



D-dimer in the diagnosis of venous thromboembolism

Insight - August 2013

- **Screening test** – D-dimer is used as a screening test to rule out venous thromboembolism (VTE). It should not be used to confirm VTE, nor should it be used to exclude VTE in **high risk patients**.
- **Confounding factors** such as infection, inflammation, malignancy, recent surgery or haemorrhage may lead to positive results and reduce the utility of d-dimer in these clinical scenarios.
- **Clinical probability**, for example, as assessed by Wells score, for DVT and/or PE is an important initial step in assessing the risk of patients for VTE, and guides testing for d-dimer.

Definitions of terms

VTE	Venous thromboembolism
DVT	Deep vein thrombosis
PE	Pulmonary Embolism
Negative predictive value (NPV)	the chances that given a negative result the condition is truly absent
Positive predictive value (PPV)	the chances that given a positive result the condition is truly present

Background

In the 2008 Access Economics report into venous thromboembolism there were an estimated 14,716 cases of VTE, leading to an incidence of 70 separations (episodes of care) for VTE per 100,000 Australians. Of these 56% were for pulmonary embolism¹. VTE is associated with significant morbidity and mortality: recognition and treatment is of vital importance.

D-dimer is one of the circulating terminal breakdown products of Fibrin formed following the action of Plasmin on clot. Levels of d-dimer reflect both the integrity of fibrinolysis (clot breakdown) as well as the activity of thrombin to turn fibrinogen into fibrin (clot formation). It can be used as a surrogate marker of both thrombogenesis and fibrinolysis and has utility both as a screening test for exclusion of venous thromboembolic disease and as an indicator of disseminated intravascular coagulopathy (DIC). Other laboratory features of DIC (thrombocytopenia, hypofibrinogenaemia and prolongation of routine coagulation studies) and an appropriate clinical context are the key to diagnosis of the latter condition.

Assay performance and reference ranges

D-dimer assessment can be performed by many different techniques, including by point-of-care devices like Simplify® and SimpliRed®. Some assays are qualitative (give a positive or negative result only) and some quantitative or semi-quantitative, ie. give a value or a range of values. Each assay type has its unique sensitivity (ability not to miss VTE) and specificity (ability to distinguish VTE from other causes) which should be determined for the particular population under test. These values may be different, for instance between community screening or hospital patient screening, because the prevalence of VTE varies between these populations.

The d-dimer assay at Melbourne Pathology is an automated, quantitative, latex agglutination assay, which has high negative predictive value for VTE: 97% in DVT²,

and 100% in PE³. A NPV <350 µg/mL gives confidence that further imaging for exclusion of DVT or PE is not required, but only when the patient has a low to medium risk by clinical assessment prior to performance of the d-dimer (see overleaf).

In regional Victoria where the quantitative test is not available, a rapid turn-around, qualitative d-dimer test is performed initially and the result confirmed within 24 hours by the latex d-dimer in the main laboratory. It should be noted that the results are sometimes discrepant (negative Simplify® and positive Lia d-dimer) due to the higher level of sensitivity of the quantitative test.

The NPV (<350 µg/mL) is not the same as the upper limit of the reference range (500 µg/mL) which is an expression of all the observed values in "normal" people unaffected by disease states known to increase thrombin or plasmin activity. Levels also increase with age and are likely to be higher than 500 µg/mL in patients over 60 years.

Confounding factors and causes of increased d-dimer

There are many conditions which lead to a rise in d-dimer. These situations include but are not limited to:

- Infection and inflammation
- Recent surgery
- Disseminated intravascular coagulation
- Malignancy
- Haemorrhage
- Pregnancy

D-dimer may not be an appropriate screening test for VTE in clinical scenarios where these conditions co-exist.

Pre-test probability

The clinical probability of VTE, based on the patient examination and history, has significant discriminative value even before laboratory testing is applied. Examples of a pre-test (pre d-dimer) probability score for DVT and PE are provided by Wells⁴. The ability of the clinical algorithm to discriminate high, medium and low risk cases was first validated in their patient population. The addition of the d-dimer reduced further the need to invest in imaging techniques to confirm or exclude VTE.

Patients who benefit most from the d-dimer assay are those at low to moderate pre-test probability. Patients who are at high risk of a pulmonary embolism on clinical grounds should proceed to further imaging investigations irrespective of the d-dimer result (and probably do not warrant having the test performed).

Case example 1

Mr NR is a 24-year-old man who presents to his GP with lower leg pain having recently undertaken a three hour car trip. The leg is not swollen, and he is previously well. The clinical diagnosis is of a muscle strain but a DVT needs to be excluded. His GP orders a d-dimer which returns a level less than the stated NPV. Given his low pre-test probability Mr NR is able to be reassured that he is highly unlikely to have a DVT, and does not warrant further investigation.

Case example 2

Mrs CA is a 56-year-old lady with a history of metastatic breast cancer who presents to the local emergency department complaining of shortness of breath, haemoptysis and pleuritic chest pain. A d-dimer was requested. A chest x-ray was clear. 30 minutes later she suffers a cardiac arrest, with autopsy findings showing a large saddle pulmonary embolism. In patients with a high pre-test probability immediate radiographic testing should be performed.

Post thrombosis testing

More recently testing for d-dimer following completion of therapy for VTE has been used to predict the risk of recurrence and to guide the need for continuing anticoagulant therapy. In a meta-analysis of eight trials a negative d-dimer (defined on the basis of the reference range of the tests used) was associated with a 3.5% annual risk of recurrent venous thromboembolism, as opposed to 8.9% annual risk in those with a positive d-dimer. The finding of a positive d-dimer is strongly influenced by clinical factors for risk of recurrence, which must be taken into account in follow-up testing. Testing is generally performed one month after cessation of anticoagulant therapy^{5,6}.

Requesting the test

All requests for d-dimer must come with clinical information identifying the indication for the test, eg. exclusion of VTE, diagnosis of disseminated intravascular coagulation or post-therapy follow-up in VTE. Given the potential morbidity and mortality from VTE this test is considered urgent. Contact details for the referring doctor MUST be provided (including out-of-hours contact details) to convey and/or discuss the result. It is not the laboratory's responsibility to manage the patient.

D-dimer is performed on citrated blood (light blue top tube). This tube must be filled to the line and received within 4 hours of collection or separated and stored appropriately awaiting transport to the laboratory.

References

1. Access Economics Pty Limited. *The burden of venous thromboembolism in Australia. Report for the Australian and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism*; 2008, 1 May 2008.
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3. Oger E, Leroyer C, Bressollette L, Nonent M, Le Moigne E, Bizais Y, Amiral J, Grimaux M, Clavier J, Ill P, Abgrall J, Mottier D, *Evaluation of a New, Rapid, and Quantitative D-dimer Test in Patients with Suspected Pulmonary Embolism*, 1998 *Am J Resp. Crit. Care Med.* July 1 1998, **158**(1) pp65 – 70
4. Bates SM, Jaeschke R, Stevens SM, et al *Diagnosis of DVT: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines*. 2012, *Chest* **141** (suppl 2): e351S – e418S
5. Verhovsek M, Douketis, JD, et al *Systematic Review: d-dimer to Predict Recurrent Disease after Stopping Anticoagulant Therapy for Unprovoked Venous Thromboembolism*, 2008, *Annals of Internal Medicine*, 7 October 2008, **149**(7): 481 – 490
6. Palareti G, Legnani C, et al *Risk of Venous Thromboembolism Recurrence: High Negative Predictive Value of d-dimer Performed after Oral Anticoagulation is Stopped*, 2002, *Thrombosis and Haemostasis*, 87(1) January: 7 – 12

Figure 1 - Wells criteria for DVT

Clinical feature	Points
High probability	3 or greater
Moderate probability	1 or 2
Low probability	0 or less
Active cancer	1
Paralysis, paresis or recent plaster immobilisation of the extremities	1
Recently bedridden for more than 3 days within the last 4 weeks	1
Localised tenderness along the distribution of the venous system	1
Entire leg swollen	1
Calf swelling by more than 3cm when compared to the asymptomatic leg (measured below tibial tuberosity)	1
Pitting oedema (greater in symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as or more likely than that of DVT	-2

Figure 2 - Wells criteria for pulmonary embolism

Clinical feature	Points
High probability	6 or greater
Moderate probability	2.0 to 6.0
Low probability	Less than 2.0
Clinical symptoms of DVT (leg swelling, pain on palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate >100	1.5
Immobilisation (≥3 days) or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1.0
Malignancy	1.0

This guideline is designed for use by referrers, both in hospital and community settings serviced by Melbourne Pathology.

If further information or guidance regarding the use of the d-dimer assay is required please contact the Laboratory Haematologist on 9287 7703 or 9287 7410.

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Dr Shaun Fleming completed his Physician training in 2009 and then entered advanced training in Haematology with a first clinical registrar year at St Vincent's and Peter MacCallum Hospitals in 2010.

He successfully passed part 1 examinations for the FRCPA while in a 2-year placement at Melbourne Pathology and will finish advanced training in 2013 at the Royal Melbourne Hospital where he is currently the bone marrow transplant registrar.



Dr Ellen Maxwell MBBS, FRACP, FRCPA

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Dr Maxwell is a University of Melbourne graduate who completed combined fellowships with the College of Physicians and the College of Pathologists in 1997.

She trained initially at the Austin and Repatriation Medical Centres and later the Alfred Hospital where she developed a keen interest in coagulation and transfusion medicine.

Dr Maxwell is a member of a number of committees and was appointed Medical Director at Melbourne Pathology in September 2009.