Pulmonary Embolism in Children

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Abstract: Pulmonary embolism is an uncommon but potentially life-threatening event in children. There has been increasing awareness of pulmonary embolism in children with improved survival in children with systemic disease and advancements in diagnostic modalities. However, literature regarding pulmonary embolism in children is sparse, and thus current guidelines for management of pulmonary embolism in children are extrapolated from adult literature and remain controversial. This article reviews the background and pathophysiology of venous thromboembolism, as well as current diagnostic approach and recommended management of pulmonary embolism in children.

Key Words: antithrombotic therapy, clot, ionizing radiation, pulmonary embolism, venous thromboembolism

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TARGET AUDIENCE

This continuing medical education activity is intended for physicians, physician assistants, nurse practitioners, and emergency medical service providers who care for pediatric patients.

LEARNING OBJECTIVES

1. Distinguish pathophysiology, clinical signs, and risk factors for pulmonary embolism in children.
2. Summarize recommended diagnostic approach and the utility of clinical prediction rules for pulmonary embolism in children.
3. Describe the therapeutic management of pulmonary embolism in children.

CASE

A 16-year-old previously healthy girl presented to her local emergency department with acute onset of chest pain and dyspnea. She localized her chest pain to the left chest wall and noted radiation to her left shoulder and upper back. Review of systems was negative for hemoptysis, fever, respiratory symptoms, leg pain, or swelling. She denied oral contraceptive use, recent travel, trauma, and any history of smoking. Physical examination was significant for dyspnea with clear breath sounds. Cardiac examination revealed regular rate and rhythm, without heart murmur or gallop, and there was good peripheral perfusion.

Initial diagnostic evaluation included a chest radiograph, which was concerning for left lower pneumonia with trace left pleural effusion, and an electrocardiogram (ECG), which demonstrated normal sinus rhythm without abnormality. Her severe pain persisted despite treatment with ibuprofen; therefore, further diagnostic testing was pursued. A D-dimer was obtained and elevated. Results of computed tomography with pulmonary angiography (CTPA) revealed a large left lower lobe pulmonary thromboembolism (Fig. 1). Anticoagulation with low-molecular-weight heparin was initiated for treatment of pulmonary embolism (PE). Additional evaluation revealed right femoral and external iliac vein thrombi, elevated left pulmonary artery pressures on echocardiogram, and presence of antiphospholipid antibodies supporting her predisposition to development of venous thrombi.

BACKGROUND

Pulmonary embolism is a rare but potentially life-threatening event in the pediatric population. Improved survival in children with chronic illnesses and minimally invasive imaging modalities have led to increased awareness and detection of PE in the pediatric population.[1] However, the incidence of PE in children is likely underreported, as evidenced by the higher proportion of PE (4.2%) confirmed in autopsy reports in children.[2] Rates of PE are likely underreported because of asymptomatic or minimally symptomatic and/or nonspecific clinical presentations, symptoms being masked by underlying disease processes, and lack of diagnostic intuition for PE. Pulmonary embolism has been shown to have a bimodal distribution occurring predominantly in neonates and then in adolescents.[3,4]

While there has been increasing recognition of PE in the pediatric population, the majority of data informing clinical suspicion and diagnostic approach in children have been extrapolated from adult literature. Thus, the evaluation and management of PE in the pediatric population remain controversial in the absence of robust evidence and standardized guidelines. In this article, we will review current pathophysiology, diagnosis, and treatment of PE in children based on available evidence.

PATHOPHYSIOLOGY

The pathophysiology of PE is based on presence of features of Virchow triad: venous stasis, injury to the vessel wall, and enhanced coagulability.[5] The subsequent interaction of red blood cells, fibrin, platelets, and leukocytes leads to the formation of a thrombus within the intact vessel wall. In the case of PE, the thrombus dislodges from a distal site and embolizes, traveling through the right atrium to the right ventricle, and then into the pulmonary arteries. The hemodynamic response to PE depends on the size of the embolus causing obstruction to blood flow, the duration over which the obstruction accumulates, and the presence of underlying cardiopulmonary disease.[6] Of note, a patient can be asymptomatic if an embolism obstructs less than 50% of pulmonary circulation; in adults, approximately 40% of patients with deep vein thrombosis (DVT) have evidence of PE on lung scans, but do not manifest symptoms.[5]

Pulmonary emboli cause increased pulmonary vascular resistance due to obstruction to blood flow and subsequent hypoxic vasoconstriction.[6] The increased pulmonary vascular resistance leads to increased right ventricular afterload. As the thin-walled right ventricle works against the heightened pulmonary resistance, right ventricular pressure rises and ultimately leads to right

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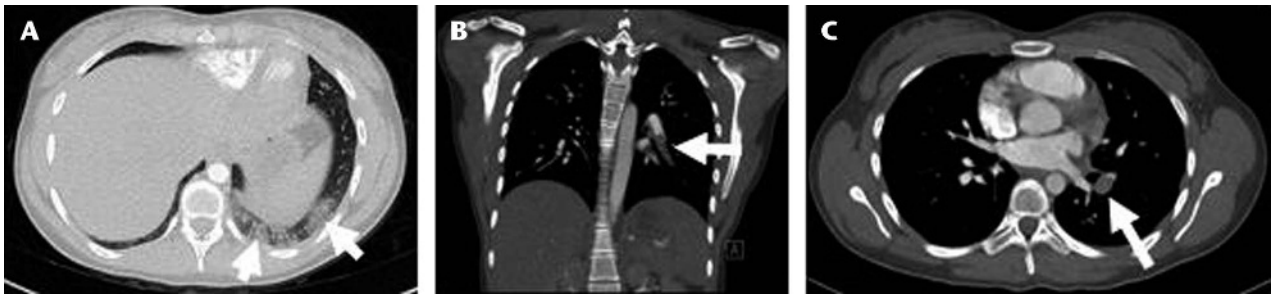

FIGURE 1. Computed tomography pulmonary angiograms illustrating segmental pulmonary arterial thromboembolism. A, Axial soft tissue algorithm image through the midthorax shows an occlusive filling defect (arrow) within the left lower lobe pulmonary artery supplying the lateral and posterior basilar segments. The remainder of the imaged pulmonary arteries enhances normally following contrast administration. B, Coronal image demonstrates an elongated occlusive thrombus (arrow) within the left lower lobe basilar pulmonary artery. C, Axial lung algorithm image through the lung bases shows multifocal patchy ground-glass opacity (arrow) in the left posterior lung base indicative of pulmonary hemorrhage and/or infarction in the distribution of the pulmonary arterial thromboembolism.

ventricular dilatation, tricuspid regurgitation, and right-sided heart failure.[7] Gas exchange is also impaired in acute PE due to ventilation-perfusion (V/Q) mismatch, intracardiac shunt, and increased pulmonary dead space.[6] Ventilation-perfusion mismatch is the most common cause of hypoxemia in PE: blood is shunted from obstructed pulmonary arteries to other available units, causing variability in the ventilation-to-perfusion ratio among different gas exchange units. Intracardiac shunting becomes prominent in the presence of a patent foramen ovale, as right atrial pressure exceeds left atrial pressure leading to venous blood flow to the systemic circulation bypassing the lungs. In cases of severe intracardiac shunting, profound hypoxia will exist despite supplemental oxygen.[5] Lastly, total dead space increases as lung units continue to be ventilated despite diminished perfusion, contributing to an increased alveolar-arterial oxygen gradient. The culmination of these processes can lead to profound hypoxia, hemodynamic instability, and ultimately cardiopulmonary collapse (Fig. 2).

RISK FACTORS FOR THROMBOSIS AND PULMONARY EMBOLISM IN CHILDREN

In children, PE frequently occurs in the presence of known comorbidities, systemic disease, or other risk factors, in contrast to the adult population where idiopathic PE is well described. Idiopathic thrombosis occurs in fewer than 4% of children with venous thromboembolism including DVT and PE.[8,9] Studies have shown that 80% to 96% of children with PE have at least 1 risk factor.[1,8–11] The most common PE risk factors described in children are indwelling venous lines, congenital heart disease, immobilization, and recent surgery.[4,9,10,12–14] Among described risk factors, central venous lines are increasingly implicated in pediatric PE. With the advent of treatments requiring long-term central venous line placement, such as parenteral nutrition, chemotherapy, and other medication administration, thrombotic complications are reported in 33% to 64% of children and 89% to 94.6% of neonates

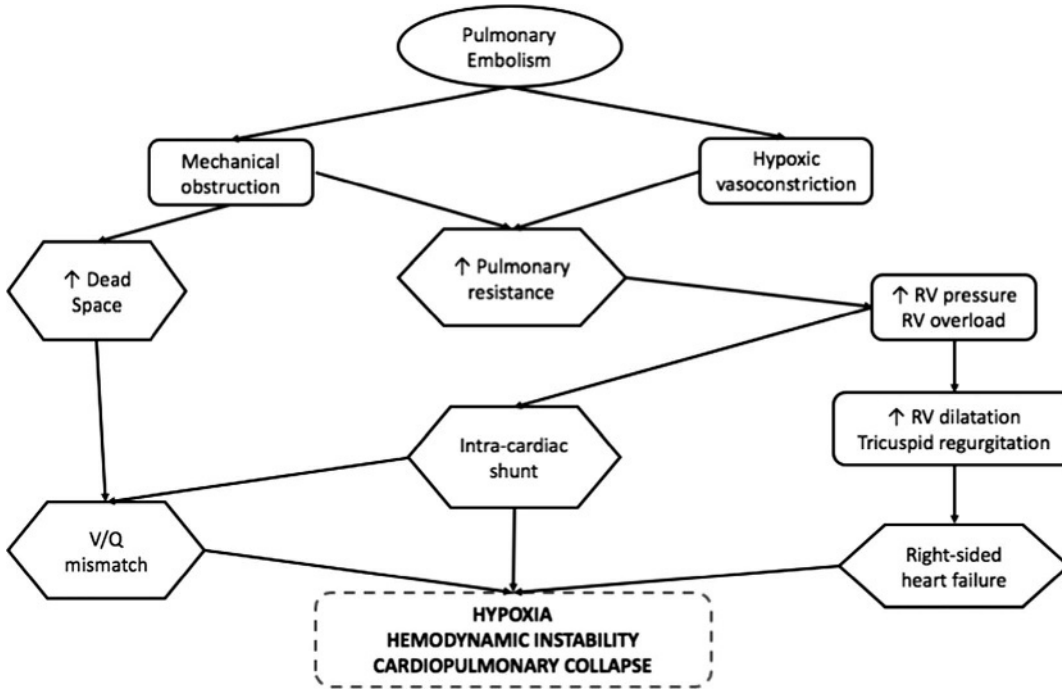

FIGURE 2. Pathophysiology of pulmonary embolism.

TABLE 1. PERC Criteria

Age <50 y
Heart rate <100 beats/min
SpO_2 >94%
No unilateral leg swelling
No hemoptysis
No surgery or trauma within 4 wk
No prior DVT or PE
No oral hormone use

PERC indicates pulmonary embolism rule-out criteria.

with central venous lines.[9,10,12,15] Pulmonary embolism is also associated with presence of DVT; as many as 72.1% of children with PE have concurrent DVT.[10] The presence of upper extremity DVT is also unique to children because of the frequent use of upper extremity and subclavian central venous lines.

Prothrombotic disorders are also an important consideration in development of PE in children. Congenital disorders, including protein C and S deficiency and factor V Leiden, have been reported in 8.8% to 16% of children with DVT or PE.[9,12] However, the true prevalence of prothrombotic disorders is unclear as not all children with venous thromboembolism were previously screened for thrombophilia. Hypercoagulable states from underlying disease processes such as malignancies, sickle cell disease, and nephrotic syndrome also increase risk of PE and can be encountered in the pediatric population. In fact, a study evaluating the risk of PE in children with nephrotic syndrome demonstrated V/Q scan changes consistent with PE in 27.9%, even without overt symptoms.[16]

Among adolescents, oral contraceptive use confers increased risk of PE.[1,17] In community-based settings, oral contraceptive use is the most important risk factor for PE, increasing risk of PE 14-fold in this age group.[18] However, oral contraceptive use alone is rarely responsible for PE in adolescents, as most patients in this age group possess other contributing risk factors including obesity, prior DVT, infection, or underlying prothrombotic disorders.[10,18]

Children suffering from traumatic injury are also at risk of PE, with an incidence of 7 per 100,000 patients reported in the National Pediatric Trauma Registry.[19] The incidence of PE in pediatric trauma patients is greater in those with central venous lines, higher injury severity scores, and older age.[20–22]

Overall, clinicians should be aware of known risk factors for PE in the pediatric population and appropriately raise their clinical suspicion for PE when these risk factors are present in the appropriate clinical setting. Moreover, determining if these PE risk factors are present can help guide clinical decisions regarding diagnostic evaluation and management.

CLINICAL SIGNS

The clinical signs and symptoms of PE in children are nonspecific. It is estimated that only 50% of children with a clinically significant PE manifest overt signs and symptoms.[2] When present, the most common signs and symptoms include chest pain, shortness of breath, tachypnea, tachycardia, and hypoxia.[1,8,10,12] In a study of adolescents evaluated for PE, 84% reported symptoms, the most common of which was pleuritic chest pain, followed by dyspnea and cough.[23] While shortness of breath is a commonly reported symptom for PE, a study evaluating children with high suspicion for PE found that children without PE were more likely to have shortness of breath than those with PE.[17] Therefore, shortness of breath itself is not a specific marker for PE, as it is frequently produced by several alternative conditions. It should be noted that, although uncommon, children with massive PE are likely to present with cardiopulmonary collapse and sudden death.[11] Overall, the clinical signs and symptoms of PE are nonspecific and cannot solely be relied upon to determine the presence or absence of PE in children.

DIAGNOSIS

Clinical Prediction Rules

In the adult population, a number of signs and symptoms are combined into a clinical probability score to determine the pretest probability for PE. The 2 most well-known and consistently used prediction rules are the Pulmonary Embolism Rule-Out Criteria (PERC) and the Wells criteria. The PERC is an 8-factor decision rule utilized to rule out PE in adults presenting with low clinical suspicion for PE (Table 1).[24,25] If a patient meets all criteria, no further testing should be performed. A systematic review and meta-analysis of the PERC in adults demonstrated excellent sensitivity (97%) and low negative likelihood ratio (0.17) in excluding PE in adults.[26] When applied to the pediatric setting, the PERC had a similar sensitivity (100%) and negative likelihood ratio (0.0), but demonstrated a high false-positive rate with up to 76% of patients without PE being PERC positive.[27] The high false-positive rate is especially important in children in whom the risk of additional testing and ionizing radiation can be harmful. Components of PERC most commonly not satisfied in the pediatric setting are the presence of tachycardia and clinical signs of DVT.[1]

The Wells criteria, which consist of weighted clinical findings to categorize patients into low-, moderate-, and high-risk groups for PE based on the presence of a number of signs and symptoms, have been shown to be accurate in predicting PE in adults (Table 2).[28,29] Scores of less than 2, 2 to 6, and greater than 6 correlate with low, moderate, and high risk, respectively. However, when applied to the pediatric population, the Wells criteria lack utility in determining pretest probability of PE in children.[1,27,30] Several components of the Wells criteria including tachycardia, hemoptysis, signs of lower DVT, and suspicion for PE as the most likely diagnosis are not discriminatory in identifying children with PE.[30] The criterion of "alternative diagnosis that is less likely than PE" is the most problematic because of its subjective nature. In a study evaluating the utility of the Wells criteria in children, only 58% of physicians had suspicion for PE in the group of children with diagnosed PE, whereas 29% had suspicion for PE in the PE-negative group.[30]

In summary, the 2 most commonly used adult-based prediction rules are not reliable in the pediatric population and should be used with caution. A single study of children evaluated for PE attempted to derive a pediatric-specific prediction rule using 3 criteria: oral contraceptive use, tachycardia, and oxygen saturation of less than 95%. This prediction rule yielded a sensitivity of 89%

TABLE 2. Wells Criteria

Clinical signs and symptoms of DVT (+3)
An alternative diagnosis that is less likely than PE (+3)
Heart rate >100 beats/min (+1.5)
Immobilization or surgery in the previous 4 wk (+1.5)
Previous DVT/PE (+1.5)
Hemoptysis (+1)
Malignancy (+1)

and specificity of 56% in identifying children with PE and thus performed similarly to the adult-based prediction rules when applied to childen.[27] To date, a valid and reliable clinical prediction rule to detect or exclude PE has not been developed for the pediatric population.

Electrocardiogram

Although ECG is frequently used in the initial evaluation for PE, findings are typically suggestive, but not diagnostic for PE. The most common ECG manifestation is sinus tachycardia, which is nonspecific and seen in a variety of clinical scenarios.[31] Manifestation of the classic S1Q3T3 pattern on ECG is thought to be pathognomonic for PE. The S1Q3T3 pattern represents right-sided heart strain and is described by the presence of a prominent S wave in lead I and a Q wave and inverted T wave in lead III. In the adult population, the S1Q3T3 pattern has been shown to be insensitive, but highly specific in the diagnosis of PE with specificities reported as high as 97%.[32] However, the predictive value of the S1Q3T3 pattern in children is unknown.[33] Reports from pediatric patients evaluated for PE suggest that the S1Q3T3 pattern may be more common among children with PE than those without PE, but there are inadequate data to examine the diagnostic utility of this finding.[18] Of note, the S1Q3T3 pattern is more strongly associated with bilateral and extensive PEs in children, similar to the adult population, although these patients frequently have overt clinical signs of PE, where suggestive evidence from ECG is not assistive.[18,33] Therefore, although it may provide suggestive evidence for PE, the overall diagnostic utility of ECG for PE in children is limited.

D-Dimer

D-Dimer is commonly used in the evaluation of PE in adult and pediatric populations. D-Dimer is released during the plasmin-mediated breakdown of fibrin, which occurs during thrombotic events. A normal D-dimer has excellent negative predictive value and can safely exclude the diagnosis of PE in adults presenting with a low pretest probability. Conversely, an elevated D-dimer suggests the need for another study to confirm or exclude presence of PE. The utility of D-dimer in children to exclude PE is not well defined.[34] In the pediatric population, D-dimer has demonstrated poor sensitivity and specificity in diagnosing PE with sensitivity and specificity reports of 79% and 69%, respectively.[8,14,27] In the community-based setting, the positive predictive value of D-dimer for PE in children is 43%, suggesting a large number of false-positive results leading to unnecessary confirmatory testing.[18] Literature in adults has demonstrated that combination of negative D-dimer and low-risk Wells score yields negative predictive values that can safely exclude PE without need for further diagnostic imaging. In children, however, the combination of a negative D-dimer and low-risk Wells score has not been documented to be effective at determining pretest probability of PE in children and should be used with caution.[30,34] Thus, D-dimer currently has limited diagnostic utility for PE in children and should not be relied upon solely in clinical decisions regarding PE.

Ventilation-Perfusion Scan

Historically, the V/Q scan was the primary test for diagnosis of PE in both adults and children. More recently, V/Q scan has fallen out of favor, in exchange for CTPA, which possesses superior diagnostic ability. However, in certain situations, such as when intravenous iodinated contrast is contraindicated, V/Q scan remains a potential option for evaluation of PE.

Ventilation-perfusion scans demonstrate the mismatch in ventilation and impaired perfusion created by a thrombus (Fig. 3) and are interpreted in conjunction with a chest radiograph. Ventilation-perfusion scans are relatively invasive but can be valuable when results are definitive.[35] In adults, a high-probability V/Q scan confers an 85% chance of having a PE.[36] However, the majority of patients have low or intermediate probability scans, and in these patients, the probability of PE is still 25%.[36] Rates of indeterminate scans are substantial, with reports as high as 33% to 49% due to interpretation difficulties and confounding V/Q mismatch, particularly in patients with underlying lung disease. Therefore, utility of V/Q scans is limited, as further diagnostic imaging is frequently necessary.[37,38] Lower indeterminate rates of V/Q scans have been reported in children without known lung disease or prior extensive PEs. However, the majority of children with PE have underlying disease processes limiting the interpretation of findings from V/Q scans.[35] Because of interpretation difficulties and frequent need for further diagnostic imaging, V/Q scans are not often utilized.

Computed Tomography Pulmonary Angiography

Computed tomography with pulmonary angiography is the diagnostic method of choice for PE in both children and adults.[39–41] In a national survey of members of the Society for Pediatric

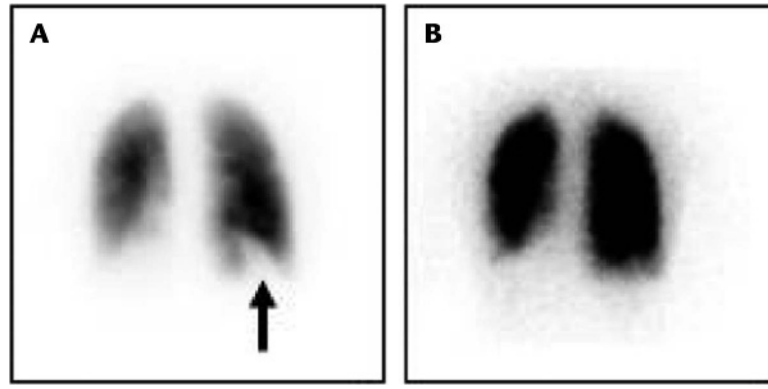

FIGURE 3. Lung ventilation perfusion (V/Q) scintigraphy images show a right lower lobe mismatched segmental perfusion defect. Note normal matched ventilation and perfusion defect within the left medial lower lung due to the heart. A, Posterior perfusion image demonstrates a wedge-shaped perfusion defect (arrow) in the right basilar lower lobe. B, Posterior ventilation image shows homogeneous tracer uptake throughout bilateral lungs without defect.

Radiology, 88% of radiologists preferred CTPA to other diagnostic modalities in children with clinical suspicion for PE.[40] In adults, CTPA has demonstrated a sensitivity of 83% and specificity of 96% in diagnosing PE.[42] Unfortunately, there are no studies evaluating the sensitivity and specificity of CTPA testing for PE in children. Computed tomography with pulmonary angiography has the additional benefit of providing comprehensive information about all intrathoracic structures and thus potential information regarding alternative diagnoses.[43] Recent technological advances such as dual-energy scanning have increased the utility of CTPA by allowing for enhanced anatomical and functional information without increasing radiation exposure.[44,45] The most significant limitation to CTPA use is the resultant ionizing radiation. However, most centers utilize radiation dose-reduction techniques in order to decrease the amount of radiation exposure in children.[40] In addition, appropriate risk factor assessment can guide appropriate use of CTPA in children to reduce radiation exposure.[14] Thus, CTPA has become the diagnostic modality of choice in the evaluation of PE because of its diagnostic performance, availability… and ability to assess for alternative diagnoses.

Magnetic Resonance Angiography

Magnetic resonance angiography has an increasing role as a diagnostic modality for PE as it does not produce radiation exposure. In addition to evaluating the pulmonary arteries, magnetic resonance angiography enables visualization of the upper body and central venous system, which confers benefit in children because of their risk of upper extremity thrombi due to central venous line use.[7] Magnetic resonance angiography is limited by the need for general anesthesia in most children, longer imaging times, and lack of availability across institutions. However, technological advances in time-resolved techniques have allowed for magnetic resonance angiography acquisition times of 4 seconds or less and for images to be obtained in a single breath hold while maintaining sufficient sensitivity and specificity.[46] As magnetic resonance imaging technology continues to improve, magnetic resonance angiography will continue to be an attractive modality for evaluation of PE in children.

Clinical Diagnostic Algorithm

Overall, the choice of diagnostic test depends on the clinical probability of PE, risk of ionizing radiation, condition of the child, and availability of diagnostic modalities. The Prospective Investigation of Pulmonary Embolism Diagnosis II formulated evidence-based recommendations for the evaluation of PE based on available literature.[47] These guidelines recommend an objective clinical evaluation with an assessment of risk factors for PE, D-dimer if initial evaluation suggests low or intermediate probability for PE, and CTPA as the first imaging test. Although these guidelines are based on adult literature and should be used with caution in children, they may provide a foundation for the initial evaluation of PE in children. (Fig. 4)

TREATMENT

Current recommendations for treatment of PE in children are primarily extrapolated from adult literature, as evidence supporting use of antithrombotic therapy in children is inadequate. Of note, guidelines for treatment of PE are based on recommendations for management of venous thromboembolism as a whole, including both DVT and PE. Treatment options include anticoagulation therapy, thrombolysis, thrombectomy, and inferior vena cava (IVC) filters (Table 3). Antithrombotic therapy in pediatric patients is challenging because of the rapidly developing hemostatic system of children and age-dependent variation in the pharmokinetics of antithrombotic drugs including distribution, binding, and clearance.[48,50] Neonates, for example, have lower plasma concentrations of several clotting factors affecting their response to various antithrombotic drugs.[50] In addition, children often have limited vascular access, and pediatric-specific formulations for antithrombotic medicines are not readily available. Current guidelines recommend at least 3 months of treatment for a venous thromboembolism caused by at least 1 identifiable risk factor and 6 to 12 months for an idiopathic venous thromboembolism. Unfortunately, adherence rates to anticoagulant therapy are reported as low as 67%, likely secondary to the need for frequent monitoring and lack of awareness of the importance of antithrombotic therapy.[51]

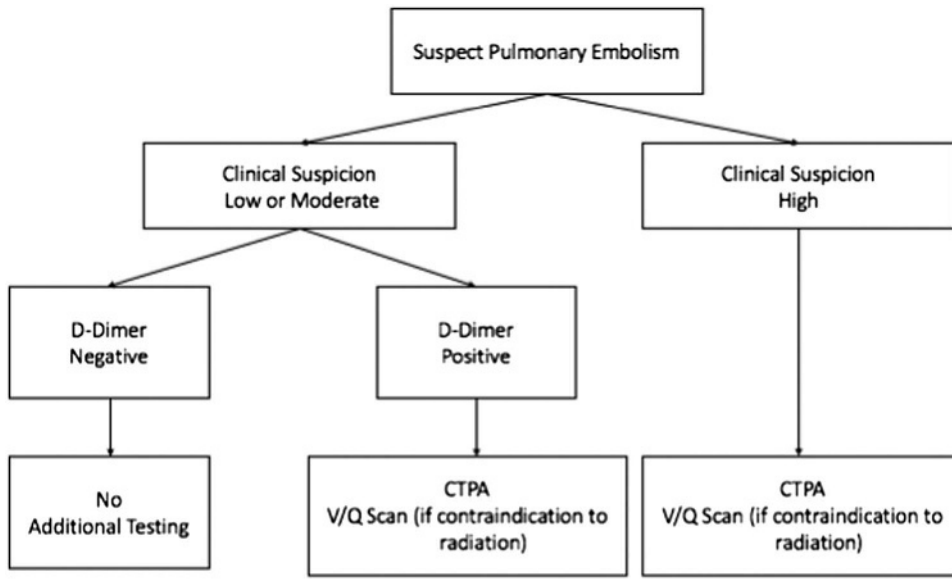

FIGURE 4. Prospective Investigation of Pulmonary Embolism Diagnosis II clinical diagnostic algorithm.

TABLE 3. Therapeutic Range and Length of Treatment for Antithrombotic Therapy[48,49]

Drug	Monitoring	Therapeutic Range	Duration of Therapy	Reversal Agent
Unfractionated heparin	Anti-Xa activity Protamine range Measure 4 h after initial bolus dose and 4 h after every change in infusion rate	0.35–0.7 U/mL 0.2–0.4 U/mL	5–10 d	Protamine
Low-molecular-weight heparin	Anti-Xa activity Measure 4–6 h after subcutaneous injection	0.5–1.0 U/mL	Initial therapy: 5–10 d Extended therapy: 1st episode Reversible risk factor: 3–6 mo Idiopathic: 6–12 mo Chronic risk factor: all year long Recurrent episode Reversible risk factor: 6–12 mo Idiopathic: 12 mo to lifelong Chronic risk factor: lifelong	Protamine (partial efficacy)
Vitamin K antagonist	International normalized ratio Frequent monitoring	2.5 (range, 2.0–3.0)	1st episode Reversible risk factor: 3–6 mo Idiopathic: 6–12 mo Chronic risk factor: all year long Recurrent episode Reversible risk factor: 6–12 mo Idiopathic: 12 mo to lifelong Chronic risk factor: lifelong	Vitamin K Prothrombin Complex concentrates
Thrombolytic therapy (tPA)	Measure CBC, PT, PTT, D-dimer, fibrinogen*	No consensus on therapeutic range		None

*Fibrinogen most helpful in determining need for cryoprecipitate or plasma replacement.

CBC indicates complete blood count; PT, prothrombin time; PTT, partial thromboplastin time.

Unfractionated Heparin

Unfractionated heparin is the most common initial anticoagulant therapy used in children.[41] Unfractionated heparin promotes antithrombin activity, which subsequently inactivates coagulation enzymes including thrombin and factor Xa. Therapeutic ranges are titrated to activated partial thromboplastin time, which corresponds to anti–factor Xa levels. Dosing is titrated to achieve a target anti-Xa activity range of 0.35 to 0.7 U/mL.[48] Advantages of unfractionated heparin include its rapid onset of action and short half-life and availability of a reversal agent (ie, protamine sulfate). The main disadvantage of unfractionated heparin is the variable clinical dose response in pediatric patients.[48] Children have reduced levels of antithrombin and a reduced capacity to generate thrombin resulting in a variable response to unfractionated heparin.[52,53] In addition, age-related differences in activated partial thromboplastin time times exist for the same anti–factor Xa level. Therefore, routine assays likely correlate poorly with true unfractionated heparin concentrations.[54]

Unfractionated heparin therapy also carries a risk of bleeding, heparin-induced thrombocytopenia, and heparin-induced osteoporosis. Rates of bleeding have been reported from 2% to as high as 24% in critically ill children receiving unfractionated heparin therapy.[55,56] Heparin-induced thrombocytopenia is extensively described as a complication of unfractionated heparin therapy in the adult population, although only case reports exist in children.[57] However, heparin-induced thrombocytopenia can lead to life-threatening thromboembolism; thus, pediatric patients should be closely monitored for signs and symptoms of heparin-induced thrombocytopenia, and alternative antithrombotic therapy should be utilized when necessary. Heparin-induced osteoporosis is another rare yet reported complication of unfractionated heparin therapy.[58,59] Heparin-induced osteoporosis has been mainly reported in long-term unfractionated heparin therapy, and thus long-term use of unfractionated heparin in children should be avoided.[48]

Low-Molecular-Weight Heparin

Low-molecular-weight heparin is the anticoagulant of choice for primary and secondary prophylaxis of venous thromboemoblism.[60,61] Low-molecular-weight heparin is safe and highly efficacious in the management and prophylaxis of venous thromboembolism in pediatric patients, with studies demonstrating clinical resolution in 94% of pediatric patients.[61] Unlike unfractionated heparin, low-molecular-weight heparin has greater activity against factor Xa compared with thrombin and thus requires only monitoring of factor Xa activity. Similar to unfractionated heparin, therapeutic ranges for low-molecular-weight heparin have been extrapolated from adult studies and may not correlate well in the pediatric population because of varying metabolism and the high degree of variation in dosing of low-molecular-weight heparin in children. For example, higher concentrations of low-molecular-weight heparin are often required in younger children and in critically ill children requiring vasoactive agents and mechanical ventilation.[62] Because of the considerable dose variation in children, current guidelines recommend close monitoring of anti–factor Xa levels and titrating low-molecular-weight heparin to achieve a therapeutic anti–factor Xa range of 0.5 to 1 U/mL.[48] However, this target has not been validated in pediatric clinical studies, and there is variability in anti–factor Xa assays contributing to poor correlation with true anti–factor Xa levels.[63] Regardless, low-molecular-weight heparin requires subcutaneous administration and has greater bioavailability and reduced risk of

heparin-induced thrombocytopenia compared with unfractionated heparin and remains the anticoagulant of choice.[64]

Vitamin K Antagonism

Warfarin is the most commonly used vitamin K antagonist in children. Warfarin inhibits the carboxylation of vitamin K coagulant factors including factors II, VII, IX, and X. Warfarin also inhibits regulatory proteins C and S, which contributes to procoagulant effects. Warfarin is an attractive therapy as it is administered orally. However, it requires frequent dose adjustments as vitamin K levels can vary with diet, various medicines, and underlying conditions.[48] Also, warfarin is available only in tablet form in most countries. Dosing is titrated to achieve a target international normalized ratio (INR) of 2.5 (range, 2.0–3.0).[48] Warfarin therapy must be administered for 5 to 7 days before it achieves a therapeutic level because of the long half-lives of procoagulant factors. Patients should be anticoagulated with unfractionated heparin or low-molecular-weight heparin prior to initiating warfarin because of the potential for transient procoagulant effects and warfarin-induced skin necrosis.[49]

Direct Anticoagulants

Direct anticoagulants are a class of anticoagulants that directly inhibit factor Xa (eg, fondaparinux) or thrombin (eg, bivalirudin and argatroban). Currently available direct anticoagulants are administered subcutaneously or intravenously. Direct anticoagulants have more predictable anticoagulant effects compared with heparin and can be used in treating heparin-induced thrombocytopenia, thus acting as an alternative to heparin in these patients.[49,65,66] However, available data pertinent to pediatric patients are limited and direct anticoagulants should be used only if contraindications to current therapies exist. Of note, there are no reversal agents for direct anticoagulants, and quick cessation of therapy is necessary.

Several direct oral anticoagulants have been approved over the past several years (eg, rivaroxaban, apixaban, dabigatran). Direct oral anticoagulants have numerous advantages including a more predictable pharmokinetic profile with less age-dependent variation and limited drug reactions allowing for fixed dosing and minimal monitoring. There is limited experience with direct oral anticoagulants in the pediatric population, and current data on safety and efficacy in children are inadequate. However, investigations in the pediatric population are underway, and pilot studies have been promising.[49]

Thrombolytics

Thrombolytic agents (ie, streptokinase, urokinase, tissue plasminogen activator [tPA]) convert endogenous plasminogen to plasmin, which is active in fibrin breakdown. Thrombolytic agents are mainly used for life- or limb-threatening thrombosis.[48] Tissue plasminogen activator is the agent of choice in pediatrics. Studies have demonstrated complete clot resolution in 55% to 65% and partial resolution in 5% to 20% of pediatric patients treated with tPA for both arterial and venous thrombi.[67,68] However, consensus recommendations do not exist regarding dose, indication, method of delivery, or duration of therapy, which are frequently based on institutional experience and guidelines.[69] In addition, studies have not evaluated the efficacy of tPA in the treatment of children with PE specifically. Plasminogen concentrations are also reduced during the first few weeks of life, as a result tPA may not be effective in this age group.[70] There are no data to suggest advantage of local over systemic thrombolytic therapy in children, but there are theoretical advantages of catheter-directed thrombolysis including ability to deliver low doses of thrombolytic directly into the thrombus.[71] While a therapeutic range does not exist, fibrinogen is the most useful assay to help determine need for cryoprecipitate or plasma replacement.[48] Complications can be severe with thrombolytic therapy, with 1 study demonstrating major complications, including bleeding requiring transfusion and central nervous system hemorrhage or ischemia, in 40% of pediatric patients treated with tPA.[67]

Thrombectomy

Thrombectomy, surgical or via transvenous catheter, is reserved for children with massive life-threatening PE, or when thrombolysis is contraindicated and there is insufficient time for anticoagulation.[4] There is no evidence demonstrating the superiority of either surgical or catheter thrombectomy. Complications from thrombectomy are significant with mortality rates reported as high as 64%.[72]

Inferior Vena Cava Filters

Inferior vena cava filters are utilized in those with contraindications to anticoagulation therapy and recurrent PEs. Inferior vena cava filters are currently recommended for children weighing more than 10 kg in body weight with lower extremity venous thromboembolism and a contraindication to anticoagulation. Inferior vena cava filters have been shown to be effective in preventing PE in children with contraindication to anticoagulation with known DVT, recurrent DVTs, and high risk of venous thromboembolism.[73] Current guidelines recommend that IVC filters be removed as soon as possible and that anticoagulation be initiated as soon as the contraindication to anticoagulation is resolved.[48] Inferior vena cava filters are less commonly placed in pediatric patients with a mean of 6 filters placed per 100,000 admissions in children annually.[74] They are more commonly placed in adolescents but have been placed in children from 1 month to 20 years of age.[74] The use of retrievable IVC filters in children has been shown to be feasible, and IVC filters have been successfully placed and retrieved even in children with maximal IVC diameter of 1 cm.[75–78] Inferior vena cava filters should be used with caution, however, as complication rates have been reported as high as 17%, and include new clot formation, migration of filter, and damage to vessel wall.[73]

OUTCOMES

Mortality rates of PE in children have been reported as high as 24%.[10] While true risks of pediatric PE are unknown and likely underreported, the cause of death in pediatric patients is usually due to underlying disease processes, such as congenital heart disease and malignancy.[10] In a Canadian registry, only 2 of the 137 children with venous thromboembolism died by PE.[9] However, the complications from PE including hospitalization, recurrent thrombosis and need for anticoagulation are not insignificant. Prevention and early recognition of PE in pediatric patients are key to mitigating complications from PE.

CONCLUSIONS

There is greater awareness of PE in the pediatric population with improved survival in children with systemic disease and increasing use of central venous lines and oral contraceptives. The evaluation and management of PE in the pediatric population are challenging as available literature is sparse and current practices are based on adult literature. While a validated pediatric-specific clinical prediction rule does not exist, a thorough risk assessment for PE should be performed in appropriate clinical settings to aid in the prompt diagnosis of PE in children. Clinicians should also be aware of the risks and benefits of the

different modalities that exist for evaluation of PE in children. While guidelines exist for the treatment of venous thromboembolism in children, providers should be aware that these guidelines are based on data from adult literature. Thus, treatment should be based on the hemodynamic status and underlying disease processes of the patient. Additional pediatric-specific literature is necessary in the evaluation and management of PE in children in order to improve the care provided to this population.

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CME EXAMINATION

February 2019

Please mark your answers on the ANSWER SHEET.

Pulmonary Embolism in Children, *Navanandan et al*

1. A 15-year-old presents to the emergency department with chest pain and shortness of breath. She started taking oral contraceptives 3 months ago. Serum diagnostic studies are obtained and are significant only for an elevated D-dimer. Which of the following is the modality of choice to confirm your clinical suspicion of pulmonary embolism?
   a. electrocardiogram
   b. chest radiography
   c. computed tomography pulmonary angiography
   d. V/Q scan

2. Which of the following are risk factors for pulmonary embolism in the pediatric population?
   a. oral contraceptives
   b. central venous lines
   c. congenital heart disease
   d. all of the above

3. An 8-year-old patient presents with 2 days of pleuritic chest pain. He has a central venous line due to need for long-term parenteral nutrition. Computed tomography with pulmonary angiography confirms the presence of a right lower lobe pulmonary embolism. The patient is hemodynamically stable. Which of the following is the most appropriate next step in management of this patient?
   a. initiate unfractionated heparin
   b. placement of an IVC filter to prevent further pulmonary emboli
   c. initiate warfarin alone
   d. initiate tPA

4. Which of the following statements regarding diagnosis of pulmonary embolism in children is true?
   a. PERC and Wells criteria are both sensitive and specific for diagnosing PE in children.
   b. D-Dimer is highly specific for diagnosis of PE in children.
   c. There is no validated clinical prediction rule for diagnosis of PE in children.
   d. The S1Q3T3 pattern on ECG is highly sensitive in the detection of PE in children.

5. Gas exchange is impaired in acute PE due to which of the following physiologic mechanisms?
   a. V/Q mismatch
   b. intracardiac shunt
   c. increased pulmonary dead space
   d. all of the above

ANSWER SHEET FOR THE *PEDIATRIC EMERGENCY CARE* CME PROGRAM EXAM
February 2019

Please answer the questions on page 152 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____
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1. (A) (B) (C) (D) (E)
2. (A) (B) (C) (D) (E)
3. (A) (B) (C) (D) (E)
4. (A) (B) (C) (D) (E)
5. (A) (B) (C) (D) (E)

Your completion of this activity includes evaluating them. Please respond to the following questions below.

Please rate this activity (1 - minimally, 5 - completely)	1	2	3	4	5
Was effective in meeting the educational objectives	○	○	○	○	○
Was appropriately evidence-based	○	○	○	○	○
Was relevant to my practice	○	○	○	○	○

Please rate your ability to achieve the following objectives, both before this activity and after it::
1 (minimally) to 5 (completely)

	Pre					Post				
	1	2	3	4	5	1	2	3	4	5
1. Distinguish pathophysiology, clinical signs, and risk factors for pulmonary embolism in children.	○	○	○	○	○	○	○	○	○	○
2. Summarize recommended diagnostic approach and the utility of clinical prediction rules for pulmonary embolism in children.	○	○	○	○	○	○	○	○	○	○
3. Describe the therapeutic management of pulmonary embolism in children.	○	○	○	○	○	○	○	○	○	○

How many of your patients are likely to be impacted by what you learned from these activities?

○ <20% ○ 20%–40% ○ 40%–60% ○ 60%–80% ○ >80%

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 - definitely will not change, 5 - definitely will change)	1	2	3	4	5
	○	○	○	○	○

How will you apply what you learned from these activities (mark all that apply):

- In diagnosing patients ○
- In monitoring patients ○
- In educating students and colleagues ○
- As part of a quality or peformance improvement project ○
- For maintenance of board certification ○
- To consider enrolling patients in clinical trials ○
- In making treatment decisions ○
- As a foundation to learn more ○
- In educating patients and their caregivers ○
- To confirm current practice ○
- For maintenance of licensure ○

Other _____

Please list at least one strategy you learned from this activity that you will apply in practice:
Please list at least one (1) change you will make to your practice as a result of this activity:

Did you perceive any bias for or against any commercial products or devices?	Yes	No
	○	○

If yes, please explain:
How long did it take you to complete these activities? _____ hours _____ minutes
What are your biggest clinical challenges related to pediatric emergency care?
[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)

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