

Two Great Tests for Shortness of Breath: BNP & D-Dimer

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Objectives

- Explain why different reference limits should be used for BNP/NTproBNP in the ER
- Define the situations in which D-Dimer should be used in the Emergency Room
- List 2 benefits of offering D-Dimer testing in the ER

COPD, Pneumonia, or CHF?

A 65 year old man arrives at the Emergency Room because of worsening shortness of breath over the past week.

Two weeks ago, he had a URI, with a mild fever, but he seemed to recover from that. His history is notable for smoking 1 pack of cigarettes a day for the past 30 years.

His physical examination is unremarkable, except for some mild wheezing in his right lung fields.

Among several blood tests ordered, his NTproBNP returns with a value of 600 pg/mL (reference interval <125 pg/mL).

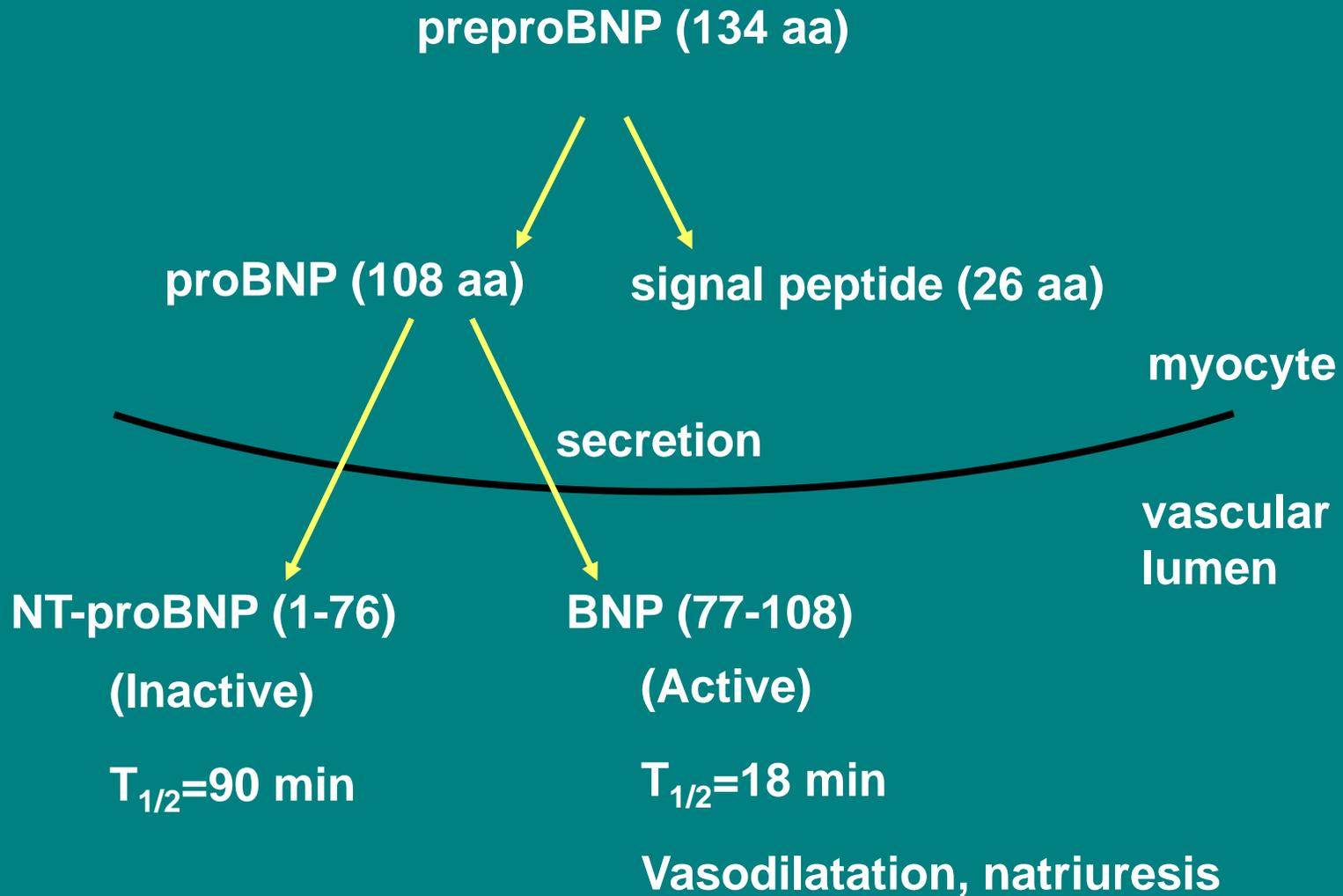
Role of Natriuretic Peptides

- In Congestive Heart Failure (CHF), the pumping action of the heart is compromised, and the heart expands
- In addition, the body retains additional sodium, which can result in fluid accumulating in tissues (legs, lungs)
- The stretching of the heart muscle not only helps the pumping action (Starlings Law) but also results in secretion of natriuretic peptides, which increase urinary sodium excretion
- A balancing act

Nomenclature of Natriuretic Peptide

- Atrial Natriuretic Peptide (ANP)
 - discovered first; isolated from atria of heart
- Brain Natriuretic Peptide (BNP)
 - isolated from brain; hence the name
 - later, isolated from ventricles of heart, too
 - more stable than ANP, easier to measure
 - re-named “B-Type Natriuretic Peptide”
- “Metabolism of BNP”
 - with stretch, heart muscle cells release proBNP, which is cleaved into NT-proBNP and BNP in equimolar amounts

“Metabolism” of BNP



A Superb Lab Test

The New England Journal of Medicine

TABLE 2. MULTIPLE LOGISTIC-REGRESSION ANALYSIS OF FACTORS USED FOR DIFFERENTIATING BETWEEN PATIENTS WITH AND THOSE WITHOUT CONGESTIVE HEART FAILURE.

PREDICTOR	P VALUE	ODDS RATIO (95% CI)*
Age	0.04	1.02 (1.00–1.03)
History of congestive heart failure	<0.001	11.08 (6.55–18.77)
History of myocardial infarction	<0.001	2.72 (1.63–4.54)
Rales	<0.001	2.24 (1.41–3.58)
Cephalization of vessels	<0.001	10.69 (5.32–21.47)
Edema	<0.001	2.88 (1.81–4.57)
Jugular venous distention	0.04	1.87 (1.04–3.36)
B-type natriuretic peptide ≥ 100 pg/ml	<0.001	29.60 (17.75–49.37)

*The odds ratio reflects the odds for patients with the characteristic in question, as compared with those without the characteristic. The odds ratio for age represents the exponent for each year of age in the logistic equation. CI denotes confidence interval.

Maisel et al. N Engl J Med 2002;347:161-7.

NTproBNP Performance in CHF (Roche Package Insert Data)

The clinical sensitivity and specificity of the Elecsys proBNP immunoassay using cut-offs of 125 pg/ml for patients younger than 75 years and 450 pg/ml for patients 75 years or older are presented below.

Sensitivity and Specificity vs. Age and Gender

Males	<45 yrs	45-54 yrs	55-64 yrs	65-74 yrs	75+ yrs	<75 yrs
% Sensitivity	81.6	88.2	89.6	91.7	86.5	89.0
95% Confidence Interval	68.00-91.24	81.27-93.24	84.47-93.42	85.58-95.77	74.21-94.41	85.95-91.58
% Specificity	95.7	93.3	87.8	86.7	88.9	90.0
95% Confidence Interval	78.05-99.89	89.07-96.31	82.33-91.99	79.59-92.07	77.37-95.81	87.14-92.32
Prevalence	0.7	1.8	6.2	6.8	9.8	1.39
Negative Predictive Value	100.0	99.8	99.2	99.3	98.8	99.8

Females	<45 yrs	45-54 yrs	55-64 yrs	65-74 yrs	75+ yrs	<75 yrs
% Sensitivity	86.7	90.5	89.3	94.3	81.8	90.6
95% Confidence Interval	59.54-98.34	69.62-98.83	78.12-95.97	80.84-99.30	64.54-93.02	84.08-95.02
% Specificity	84.9	85.5	79.9	57.8	87.9	76.7
95% Confidence Interval	68.1-94.89	80.64-89.53	74.52-84.63	50.21-65.09	77.51-94.62	73.47-79.72
Prevalence	0.5	1.3	3.4	6.6	9.7	1.16
Negative Predictive Value	100.0	99.9	99.5	99.3	97.8	99.9

Bottom Line: Excellent Negative Predictive Value
i.e., can be used to rule out CHF reliably

NTproBNP Performance in CHF (Roche Package Insert Data)

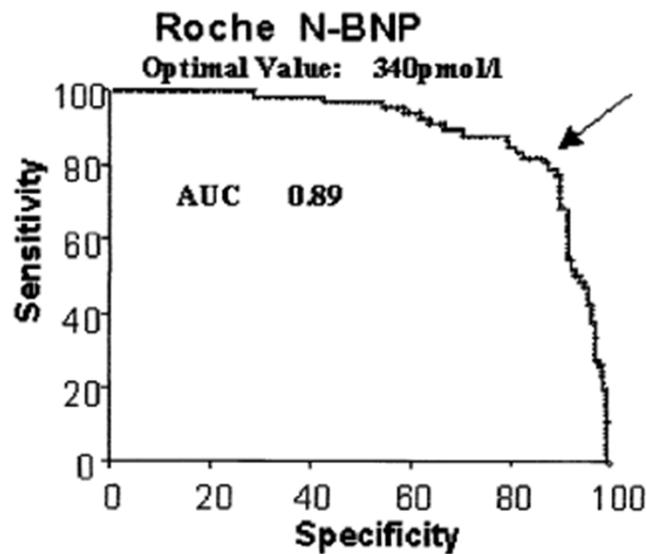
CHF Population-All

	NYHA Functional class				
	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Mean	2042	1016	1666	3029	3465
SD	3349	1951	2035	4600	4453
Median	953	342	951	1571	1707
5 th percentile	72.0	32.9	103	126	148
95 th percentile	7944	3410	6567	10449	12188
% > cutoff	89.4	76.4	93.2	94.4	97.1
Minimum	20.0	20.0	20.0	20.0	97.4
Maximum	40339	13108	10883	40339	20629
N	701	182	250	234	35

CHF Population-Males

Bottom Line: Loose Association with NYHA Class
Implications for Use in ED?

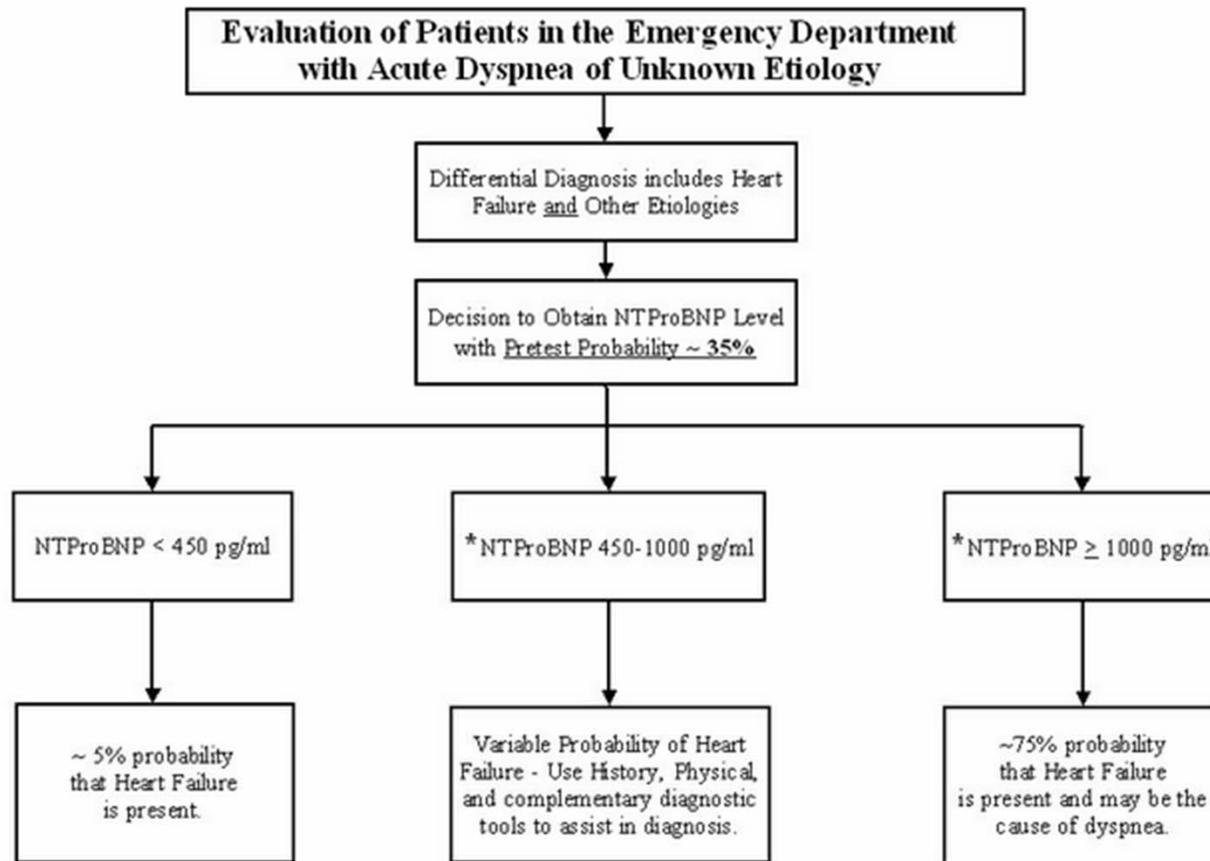
Use of NTproBNP in ED for Acute Dyspnea



Roche N-BNP (pmol/L)	Spec	Sens	PPV	NPV	ACC
140	71	87	60	91	76
240	82	83	70	90	83
340	87	80	76	89	85
440	90	74	79	87	85
540	92	68	80	84	84

Lainchbury et al. J Am Coll Cardiol 2003;42:728-735.

BIDMC Guidelines



*Please note: Patients with chronic heart failure may have persistently elevated NTProBNP levels and therefore can have acute dyspnea that is not cardiac in origin.

Adapted from Lainchbury et al, J Am Coll Cardiol 2003;42: 728- 735; Januzzi et al, PRIDE study, in press; Roche Diagnostics Elecsys ProBNP Immunoassay.

Other Uses for BNP/NT-ProBNP

- A few related clinical issues
- Natrecor™ Infusion Clinics” controversy
- Screening for CHF?
- Can these assays be used to distinguish TRALI from TACO?

Additional Issues Related to Natriuretic Peptides

- Renal insufficiency
 - may cause mild elevations, but not to levels used in ED
- Frequency of measurement
 - Not more than once per week - This is not like troponin or CK-MB
- What constitutes a significant change?
 - CV of <10%
 - Intra-individual differences much larger
 - Probably require 2-fold change to be significant

2005 Controversy – Infusion Clinics

(Topol EJ N Engl J Med 2005;353:113-6)

"It's a pattern. We saw it with Vioxx and some of the cox-2 inhibitor drugs, and we're seeing it now with Natrecor," said Dr. Eric Topol, author of the article, which appears in the July 14

Today, tens of thousands of patients in the United States are receiving "tune-ups" with the drug on an outpatient basis, an indication for which the drug is not approved, Topol said. In fact, the drug, which costs about \$500 per dose, is now being used 10 times more often in

Particularly troubling to Topol and others has been the aggressive marketing undertaken by the company even after safety issues had been raised.

Sales they According to the article, Scios is encouraging physicians to start their own "infusion centers," which would be billed to Medicare; it has also set up a toll-free telephone hotline for "Natrecor Reimbursement Support" and published a 46-page reimbursement and billing guide that provides doctors with specific Medicare billing codes.

The fact that NTproBNP could distinguish between endogenous secretion and infused BNP was little comfort

CHF : A Serious Disease

- 5 year mortality comparable to many cancers!
- increasing in prevalence because of advances in treatment of MI's
- Therapies are available to improve outcomes, especially if initiated early
- Diagnosis by physical exam is poor
- Screening with cardiac ultrasound is expensive

Screening for CHF with BNP?

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% Specificity	84.9					
95% Confidence Interval	68.1-94.0					
Prevalence	0.5					
Negative Predictive Value	100.0					

Group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence of LVD (%)
Participants aged 25-74					
All	76	87	16	97.5	3.2
With IHD	84	76	30	97.5	11
Participants aged ≥55					
All	89	71	18	99.2	5.4
With IHD	92	72	32	98.5	12.1

PPV=positive predictive value; NPV=negative predictive value; LVD=left-ventricular systolic dysfunction.

Table 5: Accuracy of BNP (cut-off 17.9 pg/mL) in detection of left-ventricular systolic dysfunction

McDonagh TA et al. Lancet 1998;351:9-13

Pulmonary Edema With RBC Transfusion

TRALI: Transfusion Related Acute Lung Injury

- cause: antibodies to HLA antigens in donor blood
- fluid therapy helps
- diuretics hurt
- mortality: 5%

- test donor for HLA antibodies

TACO: Transfusion Associated Circulatory Overload

- cause: volume overload in patients with CHF
- fluids ~~help~~ hurt
- diuretics ~~hurt~~ help
- additional transfusions to be administered slowly
- no consequences for donor

some data to suggest that TRALI is much more likely if BNP is low or increases <50% over baseline

COPD, Pneumonia, or CHF?

A 65 year old man arrives at the Emergency Room because of worsening shortness of breath over the past week.

Two weeks ago he was diagnosed with COPD. He is a heavy smoker. Even though this NTproBNP is elevated (indicating the patient may have mild CHF), it is not high enough to account for his shortness of breath at rest.

His physical exam is normal. Other causes are more likely.

Among several blood tests ordered, his NTproBNP returns with a value of 600 pg/mL (reference interval <125 pg/mL).



Is It or Isn't PE/DVT?

A 28 year old woman arrives at the Emergency Room with acute shortness of breath occurring just after arriving in Philadelphia after an overnight flight from Europe.

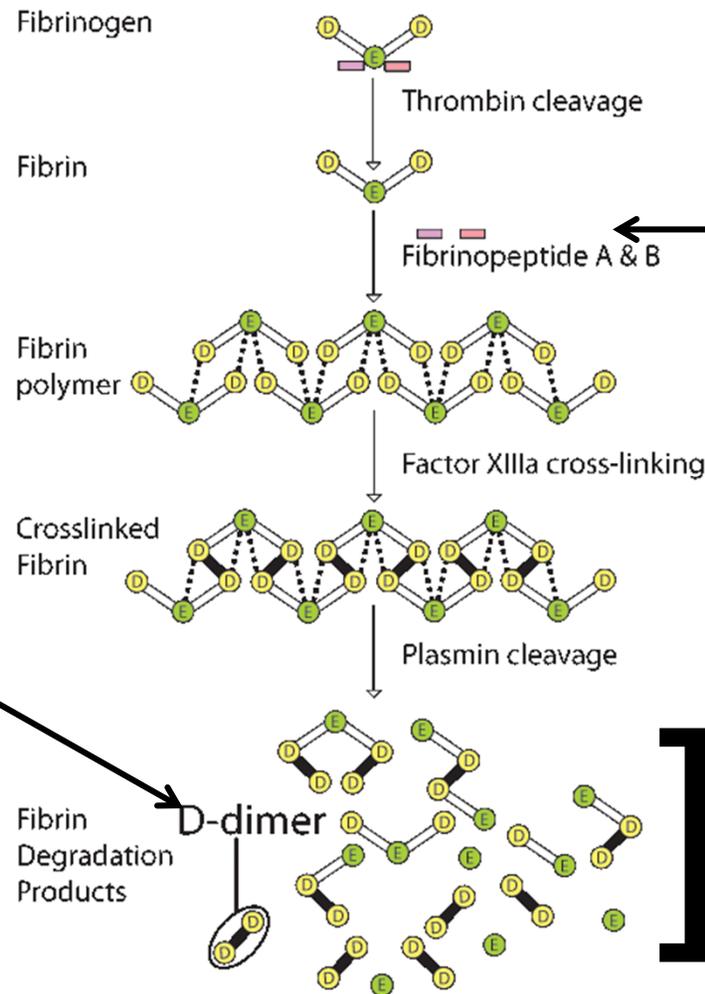
She is a very healthy individual, who sees her primary care physician annually. Of note, she takes oral contraceptives.

Her physical examination is unremarkable, except for some mild wheezing in her right lung fields.

Among several blood tests ordered, her D-Dimer value is reported as 250 ng/mL (reference interval <500).

Understanding What D-Dimer Is

Generation of D-dimer from cross-linked fibrin



These molecules do ****not**** originate from clot

Single species
Standardizable

Heterogeneous
collection of molecules
occurring in differing
combinations

<http://ahdc.vet.cornell.edu/coag/test/D-dimer.gif>

Similarities to Bone Turnover Markers

- In the old days, bone resorption markers included calcium, phosphate, collagen, etc., none of which were specific for bone destruction
In that sense, they were like FDPs

Telopeptides are the like the “D-Dimer” of bone,
in that they can form only after bone is destroyed

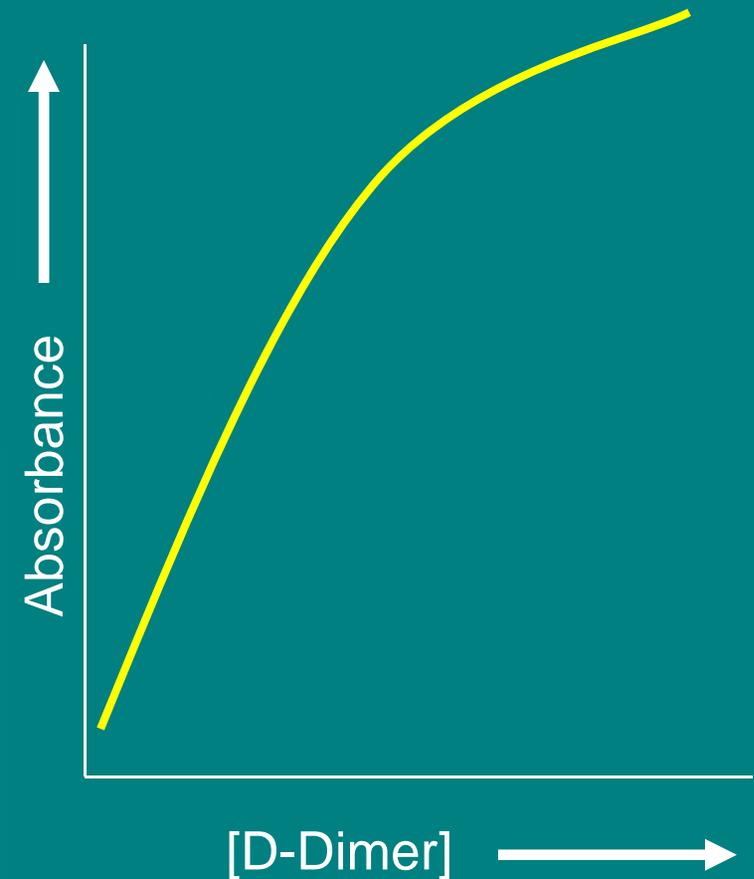
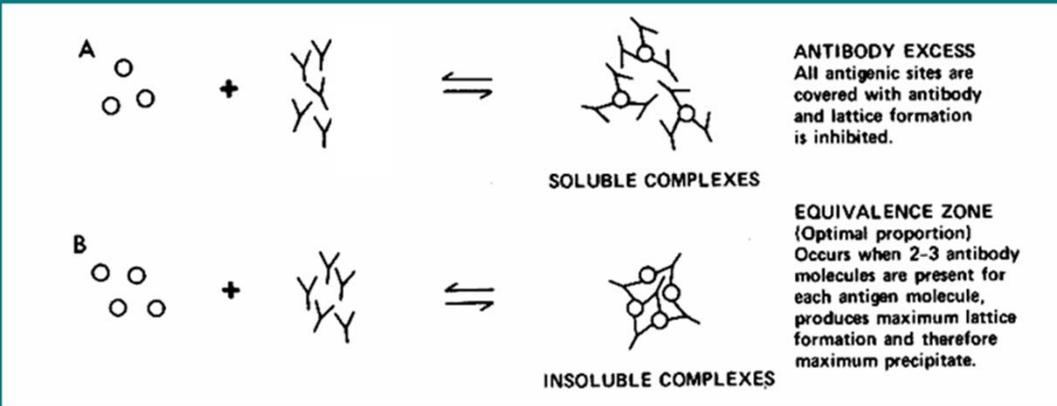
- There may be more on this topic later in the course
- Also, note that alkaline phosphatase is a marker of bone formation

A Typical Immunospectrometric Assay

Test principle

Latex particles of uniform size are coated with monoclonal antibodies (F(ab')₂ fragments) to the D-Dimer epitope. The antigen/antibody complexes produced by the addition of samples containing D-Dimer lead to an increase in the turbidity of the test reactants. The change in absorbance with time is dependent on the concentration of D-Dimer epitopes in the sample.

Reagents: working solutions



“Wells Criteria” & PE/DVT

Thromb Haemost 2000; 83: 416–20

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Derivation of a Simple Clinical Model to Categorize Patients Probability of Pulmonary Embolism: Increasing the Models Utility with the SimpliRED D-dimer

Philip S. Wells, David R. Anderson, Marc Rodger, Jeffrey S. Ginsberg, Clive Kearon, Michael Gent, Alexander Klok, Michael Chamberlain,

Wells' Criteria: Clinical Assessment for Deep Venous Thrombosis	
Criteria	Points
Malignancy (on treatment, treated in the past six months or palliative)	1.0
Paralysis, paresis, or recent lower extremity immobilization.	1.0
Localized tenderness.	1.0
Entire leg swollen.	1.0
Bed rest > 3 days or Surgery ≤ 4 weeks ago.	1.0
Calf swelling > 3cm when compared to asymptomatic leg.	1.0
Pitting edema (greater in symptomatic leg).	1.0
Collateral superficial veins (non varicose).	1.0
Alternative diagnosis as or more likely than DVT.	- 0.2
Score range	Interpretation of risk
0 points	Low
1 or 2 points	Intermediate
≥ 3 points	High

Data from Wells, PS, et al. Lancet 1997; 350:1795

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irsh

Modified Wells' Criteria: Clinical Assessment for Pulmonary Embolism			
Criteria	Points		
Clinical symptoms of DVT	3.0		
An alternative diagnosis is less likely than PE	3.0		
Heart rate >100 beats per minute	1.5		
Immobilization or surgery in the previous four weeks	1.5		
Previous DVT or PE	1.5		
Hemoptysis	1.0		
Malignancy (on treatment, treated in the past six months or palliative)	1.0		
Score range	Mean probability of PE, %	% with this score	Interpretation of risk
<2 points	3.6	40	Low
2 to 6 points	20.5	53	Moderate
>6 points	66.7	7	High

Data from Wells, PS, et al. Ann Intern Med 2001; 135:98.

BIDMC OnLine Lab Manual: D-Dimer

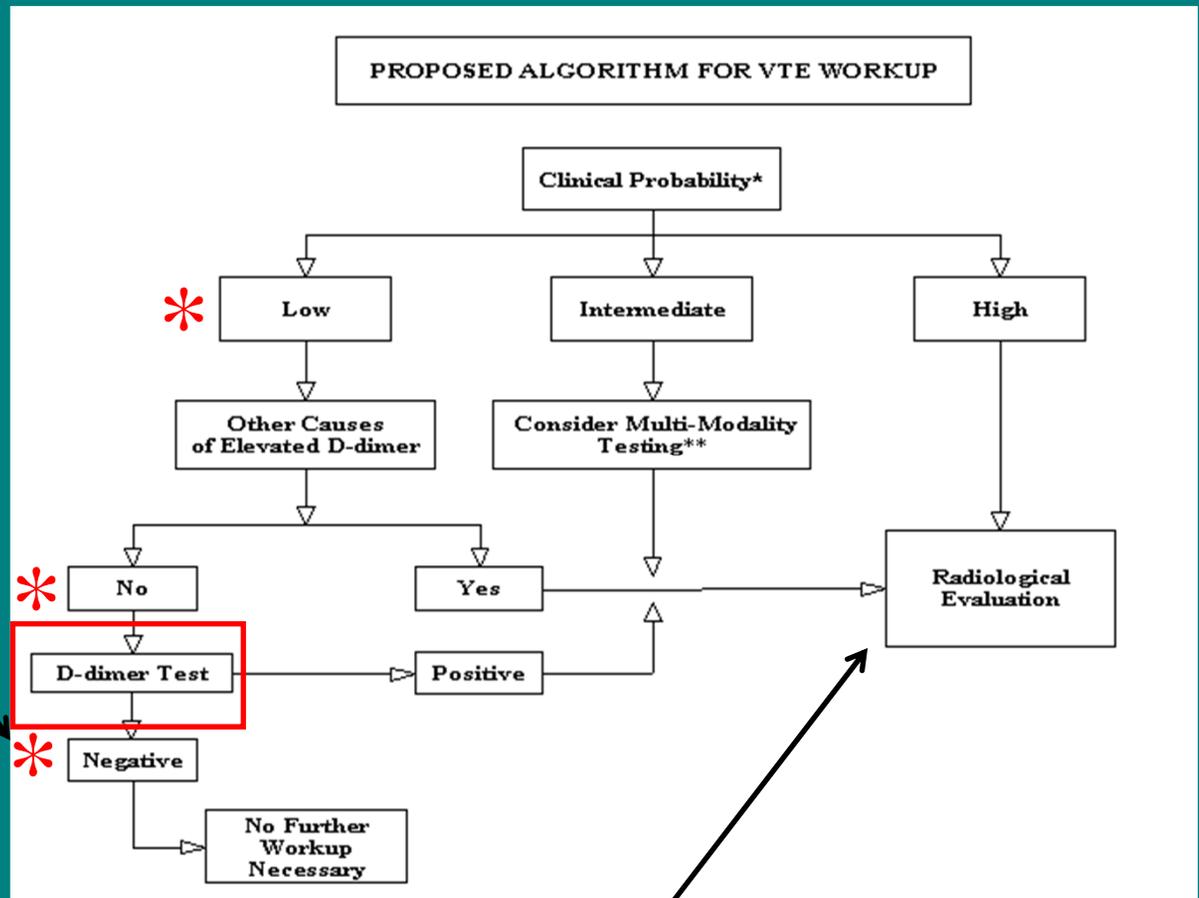
Cross-linked fibrin degradation product generated by lysis of fibrin (and not fibrinogen).

The D-Dimer assay should NOT be used to exclude venous thromboembolism (VTE) in hospitalized patients since they often have co-morbid diseases associated with elevated D-Dimer levels.

Doing so will lead to false positive results and prompt further unnecessary testing.

The current literature only supports the use of this assay to exclude VTE among outpatients with a **LOW PRETEST PROBABILITY** of disease who are being evaluated in the Emergency Department or Ambulatory setting.

BIDMC Implementation



“High Sensitivity” Assay
<500 ng FEU/mL

Computed Tomography Angiogram

BIDMC Experience

(Sanchez L et al Acad Emerg Med 2011;18:317-321)

- 6-month study, encompassing 25,917 ED visits
- 859 D-Dimers ordered (565 females, 294 males)
 - 346 < 500 ng/mL → discharged without imaging
 - 219 > 500 ng/mL
 - 187 had imaging
 - 17 (9.1%) had PE
- effects on resource utilization (compared to previous high sensitivity D-Dimer assay)
 - decreased ED length of stay of 45 minutes
 - decreased radiation exposure (CTAs decreased 16%)
 - higher yield (4.2% to 9.1%), same number of positives

“High Sensitivity”: An Increasingly Used Term

- Implies greater precision at low concentrations
- Assays affected:
 - CRP vs hs-CRP
 - 3rd generation TSH
 - D-Dimer
- Original D-Dimer assays
 - used in DIC (disseminated intravascular coagulation)
 - designed to detect very high levels
 - cannot be used to categorize values for DVT/PE
 - check your package insert to be sure it's approved for use in DVT/PE

Units: Not As Easy As You'd Think

- email from a colleague working in the Emergency Room at a different hospital in our “network”:
“How should I interpret a value of 350 ng/mL?”
- lab report indicates values >237 ng/mL are abnormal, but he’s used to our assay with a threshold of 500 ng/mL
- 2 units (both, unfortunately, in ng/mL):
Fibrinogen Equivalent Units (FEU)
D-Dimer Units (DDU)
1 DDU ~ 2 FEU, so the thresholds are equivalent
most labs use FEUs for DVT/PE

CAP Accreditation Checklist

****NEW** 04/21/2014**

HEM.37924 D-dimer Unit Results

Phase I

The unit results in the laboratory report are the units generated directly by the D-dimer method, including both the unit type (e.g. FEU or D-DU) and unit of magnitude (e.g. ng/mL).

NOTE: The units generated directly by the D-dimer method can be determined from the package insert. If units are not stated in the package insert, consult with the manufacturer of the D-dimer method.

D-dimer units include both a type (i.e. D-DU or FEU) and magnitude (e.g. ng/mL). Both of these components must be used as generated by the method. Reporting the unit of magnitude without the type of unit or vice versa is unacceptable. Calculations for the conversion of the type and/or unit of magnitude are not acceptable.

REFERENCES

Final Words on D-Dimer

- Use D-Dimer to rule out DVT/PE only when suspicion is low (Wells criteria)
- If suspicion is moderate or high, imaging is absolutely ****necessary****, regardless of D-Dimer result
- Make sure the D-Dimer assay is high sensitivity and that you know which units are used

Is It or Isn't PE/DVT?

A 28 year old woman arrives at the Emergency Room with acute shortness of breath occurring just after arriving in Philadelphia after an overnight flight from Europe.

She is
physic

This patient has a low Wells score, so it was totally appropriate to order the D-Dimer.

The value is below 500 FEU ng/mL.

Her p
mild v

She does not need an imaging study and can be safely discharged home

Among several blood tests ordered, her D-Dimer value is reported as 250 ng/mL (reference interval <500).

Final Words on Shortness of Breath in the ED

- BNP (or NTproBNP) and D-Dimer are superb tests, among the best assays in Clinical Chemistry
- They are used daily by Emergency Department physicians across the country to make critical decisions about their patients

Self-Assessment Question 2

Which of the following patients can be screened with D-Dimer levels as a means of ruling out DVT or PE?

- A) A hospitalized patient
- B) A patient with history of DVT and heart rate > 100
- C) A patient with a swollen, tender leg
- D) A patient on chemotherapy for breast cancer

Self-Assessment Question 3

Which of the following is an advantage of offering D-Dimer testing in the Emergency Room?

- A) Increased numbers of patients admitted to hospitals for thorough examinations
- B) Decreased numbers of patients exposed to radiation
- C) Increased revenue to radiologists for performing CTAs
- D) No need for physicians to carefully evaluate patients