Hematologist Intervention in Disseminated Intravascular Coagulation - Has Something Changed in 2018?

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Abstract

Disseminated intravascular coagulation (DIC) is a systemic condition secondary to an underlying process that affects hemostasis, causing thrombocytopenia and coagulation factor consumption. Severe sepsis, polytraumatic lesions, obstetric complications, cancer, and acute promyelocytic leukemia are, some of the pathologies that can trigger this hemostatic disorder. Despite the severity of DIC, there have been minimal changes in the therapeutic approach over time. The cornerstone of treatment is to identify the etiology and eliminate the underlying cause. On the other hand, it is necessary to replace the lack of blood elements such as platelets and coagulation factors, using fresh frozen plasma or clotting factor concentrates. In this paper, we have reviewed the timeline over 30 years regarding the evolution of therapeutic hematologic support for DIC.

KEY WORDS: Coagulation. Treatment. Disseminated intravascular coagulation. Hemorrhage. Plasma. Platelets.

Introduction

In everyday practice, hematologists, internists or intensive care physicians face relatively often the combination of thrombocytopenia, prolonged prothrombin, and thromboplastin times in the context of a patient with hemorrhage. If we rule out acute or chronic liver disease, which is crucial, this combination of laboratory alterations forces us to think in disseminated intravascular coagulation (DIC). This is often a complication secondary to a severe problem which compromises patient's life. As previously indicated, the patient usually presents some type of acute or chronic but worsening basal disease such as sepsis and some type of cancer, i.e., promyelocytic leukemia, severe trauma, obstetric complications, and, in some cases, intravascular hemolysis. DIC can then be defined as an "acquired syndrome, characterized by the intravascular activation of

the coagulation system in a generalized way and which may have different causes."¹ The definition by itself is not specific and denotes the lack of an in-depth knowledge on this catastrophic phenomenon.

DIC is classically described as an abnormal response of hemostasis to an underlying condition. In physiological conditions, hemostasis is regulated by multiple regulatory mechanisms which in DIC do not work properly, this combined with the endothelial damage contributes to the massive production of thrombin in a systemic way².

To confirm the diagnosis, ideally, the combination of thrombocytopenia, elevated D-dimer, and hypofibrinogenemia in the presence of prolonged prothrombin and thromboplastin times leads us to be reasonably sure of the diagnosis^{3,4}. Some pathologies can be distracting, foremost among them are severe hepatopathy, thrombotic thrombocytopenic purpura, and hemolytic uremic

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Figure 1. Diagnostic algorithm for patients with suspicion of disseminated intravascular coagulation⁹.

Table 1. Laboratory findings in patients with DIC⁴

Laboratory parameter	Expected result	Acute versus chronic
Platelet count	↓	Acute
FDP, D-dimer	↑	Both
Fibrinogen	↓	Acute
PT	↑	Acute
aPTT	↑	Acute

DIC: disseminated intravascular coagulation.

syndrome. The presence of thrombosis can cause D-dimer elevation but not other major hemostatic alterations. In [table 1](#), the main laboratory findings are described in patients with DIC, and in [figure 1](#), a practical diagnostic algorithm is described to suspect or rule out this disease.

Analysis and discussion of the therapeutic options of DIC

In this paper, we decided to evaluate review articles and clinical guidelines found in the MEDLINE database linked to the recommendations for DIC management. From the consulted articles, we chose seven according to the impact of such publications during the past three decades ([Table 2](#))⁵⁻¹¹.

The question to answer is quite simple - are there any significant practical changes in the treatment of

DIC on the hematologist perspective? At first, all seven publications concur that treatment is based on support for the patient and solving the triggering cause as it may be treating an infectious process, using a target treatment for promyelocytic leukemia or solve an obstetric complication.

The first article evaluated data from 1987⁵ where the therapy used for DIC was based on the application of fresh frozen plasma, cryoprecipitates, and platelet transfusion. In 2018, according to the article published in the section “How I treat” from the journal *Blood*¹¹, the treatment is still based on in these principles; however, it makes a reference to the utility of purified clotting factor concentrates in patients with a high risk of bleeding or with active bleeding.

Evaluating the main antihemorrhagic options for DIC management, Carr Jr.⁵ mentions in his article of 1987 that replacement therapies were previously contraindicated in acute DIC processes. Nevertheless, the use of fresh plasma became accepted as the first line in case of bleeding, and it remains to be recommended today¹¹. In 2005, Levi⁸ mentioned that the use of fresh plasma should not be based solely on laboratory studies but to make the decision taking into consideration the clinical state of the patient.

Regarding cryoprecipitates, Car Jr.⁵ stresses in the late 80s that its use ought to be reserved for patients with severe hypofibrinogenemia (< 50 mg/dL) or in cases of active bleeding with fibrinogen levels lower than 100 mg/dL. In 2009, the British Society of Hematology guidelines mentioned that the use of cryoprecipitates

Table 2. Recommended therapeutic strategies in DIC during the past three decades

Emergency treatment	Carr ⁵	Rubin and Colman ⁶	Levi and Ten ⁷	Levi ⁸	Levi ⁹	Wada et al. ¹⁰	Levi ¹¹
Treat the underlying condition	✓	✓	✓	✓	✓	✓	✓
Life support measures	✓	✓	✓	✓	✓	✓	✓
Prevention or treatment of bleeding							
Purified coagulation factor concentrates	NM	NM	×	?	?	✓	✓
			PCP might exacerbate the coagulation disorder	PCC controversial. Use in specific coagulation factor deficiencies can be corrected (e.g., fibrinogen)	PCC controversial. Use fibrinogen concentrates in severe hypofibrinogenemia that persists despite FFP replacement	PCC might be considered when FFP transfusion is not possible in active bleeding patients. Fibrinogen concentrates recommended in severe hypofibrinogenemia	
Fresh frozen plasma	✓	✓	✓	✓	✓	✓	✓
	First-line therapy		In patients with high risk for bleeding or active bleeding	Its administration should not be based on laboratory results alone		Patients with active bleeding with prolonged coagulation times or decreased fibrinogen	Recommended; no randomized controlled trials exist
Cryoprecipitate	✓	✓	NS	NS	✓	✓	✓
	Fibrinogen <50 mg/dL; or <100 mg/dL plus active bleeding				Severe hypofibrinogenemia that persists despite FFP replacement	In actively bleeding patients with persisting severe hypofibrinogenemia	Recommended; no randomized controlled trials exist
Platelet transfusion	✓	✓	✓	✓	✓	✓	✓
	<50,000/μL; or <100,000/μL plus active bleeding		In patients with high risk of bleeding or active bleeding	<10,000-20,000/μL or <50,000/μL plus active bleeding		<20,000/μL plus high risk of bleeding; or <50,000/μL plus active bleeding	Recommended; no randomized controlled trials exist
Antifibrinolytic agents	×	×	×	NS	×	×	?
		They may worsen the thrombotic state	Might be useful in patients with acute promyelocytic leukemia			Might be considered in patients with acute promyelocytic leukemia/trauma with severe bleeding	In case of excessive hyperfibrinolysis

(Continues)

Table 2. Recommended therapeutic strategies in DIC during the past three decades (Continued)

Prevention or treatment of thrombosis									
Heparin	?	✓	✓	✓	✓	✓	✓	✓	✓
	Routine use was controversial; heparin trial in progressive cases; purpura fulminans	Therapeutic doses followed by infusion of platelets and FFP	Useful in patients with overt thromboembolism; continuous infusion of 300-500 U per hour	Useful in patients with overt thromboembolism; prophylaxis to prevent venous thromboembolism	Therapeutic and prophylactic use	Therapeutic and prophylactic use	Therapeutic and prophylactic use	A randomized controlled trial of heparin is needed	
Antithrombin III concentrates	✓	?	✓	?	✕	?	?	?	
	In refractory cases		Supportive therapeutic option in patients with severe DIC	Some beneficial effects that need further validation	Lack of controlled clinical trials that confirm a beneficial effect	Further, prospective evidence is needed	Further, prospective evidence is needed	Further, prospective evidence is needed	
Activated protein C	NM	NM	NM	✓	✓	?	?	✕	
					In patients with severe sepsis; contraindicated in patients with high risk of bleeding	Further prospective evidence is needed	Further prospective evidence is needed	The absence of significant advantages; the product has been withdrawn from the market	
Other recommended therapies	NM	NM	NM	Administration of Vitamin K; recombinant tissue factor pathway inhibitor	NM	NM	NM	Administration of Vitamin K; recombinant thrombomodulin in septic patients has shown encouraging results	

✓: recommended; ✕: not recommended; ?: controversial; NM: not mentioned; DIC: disseminated intravascular coagulation; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate

or fibrinogen concentrates ought to be used when there is a persisting hypofibrinogenemia lower than 100 mg/dL despite fresh frozen plasma replacement⁹. In 2013, its indication was the same but in cases with active bleeding¹⁰.

Recently, indications for platelet transfusions have decreased cutoff values from 20,000/ μ L in patients with a risk of bleeding and 50,000/ μ L with active bleeding⁸⁻¹¹. Three decades ago, the recommendation for platelet administration in DIC was when having counts lower than 50,000/ μ L or under 100,000/ μ L with active bleeding⁵.

When evaluating recommendations about the use of purified clotting factor concentrates, we did not find evidence of its use in two of the oldest articles cited^{5,6}. It is up to 1999 that Levi and Ten⁷ discussed its application in DIC and did not recommend its application since it could worsen coagulative disorder. In 2005 and 2009, its use remains under controversy since it mentions its possible application in cases with severe hypofibrinogenemia^{8,9}. It is until 2013 that Wada et al.¹⁰ recommend its use in patients with active bleeding where the administration of fresh plasma is not possible or in cases with severe hypofibrinogenemia.

Up to present, there are few randomized clinical studies in adults evaluating or comparing the effectiveness of the standard treatments due to their critical clinical conditions. This is discussed by Squizzato et al.¹², who tried to find randomized clinical studies which answered to fictional clinical scenarios of DIC, but representative of the most common triggering causes; and at the same time, it is stressed in the article by Levi¹¹ published in 2018, obviously, the resulting evidence of this imaginary essay was poor. In his 2005 article, Levi⁸ mentions that even though the administration of hemocomponents can “add fuel to the fire,” the administration of plasma and platelets is clearly necessary in those cases with active bleeding or when there is a high risk of bleeding and/or depletion of these components.

The use of heparin in the context of the DIC has been part of a vicious cycle due to the lack of overwhelming scientific evidence supporting its benefits¹¹. However, since 1992, Rubin and Colman⁶ indicated its therapeutic use along with platelets, plasma, and cryoprecipitates when required. As of 2005, its benefits have been considered prophylactically in these patients⁸. On the other hand, it is interesting noting that the use of Vitamin K continues to be recommended¹¹. In addition, thrombomodulin has been utilized with possible benefits due to its interaction with protein C¹³ yet with low

and questionable clinical evidence. It is important to note that the product is not approved for its clinical use in most of the countries around the globe. The use of other products like antithrombin III is yet more objectionable and does not seem to be of any use¹⁴. Finally, the lack of commercial availability of activated protein C, in part due to its doubtful usefulness, limits its clinical use¹⁵.

Conclusion

Nowadays, DIC represents a severe hemostatic condition; the foundation for its treatment is based on solving the triggering cause and support therapies. For more than 30 years, clotting factor replacement with plasma and platelets has remained as the first-line therapy in the management of bleeding. Recently, the use of other alternatives has been proposed, alternatives with high costs and doubtful benefits like the administration of recombinant clotting factors. It is reasonable to accept that critical conditions in patients to evaluate new treatments difficult, being complicated to carry out all the clinical studies with enough evidence which support their benefits. Unfortunately, there does not seem to be anything new in the treatment of DIC, at least something significant or practical, that is, based on the reports by the experts in the past 30 years.

Conflicts of Interest

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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