The Weekly Probe

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UP UP CRONULLA !!

THIS WEEK

D-dimer

A 65yo lady presents with cough and SOB. The GP has performed a d-dimer – 0.6 mcg/ml. (upper limit of normal 0.5) What do we do now?

When looking at a patient with possible PE there is a number of steps we need to consider.

1) History and Examination - who gets PEs and how do they present?
2) Using this features then stratify “pre-test probability” – risk of PE prior to more invasive tests- use gestalt + clinical decision tools
3) Consider d-dimer to rule out PE
4) Investigate - depending on patient or test characteristics - CTPA, VQ, US
5) Consider the limitations of the tests if “normal”
6) Treat – multiple options now with NOACs

Each of these topics is a significant issue for discussion but our focus today is on the d-dimer test.
However we must remember that the test cannot be considered in isolation and the decision to perform the test and its subsequent interpretation depends on all the above considerations.

D-DIMER

D-dimers are the products of degradation of cross-linked fibrin by plasmin-
Cross linking occurs in thrombotic states such as DIC, DVT/ PE but also in malignancy, post-operative states, trauma and pre-eclampsia

Thus elevated levels are not specific for thromboembolism

D-dimer assays are not the same – they recognise different epitiopes of d-dimer & use different technologies which impact on the diagnostic characteristics & performance. When looking at the literature, we then need to ask:
- what was used in the study?
- what was the cut-off for normal – abnormal?
- what do we use?

We could look at all the tests available and assessed in the literature and see what is the best or the worst performing test. However it makes more sense to look at the tests we have available today in our ED.

The most common d-dimer test used in SWSAHS and SESIAHS is the Stago STA LIATEST - this is what you'll get when you request a "d-dimer". Some hospitals also have access to SimpliRED testing which you'll need to specifically ask for. We'll focus on these 2 tests.

STA LIATEST - is an immunoturbidometric test. Latex micro-particles coated with antibodies specific to d-dimer is mixed with the sample. When the antigen-antibody reaction takes place, there is a change in the turbidity and absorbance - this is detected photometrically.

- normal level is generally less than 0.5 mcg/ml - "each lab should determine its own normal d-dimer level" - this is a quantitative test ie you get a number reading

Units- Units are expressed as mg/L, µg/L, or ng/mL. However there are 2 ways to report the d-dimer levels.
Most labs have a cut off of less than 0.5 mg/L fibrinogen-equivalent units (**FEU**)
Some labs use d-dimer units or **DDU with a cut off of 0.25mg/L**-
1 FEU = 2 X D-DU
This explains why some labs (eg SESIAHS including Sutherland, and outside labs including Laverty and Douglas Hanley Moir) have a cut off of 0.5 mg/L (500mcg/L) FEU
and others such as SSWAHS (including Liverpool, Fairfield and C'town) at 0.25 mg/L (250 mcg/L) DDUs.
DDimer 0.25 mg/L (DDU) = 250mcg/L (DDU) = 0.5 mg/L (FEU) = 500mcg/L (FEU)

SimpliRED is a whole blood agglutination test - a congugate of d-dimer antibodies combined with antibodies to red cells is mixed with the sample- if d-dimer is present above a threshold of 0.2mcg/ml then the sample agglutinates and is read as positive (this is a qualitative test ie +ve or -ve)

When looking at how good any test is, the three main questions are:

- prevalence of disease (ie PE or DVT) in the patient population
- the sensitivity of your test and
- the specificity

A pre-emptive apology but just a quick reminder on these terms with 2 examples :
(TN= true –ve / FP=false +ve)

Group A

	No PE	PE
-ve d-dimer	45 TN	1 FN
+ve d-dimer	45 FP	9 TP

Group B

	No PE	PE
-ve d-dimer	20 TN	6 FN
+ve d-dimer	20 FP	54 TP

- Sensitivity (= True +ve / (True +ve + False -ve) "SNOUT - sensitivity - rules you out"- higher sens with less false -ves

- Specificity (true -ve / (True -ve + False +ve) SPIN - "specificity - rules you in" - higher specificity = less false +ves

Depending on the prevalence of disease we can also work out the Negative Predictive Value (NPV) and Positive predictive value (PPV)
- as the prevalence increases (with the same sensitivity and specificity) the number of false +ve results decrease but the number of false –ves increases.

- Negative Predictive Value = True -ve / (True -ve + False -ve)- the higher prev, the more FNs- / negative result less helpful

- Positive predictive value = true +ve / (True +ve + False +ve) - the higher prevalence the less FPs / positive result more helpful

Example A (prevalence 10%) – Spec 50% / Sens 90% / NPV 98% / PPV 17 %

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Example B (prevalence 60%)– Spec 50% / Sens 90% / NPV 77% / PPV 73%

(for more detailed info re Likelihood ratios (which can also be corrected for prevalence) showing the same directions or trends , see http://vassarstats.net/index.html and type the above examples in.

Study Results

A couple of studies which echo a number of key points:

DVTs

In van der Graaf study of 99 ED pts , of which 50 had venographic proven DVTs (prox or distal). Tests were performed with both techniques

	sens	spec	+ve pred val	-ve pred val
LIATEST (>0.5)	96%	47%	60%	92% (100% if < 0.35)
SimpliRED	80%	94%	93%	82%

They report on a common finding that age affects the results esp specificity

LIATEST- sens < 60yo - 100% / > 60yo 10% - spec <60yo - 55% / > 60% - 0%

Simplired- sens < 60yo - 79% / > 60yo - 81% - spec < 60% - 90% / > 60yo - 90%

Ie the older you get the lower the less specific the test becomes

In the same study they also found lower sensitivity with distal c/w proximal clots, a function the amount of clot.

In another study of DVTs , Englehardt looking at 344 outpatients with suspected DVT (100 had confirmed DVT, when using a LIATEST at a threshold of 0.5 , found a 94% sensitivity, 48% specificity with a 95% negative predictive vaue (sens 97% at <0.3)

Oncology pts - less specific 29% vrs 51% (ELISA study for DVTs)

PEs

The specificity of all d-dimer tests is lower in studies which involve inpatients c/w outpatients

- one study 11% vrs 32 %
- Note that the line between our in-patients and outpatients is a blurry one - relatively immobile 85yo with CCF from home c/w 32yo mobile inpatient post-op lap chole

Di Nisio looked 217 d-dimer studies for DVT and 111 for PE – of which 45 latex tests for DVT (39% prevalence) and 23 were for PE (29% prevalence). He found that for the LIAtest

	Sensitivity (range)	Specificity (range)
DVT	94% (83-98)	44 (36-52%)
PE	96% (80-99%)	43% (20-68%

For the Simplired

- DVT – sensitivity 82% (59-93%) / specificity 72% (56-84%)
- PE – sensitivity 86% (43-97%) / specificity 70 % (44-87%)

So the Simplired is less sensitive (ie worse to rule out) yet more specific (ie better to rule in)

A metaanlysis by Brown which looked at only immunoturbidometric tests (9 studies - 1901 pts - 3 studies used the LIA test) - prevalence of PE varied form 9-62%!- threshold of 0.5 mcg/L in LIAtests) -

Looking only at the studies using the LIATEST-

Study	PE prevalence	No. (% outpatients)	Sens (95% CI)	Spec
Bruns	9%	234 (100%)	90 (67-98%)	48% (41-55)
Myer	40%	142 (80%)	93 (82-98%)	44% (33-55)
Reber	30%	501 (100%)	99 (96-100%)	44% (38-49)

Overall Brown et al (looking at all 9 studies) found a sensitivity of 93% (95% CI 89-96%) (note it is not 100%) and a specificity of 51% (95%CI 42-59%). They equate this to a:
- -ve likelihood ratio of 0.14
- +ve likelihod ratio of 1.9

So as mentioned as the prevalence increases (with the same sensitivity and specificity) the number of false +ve results decrease but the number of false –ves increases.

- with more false –ves , the negatives predictive value drops ie a negative result is less reliable to rule out a PE.

Brown thus adds that **if you want to use the negative result to rule out a PE (post test probability of < 1%) you can only use it on a group where the prevalence is low ie pre-test probability is < 10% ie low risk groups only.**

Older (more mature) patients
As mentioned earlier it is known that as patients age the normal values increase the utility of the d-dimer changes.
One study looked at whether we could use a different cut off value (10 X age) in those > 50yo
What group was studied and how?

- A multicenter, multinational, prospective study in 19 centers in Belgium, France, the Netherlands, and Switzerland over 3 years - all ED patients presenting with suspected PE were included
- All apatient very stratified using a simplified, revised Geneva score or the 2-level Wells score for PE – see table below for these scores– patients were classified into high risk / likely PE and non-high risk groups
- High risk or likely PEs went straight to CTPA
- D-dimer was performed in those with non-high risk groups (6 different highly sensitive d-dimer assays) – normal < 500mcg/L – separate analysis of those with d-dimer **> 500 yet less than 10X age**
- CTPA was performed on those with +ve d-dimer tests
- "Patients with a positive CTPA result were started on anticoagulant therapy, and patients with a negative CTPA result were left without anticoagulant treatment. Patients with inconclusive CTPA (technically inadequate for interpretation or isolated subsegmental PE) results underwent additional testing with compression ultrasonography, ventilation-perfusion lung scan, or pulmonary angiography. Given the uncertainty regarding the clinical relevance and optimal management of isolated subsegmental PE, it was decided to consider CTPA showing isolated subsegmental PE as inconclusive and to recommend further testing."
- 3 month followup for thromboembolic events in those not treated

Results

- 3346 patient > 50yo studied – 19% incidence of PE
- 2988 patients were non-high risk groups (< 500)
    - 28.2% - d-dimer < 500
    - 11.6% (337 pts) - dimer > 500 yet less than age adjusted cut off (10X age)
        - Of this group **1/331 at the 3 months followup (0.3%)** had a thromboembolic event at 3 months (6 of the 337 had anticoagulation for other reasons) (0/47 with LIA test)

THP – Remember that high risk patients or PE likely patients are not included- remember your units (DDUs vrs FEUs)-consider using the age adjusted cut off

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Pregnant Pts

As an aside, what about pregnant patients?

- Pregnancy - even in normal pregnancy there is significant haemostatic activation - with a rise in d-dimer values-
- 48 women IL d-dimer test (ng/ml)- similar immunoturbidometric test- mean values
    - control range 0.14+/-0.58
    - 16 weeks 0.191 +/- 0.25
    - 26 weeks 0.39 +/- 0.72
    - 34 weeks 0.54 +/- 0.96

Kline looked at 23 women throughout their pregnancy and assessed d-dimer levels with an immunoturbidomeric technique. Some pretty revealing charts in the study but the most important part was the % of women with a d-dimer < 0.5 at different stages of their pregnancy.

Preconception	1st Trimester	2nd trimester	3rd Trimester	4 weeks post partum
79%	50%	22.6%	0	69%

Some really helpful (not!) info comes from STAGO , the manufacturer of the d-dimer test kits which publishes their **references ranges for pregnant women** based on the work of Szecsi (in brackets is the number of samples)

Control	13-20 weeks	21-28 weeks	29-34 weeks	35-42 weeks
<0.5	0.2-1.4 (537 pt)	0.3-1.7 (369 pt)	0.3-3 (178 pt)	0.4-3.1 (362 pt)

ie a significantly positive result can be normal in a pregnant woman

Note also that:

- No validated risk scores exist at present for pregnant patients. During the derivation of the Wells score, pregnant women were specifically excluded. External validity is therefore uncertain.
  - We can see how many false positive tests arise with normal pregnant patients but there is also little understanding on the sensitivity and specificity of d-dimer in pregnant patients with PE.
- Pregnant patients have a thromboembolism rate of ~ 4 times non-pregnant controls.
  - One could therefore argue that pregnant women will always be at least at moderate clinical risk by default.

  Take Home Point (THP) - At present, therefore, D-dimer is an inappropriate diagnostic test for suspected PE in pregnancy especially late pregnancy.

So going back to the general patient, one process we must consider before ordering the d-dimer is looking at the pre-test probability of a PE or a DVT. What is the likelihood of the patient having the condition? Only then can you followup with "what is the likelihood the test is positive or negative , and then "what am I going to do if the test is positive or negative?"

What is the odds that the patient has a PE? Clinical gestalt is important. However there are two main clinical prediction rules which have been widely validated- the Wells and Geneva scores.

Table 7 Clinical prediction rules for PE: the Wells score and the revised Geneva score

Revised Geneva score[64]

Variable	Points
Predisposing factors	
Age >65 years	+1
Previous DVT or PE	+3
Surgery or fracture within 1 month	+2
Active malignancy	+2
Symptoms	
Unilateral lower limb pain	+3
Haemoptysis	+2
Clinical signs	
Heart rate	
75–94 beats/min	+3
≥95 beats/min	+5
Pain on lower limb deep vein at palpation and unilateral oedema	+4
Clinical probability	**Total**
Low	0–3
Intermediate	4–10
High	≥11

Wells score[65]

Variable	Points
Predisposing factors	
Previous DVT or PE	+1.5
Recent surgery or immobilization	+1.5
Cancer	+1
Symptoms	
Haemoptysis	+1
Clinical signs	
Heart rate	
>100 beats/min	+1.5
Clinical signs of DVT	+3
Clinical judgement	
Alternative diagnosis less likely than PE	+3
Clinical probability (3 levels)	**Total**
Low	0–1
Intermediate	2–6
High	≥7
Clinical probability (2 levels)	
PE unlikely	0–4
PE likely	>4

With the Wells here is high inter-observer variability due to the 3 point "alternative diagnosis is less likely than PE"- this factor alone is thought by some to be as predictive as the rest of the score. Whichever rule is used, the proportion of patients with PE is:

- 10% with the low probability,
- 30% with the intermediate and
- 65% in the high probability group.

(PS also note the inclusion of a 2 level probability - PE unlikely 0-4 /PE likely > 4)

Based on the above information combined with LIATEST sensitivities of ~ 92% the likelihood of a PE with **when we have a -ve d-dimer result** are;
- low probability ~ 2.5%
- intermediate probability ~ 6%
- high probability ~29%

Combining the 2 principles the European Society for cardiology in their 2008 guidelines, they suggest:
- the use of high sensitivity d-dimer assays (sensitivity > 95%) in low and intermediate prob patients
- the use of intermediate sensitivity assays (sensitivity 85-90%) in only low probability patients

- As noted above the LIATEST sensivities for sit around the 90-95% range so we should limit using the test to "de-stratify" PE in low (and potentially intermediate patients) probability patients. Consider using the 2 part Wells' score "PE unlikely" which includes the lower end of the intermediate range with score of 2-4 – see above
- **Note it is not a 100% "rule out".**

THPs

- specificity LIATEST overall is ~ 40- 50%- ie if you want to use LIATEST to decide if you want to rule it in, easier to toss a coin
- thus a +ve result has no value of ruling in a PE
- (if you have access to a simplired, the specificity is better yet not perfect)
- only -ve results help us yet only in the "unlikely" patients (and we have to be even more cautious when using a Simplired to a DVT)

Refs

Editor: Peter Wyllie

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NEXT WEEK

The PERC rule and trying to tie it together

JOKE / QUOTE OF THE WEEK

Please forward any funny and litigious quotes you may hear on the floor (happy to publish names if you want)

THE WEEK AHEAD
Tuesdays - 14:30 – 15:30 Intern & JMO teaching -Thomas & Rachel Moore
Wednesday- 0800-0900 Critical Care Journal Club. ICU Conf Room / 14:30 – 15:30 Intern & JMO teaching -Thomas & Rachel Moore
Thursday 0730-0800 Trauma Audit. Education Centre / 0800-0830 MET Review Education centre / 1300-1400 Medical Grand Rounds. Auditorium.

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