CASE: 33 year old woman with no known medical history presents to the Emergency Department complaining of sudden onset shortness of breath and pleuritic chest pain. What is your differential diagnosis? What is the pre-test probability for venous thromboembolism? What is important in the history? What would you expect to find on exam and what tests are useful? How would you treat this patient?

Venous Thromboembolic Disease (VTE)

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Clinical findings: Common symptoms include pleuritic chest pain or hemoptysis (65%) and isolated dyspnea (25%). Syncope can be seen with large embolus (5-10%). These symptoms are relatively nonspecific. History is key. Risk factors will change pre-test probability and guide your testing.

Risk factors: Recent travel such as flight >3000 miles and long car/bus/train trips; recent immobility due to hospitalization in past 4 weeks (major hip and knee surgery is greater risk (>) than neurosurgery > trauma > cancer surgery); medical illness including cancer, CHF, CVA, COPD, obesity; recent central line; estrogen use as with oral contraceptive pills, hormone replacement, pregnancy; tobacco use; and personal or family history of VTE. A personal history of DVT confers recurrence risk for ten years.

Use Wells Score to guide workup. If 4 points or fewer, VTE probability is < 5%.
1. Clinical signs and symptoms of pulmonary embolus (PE)—3 /pts.
2. An alternate diagnosis is less likely than PE —3pts.
3. Heart rate above 100—1.5pts.
4. Immobilization or surgery in the previous 4 weeks—1.5pts.
5. Previous DVT or PE—1.5pts.
6. Hemoptysis—1pt.
7. Cancer treatment now or within the last 6 months, or palliative—1pt.

The **Revised Geneva Score** can guide the work up and removes the ambivalence of determining the alternate diagnosis in the Wells score. 0-3 points has a probability of 8%.
1. Age > 65—1 pt.
2. Previous DVT or PE —3pts.
3. Surgery (under general anesthesia) or fracture (of lower limb) within 1 mo —2pts.
4. Active malignant condition (currently active or considered cured <1y) —2pts.
5. Unilateral lower-limb pain —3pts.
6. Hemoptysis —2pts.
7. Heart rate
   - 75-94 beats/min —3pts.
   - Greater than or equal to 95 beats/min —5pts.
8. Pain on lower-limb deep venous palpation and unilateral edema —4pts.

COPD
Patients with severe COPD exacerbations without a known trigger have a VTE prevalence of 25%. In these patients, history of previous VTE, malignancy, and a decrease in PaCO2 of at least 5 mm Hg from baseline values were associated with PE.

Physical Exam: Tachycardia is the only exam finding that supports diagnosis of VTE; the absence of tachycardia argues against it. Other findings may include: diaphoresis, tachypnea (RR > 25), fever, pulmonary crackles or pleural rub, elevated neck veins, loud P2, presence of S3 or S4, tender or swollen calf, and calf asymmetry. None are sensitive or specific.

Diagnosis

•CXR - helpful to in/exclude other diagnosis; not helpful for VTE. Classic finding is Westermark's sign (localized area of peripheral oligemia +/- distended pulmonary arteries), seen in ~6% of patients with PE. Look for Hampton's hump (infarcts seen as rounded opacities near costophrenic sulcus above an elevated diaphragm). Most common finding is cardiomegaly.

•EKG - unusual to have NORMAL EKG. Usually, tachycardia and/or signs of right heart strain; right bundle branch block, rarely S1, Q3, T3. Helpful to rule out acute ischemia, pericarditis.

•Arterial Blood Gas - hypoxemia is not specific and is not helpful as a screening tool. A-a gradient may be abnormal; one study showed a normal A-a gradient in 20% of patients with VTE. ABG can help identify respiratory fatigue.

•D-dimer - Becoming the standard lab to *rule out* VTE. In the outpatient or ED setting, D-dimer is useful if negative AND if test is an ELISA (as at HMC and UWMC and if pre-test probability is not high). Sensitivity is 95-96% for VTE; negative predictive value 99.6%, in one study. High-risk patients still usually require imaging

CAVEAT: D-dimer is NOT useful in inpatients! In one study, 19 of 45 inpatients had false negative D- dimer valves and did in fact have VTE; most inpatients will have an elevated D-dimer, for reasons yet unknown. D-dimer should not be checked on patients hospitalized more than 3 days.

•Cardiac markers – may be helpful for prognostication. Elevated troponin and brain natriuretic peptide (BNP) predict adverse outcomes. If you think your patient has VTE and there is a mildly elevated troponin, it still could be VTE.

Additional Imaging

•Pulmonary arteriograpy - considered the gold standard but rarely used as it is costly, invasive, and involves a significant contrast load; it is not great for subsegmental pulmonary embolism.

•V/Q scan – most helpful if the patient has a normal CXR. Multiple studies have shown that a low probability V/Q scan excludes VTE. Especially useful if patient has contrast allergy or renal failure. Indeterminate scans do not rule out VTE. At HMC, V/Q is challenging to obtain rapidly at night or on weekends.

•Spiral CT – imaging of choice at HMC. Quick and easy to do; the patient needs an 18-gauge IV in the antecubital space or higher. 69-92% sensitive; 86-96% specific for segmental or larger PE; not great for subsegmental PEs. Most studies were done with larger cuts and newer CT scanners are faster and using smaller (1mm) cuts and detecting 40% more subsegmental PEs. In addition, CT scans can evaluate deep pelvic veins and are 100% specific and 97% sensitive for DVT. The three-month VTE risk for patients with a negative multidetector CT scan who are left untreated is 1.5 %, similar to that of pulmonary angiography. HMC and UWMC use 1.5 mm cuts in their spiral CTs.

•MRA - not done often at HMC. Time consuming, expensive, difficult to monitor unstable patients. However, no contrast is needed; 85-100% sensitivity and 95-96% specificity for VTE.

•Echo - not useful to diagnose VTE but can be helpful for risk stratification.

Management Principles: Prognosis/risk stratification: Adverse outcome predicted by the Geneva prognostic index. If patients have cancer, heart failure, prior VTE, hypotension, hypoxemia or deep vein thrombosis on ultrasound, they had more complications in one study. The Geneva Index is not used to direct therapy. If transthoracic echo shows RV dysfunction, there is a higher risk of shock and death.

Treatment

If unstable (hypotensive, hypoxic) patient: consider directed thrombolysis, embolectomy, or lytics, such as Alteplace 100 mg, together with un-fractionated heparin. It is unclear if patients with echocardiographic right heart strain but normal blood pressure should receive lytics. One prospective study of heparin plus alteplase compared with heparin alone in sub-massive VTE showed that patients who received lytics had better outcome, less recurrence of VTE, and fewer complications. There was no mortality benefit.

•Stable patients: Treatment with IV anticoagulation, either un-fractionated heparin with a bolus of 80U/kg and 18U/kg/hr infusion, adjust per protocol OR low molecular weight heparin (LMWH) 1mg/kg Subcutaneous BID also appears to be effective treatment.
►Recent Cochrane review: LMWH is as effective as un-fractionated heparin for treatment of DVT. LMWH significantly reduces the occurrence of hemorrhage during initial treatment and overall mortality at end of follow up. A recent Meta-analysis found LMWH equivalent to un-fractionated heparin in stable PEs. However, if patient is unstable, most would still recommend un-fractionated heparin.
►Recent JAMA article compared subcutaneous heparin (330U/Kg for the first dose, then 250U/Kg Q12) with LMWH and found them to be equally efficacious.
•Hypercoaguable workup: If there isn't an obvious cause for VTE such as trauma or surgery, if this is recurrent clot or in a strange place such as an artery, an upper extremity without instrumentation, personal or family history of VTE, or abdominal clots, consider hypercoaguable workup. Acute VTE may affect antithrombin III and protein C levels and warfarin affects Protein C and S levels. Thus, test prior to starting anticoagulation OR 4-6 weeks after discontinuing anticoagulation. If antithrombin III and Protein C levels are low prior to starting anticoagulation, retest after treatment to ensure they are truly low. Send: **Factor V Leiden mutation, prothrombin gene mutation, homocysteine levels, antiphospholipid antibody syndrome screen, antithrombin III, protein C and Protein S levels and activity. Consider Factor VIII or XI levels and lipoprotein (a).**
•Filter: If patient isn't an anticoagulation candidate, consider a removable IVC filter, which usually must be removed within 4 weeks.
•Warfarin should be started on the first hospital day, usually at a dose of 5 mg at bedtime, unless there are contraindications such as pregnancy. High dose loading is not indicated. PT/INR should be followed and the dose should be adjusted accordingly. No good evidence for continuing heparin until warfarin has been therapeutic for 2 days. Goal INR is 2-3. Treatment should last 6 months, unless the patient is found to have an inherited disorder.

Case Follow-up
On history, the patient noted smoking 1 pack of cigarettes a day and had just begun taking oral contraceptives. On exam, she had a heart rate of 109, a BP of 132/68 and a room air saturation of 95%. Her CXR was clear, her EKG showed a partial right bundle block with sinus tachycardia, and her D-dimer was positive. Cardiac enzymes were normal. Spiral CT revealed an embolus in the sub-segmental pulmonary artery of the left lower lobe. She was started on LMWH 1mg/kg, started on Coumadin and remained stable. She was encouraged to stop smoking and find a different form of birth control. Genetic testing was not done.

Clinical Pearls
- History is critical in determining pre-test probability.
- Consider VTE in unexplained COPD exacerbations.
- Presence or absence of tachycardia is the most useful physical exam finding.
- D-dimer is NOT helpful in patients hospitalized more than 3 days.
- LMWH and heparin are equivalent for treatment of VTE in stable patients.

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