

CLINICAL DECISIONS

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Anticoagulation for Subsegmental Pulmonary Embolism

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Man with a Subsegmental Pulmonary Embolus

Amanda Fernandes, M.D.

Mr. Jackson is a 55-year-old man who has come to the emergency department with a 1-day history of fever and pain in the right upper quadrant. Five days ago, he presented with right upper quadrant pain and underwent laparoscopic cholecystectomy for acute calculous cholecystitis. He had done well after the procedure and had been discharged home.

At the current presentation, the patient's temperature is 39.5°C, blood pressure 135/88 mm Hg, pulse 95 beats per minute, and respiratory rate 22 breaths per minute; a pulse oximeter reading indicates that his oxygen saturation is 99% while he is breathing ambient air. On examination, he has mild tenderness on palpation of the right upper quadrant. Electrocardiography shows sinus rhythm with no evidence of right bundle-branch block or right ventricular strain. Laboratory testing shows no elevation in creatine kinase or troponin levels. A computed tomographic (CT) scan of the abdomen shows no evidence of

an abscess in the right upper quadrant but reveals a single subsegmental embolus in the lower lobe of the right lung. Mr. Jackson has no history of a clotting disorder, and there is no family history of coagulopathy. However, given the CT evidence of a subsegmental embolus, you must decide whether to advise Mr. Jackson to begin anticoagulation therapy.

TREATMENT OPTIONS

Which one of the following approaches would you take for this patient? Base your choice on the published literature, your own experience, published guidelines, and other information sources.

1. **Recommend anticoagulation therapy.**
2. **Do not recommend anticoagulation therapy.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

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From the Department of Endocrinology, Warren Alpert Medical School of Brown University, Providence, RI.

OPTION 1

Recommend Anticoagulation Therapy

Jean M. Connors, M.D.

Five days after undergoing major surgery, Mr. Jackson is found to have a subsegmental pulmonary embolus, with symptoms for which no alternative diagnosis is found. Regardless of whether we consider this to be a symptomatic or incidental embolus, the patient would require a limited

3-month course of anticoagulation therapy, a regimen that is safer now than in years past. Even if the results of ultrasound testing of the legs are negative, anticoagulation with a direct oral anticoagulant agent is prudent until good-quality data are available to inform us of the risk of progressive or recurrent venous thromboembolism associated with not treating a subsegmental pulmonary embolus in a patient who has just undergone surgery, a known major risk factor for development of venous thromboembolism.

The ability to diagnose subsegmental pulmonary embolism has increased owing to improved CT resolution,¹ although among patients presenting with symptoms, subsegmental pulmonary embolism is diagnosed in many fewer patients than proximal pulmonary embolism.^{2,3} Whether the diagnosis of subsegmental pulmonary embolism is of clinical consequence and merits treatment is unclear. Although the American College of Chest Physicians is widely quoted as suggesting that this condition not be treated with anticoagulation (grade 2C, indicating weak recommendation and low-quality evidence for treatment), caveats accompany this suggestion, including the observation that uncertainty about the use of anticoagulants in these patients remains; such patients require negative results on evaluation of deep-vein thrombosis in the legs and close follow-up if anticoagulation is not initiated.⁴

Pulmonary embolism can be fatal. The diagnosis is often overlooked, with symptoms attributed to other causes. Clinical prediction rules, such as the Wells score⁵, PERC (pulmonary embolism rule-out criteria) rule⁶ and YEARS algorithm,⁷ were developed because it is difficult to determine which patients should undergo imaging when pulmonary embolism is suspected. These rules often require testing of D-dimer levels. A prospective study showed that D-dimer levels were unable to distinguish between a proximal pulmonary embolus and a subsegmental pulmonary embolus subsequently detected by CT pulmonary angiography but did distinguish between any pulmonary embolus and no embolus.³ The patients with subsegmental pulmonary embolism had D-dimer levels well above the normal range (median, 2520 mg per deciliter), a finding that suggests true thrombus, with a significant difference between patients with a subsegmental pulmonary embolus and those with no pulmonary embolus but not between patients with a subsegmental pulmonary embolus and those with a proximal pulmonary embolus.

Patients with a negative result on CT pulmonary angiography have a 3-month risk of venous thromboembolism of 0.5%⁸ to 1.3%,⁹ but the risk in patients with untreated subsegmental pulmonary embolism is unknown. In a combined analysis of two large prospective studies of 3728 consecutive patients with suspected pulmonary embolism, 15.5% of 748 patients with

confirmed pulmonary embolism had subsegmental pulmonary embolism and were treated with anticoagulation. In this analysis, no difference in the incidence of recurrent venous thromboembolism or death was observed between patients with subsegmental pulmonary embolism and those with more-proximal pulmonary embolism. Patients with subsegmental pulmonary embolism had a higher risk of venous thromboembolism during follow-up than those without pulmonary embolism (hazard ratio, 3.8; 95% confidence interval, 1.3 to 11.1). In addition, among the patients with pulmonary embolism, the risk factors for venous thromboembolism were similar in those who had subsegmental pulmonary embolism and those with more-proximal pulmonary embolism.² The cumulative risk of recurrent venous thromboembolism among the patients who received anticoagulation therapy was 3.6% among those with subsegmental pulmonary embolism and 2.5% among those with proximal pulmonary embolism, with no change after adjustment for malignant disease or other variables. The rate of major bleeding was lower (1.7% among patients with subsegmental pulmonary embolus and 1.6% among those with proximal pulmonary embolism) than the risk of recurrent venous thromboembolism.

Data on incidental and subsegmental pulmonary embolism in patients with cancer show that the benefit of anticoagulation therapy for subsegmental pulmonary embolism is similar to that for proximal pulmonary embolism.¹⁰ The natural history of untreated subsegmental pulmonary embolism in other populations is not known. No data from prospective randomized, controlled trials suggest that subsegmental pulmonary embolism should be managed differently than proximal pulmonary embolism or that not treating subsegmental pulmonary embolism, even if detected incidentally, is safe. A meta-analysis of a small number of patients with subsegmental pulmonary embolism treated with or without anticoagulation showed a lack of precision in pooled data and high heterogeneity of the outcomes, which suggests that no conclusion can be made about the benefit or harm of anticoagulation therapy.¹¹ Data do indicate that for treatment of pulmonary embolism, anticoagulation therapy with one of the direct oral anticoagulants available now is associated with an incidence of bleeding that is 39% lower than the

incidence associated with previously used low-molecular-weight heparin and vitamin K antagonists,¹² with no fatalities due to major bleeding seen with direct oral anticoagulants in one pooled analysis.¹³

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OPTION 2

Do Not Recommend Anticoagulation Therapy

Marc Carrier, M.D.

The increasing availability of CT in hospital emergency departments and recent advances in technology have led to a substantial rise in the reporting of acute pulmonary embolism, especially of emboli localized in small-caliber vessels such as the subsegmental pulmonary arteries.¹⁴ The validity of a diagnosis of subsegmental pulmonary embolism is questionable. The interobserver agreement among radiologists assessing this type of embolism on CT pulmonary angiography has been reported to be low (kappa statistic, 0.38).¹⁵ The subsegmental pulmonary embolus in Mr. Jackson was diagnosed on CT of the abdomen and not on CT pulmonary angiography. Therefore, given the uncertainty regarding the validity of the diagnosis, clinicians should review the results of the diagnostic imaging and confirm the diagnosis with an experienced radiologist before contemplating anticoagulation therapy, to avoid exposing Mr. Jackson to the bleeding risks associated with anticoagulation therapy for an artifactual finding. In this case, CT pulmonary angiography would be necessary also to ensure that there are no other more-proximal defects in parts of the lungs that were not visualized.

Assuming that the diagnosis of subsegmental pulmonary embolism in this patient is confirmed by the radiologist, its clinical significance remains unknown. Although the incidence of diagnosis of pulmonary embolism has been increasing over the past decades, there have been minimal changes in the overall mortality associated with the diagnosis, and its case fatality rate has been decreasing, which suggests that overdiagnosis and a lower severity of illness challenge

the benefits of anticoagulation therapy.¹⁴ A systematic review with meta-analysis has shown no increase in the rate of recurrent venous thromboembolism or death among patients with subsegmental pulmonary embolism that has been left untreated, a finding that suggests clinical equipoise for the role of anticoagulation.¹¹ Therefore, Mr. Jackson's case could potentially be managed conservatively with clinical surveillance without anticoagulation, an approach that would mitigate the risk of bleeding in the postoperative period.

Subsegmental pulmonary emboli are not diagnosed only in patients who have undergone CT pulmonary angiography. They are also frequently present in patients with suspected pulmonary embolism and nondiagnostic ventilation-perfusion scans. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 17% of patients with a low-probability ventilation-perfusion scan had evidence of subsegmental pulmonary embolism on pulmonary angiography.¹⁶ Prospective management studies have shown that patients with suspected pulmonary embolism and nondiagnostic ventilation-perfusion scans can be safely treated without the use of anticoagulation therapy, provided there is no deep-vein thrombosis.¹⁷ Therefore, treatment for the subsegmental pulmonary embolus in Mr. Jackson can be similar to the treatment in a patient with a nondiagnostic ventilation-perfusion scan. Mr. Jackson has good pulmonary reserve and no additional risk factors for recurrent venous thromboembolism. He should receive treatment for his pain (e.g., acetaminophen or nonsteroidal antiinflammatory drugs) and undergo Doppler ultrasonography of both legs. If there are no deep-vein thrombi, anticoagulation therapy does not need to be started.

Managing the subsegmental pulmonary embolism in Mr. Jackson without anticoagulation aligns with the recommendations in the most recent version of the American College of Chest Physicians clinical practice guidelines.⁴ The guidelines suggest using clinical surveillance rather than anticoagulation therapy in patients with subsegmental pulmonary embolism and no deep-vein thrombosis in the legs who have a low risk of recurrent venous thromboembolism (evidence grade 2C).⁴ An ongoing international prospective cohort study (ClinicalTrials.gov number, NCT01455818) in which subsegmental pulmonary

embolism is managed conservatively should provide more insight to address this important knowledge gap.

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