coagulation system. Additionally, the activation of inflammatory and coagulation cascade in septic burn patients can lead to microvascular injury and subsequent multiple organ dysfunction or failure.<sup>3,6</sup>

The literature on coagulopathy in burn patients is relatively

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heterogeneous, so the incidence of coagulopathy in burns is still undefined and depends on diagnostic criteria and the definitions used in each study. In terms of diagnosis, assessment of the levels of specific coagulation markers has been reported to be helpful.<sup>7,8</sup> The use of new diagnostic methods such as thromboelastometry and thromboelastography may also improve our diagnostic abilities in coagulopathy. Although a few studies have recently been published on the use of thromboelastography in burn patients,<sup>9,10</sup> there are still insufficient data on the use of the tool in this specific area. Controversies persist over the treatment of coagulopathy in burn patients. Modern treatment strategies suggest using specific coagulation factors instead of plasma, in an effort to minimize patients' exposure to blood products. The use of specific coagulation factors in burn patients seems to be effective and reduces allogeneic blood product requirements perioperatively.<sup>10,11</sup>

Although there is extensive literature exploring the attitudes of physicians on diagnosis and management of trauma-induced coagulopathy treatment over the last decade,<sup>12-18</sup> still little is known about practices in specialised burn units. The questionnaire used in our study was created to evaluate aspects of monitoring and treatment of coagulation abnormalities in burn patients.

### Materials and methods

The questionnaire was designed by the authors and was assessed by two intensive care consultants who work in the specialised burn ICU of the first author. The reviewing consultants were not involved in conducting the survey, and their comments resulted in minor modifications to improve the clarity of the questionnaire.

A total of 350 questionnaires were distributed electronically to burn ICU physicians. Participation in the survey was voluntary and anonymous. Collection time (time the survey remained open) was 2 months.

The questionnaire consisted of three parts: the first part collected physician and institutional demographics, the second part explored the opinions and attitudes of the burn specialists regarding diagnostic approach to coagulopathy, and the third explored their opinions and attitudes regarding therapeutic approach to coagulopathy in burn patients.

#### Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Appropriate descriptive statistics were used to explore basic response rates in every question, while the chi-square test was utilized to reveal differences between the responses of burn specialists in different regions or from different backgrounds. Test results were considered to be statistically significant if the p value was less than 0.05.

### Results

Of the 350 questionnaires distributed, 55 (15.7%) were returned. Regarding the geographic distribution of respondents, 54.5% were from centres in Europe, 20% in North America, and 25.5% in other regions. The majority of respondents were from burn centres with more than 60 admissions per year (80% of centres in Europe, 100% in North America, and 71% in other regions). Most of the physicians (89.1%) were senior members of staff (heads of department and consultants); 56.4% of re-

**Table I** - Characteristics of respondents and burn centres

	Responses n.	Responses %
<b>Region</b>		
1. Europe	30	54.5
2. North America	11	20.0
3. Other regions, all	14	25.5
Southeast Asia	5	9
Africa	4	7.3
Eastern Mediterranean	2	3.6
South and Central America	2	3.6
Western Pacific	1	1.8
<b>Position</b>		
1. Trainee	6	10.9
2. Consultant	26	47.3
3. Head of department	23	41.8
<b>Specialty</b>		
1. Surgery	31	56.4
2. Anaesthesiology and/or Intensive care	24	43.6
<b>Affiliation of the burn centre with a university or teaching hospital</b>	49	89.1
<b>Number of admissions to the burn centre per year</b>		
1. ≤60	10	18.2
2. >60	45	81.8

spondents were surgeons and 43.6% were anaesthesiologists or intensivists.

Physician and institutional demographics are shown in *Table I*. Diagnostic approaches to coagulopathy are displayed in *Table II*. The majority of participants (74.5%) declare that they do not use any specific definition and scoring system in their department to detect coagulopathy. One third of physicians (30.9%) claim that there is not enough data to support the use of viscoelastic tests in burn patients, and 25.5% of respondents state that they are not aware of these techniques.

Treatment approaches to coagulopathy are shown in *Table III*. The minority of burn specialists (16.8%) use a transfusion protocol with a fixed blood product ratio; 43.6% of respondents suggest an optimal red blood cell:plasma ratio of at least 1:3 and 36.4% of respondents suggest at least 1:1. The most frequent indications for plasma transfusion are massive bleeding (32.8%) and Disseminated Intravascular Coagulation syndrome treatment (20%). A platelet count  $<50 \times 10^9 /L$  is a common trigger for perioperative platelet transfusion for 31.9% of burn specialists, however 33.3% of respondents use individualized platelet substitution in each patient. The most used specific factors reported by participants in our study are cryoprecipitate (23.2%) and fibrinogen concentrate (18.9%), while 21.1% of respondents state that they do not use any specific coagulation factor substitution in burn patients. We observed statistically significant differences in replies to particular questions about origins and kind of treatments for coagulopathy between regions and respondents' specialties (*Table IV*).

### Discussion

The magnitude of coagulation abnormalities, and the definition and treatment of coagulopathy in burn patients are inadequately understood and continue to be discussed in the literature.<sup>4-8,19,20</sup> Furthermore, the majority of studies on coag-

**Table II** - Diagnostic approaches to coagulopathy

	Responses n.	Responses %
<b>In your opinion, which kind of coagulopathy prevails in burn patients?</b>		
1. Acute burn-induced coagulopathy (coagulation activation and consumption of coagulation factors early after burn injury)	27	24.5
2. Dilution coagulopathy due to volume resuscitation with crystalloids and colloids	26	23.6
3. Perioperative consumption coagulopathy	21	19.1
4. Sepsis-induced coagulopathy	36	32.7
<b>Which tests do you use to detect post-burn coagulopathy in your routine practice?</b>		
1. Our routine practice includes the early, repeated and combined measurement of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen and platelets	46	70.8
2. Our routine practice includes the use of standard tests and the measurement of antithrombin III (AT III), Protein C (PrC) activities, and D-dimer levels	12	18.5
3. Viscoelastic methods (thromboelastometry, thromboelastography) are also used to assist in characterising the coagulopathy and in guiding haemostatic therapy in burn patients	7	10.8
<b>Which scoring system do you use to diagnose coagulopathy in burn patients?</b>		
1. Acute trauma-induced coagulopathy criteria	3	5.5
2. Disseminated Intravascular Coagulation (DIC) criteria of the International Society for Thrombosis and Hemostasis (ISTH) for overt and non overt DIC diagnosis	11	20.0
3. No specific scoring system is used in my department to detect coagulopathy	41	74.5
<b>Which coagulation tests do you use to guide intra/perioperative haemostatic therapy in burn patients?</b>		
1. Standard laboratory tests (prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen and platelets)	46	70.8
2. Standard tests and AT III, Pr C, D-dimer	12	18.5
3. Viscoelastic point-of-care monitoring	7	10.8
<b>Choose one of the following statements:</b>		
1. Thromboelastography or thromboelastometry can identify coagulopathy and hyperfibrinolysis and guide haemostatic therapy in burn patients	24	43.6
2. There is not enough data to support the use of thromboelastography or thromboelastometry in burn patients	17	30.9
3. I am not aware of these techniques	14	25.5

ulopathy in burns were conducted more than a decade ago, before the dramatic increase in the use of specific coagulation factors and before the implementation of new monitoring tools such as the measurement of specific coagulation factors and the use of viscoelastic tests. Our questionnaire aimed to explore the views and practices of burn ICU physicians regarding this challenging matter.

Combined mechanisms contribute to coagulopathy in burn patients, such as excessive consumption of coagulation factors and platelets, dilution coagulopathy due to administration of large volumes of fluids and sepsis-induced coagulopathy.<sup>4-6</sup> More than thirty percent of the study participants (32.7%) consider sepsis-induced coagulopathy to be the most frequent coagulopathy in burn patients, followed by early post-burn coagulopathy (24.5%) and dilution coagulopathy (23.6%) due to volume resuscitation. Interestingly, differences were observed between surgeons and anaesthesiologists/intensivists; the prevailing coagulation disorder reported by 62.5% of anaesthesiologists/intensivists was dilution coagulopathy, whilst only 35.5% of surgeons considered dilution coagulopathy to be the principal cause of coagulation disorders in burns.

The majority of the respondents (70.8%) report that their routine practice includes the use of standard coagulation tests (measurement of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen and platelets). More recent evidence, however, suggests that classical tests for coagulation, such as international normalized ratio, PT and PTT are not reliable, and fail to accurately describe the complex processes occurring in acute trauma patients.<sup>12,13,15,18</sup>

Major differences in the definitions and criteria used and,

consequently, the incidence of coagulation abnormalities can be noted in recent literature. Coagulopathy is defined as acute traumatic coagulopathy, acute burn-induced coagulopathy or overt and non-overt disseminated intravascular coagulation.<sup>4-7,21,22</sup> Surprisingly, 74.5% of participants declare that they do not use any specific definition and scoring system in their department to detect coagulopathy, and only a few of them (5.5%) use the acute trauma-induced coagulopathy criteria. Conventional plasma-based coagulation tests (prothrombin time, international normalized ratio and activated partial thromboplastin time) are used by most respondents (70.8%) to assess haemostatic status of bleeding patients, and to guide intra/perioperative haemostatic therapy. This is of particular interest, as recent publications found no evidence that standard coagulation tests are predictive of bleeding or have the potential to guide coagulation therapy.<sup>13,23</sup>

Viscoelastic tests such as TEG (thrombography) or ROTEM (rotational thromboelastometry), which use whole blood and provide measurements of the entire clotting mechanism, have become more popular in the management of trauma patients.<sup>13,18</sup> The use of Point of Care coagulation monitoring (POC), which is based on viscoelastic tests, may improve our understanding and diagnostic abilities in coagulopathy, and additionally, seems to lower transfusion-related costs in cardiac surgery, trauma and liver transplantation.<sup>13</sup> The use of a specific coagulopathy treatment algorithm, based on viscoelastic techniques, has reduced allogeneic blood product requirements in burn patients perioperatively.<sup>10</sup> Our study reveals that only the minority of respondents (10.8%) use viscoelastic point-of-care monitoring to guide haemostatic therapy in their routine prac-

Table III - Therapeutic approaches to coagulopathy

	Responses n.	Responses %
<b>Does your institution implement an evidence-based treatment algorithm to guide clinical management for bleeding burn patients with coagulopathy?</b>		
1. Yes	41	25.5
2. No	14	74.5
<b>Does your institution implement a treatment checklist to guide clinical management for bleeding burn patients?</b>		
1. Yes	46	83.6
2. No	9	16.4
<b>What are the indications for transfusion with fresh frozen plasma (FFP) in burn patients in your department?</b>		
1. Use of transfusion protocol with a fixed blood product ratio, red blood cell transfusion is always accompanied by FFP transfusions	21	16.8
2. Elevated international normalized ratio and prolonged activated partial thromboplastin time	29	23.2
3. Massive bleeding	41	32.8
4. Prophylactic transfusion before major surgery	9	7.2
5. Treatment of Disseminated Intravascular Coagulation	25	20.0
<b>In patients with massive bleeding: if plasma is administered, you suggest an optimal red blood cell:plasma ratio of at least</b>		
1. 1:1	20	36.4
2. 1:3	24	43.6
3. 1:2	11	20.0
<b>What are the indications for transfusion with platelets?</b>		
1. Use of transfusion protocol with a fixed blood product ratio, in which red blood cell transfusion is accompanied by platelet transfusions	7	9.7
2. A platelet count $<20 \times 10^9$ /L is a common trigger for perioperative platelet transfusion	15	20.8
3. A platelet count $<50 \times 10^9$ /L is a common trigger for perioperative platelet transfusion	23	31.9
4. A platelet count $<100 \times 10^9$ /L is a common trigger for perioperative platelet transfusion	3	4.2
5. We use individualized platelet substitutions in each patient	24	33.3
<b>Which kind of specific coagulation factor replacement therapy do you use in burn patients with massive bleeding?</b>		
1. Administration of fibrinogen concentrate	18	18.9
2. Administration of prothrombin complex concentrate	14	14.7
3. Administration of recombinant activated factor VII	7	7.4
5. Administration of cryoprecipitate	22	23.2
5. Administration of factor XIII concentrate	6	6.3
6. Administration of antithrombin concentrate	8	8.4
7. We don't use any specific coagulation factor in our department	20	21.1
<b>If you use specific coagulation factors, what are the criteria of treatment with these specific factors?</b>		
1. Viscoelastic methods: thromboelastometry, thromboelastography findings	13	16.9
2. Levels of specific factors	26	33.8
3. Clinical criteria of massive bleeding	38	49.4
<b>In your opinion, what are the indications for fibrinogen substitution with fibrinogen concentrate or cryoprecipitate?</b>		
1. We recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit	0	0
2. Plasma fibrinogen concentration $<2.9$ g/L indicates an increased risk of bleeding and triggers fibrinogen transfusion	5	9.1
3. We recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5 to 2.0 g/L.	29	52.7
4. We do not use fibrinogen concentrate or cryoprecipitate in our department	21	38.2

tice, with 25.5% of respondents claiming that they are not aware of these techniques. Interestingly, differences were observed on this point between surgeons and anaesthesiologists/intensivists; a much greater percentage of surgeons (36.7%) were unaware of the use of viscoelastic tests compared to anaesthesiologists and intensivists (12.5%).

With growing concern about the need for optimizing transfusion practices and improving treatment of bleeding patients, algorithms for the clinical evaluation and control of bleeding in perioperative clinical settings have been created.<sup>10,13,24</sup> The

majority of respondents (74.5%) report that they do not implement an evidence-based treatment algorithm to guide clinical management of a bleeding burn patient with coagulopathy. These findings highlight the importance of a structured approach for clinicians in order to achieve earlier and more effective bleeding control.

Many treatment protocols for perioperative bleeding use fixed ratios of allogeneic blood products. Studies from both military and civilian trauma centres have shown that early transfusions with a high ratio of fresh frozen plasma to red cells

Table IV - Differences between regions and specialties

Question	Answer	Europe	North	Other America	Surgeons' regions	Anaesthesiologists/ Intensivists	P
<b>In your opinion, what kind of coagulopathy prevails in burn patients?</b>	Dilution coagulopathy due to volume resuscitation with crystalloids and colloids				35.5%	62.5%	0.047
<b>What kind of specific coagulation factor replacement therapy do you use in burn patients with massive bleeding?</b>	Administration of prothrombin complex concentrate (PCC)	40%	9%	7.1%			0.025
	Administration of fibrinogen concentrate				19.3%	50%	0.016
<b>I am not aware of thromboelastography or thromboelastometry</b>					36.7%	12.5%	0.04

and platelet concentrates to red cells are linked to improved outcomes in trauma patients with severe hemorrhage.<sup>18,25-27</sup> However, transfusion of allogeneic blood products increases morbidity and mortality, and fixed ratios might not improve outcomes.<sup>13</sup> Our study reveals that only a low percentage of burn specialists (16.8%) use a transfusion protocol with a fixed blood product ratio, where red blood cell transfusion is always accompanied by FFP transfusion, and only 9.7% of respondents use a transfusion protocol with a fixed blood product ratio, in which red blood cell transfusion is accompanied by platelet transfusions. Interestingly, 20% of respondents consider the use of plasma transfusion for Disseminated Intravascular Coagulation syndrome treatment, despite the fact that the use of plasma for this purpose is no longer recommended.<sup>3,13</sup>

Modern treatment strategies suggest using specific coagulation factors instead of plasma, thus minimizing patients' exposure to blood products. The principal advantages of specific coagulation factors include their immediate availability, defined and high concentrations of the coagulation factors which can be administered without volume expansion.<sup>13,16,18</sup> We searched for evidence on the use of fibrinogen concentrate, cryoprecipitate, factor XIII concentrate, recombinant activated factor VII (rFVIIa), prothrombin complex concentrate and antithrombin concentrate in severe perioperative bleeding. Our results show that in 49.4% of centres, treatment with specific coagulation factors is mainly based on pragmatic clinical aspects (clinical signs of massive bleeding) rather than guided by specific tests. The most frequently used specific factors reported by participants in our study are cryoprecipitate (23.2%) and fibrinogen concentrate (18.9%), while 21.1% of respondents state that they do not use any specific coagulation factor substitution in burn patients. The potential concerns about the treatment-associated cost of these factors might partially explain the last finding, although current guidelines report that goal-directed therapy with specific coagulation factor concentrates may reduce transfusion-associated costs.<sup>13</sup> However, specific administrative rules and cost control initiatives of hospitals could be an additional factor that affected the burn specialists' decision about the replacement of specific factors in our study.

We observed statistically significant differences regarding the use of specific coagulation factor replacement therapy when comparing different regions and specialties. The use of prothrombin complex concentrate is more frequent in Europe (40%), whereas in N. America and other regions it accounts for 9% and 7.1% of specific factors, respectively. Anaesthesiologists and/or intensivists administer fibrinogen concentrate more frequently in comparison to surgeons (50% vs. 19.5%). Lack of sufficient evidence that using specific coagulation fac-

tors improves outcome in burn patients, and the high cost of treatment with specific factors, may partially explain the observed reluctance of burn physicians to use this treatment option. Low availability of coagulation factor concentrates and point-of-care testing might also lead to insufficient use of targeted therapy for haemostatic defects. More clinical trials should aim to extend our knowledge of the effects of specific coagulation factors and should therefore address important biologically-based coagulopathy treatment uncertainties in burn patients. Clear indications, efficacy, and the economic feasibility of the use of specific coagulation factors in burn patients should be targeted in these future trials.

Our study was the first international study evaluating the opinions and attitudes of burn specialists regarding diagnostic and therapeutic approaches to coagulopathy in burn patients. However, there were several limitations: the use of the questionnaire was not formally validated and the response rate was unfortunately low. This might be attributed partly to the absence of support by an official scientific association, which would make completion of the questionnaire more appealing. The resulting small number of responses did not allow us to analyse differences between geographic regions and countries in depth, although our sample was not country specific. Additionally, the small number of respondents makes the results of this study susceptible to randomization errors. Another limitation is that the study was limited to burn specialists and did not address a multidisciplinary group of specialists involved in burn care, which could be an interesting target group for analogous future investigations.

In conclusion,

- The majority of burn specialists consider sepsis-induced coagulopathy to be the most frequent coagulopathy in burn patients.
- The majority of burn specialists do not use any specific scoring system to detect coagulopathy.
- Standard coagulation tests are the most commonly used coagulation tests in burn units.
- Very few burn physicians use viscoelastic point-of-care monitoring to guide haemostatic therapy in their routine practice.
- Specific coagulation factor replacement therapy includes the use of cryoprecipitate, fibrinogen concentrate and prothrombin complex concentrate; however, quite a few physicians do not use any specific coagulation factor substitution in burn patients.
- Additional clinical trials should aim to extend our knowledge about diagnostic and therapeutic approach to coagulopathy in burn patients.

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