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How we manage a high D-dimer

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Contributions

All the authors collaborated in writing and reading the manuscript
Abstract

D-dimer, a soluble fibrin degradation product that originates from plasmin-induced degradation of cross-linked fibrin, is an important biomarker of coagulation activation and secondary fibrinolysis that is routinely used to rule out venous thromboembolism (VTE), to evaluate the risk of VTE recurrence as well as the optimal duration of anticoagulant therapy. Besides VTE, D-dimer may be high due to physiologic conditions, including aging, pregnancy and strenuous physical activity. In addition, several disorders have been associated with increased D-dimer levels, spanning from disseminated intravascular coagulation to infectious diseases and cancers. Thus, it is far from unusual for hematologists to have to deal with ambulatory individuals presenting with increased D-dimer without signs or symptoms of thrombus formation. To the management of these cases by the hematologist is dedicated this narrative review.

Key words: D-dimer, bleeding, thrombosis, management.
Introduction

Hemostasis can be schematically represented as a balance, which is in a constantly delicate equilibrium between anticoagulant and procoagulant strengths in order to maintain the blood in physiological conditions of fluidity. The primary function of hemostasis is the generation of a stable clot in the event of vascular injury, thereby preventing excessive blood loss.1 While the formation of a clot, composed essentially of fibrin and blood cells (i.e., erythrocytes, leukocytes and platelets), is essential to stop bleeding, its timely removal by the fibrinolytic system is also needed to restore blood flow within the repaired blood vessel.2 Clot lysis, made by plasmin and other proteases, is accompanied by the generation of fibrin degradation products. Among the laboratory biomarkers of fibrinolysis, D-dimer is currently considered the gold standard, due not only to high sensitivity but also rapidity of performance, widespread availability and relatively low cost of the assays.3-5 Beside thromboembolic diseases, several physiological and pathological conditions (i.e., aging, pregnancy, cancer, inflammation, infection), not necessarily characterized by thrombus formation, have been associated with increased D-dimer.6

In this narrative review focused for the hematologist, following a paradigmatic clinical case and the description of the physiology and physiopathology of D-dimer formation, we summarize the main conditions associated with increased D-dimer and propose an approach to their management, based on both literature evidence and personal experiences. COVID-19-associated increased D-dimer levels will be not discussed herewith, because already extensively addressed.7-9 It is, however, undeniable that during the three year period of the pandemic an overuse of D-dimer has been done in many patients infected (or recovered) from SARS-CoV-2 infection, thereby creating a generalized and often unjustified alarm among patients and their treaters.10 Accordingly, hematologists have frequently met cases concerned by isolated increased D-dimer levels with no apparent thrombotic process and have been thus called to make important decisions on their management.
Methodology

For this narrative review, we reviewed the medical literature for fully published studies on the management of patients with increased D-dimer. A literature search of PubMed (through Medline) electronic database was carried out without temporal limits using English language as restriction. The Medical Subject Heading (MeSH) and keywords used were: “D-dimer”, “thrombosis”, “venous thromboembolism”, “pulmonary embolism”, “deep vein thrombosis”, “cancer”, “management”, “treatment”, “inflammation”, “disseminated intravascular coagulation”, “trauma”, “surgery”, “infection”, “sepsis”, “pregnancy”, “joint arthroplasty”, “cardiovascular disease”, “acute aortic dissection” and “coronary artery disease”. We also screened the reference lists of the most relevant articles for further studies not captured in the initial literature search.

Clinical case

In order to show that D-dimer testing is often misused, not rarely leading to inappropriate diagnosis and therapies, we present herewith a paradigmatic case involving a 76-year-old woman referred to us three years after an unprovoked DVT of the popliteal vein of the left leg. All the screenings for thrombophilia or para-neoplastic syndrome were negative. After six months of antithrombotic therapy with a direct oral anticoagulant (DOAC) and negative venous ultrasonography she started a risk stratification protocol measuring D-dimer twice, at the time of stopping anticoagulant therapy and one month afterwards. Both results being negative (below the fixed cut-off value of 500 ng/mL) stopping of anticoagulation had been decided.

After a few months her general practitioner, prompted by nonspecific complaints of a “swollen and heavy leg”, prescribed D-dimer testing that showed elevated levels (1350 ng/mL), so that the patient was instructed to resume anticoagulation with a DOAC. During the last two years anticoagulation
had been stopped and started again several times due to patient concerns about a possible hemorrhage and the fluctuation of D-dimer levels. Finally, the case had been referred to our attention by the general practitioner. Medical history and physical examination revealed that in the last five years she had been suffering from severe coxarthrosis and gonarthrosis of the left leg. Surgery had been postponed and the patient made frequent use of anti-inflammatory drugs when pain was unbearable (from which her fear of a possible hemorrhage if anticoagulated). A recent venous ultrasonography was negative. Because we observed that D-dimer levels fluctuated according to the degree of pain and inflammation, she has been instructed not to resume the anticoagulant therapy, to stop measuring randomly D-dimer and to refer to an orthopedic surgeon to tackle her joint problems.

What is D-dimer?

Coagulation is the physiological process that leads to blood “solidification” through the conversion of soluble fibrinogen into insoluble fibrin through the enzymatic action of the thrombin, derived by conversion from its zymogen prothrombin. Once the coagulation mechanisms have started there is the secondary activation of fibrinolysis meant to prevent the uncontrolled propagation of fibrin formation and facilitate the repair of the lesion.1

However, to better understand D-dimer formation we need to sketch more deeply the molecular mechanisms underlying the physiological coagulation process. Circulating fibrinogen is made of three paired protein chains, Aα, Bβ e γ. When needed at the vascular injury site, thrombin cleaves fibrinopeptides A and B from fibrinogen to form fibrin monomers that polymerize in the frame of a non-enzymatic process. Finally factor XIII (FXIII) provides monomer stabilization through covalent binding involving the γ chains, so that the insoluble fibrin net is ready to act as the main backbone of the coagulation process and related repair of the vascular lesion. Then the fibrinolytic process begins locally and converts insoluble fibrin to soluble products that can be cleared from the
bloodstream by the liver. This process depends on the enzyme plasmin, derived from activation from its zymogen plasminogen that circulates in the blood and is localized inside the forming clot together with fibrinogen. The plasminogen to plasmin activation and its progressive action upon the fibrin net produces a number of soluble products among which these are the D-dimer fragments (Figure 1), which are present only if there is a stabilized fibrin net but do not form with fibrinogen alone.11,12

The presence of D-dimer in the bloodstream is physiological, representing the continuous balance between coagulation and fibrinolysis. Only when D-dimer exceeds the cutoff value it is considered pathologic. Cutoff values, earlier considered fixed and universal, are now considered variable and age dependent, perhaps reflecting the physiological changes of the homeostatic system with the increased prevalence with aging of inflammatory – coagulative – reparative processes. From the time of its formation, D-dimer begins to be detectable in blood within approximately two hours with a half-life of approximately six hours. After surgery D-dimer increases peaking at about one week and thus decreasing by 5-10% daily, being detectable for at least one month.13-15

Regarding the laboratory measurement of D-dimer, numerous assays are commercially available. Most of them rely on monoclonal antibodies and are typically enzyme-linked immunosorbent assays (ELISA), but other methods use microparticles covered with monoclonal antibodies that bind D-dimer and cause agglutination detected and quantified by nephelometry or turbidometry. There are point of care (POC) assays that produce both qualitative and quantitative results and provide faster results in emergency care settings. Quantitative ELISA have a high sensitivity (>95%) but a low specificity for VTE and thus are principally used for exclusion purposes. For this important reason, establishing a cutoff value is very important, but these values greatly differ among the various assays used, perhaps due to the different specificity and epitope affinity of the different monoclonal antibodies. Thus, it is of paramount importance to use an assay method for which the cutoff value has been determined by association of the D-dimer results with the clinical and
instrumental diagnostic findings of VTE.\textsuperscript{3-5} D-dimer results can be expressed in two different units: FEU (Fibrinogen Equivalent Units) that correlates the mass of the D-dimer to that of fibrinogen, or DDU (D-dimer Units) that relates to the mass of the D-dimer itself. It is important not to exchange or confuse a result expressed in FEU with one expressed in DDU, because they differ by a 1.75 factor.\textsuperscript{5}

**Conditions associated with increased D-dimer**

As mentioned upfront, D-dimer is used to guide the diagnostic procedure of venous thromboembolism (VTE, which includes deep vein thrombosis and pulmonary embolism). However, while patients with pulmonary embolism or deep vein thrombosis in the acute phase usually have high D-dimer levels, individuals with high D-dimer not necessarily have an underlying thromboembolic disease, but they could have several other pathological and non-pathological conditions (Table 1).

**Venous thromboembolism**

To begin, a concise description of the D-dimer based diagnostic workup of this thrombotic disorder is provided herewith. VTE affects nearly 10 million people every year worldwide, with an annual incidence of 1-2 cases per 1000 population, being the third most frequent cardiovascular disease.\textsuperscript{16,17} Although its incidence increases with aging both in men and women, women have a higher risk of developing VTE at the young age of 20-40 years due to hormonal-related factors (i.e., pregnancy or oral contraceptive use).\textsuperscript{16,17} Owing to the substantial global burden of VTE, a timely and preferentially non-invasive diagnostic weapon is warranted when it is suspected. In this context, thanks to the high sensitivity (close to 100\%) of quantitative ELISA, D-dimer measurement plays a key role in the diagnostic workup. However, due to its low specificity (high negative and low positive predictive value), the test should only be used to exclude VTE.\textsuperscript{18-20} This means that a D-
D-dimer negative result (i.e., less than 500 μg/L) categorize patients as having a low to moderate clinical pretest probability of VTE. Several scores have been developed in order to assess the clinical probability of VTE. The most used are the Wells and Geneva scores,\(^{21,22}\) of which a simplified and validated version has been developed to increase adoption in clinical practice.\(^{23,24}\) The combination of negative D-dimer ELISA and low-intermediate pre-test clinical probability excludes deep vein thrombosis or pulmonary embolism in approximately 30% of the cases with suspected VTE with no need for imaging (i.e., venous ultrasonography for a suspected deep vein thrombosis and computed tomography [CT] pulmonary angiogram for a suspected pulmonary embolism).\(^{25}\) Conversely, D-dimer is not recommended in patients with a high clinical probability, because a normal result does not exclude VTE, even when a highly sensitive assay is used, so that these cases should directly undergo imaging without D-dimer testing (Figure 2).\(^{26}\) Notably, as D-dimer levels increase with aging, an age-adjusted (age x 10 μg/l in patients aged >50 years) rather than a fixed cut-off (< 500 μg/L) is warranted to exclude VTE in patients with low or intermediate pre-test clinical probability.\(^{27}\) Although impaired renal function has been suggested to affect D-dimer levels in individuals suspected of having VTE,\(^{28}\) its influence seems to be less important than that of age.\(^{29}\)

D-dimer testing in combination with a clinical pretest probability assessment (YEARS criteria or revised GENEVA score) have also been used for the exclusion of pulmonary embolism in pregnant women with the aim of avoiding unnecessary imaging.\(^{30,31}\) In addition, D-dimer testing provides important information not only for the diagnosis of VTE but also for the anticoagulant management of VTE. Current evidence indicates that a positive D-dimer after completion of 3 months of anticoagulant therapy in patients with a first unprovoked VTE is associated with a twofold higher risk of VTE recurrence than a negative test.\(^{4}\) Thus, following the demonstration of the strong association between D-dimer and VTE recurrence,\(^{32}\) D-dimer testing is often included in the prediction models designed to guide decisions for stopping anticoagulant therapy.\(^{33,34}\) On the other
hand, persistently elevated D-dimer after stopping a 3-month anticoagulant treatment argues in favor of therapy prolongation in cases with unprovoked VTE.35

The role of D-dimer for the diagnosis of cerebral vein thrombosis (CVT) has been the object of research in the last 20 years. A systematic review and meta-analysis by Dentali and colleagues (14 studies including 1134 patients) found high sensitivity and specificity for D-dimer (93.9% and 89.7% respectively), in patients with suspected CVT.36 Another meta-analysis performed by Alons et al (8 studies including 636 patients) showed that D-dimer had a high negative predictive value for CVT in low-risk patients (defined as those with normal neurological examination, normal standard head CT scan and absence of such risk factors as puerperium and pregnancy) and isolated headache.37 A recent prospective study proposed a new score that, combining clinical data with normal D-dimer (i.e., < 500 μg/L), was very effective in predicting CVT, thus reducing unnecessary neuroimaging.38 Finally, D-dimer testing should not be currently recommended as a first line diagnostic tool for the diagnosis of venous thrombosis in unusual sites (upper limbs, retinal veins, arterial veins.39

Physiological conditions

It was previously pointed out that the detection of raised D-dimer levels does not necessarily imply the presence of an underlying disease, because a number of physiological conditions are accompanied by abnormal values (Table 1).40 D-dimer increases with age, thus leading to a greater proportion of older patients (> 50%) with values higher than the conventional cutoff of 500 μg/L.41 The lower specificity of D-dimer for VTE in older than younger people implies that the former are unlikely to have negative D-dimer results even when VTE is absent, with a related high rate of unnecessary use of imaging tests.42 For this reason, an age-adjusted cutoff has been validated and recommended in the diagnostic workup of VTE.43 However, in patients >80 years of age, the use of the D-dimer is not recommended for the exclusion of VTE, because high baseline levels lead to unacceptably high false positive results in cases with no VTE.44
Similarly, D-dimer levels increase physiologically during pregnancy and in the post-partum period. D-dimer levels are also higher in women taking oral contraceptives than in non-users, perhaps reflecting their hypercoagulable state.

Exercise has effects on hemostasis, that are dependent on the duration and intensity of the physical activity. D-dimer levels significantly increase following short-duration strenuous exercise and exercise-induced fibrinolytic activity in healthy subjects is proportional to the amount of exercise. Changes of cardiac and hemostatic biomarkers (including D-dimer) after strenuous endurance exercise can wrongly mimic pulmonary embolism and myocardial injury.

**Disseminated intravascular coagulation**

Disseminated intravascular coagulation (DIC) is a severe, often life-threatening, syndrome characterized by diffuse and persistent activation of the hemostatic system with intravascular thrombin generation, fibrin formation and degradation. Early recognition of DIC is crucial to promptly initiate treatment, aimed first at eliminating the underlying condition (i.e., sepsis, malignancy, trauma, obstetrical diseases). D-dimer has become a cornerstone in the diagnosis of DIC because, thanks to its excellent negative predictive value, D-dimer measurement has been endorsed by all national and international guidelines in order to diagnose DIC. For instance, the International Society of Thrombosis and Hemostasis (ISTH) not only validated a scoring system (including prothrombin time, platelet count, fibrinogen and d-dimer levels) for its diagnostic and prognostic value, but also recommended sequential D-dimer measurements to monitor DIC evolution and to guide clinical and therapeutic management.

**Cancer, inflammation and infection**

The activation of coagulation is a common finding in most malignant tumors, being associated with growth and progression. As a consequence, up to 20% of cancer patients develop VTE, which is the second leading cause of death. D-dimer is over-produced in the presence of active malignancy
and its levels are increased in an array of tumors.\textsuperscript{57} However, the common finding of high D-dimer in cancer even in the absence of thrombosis limits the diagnostic usefulness of this test. Nevertheless, incorporating D-dimer measurement in appropriate scoring systems including other biomarkers may help to identify cancer patients at increased risk of developing VTE and thus candidate for primary thromboprophylaxis.\textsuperscript{58-62} In addition, although the value of screening patients with increased D-dimer for occult cancer is still debated, an occult cancer may be considered as the potential source for a substantial D-dimer elevation when other physiological or pathological causes are ruled out.\textsuperscript{48} The usefulness of this approach has been highlighted in a clinical study in patients with unprovoked VTE, demonstrating that extremely high D-dimer (>4000 ng/mL) is independently associated with the likelihood of an occult cancer.\textsuperscript{63}

There is a close link between fibrinogen, thrombus formation, fibrinolysis and the inflammatory process.\textsuperscript{10} Fibrinogen, an acute phase reactant, leaks out of the vasculature exerting an aid to the inflammatory process.\textsuperscript{64} The involvement of clotting factors (i.e., factor VIII end others) helps to form fibrin in the extravascular space, which functions as a scaffold for the inflammatory cells of the immune system to exert their functions.\textsuperscript{64} As a result of fibrin formation, secondary fibrinolysis does occur and generates D-dimer, with levels paralleling the degree of inflammation.\textsuperscript{65} Several diseases are characterized by low-grade chronic inflammation and thus high D-dimer, the most common being autoimmune diseases and diabetes. Although D-dimer is considered a marker of inflammation (the so call “D-dimeritis”), finding of high values not necessarily implies the presence of an increased thrombotic risk,\textsuperscript{10} because D-dimer increases exponentially in parallel with increasing C-reactive protein.\textsuperscript{66}

Inflammation also provides the molecular basis for the explanation of the detection of high D-dimer during infections. The best example is sepsis, a life-threatening systemic infection-related condition associated with defects of hemostasis and, as forementioned, with DIC.\textsuperscript{67} Marked elevations of D-dimer have been observed in sepsis, demonstrating the prognostic importance of D-dimer in relation
to the severity of the patient state.\textsuperscript{68,69} Beside SARS-CoV-2 infection, several viral infections (i.e., Ebola virus, influenza A virus, human immunodeficiency virus (HIV), hepatitis C virus, Coxsackievirus, herpes simplex virus and parvovirus B19) are characterized by marked elevations of plasma levels of hypercoagulability markers, such as D-dimer and thrombin-antithrombin complex.\textsuperscript{70} The endothelial dysfunction and the inflammatory state associated with infections drive patients towards a hypercoagulable condition, that translates into an increased thromboembolic and cardiovascular risk.\textsuperscript{66} This is particularly evident in HIV-infected patients.\textsuperscript{71} In addition to chronic, low grade inflammation, an important mechanism for their enhanced risk of cardiovascular disease, people living with HIV have increased D-dimer that correlate with VTE and mortality risks.\textsuperscript{72}

A special mention deserves the role of D-dimer in the diagnosis of periprosthetic infections.\textsuperscript{73,74} A systematic review and meta-analysis, based upon 12 studies totaling 1818 patients, concluded that D-dimer has sufficient diagnostic accuracy to exclude peri-prosthetic joint infection.\textsuperscript{75} In addition, the updated 2018 Musculoskeletal Infection Society criteria did validate a score for the diagnosis of periprosthetic hip and knee infections which included D-dimer levels > 860 \(\mu\text{g/L}\).\textsuperscript{76}

\textit{Other conditions}

Several other disorders have been associated with abnormal D-dimer.\textsuperscript{77} Among cardiovascular diseases, atrial fibrillation is accompanied by high D-dimer, which decrease during anticoagulant treatment or after successful cardioversion.\textsuperscript{78,79} Because D-dimer is higher in atrial fibrillation patients with such additional risk factors for stroke as hypertension, diabetes or heart failure, its measurement has been proposed as a biomarker for predicting the risk of stroke.\textsuperscript{80} Notably, a recent study demonstrated the efficacy of an age-adjusted D-dimer cut-off to exclude the presence of left atrial thrombi in patients with atrial fibrillation.\textsuperscript{81} However, predictive value is less powerful than that of other biomarkers (i.e., troponin, N-terminal pro-B-type natriuretic peptide), which are preferentially incorporated into the available risk prediction models.\textsuperscript{82} Prospective studies have also evaluated the utility of D-dimer measurement to predict other cardiovascular adverse events (i.e.,
myocardial infarction and cardiovascular death), but with conflicting results.77 Likewise, in patients with a preexisting coronary artery disease, D-dimer is of uncertain value for the prediction of incident cardiovascular events.82 A separate mention pertains to acute aortic dissection, an extremely severe condition for which a rapid diagnosis is essential. As D-dimer levels are high in the presence of acute aortic dissection and low in absence, a normal D-dimer helps to exclude this diagnosis.83 The diagnostic value of this measurement was recently assessed by a systematic review and meta-analysis including 16 clinical studies and 1135 patients, that concluded that a D-dimer < 500 μg/L had excellent exclusion diagnostic sensitivity (96%), thus playing a crucial role for the differential diagnosis of acute aortic dissection.84

The role of D-dimer for the diagnosis of acute intestinal ischemia has also been acknowledged in the literature.85 A systematic review and meta-analysis including 12 studies with 1300 patients calculated a sensitivity of 94%, suggesting a potential diagnostic role for this biomarker.86

Beside these thrombotic or prethrombotic conditions, the clinical usefulness of D-dimer has also been studied in hemorrhagic conditions, including intracerebral and subarachnoid hemorrhages. A retrospective study of 1332 consecutive cases with spontaneous intracerebral hemorrhage found that high D-dimer (> 550 μg/L) was an independent predictor of poor functional outcome and mortality.87 Similar results were obtained by retrospective study of 2056 patients with aneurysmal subarachnoid hemorrhage.88

High D-dimer have also been reported in the HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome, a rare complication of pregnancy usually considered a variant of pre-eclampsia.48 This biomarker has therefore been proposed for the early identification of patients with pre-eclampsia at risk of developing a severe HELLP syndrome, although its clinical utility is questionable due to increased D-dimer during physiological pregnancy (see above). D-dimer is also increased in liver cirrhosis and, being positively associated with the severity of liver dysfunction and the presence of portal vein thrombosis, have been proposed as a predictor of adverse outcomes
in these patients. Finally, inflammation-related raised D-dimer levels have been reported in other conditions, including pancreatitis and diabetes. For instance, the marker has been recently proposed for cardiovascular risk stratification in patients with type 2 diabetes.

Proposal of management of ambulatory individuals with high D-dimer

While there is little doubt on the role of D-dimer in the diagnostic workup of patients affected by acute illnesses such as VTE, DIC and sepsis (Table 1), more challenging is the management of ambulatory individuals characterized by the detection of high D-dimer levels but no evidence of thrombosis. This issue has been focused and heightened by the generalized and indiscriminate dispensation of D-dimer testing during and following the last COVID-19 pandemic. When an ostensibly healthy and asymptomatic person is referred for persistently high D-dimer, he should first be reassured by explaining all the possible reasons other than disease that may underly this abnormality. Yet, an abnormal D-dimer should not be overlooked in otherwise asymptomatic subjects. Thus, they should be given a chance to receive a diagnosis and all possible conditions associated with increased D-dimer should be taken into consideration in the process of differential diagnosis.

Figure 3 summarizes a flow chart for the evaluation by hematologists of ambulatory cases with increased D-dimer levels following age adjustment. The flow-chart is based mostly on our personal experience rather than on scanty literature data. First and most importantly, physical examination is crucial for excluding the presence of signs and/or symptoms related to VTE. It is also essential to rule out not only current symptoms but also those that arose in the previous few days. For instance, we recently observed an asymptomatic patient with raised D-dimer who reported that in the previous few days he had some respiratory symptoms that had gradually disappeared. A
precautionary CT pulmonary angiogram was done and a pulmonary embolism was diagnosed. In cases with clinical signs/symptoms potentially suggestive of VTE we suggest performing a leg venous ultrasonography for the detection of occult DVT plus, when pulmonary embolism is suspected, a CT angiogram according to the flow chart shown in the figure 3. If negative, the individual should undergo a blood screening to unravel conditions possibly associated with increased D-dimer. Again, a personal history and physical examination are essential to restrict the range of blood tests to be performed. The individual should also be interviewed for the presence of autoimmune or rheumatic disorders, diabetes, chronic inflammatory disorders, renal disease, active or previous cancer, chronic infection, liver disease and cardiovascular disorders. All physiological causes of high D-dimer (ongoing or recent pregnancies, strenuous physical exercise) should also be ruled out. Blood tests should be therefore focused on those able to confirm or diagnose an underlying disorder. In case of identification of a pathological condition, the patient should be referred to the specialist for the most appropriate care. In addition to physical examination, we suggest performing an abdominal ultrasound in order to exclude aortic dissection. If no underlying conditions is identified, we suggest a clinical follow-up of the individual, that should however be reassured.

**Conclusions**

D-dimer testing is unequivocally a useful tool for the diagnosis of VTE. However, owing to its intrinsic poor positive predictive value, D-dimer is not specific for thromboembolic disease, because elevations are also observed in many other conditions, ranging from DIC to infections and malignant neoplasms. In other words, raised D-dimer levels may be encountered as part of an inflammatory state or cancer without being the sign of intravascular thrombus formation. Thus, while D-dimer measurement must be incorporated in multi-test algorithms for the evaluation of patients with suspected VTE, this measurement has limited clinical utility in unselected ambulatory
cases and therefore should only be performed in specified clinical situations. Yet, the detection of raised D-dimer cannot be ignored but warrants a series of diagnostic procedures aimed at the proper management of these cases, which encompass on one hand the exclusion of any associated thromboembolic complication and on the other hand the identification or exclusion of conditions associated with D-dimer increase. When the latter remain the only abnormality, the individuals should be reassured about their health status and encouraged to avoid the repeated obsessive measure of D-dimer.
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function-adjusted testing in individuals suspected of having venous thromboembolism.

Pulmonary Embolism During Pregnancy: A Multicenter Prospective Management Outcome

Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. N Engl J


Table 1. Pathological and non-pathological conditions associated with high D-dimer levels.

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¹Conditions for which the usefulness of D-dimer testing is supported by clinical studies.
Legend to the figures

**Figure 1.** Mechanism of D-dimer formation.

Legend to Figure 1.

Top (coagulation process): circulating human fibrinogen is made up of three pairs of polypeptide chains, designated Aα, Bβ and γ. Thrombin converts plasma fibrinogen to fibrin monomers by cleaving fibrinopeptides A and B. Polymerized fibrin monomers are stabilized by factor XIII (activated by thrombin) into an insoluble crosslinked fibrin net.

Bottom (fibrinolytic process): plasminogen is activated to plasmin, which releases soluble D-dimers and other fragments, including E-fragments, from fibrin polymers. Finally, these soluble products are cleared from the bloodstream by the liver.

**Figure 2.** Proposed algorithm for the diagnostic evaluation of venous thromboembolism (VTE).

**Figure 3.** Proposed algorithm for the management of cases with raised D-dimer levels.
**Coagulation process**

- Aα
- Bβ
- γ
- D
- E
- Fibrinogen
- Thrombin
- Fibrinopeptides A & B
- Factor XIII
- Insoluble
- Crosslinked fibrin net

**Fibrinolytic process**

- Plasminogen → Plasmin
- D-dimers
- E fragments
- Liver
Algorithm for the diagnostic of venous thromboembolism (VTE)

1. Suspected VTE
   - Pre-test clinical score
     - High probability
       - Imaging
         - VTE diagnosis
         - Treatment
     - Low / intermediate probability
       - D-dimer test
         - ≥ age-adjusted cutoff
           - VTE excluded
         - < age-adjusted cutoff
           - VTE excluded
Proposed algorithm for the management of cases with raised D-dimer levels

Ambulatory individual with high age-adjusted D-dimer

- Signs and/or symptoms of VTE
  - Imaging
    - Treatment for VTE
      - Physical examination, clinical history, blood test screening, abdominal ultrasound
        - Refer the case to the specialist
        - Careful clinical follow-up