September 2013

Washington University Emergency Medicine Journal Club
Outpatient Management of Selected PE Patients

Vignette

Your emergency department's Urgent Care area – the land of the relatively healthy. Your first mission of the day is a healthy undergraduate teenager referred from the campus clinic for evaluation of acute onset, unilateral, pleuritic chest pain. The referring physician's specific concern is pulmonary embolism (PE). Your young patient denies any significant past medical or surgical history, including no (personal or family) history of prior venous thromboembolism. However, she does use birth control pills. She has had no recent chest trauma, upper respiratory infection, or skin rash.

Her vitals are BP 120/80, P 60, RR 16, T 37.1°C, and her room air pulse ox is 100%. She is lean and muscular without any other remarkable findings on physical exam, including no chest wall tenderness. Active twisting/bending range of motion of her trunk and chest wall is pain-free for her. You follow the Washington University pulmonary embolism diagnostic protocol and because she uses birth control pills, she is non-low risk by the PERC criteria. Therefore, per the protocol, you order a D-dimer, which is elevated, and a subsequent PE protocol CT demonstrates a peripheral PE. You notify the patient of these findings, call the referring physician to notify her, and prepare to admit the patient. However, the admitting service calls you to discuss outpatient management of PE, which the Hospitalist insists is a common practice and based upon high-quality research. You decide to review the literature yourself before discharging your young patient home.

PICO Question

Population: Adult patients with pulmonary embolism
Intervention: Outpatient management (heparin/LMWH anticoagulation)
Comparison: Inpatient management (heparin/LMWH anticoagulation)
Outcome: Morbidity, mortality, ED recidivism, cost, side effects

Search Strategy

You use PUBMED to conduct a "broad" therapy study Clinical Query using the search term "pulmonary embolism" yielding 16242 citations which you subsequently combine with the search terms "emergency*" and "outpatient management" (27 citations – see **http://tinyurl.com/m8nq8yg**). The first citation is a recent meta-analysis which points you to all of the other references, including two observational trials and one randomized controlled trial.

Article 1: Vinson DR, Zehtabchi S, Yealy DM. Can selected patients with newly diagnosed pulmonary embolism be safely treated without hospitalization? A systematic review. Ann Emerg Med. 2012 Nov;60(5):651-662. Answer Key.

Article 2: Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, Renaud B, Verhamme P, Stone RA, Legall C, Sanchez O, Pugh NA, N'gako A, Cornuz J, Hugli O, Beer HJ, Perrier A, Fine MJ, Yealy DM. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet. 2011 Jul 2;378(9785):41-8. Answer Key.

Article 3: Zondag W, Mos IC, Creemers-Schild D, Hoogerbrugge AD, Dekkers OM, Dolsma J, Eijsvogel M, Faber LM, Hofstee HM, Hovens MM, Jonkers GJ, van Kralingen KW, Kruip MJ, Vlasveld T, de Vreede MJ, Huisman MV; Hestia Study Investigators. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost. 2011 Aug;9(8):1500-7. Answer Key.

Article 4: Agterof MJ, Schutgens RE, Snijder RJ, Epping G, Peltenburg HG, Posthuma EF, Hardeman JA, van der Griend R, Koster T, Prins MH, Biesma DH. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. J Thromb Haemost. 2010 Jun;8(6):1235-41. Answer Key.

Bottom Line

PE Epidemiology and Overdiagnosis

According to Rosen's textbook of emergency medicine, approximately 1 in every 500 to 1000 (0.1%-0.2%) ED patients have a pulmonary embolism (PE). Autopsy data ranges from 0.07% (Silverstein 1998) to 0.2% (Anderson 1991, Hansson 1997), although experts believe that clinical estimates of PE incidence underestimate the true value as opposed to autopsy, which often overestimates the true incidence (White 2003). In fact, some autopsy data suggests that 60% of consecutive individuals have PE if we look hard enough. Indeed, pundits increasingly suggest that contemporary CTs may too accurately diagnose PE's – meaning that clinically insignificant PEs are being detected by modern CT scanners (i.e. PE not the cause of the patient's symptoms, PE not destined to cause patient death or permanent disability).

In support of this observation, there is a significant temporal trend of increased PEs diagnosed since CT became widely available in 1998 in the United States and Australia. If clinically significant PEs were truly becoming more common since 1998 (as opposed to being overdiagnosed due to overtesting), then PE-related mortality

should be increasing, but it is stable over the last 40-years – thus meeting one defining element of "overdiagnosis" (Hoffman 2012, Moynihan 2012, Carpenter 2013, Preventing Overdiagnosis Consortium).

Furthermore, we are harming patients in the attempt to diagnose 100% of PEs. Newman estimates that in the pulmonary embolism rule-out criteria study, testing for PE prevented 6 deaths and 24 major/non-fatal PE events, while causing 36 deaths and 37 non-fatal major medical harms (renal failure, major hemorrhage, cancer). Overtesting inextricably links to overdiagnosis and in the case of PE, ↑ testing →↑harm. Harms extend beyond iatrogenic injury, too, including patient anxiety for a PE diagnosis (of which they never would have been aware with no ill effect in many cases), as well as current and future costs (individual patient insurance premiums). Per-patient inpatient admission costs for PE in the United States ranged from $25,000 to $44,000 between 1998 and 2006 with post-hospitalization warfarin and lab testing estimated at $2694.

Roots of the Overdiagnosis Problem

Why is there a problem with overtesting for PE? Multiple reasons exist in the United States, including

- an unfriendly malpractice environment,
- distrust by patients or clinicians of existing non-imaging clinical decision aids (Well's, PERC),
- patient/family belief that more testing equates to better care,
- reimbursement streams that reward more testing (or fail to reward less testing),
- physician perception that all PEs are potentially lethal and therefore merit inpatient monitoring (Futterman 2004, Calder 2005, Kabrhel 2010).

Based upon two studies (Goldhaber 1999, Kline 2003), Rosen's emergency medicine textbook reports that 10% of ED patients die within 30-days of diagnosis, even if promptly diagnosed and treated. However, this mortality estimate lumps all PE patients (sub-segmental versus segmental versus saddle embolus) into one large group and assumes that mortality is secondary to the PE. Based upon data from Kline, Newman estimated that PE-related mortality is 0.2%. What we really need to know is which PE patients benefit from anticoagulation? Unfortunately, CT does not usually provide us with that answer so what options are available to maximize the risk-to-benefit ratio of PE testing and treatment?

What Can We Do?

The first line defense against PE overdiagnosis is to use evidence-based diagnostics to guide which patients to evaluate with D-dimer and advanced imaging. We discussed this extensively at the August 2011 Journal Club (see http://tinyurl.com/ED-PE-Testing) which was based on 5 prior Journal Clubs and includes an algorithm that was accepted by Wash U Risk Management, Radiology, and Emergency Medicine, as well as the majority of the emergency departments across the St. Louis

metropolitan area. Note that the algorithm includes a recommendation to contemplate V/Q scanning rather than PE. Why? Only 1% of "high probability" V/Q scans correspond to isolated sub-segmental PE as compared with 15% of CT pulmonary angiograms.

The second line of defense against PE overdiagnosis-related overtreatment in the ED is to risk stratify patients once we have diagnosed acute PE since some of them may be safely discharged home. Some EM faculty argued for more ED-based testing of PE patients "using a thoughtful approach", including troponin, ECG, BNP, and echocardiography as surrogate markers of right ventricular strain. However, the subset of PE patients who benefit from additional testing remains undefined and could lead us down yet another path towards overtesting →overdiagnosis → overtreatment so this opinion did not reflect the majority.

At least two PE risk stratification instruments exist, but our group agreed that the Pulmonary Embolism Severity Index (PESI) was the preferred risk stratification tool (based upon current evidence [Donzé 2008, Choi 2009] and in order to replicate the highest quality ED-based outpatient PE management evidence trials). The PESI can be computed online and consists of the following questions:

	Score
1. Patient Age	1 point per year
2. Male Patient	+10
3. History of cancer	+30
4. History of heart failure	+10
5. History of chronic lung disease	+10
6. Heart rate ≥ 110	+20
7. Systolic BP < 100 mm Hg	+30
8. Respiratory rate ≥ 30	+20
9. Temperature <36°C/96.8°F	+20
10. Altered mental status	+60
11. Room air O_2 saturation < 90%	+20

The PESI Score predicts 30-day PE-related mortality.

Score	Class	30-day PE-related mortality
≤ 65	I	0-1.6%
66-85	II	1.7%-3.5%
86-105	III	3.2%-7.1%
106-125	IV	4.0%-11.4%
>125	V	10.0%-24.5%

If a subset of PE patients are discharged home, PESI Class I patients are the most obvious target.

Is Outpatient Management Safe and Effective?

ED physicians currently discharge 1% of PE patients, but are asked to do so by admitting services in 21% of cases. One recent systematic review identified 8 studies that diagnosed acute PE and discharged a portion home. Seven of these studies were observational (i.e. not randomized controlled trials), only 4 included ED patients and only 1 included U.S. patients. All of the studies had extensive exclusion criteria, including social factors (living alone, indigent, lack of transportation for outpatient follow-up) that prohibited outpatient PE management – all of which are reflected in the protocol that we derived with Hospitalists (see below). In addition, all of the available studies used low molecular weight heparin + warfarin (not dabigatran or one of the other newer anticoagulation therapies) so this data cannot be extrapolated to these newer agents. No cases of venous thromboembolism (VTE) or hemorrhage-related death were noted across 7 studies with 90-day follow-up (0%, 95% CI 0-0.62%), while one study reported two deaths at 180-days (if this occurred at 90-days, estimated risk 0.26%, 95% CI 0-1%). Recurrent VTE ranged from 0-6.2% and non-fatal hemorrhage ranged from 0-1.2% at 90-days. Another systematic review published in August 2013 confirms the safety of outpatient PE management, if home circumstances are adequate.

The single randomized trial was an open-label non-inferiority trial across 19 EDs in four countries (including the U.S.) from 2007-2010. They included non-pregnant, PESI Class I or II patients without renal dysfunction, recent bleed, or social issues. They hypothesized a non-inferiority margin of 4% and in the per-protocol analysis outpatient management was non-inferior to inpatient care for 90-day recurrent VTE (0.6% difference, upper limit of 95% CI 2.9%, p = 0.014). However, the upper limit of the confidence interval for major bleeding exceeded the 4% threshold at 90 days (3/163 = 1.8%, upper limit of 95% CI 4.5%) so outpatient PE management is not non-inferior to inpatient management with respect to major bleed risk. No major bleeds occurred in the inpatient group. The three major bleeds in the outpatient group were intramuscular hematomas on days 3 and 13 and one episode of menometrorrhagia on day 50. No differences in mortality were identified (0%, upper limit 95% CI 2.1%). No differences in patient satisfaction were observed between inpatient and outpatient management (92% outpatients versus 95% inpatients satisfied or very satisfied). Hospitalization time was 0.5 days in the outpatient group versus 3.9 days in the inpatient group.

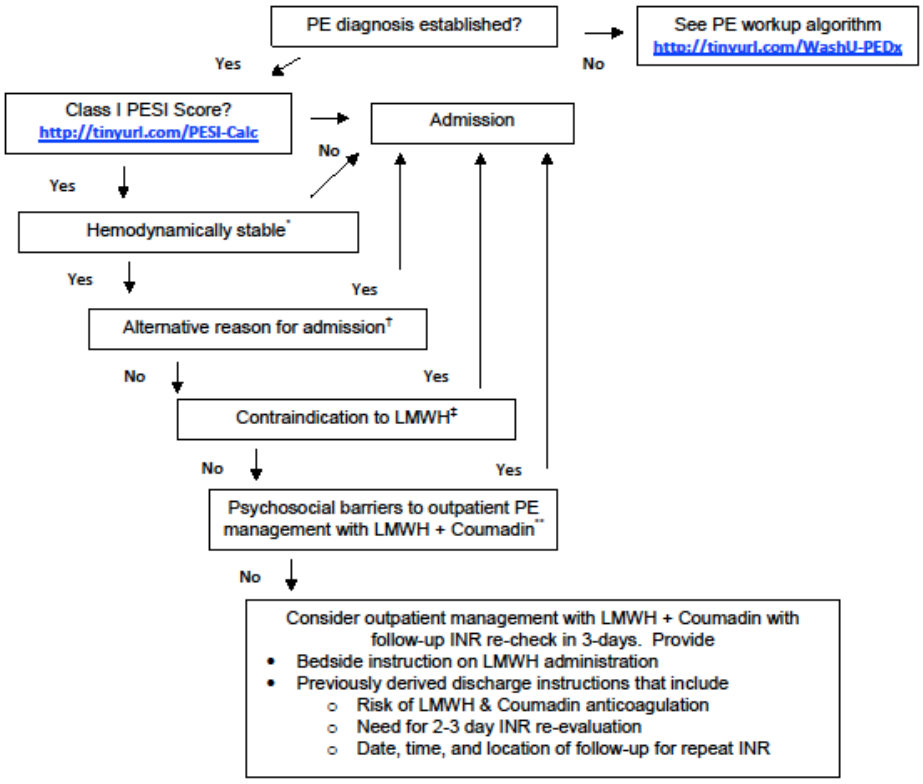
Multiple uncertainties remain.

- Can and will EP's accurately and reliably risk stratify PE patients?
- Which risk-stratification instrument should be used?
- Is LMWH available to destitute ED patients 24/7?
- Who will provide LMWH teaching and is this instruction reliable?
- How will follow-up be assured and what QI process will close the loop?
- Our Hospitalist colleagues question whether future studies of outpatient PE management evaluate whether inpatient is superior to outpatient, rather than whether outpatient management is non-inferior to admission.

In terms of facilitating shared decision making with PE patients who might be appropriate for outpatient management, the consensus was that a statement like the following was appropriate: "A single moderate quality study from 19 ED's in Europe and the U.S. demonstrates that certain PE patients can be safely and effectively treated with blood thinners at home, although there is a chance of increased bleeding risk at 90 days (< 5% at most) with home management."

The role of alternative shared decision-making models to summarize study results from non-inferiority studies (such as Cates plots, site 1 and site 2), natural frequencies, or number needed to treat) remains uncertain. Hospitalists and emergency medicine ultimately agreed upon the attached algorithm, which is also reproduced below.

Protocol for Outpatient Management of Low Risk, Non-Pregnant, Newly Diagnosed PE Patients



* sBP > 90, heart rate < 100, room air oxygen saturation > 90%.
† Pain control, cancer management, etc.
‡ Allergy, GI bleed or surgery within 14 days, stroke within 4 weeks, renal impairment, thrombocytopenia, active bleeding or high-risk for bleeding (coagulation disorder).
** High-risk of non-compliance = debilitating psychiatric disorder, dementia, lack of access to primary care or Thrombo Clinic, lack of insurance to pay for LMWH, limited health literacy