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Review

DIC: Which laboratory tests are most useful

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ABSTRACT

In patients with disseminated intravascular coagulation (DIC) a variety of altered coagulation parameters may be detectable, such as thrombocytopenia, prolonged global coagulation times, reduced levels of coagulation inhibitors, or high levels of fibrin split products. In addition, more sophisticated tests for activation of individual factors or pathways of coagulation may point to specific involvement of these components in the pathogenesis of the disorder. There is not a single test, however, that is sufficiently accurate to establish or reject a diagnosis of DIC. Nevertheless, a combination of widely available tests may be helpful in making the diagnosis of DIC and can also be helpful to guide in the selection of DIC patients that require specific, often expensive, interventions in the coagulation system. More recently developed dynamic algorithms, assessing changes in coagulation parameters over sequential days, could further increase the diagnostic accuracy for DIC and may be helpful to detect early stages of coagulopathy potentially evolving into DIC.

1. Introduction

Disseminated intravascular coagulation (DIC) is an extreme form of coagulation activation that may complicate a myriad of clinical situations, most of which are characterized by some form of local or systemic inflammation.[1] Intravascular activation of coagulation, inadequately balanced by physiologic anticoagulant systems and aggravated by impaired endogenous fibrinolysis, may contribute to (micro)vascular fibrin deposition and thrombotic microangiopathy.[2] The sometimes massive and ongoing activation of coagulation may lead to exhaustion of coagulation factors and platelets, thereby predisposing the patient with DIC for severe bleeding complications, which in some cases may dominate the clinical picture. In recent years, the insights into contributory pathogenetic pathways in DIC have been largely increased, which could result in more precise diagnostic tests for this condition.[3] However, the clinical and laboratory diagnosis of DIC may remain difficult, since most tests focus on the consumption of coagulation factors or platelet, whereas molecular markers that are more sensitive for coagulation activation are usually insufficiently specific and are often not available in most settings for daily clinical care.[4,5] In this review manuscript we focus on both routinely available and more sophisticated laboratory tests that may be useful in the diagnosis of DIC.

2. Platelet count

Thrombocytopenia or a rapidly declining platelet count is an important diagnostic hallmark of DIC. As the incidence of thrombocytopenia (platelet count $<150\times10^9$/l) in critically ill medical patients is 35–44%,[6–8] the specificity of thrombocytopenia for the diagnosis of DIC is limited. A platelet count of $<100\times10^9$/l is seen in 50–60% of DIC patients, whereas 10–15% of patients have a platelet count of $<50\times10^9$/l. In surgical and trauma patients with DIC the incidence of thrombocytopenia is higher with >80% of patients having less than 100×10^9/l platelets.[9,10] The relevance of thrombocytopenia in patients with DIC is indeed related to an increased risk of bleeding. In particular patients with a platelet count of $<50\times10^9$/l have a 4- to 5-fold higher risk for bleeding as compared to patients with a higher platelet count, in particular when anticoagulants are used.[6,8,11] The risk of intracerebral bleeding in patients with DIC is relatively low (0.3–0.5%), but in 88% of patients with this complication the platelet count is less than 100×10^9/l.[12] Regardless of the cause, thrombocytopenia is an independent predictor of ICU mortality in multivariate analyses with a relative risk of 1.9 to 4.2 in various studies.[6,8,9] In particular, a sustained thrombocytopenia during more than 4 days after ICU admission or a drop in platelet count of >50% during ICU stay is related to a 4- to 6-fold increase in mortality.[6,13] The platelet count was shown to be a stronger predictor for ICU mortality than composite scoring systems, such as the Acute Physiology and Chronic Evaluation (APACHE) II score or the Multiple Organ Dysfunction Score (MODS). A platelet count of $<100\times10^9$/l is also related to a longer ICU stay but not the total duration of hospital admission.[8]

3. Global clotting times and coagulation factors

Consumption of coagulation factors leads to low levels of coagulation factors in patients with DIC. In addition, impaired synthesis, for example due to impaired liver function or a vitamin K deficiency, and loss of

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coagulation proteins, due to massive bleeding, may play a role in DIC as well.[14,15] Although the accuracy of the measurement of one-stage clotting assays in DIC has been contested (due to the presence of activated coagulation factors in plasma), the level of coagulation factors appears to correlate well with the severity of the DIC. The low level of coagulation factors is reflected by prolonged coagulation screening tests, such as the prothrombin time (PT) or the activated partial thromboplastin time (aPTT). A prolonged PT or aPTT occurs in 14 to 28% of intensive care patients but is present in more than 95% of patients with DIC.[16,17] A PT or aPTT ratio >1.5 was found to predict excessive bleeding.[16] It is important to emphasize that global coagulation tests, such as the PT and aPTT, poorly reflect *in vivo* hemostasis. However, these tests are a convenient method to quickly estimate the concentration of one or at times multiple coagulation factors for which each test is sensitive.[18] In general, coagulation tests will prolong if the level of coagulation factors is below 50%. This is relevant since the levels of coagulation factors, that are needed for adequate hemostasis, are somewhere between 25 and 50%.[19] The normal values and the sensitivity of these tests for deficiencies of coagulation factors may vary markedly between tests, dependent on the reagents used. Therefore, an increasing number of laboratories use the International Normalized Ratio (INR) instead of the prothrombin time. While this may carry the advantage of increased standardization between centers, it should be mentioned that the INR has only been validated for control of the intensity of vitamin K antagonist therapy and has never been developed for the use as a screening test for coagulation abnormalities.[20]

Plasma levels of factor VIII are paradoxically increased in most patients with DIC, probably due to massive release of the von Willebrand factor from the endothelium in combination with the acute phase behaviour of factor VIII. Recent studies have pointed to a relative insufficiency of the von Willebrand cleaving protease ADAMTS-13, thereby causing high concentrations of ultralarge von Willebrand multimers in plasma, which may facilitate platelet–vessel wall interaction and the subsequent development of thrombotic microangiopathy, which may contribute to organ dysfunction.[21]

Measurement of fibrinogen has been widely advocated as a useful tool for the diagnosis of DIC but in fact is not very helpful to diagnose DIC in most cases.[22] Fibrinogen acts as an acute phase reactant and despite ongoing consumption plasma levels can remain well within the normal range for a long period of time. In a consecutive series of patients the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28% and hypofibrinogenemia was detected in very severe cases of DIC only.[23]

4. Fibrin-related markers

Theoretically, measurement of soluble fibrin or fibrin monomers in plasma could be helpful to diagnose intravascular fibrin formation in DIC. Indeed, initial clinical studies indicate that if the concentration of soluble fibrin has increased above a defined threshold, a diagnosis of DIC can be made.[24–26] The only problem so far is that a reliable test is not available for quantitating soluble fibrin in plasma. Since soluble fibrin in plasma can only be generated intravascularly, this test will not be influenced by extravascular fibrin formation, which for example may occur during local inflammation or trauma.

Other more frequently used tests include elevated fibrin split products. Fibrin split products are detectable in 42% of a consecutive series of intensive care patients, in 80% of trauma patients and in 99% of patients with sepsis and DIC.[27–29] Fibrin degradation products (FDP's) may be detected by specific ELISA's or by latex agglutination assays, allowing rapid and bedside determination in emergency cases.[3] None of the available assays for fibrin degradation products discriminates between degradation products of cross-linked fibrin and fibrinogen degradation, which may cause spuriously high results.[30] The specificity of high levels of fibrin degradation products is therefore limited and many other conditions, such as trauma, recent surgery, inflammation or venous thrombo-embolism, are associated with elevated FDP's. Because FDP's are metabolized by the liver and secreted by the kidneys, FDP levels are influenced by liver and kidney functions.[31] Other tests are specifically aimed at the detection of neo-antigens on degraded cross-linked fibrin. One of such tests detects an epitope related to plasmin-degraded cross-linked γ-chain, resulting in fragment D-dimer.[32] These tests better differentiate degradation of cross-linked fibrin from fibrinogen or fibrinogen degradation products.[27] D-dimer levels are high in patients with DIC, but also poorly distinguish patients with DIC from patients with venous thrombo-embolism, recent surgery or inflammatory conditions.

5. Natural coagulation inhibitors

Plasma levels of physiological coagulation inhibitors, such as antithrombin III or protein C, may be useful indicators of ongoing coagulation activation.[33] Low levels of these coagulation inhibitors are found in 40–60% of critically ill patients and in 90% of DIC patients.[29,34] Antithrombin is the principal inhibitor of thrombin and may be readily exhausted during continuous thrombin generation. Plasma levels of antithrombin have been shown to be potent predictors for survival in patients with sepsis and DIC. During severe inflammatory responses, antithrombin levels are markedly decreased not only due to consumption but also due to impaired synthesis (as a result of a negative acute phase response) and degradation by elastase from activated neutrophils.[35] A reduction in glycosaminoglycan availability at the endothelial surface (due to the influence of pro-inflammatory cytokines on endothelial synthesis) will also contribute to reduced antithrombin function, since glycosaminoglycans act as physiological heparin-like cofactors of antithrombin. Binding of glycosaminoglycans to antithrombin induces a conformational change at the reactive center of the antithrombin molecule, thereby rendering this protease inhibitor from a slow to a very efficient inhibitor of thrombin and other active coagulation factors.[36]

Levels of protein C may also indicate the severity of the DIC. In patients with meningococcal septicemia, very low plasma levels of protein C are observed and this may play a pivotal role in the occurrence of purpura fulminans in these patients.[37] In fact, also the plasma level of protein C may be regarded as a strong predictor for the outcome in DIC patients. Endothelial dysfunction is even more important in the impairment of the protein C system during DIC. Under physiologic conditions protein C is activated by thrombin bound to the endothelial cell membrane-associated thrombomodulin. Thrombomodulin is a membrane protein with several domains, including a lectin-like domain, six epidermal growth factor (EGF)-like repeats, a transmembrane domain and a short cytoplasmatic tail.[38] The binding of thrombin to thrombomodulin occurs at the site of the EGF-repeats.[39] This binding not only results in an about 100-fold increase in the activation of protein C, but also blocks the thrombin-mediated conversion of fibrinogen into fibrin and inhibits the binding of thrombin to other cellular receptors on platelets and inflammatory cells. In addition, thrombomodulin accelerates the activation of the plasma carboxypeptidase thrombin-activatable fibrinolysis inhibitor (TAFI), an important inhibitor of fibrinolysis.[40] Binding of protein C to the endothelial protein C receptor (EPCR) results in a 5-fold augmentation of the activation of protein C by the thrombomodulin–thrombin complex.[41] However, during severe inflammation and DIC the protein C system is defective due to downregulation of thrombomodulin at the endothelial surface, mediated by the pro-inflammatory cytokines TNF-α and IL-1β.[42] Observations in patients with severe Gram-negative septicemia indeed confirmed the downregulation of thrombomodulin *in vivo* and impaired activation of protein C.[43] Low levels of free protein S (the cofactor of activated protein C) may further compromise an adequate function of the protein C system. In plasma, 60% of protein S is complexed to a complement regulatory protein, C4b binding protein (C4bBP). Increased plasma levels of C4bBP as a consequence of the acute phase reaction in inflammatory diseases may result in a relative free protein S deficiency.