Pulmonary Embolism in Children

Approach to Diagnosis, Risk Stratification and Management

Disclaimer

This clinical pathway is not intended to replace clinical judgment. It is meant to assist licensed independent practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches to the diagnosis and management of a particular condition. A particular patient's circumstances should always be taken into account when a practitioner is deciding on a course of management.

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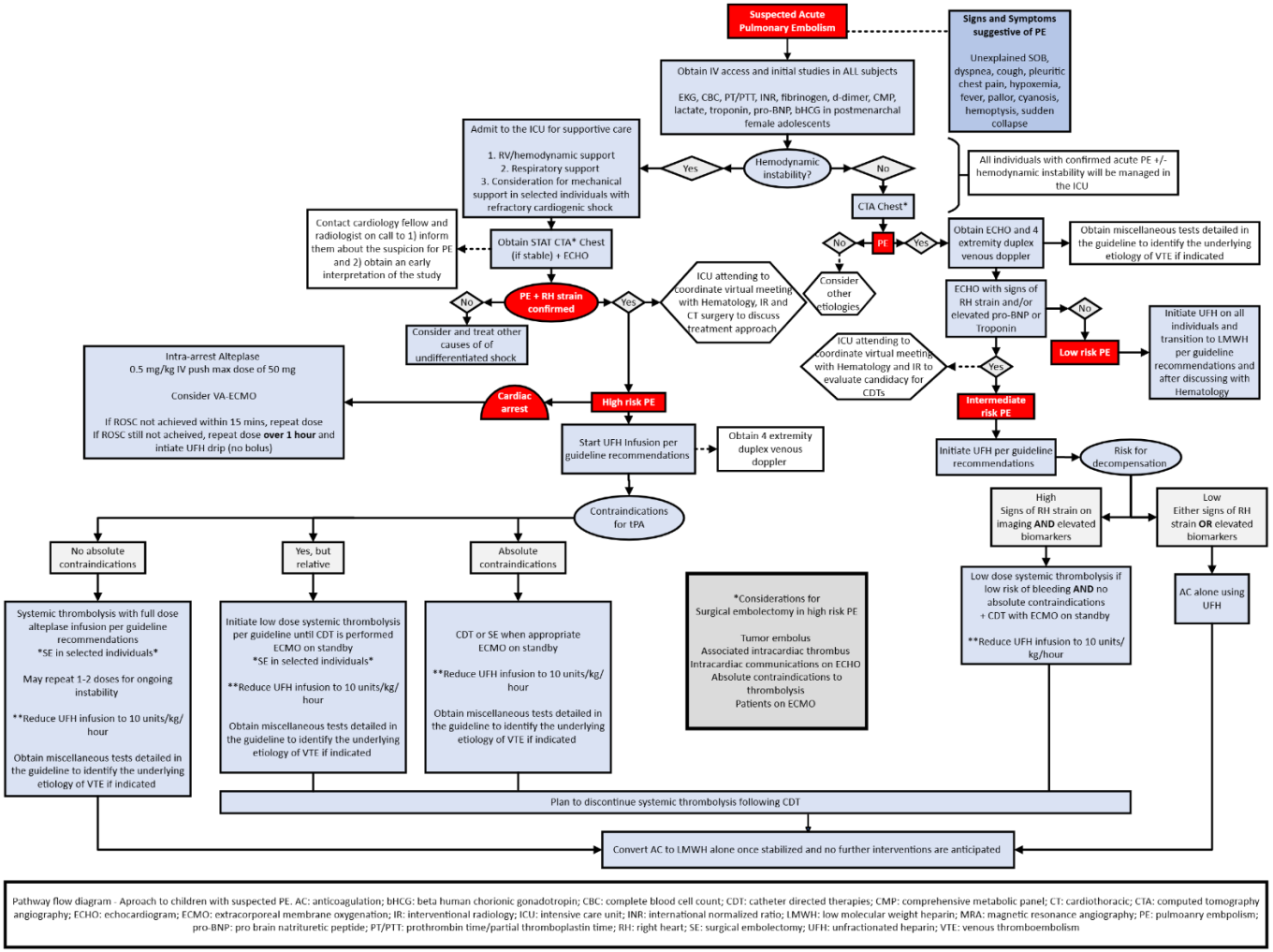
Pathway Flow Diagram / Algorithm



Pathway flow diagram - Aproach to children with suspected PE. AC: anticoagulation; bHCG: beta human chorionic gonadotropin; CBC: complete blood cell count; CDT: catheter directed therapies; CMP: comprehensive metabolic panel; CT: cardiothoracic; CTA: computed tomography angiography; ECHO: echocardiogram; ECMO: extracorporeal membrane oxygenation; IR: interventional radiology; ICU: intensive care unit; INR: international normalized ratio; LMWH: low molecular weight heparin; MRA: magnetic resonance angiography; PE: pulmoanry embpolism; pro-BNP: pro brain natriturectic peptide; PT/PTT: prothrombin time/partial thromboplastin time; RH: right heart; SE: surgical embolectomy; UFH: unfractionated heparin; VTE: venous thromboembolism

*Ok to obtain a contrast-enhanced MRA of the Chest if there is an absolute contraindication to CTA chest (severe anaphylactic reaction to iodinated contrast). Please discuss with Radiology to coordinate the logistics of the test

**Recommendations for modification of the UFH infusion may be made at the discretion of the hematology consultant, based on individual patient risk factors for bleeding and thrombosis

Scope

Definition

Pulmonary embolism (PE) is a potentially life-threatening condition typically resulting from dislodged thrombus occluding the pulmonary arteries. Right heart failure and cardiac arrest may ensue if the PE is not quickly diagnosed and aggressively treated. PE is relatively rare in the pediatric population when compared to adults; however, the incidence is increasing. A high clinical index of suspicion is warranted as in children PE often is unrecognized leading to misdiagnosis and potentially increased morbidity and mortality. PE in children can occur in the setting of infection, but it is also associated with cancer, congenital heart disease, acquired and inherited thrombophilias, and the presence of central vascular access devices. The clinical severity of PE varies widely. Unlike in adults, pediatric PE often appears clinically silent. Classic symptoms when present include increased shortness of breath, pleuritic chest pain, hemoptysis, cough, syncope and in severe cases, cardiovascular collapse. PE is definitively confirmed by an imaging study, most commonly chest computed tomography angiography (CTA). After the diagnosis of PE is made, an attempt should be made to categorize the patients into risk categories that can predict adverse outcomes. Risk stratification can be done by using clinical criteria, cardiac biomarkers, and imaging tests to identify patients with low, intermediate, and high risk of adverse events. The management of children with PE should be tailored based on risk stratification. Low-risk patients are treated with anticoagulation alone. In children with intermediate and high-risk PE, besides the use of systemic anticoagulation, additional interventions such as systemic thrombolysis, catheter directed therapies and/or surgical thrombo-embolectomy (SE) may be warranted. Follow-up is necessary to establish resolution, progression, or recurrence and monitor potential long-term complications, such as pulmonary hypertension and chronic PE.

Inclusion Criteria and PE Risk Factors:

- Recent onset/worsening of unexplained shortness of breath or pleuritic chest pain in the absence of known underlying cardiac disease, lung disease, or suspected acute pneumonia.
- Recent onset/worsening of shortness of breath or pleuritic chest pain, in the presence of known underlying cardiac disease, lung disease, or suspected acute pneumonia, and with one or more of the following PE risk factors:
    - Painful leg swelling or known recent diagnosis of deep vein thrombosis (DVT)
    - Family or personal history of DVT or PE
    - Known hypercoagulable state predisposing to DVT or PE
    - Recent or current indwelling central venous catheter
    - Pregnancy or use of oral contraceptive pills
    - Immobility
    - Recent major or orthopedic surgery
    - Acute or chronic inflammatory condition
    - Obesity

Exclusion Criteria:

- No suspected PE

Pathway Goals

The purpose of this guideline is to improve the recognition and early risk stratification of PE in pediatric patients aged 30 days to 18 years and to help guide clinicians through the inpatient management of low, intermediate, and high-risk PE with the ultimate goal of reducing morbidity and mortality.

Key Clinical Recommendations with Evidence Based Supporting Material

Introduction and risk factors for pulmonary embolism

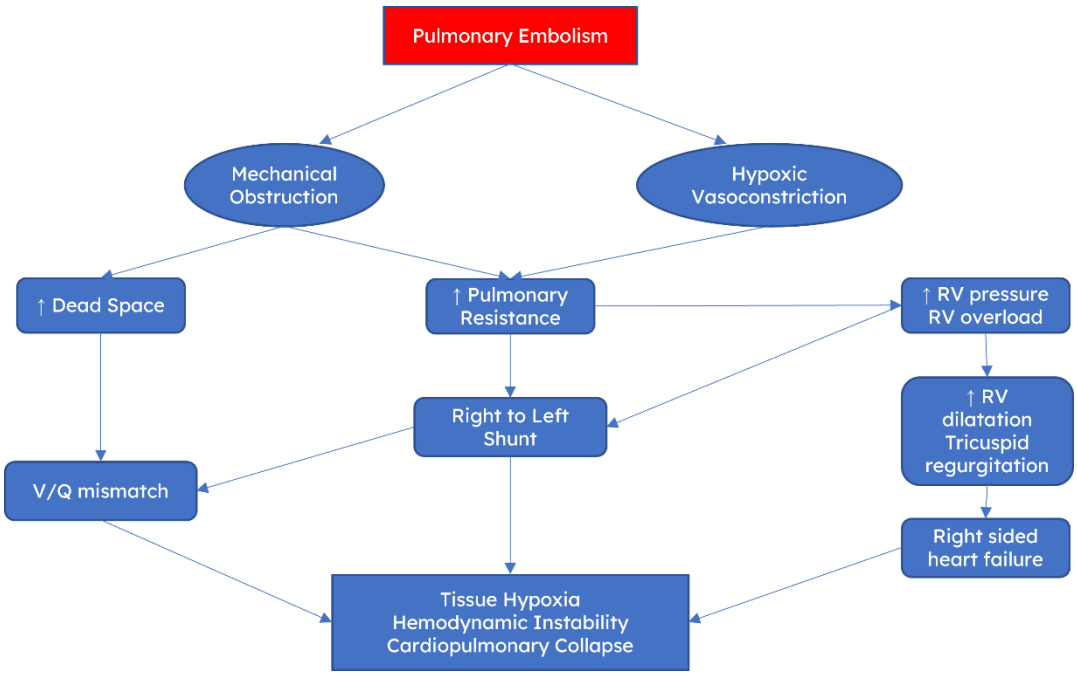
While PE is rare in pediatrics, intermediate and high-risk PE are associated with significant morbidity and mortality making the diagnosis and management critical. The incidence of PE in hospitalized pediatric patients varies but is estimated to be between 8.6-57 in 100,000 patients. This number is likely underestimated due to both silent PEs and under recognition by providers. Several factors have led to an increase in the incidence of pediatric PE including an increase in complex pediatric patients, increased use of central venous catheters, and improved awareness and recognition of PE in children. Risk factors for PE are shown in Table 1. Most children with PE will have at least one underlying risk factor with the most common risk factor for hospitalized patients being the presence of a central venous catheter. The most common risk factor for community-based children is use of oral contraceptive pills or hormonal supplementation.

Table 1. Risk Factors for Venous Thromboembolism (VTE)
• Central venous catheters • Malignancy • Congenital heart disease • Surgery • Immobility • Trauma • Obesity • Local or systemic bacterial infections • Select medications (oral contraceptives, systemic corticosteroids, L-asparaginase) • Hematological Diseases (sickle cell disease, paroxysmal nocturnal hemoglobinuria) • Dehydration • Systemic inflammatory diseases (antiphospholipid syndrome) • Thrombophilia • Family history of pro-thrombotic states • Prothrombotic states (nephrotic syndrome, pregnancy)

Pathophysiology of Pulmonary Embolism

The presence of a PE leads to anatomic obstruction to pulmonary artery flow as well as impaired gas exchange from alterations in the ventilation to perfusion ratio (Figure 1). Obstruction to blood flow can lead to pulmonary artery hypertension causing right ventricular dilation and, in severe cases, acute right heart dysfunction or failure. Once the right ventricular pressure is increased above systemic pressure the right ventricle may bow into the left ventricle. Left ventricular dysfunction and systemic hypotension may then occur due to decreased preload from bowing of the right ventricle and decreased pulmonary blood flow. The cycle can continue with systemic hypoperfusion, increased myocardial oxygen demand, and progressive biventricular failure culminating in severe cases in a cardiac arrest.

Figure 1. Pathophysiology of Pulmonary Embolism



Presentation

The classic symptoms of PE include shortness of breath, pleuritic chest pain, hemoptysis, and cough. However, a high index of suspicion is needed to diagnose PE in children as many symptoms mimic more common pediatric conditions such as pneumonia and approximately 15% of children may be asymptomatic. In high-risk PE, children present with signs of shock and complete cardiovascular collapse. Unfortunately, the diagnosis prediction tools used for adults to detect PE such as the Well's criteria and pulmonary embolism rule-out criteria (PERC) have not been validated in children.

Diagnostic Work Up

Diagnostic tests for evaluation of PE can be divided into those needed for the definitive diagnosis of PE, tests that aid in risk stratification, and miscellaneous tests (Tables 2, 3 and 4).

Table 2. Diagnostic Tests	
Initial tests: pro-BNP, troponin, CBC, PT/PTT, INR, fibrinogen, D-dimer*, CMP, bHCG in postmenarchal female adolescents, 12-lead EKG**, 4 extremity duplex venous doppler US to evaluate for DVTs	
Confirmatory test: CT Angiography (CTA) Chest is the diagnostic method of choice for PE in both children and adults. In children in whom ionizing radiation is contraindicated, discuss available MRA techniques or other imaging modalities with Radiology.	
Risk Stratification	Miscellaneous Tests to identify the underlying etiology of VTE
Echocardiography*** CTA Chest**** Biomarkers (pro-BNP, troponin)	Thrombophilia testing: Protein C, S, antithrombin III deficiency, factor V Leiden, prothrombin gene variant, elevated homocysteine, lupus anticoagulant, anticardiolipin antibodies, anti-B2-glycoprotein antibodies

*D-Dimer is commonly used in the evaluation of PE. D-Dimer is released during the plasmin-mediated breakdown of fibrin, which occurs during thrombotic events. In adults, a normal D-dimer has excellent negative predictive value and can safely exclude the diagnosis of PE 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. 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. Thus, D-dimer currently has limited diagnostic utility for PE in children and should not be relied upon solely in clinical decisions regarding PE.

**See appendix for Right Heart (RH) strain findings on EKG

***If an immediate read for the echocardiogram is needed, the echocardiogram should be ordered "STAT" and Cardiology should be notified immediately.

****Contrast-enhanced MRA of the Chest if there is an absolute contraindication to CTA chest (severe anaphylactic reaction to iodinated contrast).

Table 3. Echocardiographic findings concerning for Right Heart Strain	
Presence of one or more findings below is concerning for right heart strain:	Other supportive findings of right heart strain:
Greater than mild RV dilatation Paradoxical septal motion More than mild RV dysfunction Estimated RVSP >50% systemic Systolic flow reversal noted in the IVC and hepatic veins	Presence of moderate/severe tricuspid regurgitation < 50% collapse of the IVC during inspiration RV free wall hypokinesis that does not affect the apical segment Abnormal RV myocardial strain rate

Table 4. Chest CTA Findings Suggestive of Right Heart Strain
Ventricular Septum Position: Leftward Hepatic vein and/or IVC Reflux: Present

Classification

Acute pulmonary embolus can be classified into low, intermediate, and high-risk categories based on the presence or absence of hypotension, laboratory evidence of right heart strain and dysfunction and imaging findings (Table 5). This guideline will cover management of intermediate and high-risk patients primarily.

Low risk PE is defined as an acute PE with stable hemodynamics with normal laboratory findings and no evidence of RH strain.

Intermediate risk PE is defined as acute PE with normal blood pressure for age and either laboratory evidence of RV dysfunction (elevated troponin or pro-BNP) and/or echocardiogram/CTA findings of RH strain. Intermediate risk can be subclassified into high risk and low risk of decompensation.

High risk PE is defined as an acute PE with presence of hypotension (blood pressure < 5th percentile by age), need for vasoactive support, PE causing a cardiopulmonary arrest, or normotension with signs of shock.

Table 5. Classification of PE		
Low Risk	Intermediate Risk	High Risk
Acute PE with stable hemodynamics and no evidence of RH strain	Acute PE with stable hemodynamics but with echocardiographic/CTA or laboratory evidence of RH strain Subclassification: 1. Intermediate risk with high risk of decompensation: ECHO/CTA findings of RH strain AND elevated biomarkers 2. Intermediate risk with low risk of decompensation: Either ECHO/CTA findings of RH strain OR one or more elevated biomarkers alone	Acute PE with hemodynamic instability attributable to PE Criteria for hemodynamic instability include one of the following: 1. Systolic Hypotension (defined as systolic BP < 5th percentile by age) with end-organ hypoperfusion 2. Need for vasoactive support 3. Normotension with signs of shock 4. Cardiac arrest

Management

Early recognition and diagnosis are extremely important to not only prevent progression and adverse consequences of underlying PE but also to avoid unnecessary interventions. Recommendations for management of pediatric PE have been extrapolated from adult data. Given the differences in etiologies of PE and pharmacokinetics of drugs used to treat PE among children compared to adults, management decisions should be specifically tailored toward this particular population. There is no widely accepted algorithm for management of pediatric PE. Treatment varies depending on the risk stratification and the center's expertise and resources.

Once the diagnosis of an acute PE is confirmed and patients are risk-stratified into low, intermediate (further divided into low and high risk for decompensation), and high risk, hematology should be consulted, and anticoagulation should be initiated.

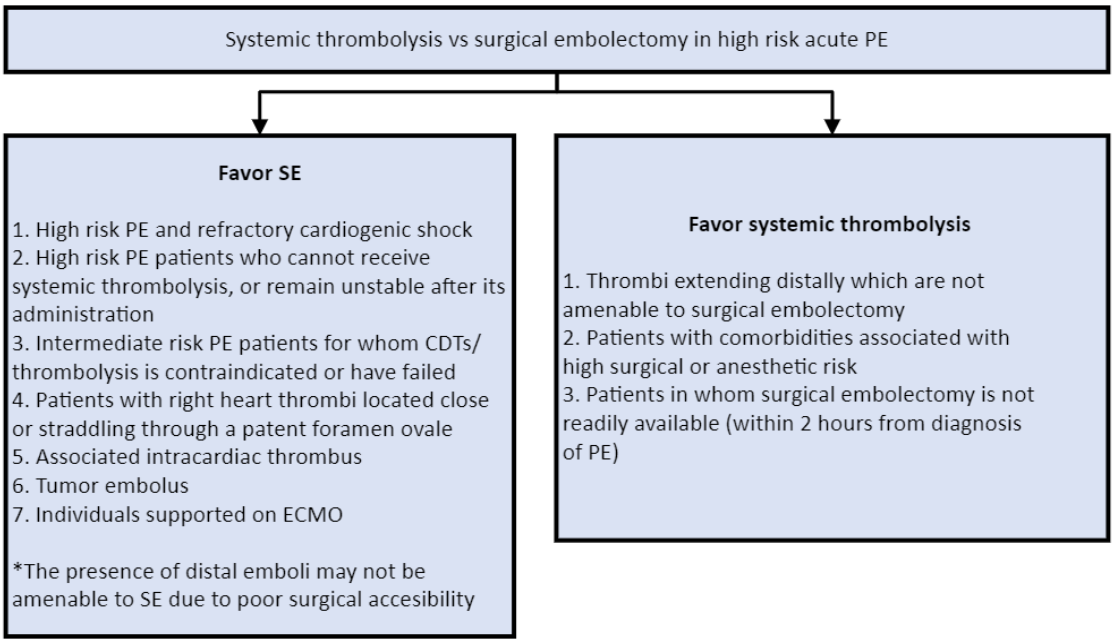
Patients with acute PE stratified into intermediate risk or high risk:
For acute PE patients at intermediate risk or high-risk, a multidisciplinary discussion including ICU (PICU or CVICU), IR, Hematology, and general or CT surgery is suggested. After risk stratification into intermediate risk or high-risk, the attending ICU physician will coordinate this discussion via Microsoft Teams (or in person). If surgical procedures are planned for patients, the ICU attending physician should also immediately contact the Anesthesia manager (aka the Anesthesia board runner) to discuss the anesthetic plan and risk/benefits. See also Supportive Care: Mechanical Support section for discussion of ECLS.

Overview of Surgical and Pharmaceutical Management Based on Risk Stratification

High Risk
Primary reperfusion for high-risk PE should be achieved by using either systemic thrombolytic therapy or surgical embolectomy (SE) due to observed reduction in mortality and recurrence in this patient population. We propose the use of systemic thrombolysis with alteplase in all individuals with high-risk PE unless there is an absolute contraindication for its use and/or in specific patient population where SE has been shown to improve the overall outcome of the individual (Table 8). During the alteplase infusion, the UFH infusion rate should be decreased to 10 units/kg/hour. Recommendations for modification of the UFH infusion may be made at the discretion of the hematology consultant, based on individual patient risk factors for bleeding and thrombosis. For individuals with relative contraindications but no absolute contraindications for alteplase use, low dose alteplase therapy can be considered in selected cases.

Considerations to perform SE vs thrombolysis include the availability and experience of the cardiothoracic surgeon and anesthesia team, anticipated delays for either therapy, relative and absolute contraindications for either strategy and surgical accessibility of the emboli (distal emboli may not be amenable to SE). If the suspicion for tumor embolism is high, SE is the preferred approach as well (for example with Wilms tumor, Ewing's sarcoma and osteosarcoma). In PE with associated intracardiac thrombus and/or when intracardiac communications are identified on echocardiogram, SE is also the preferred approach. Individuals supported on ECLS may have improved outcomes after SE rather than systemic thrombolysis.

Catheter-directed therapy (CDT) is an alternative approach in children with high-risk PE with absolute contraindications to either full dose systemic thrombolysis, anticoagulation or SE. Our institutional approach for these subjects is to initiate low dose systemic thrombolysis in combination with CDT. If there is an absolute contraindication to use systemic thrombolysis in general, CDT alone is preferred (or SE in selected individuals). If there are relative contraindications only (and no absolute contraindications), low dose systemic alteplase may be used in conjunction with CDT. Given the paucity of data on the use of CDT in high-risk PE and the variability in outcomes when this approach is implemented, a multidisciplinary discussion including ICU, surgery, IR, and hematology teams is warranted prior to CDT intervention in high-risk patients. If CDT is the decided approach, prior to CDT, patients should be initiated on UFH at 10units/kg/hr and IV low-dose alteplase at a fixed dose of 0.03-0.06mg/kg/hour (max 2mg/hr). Of note, UFH should not be titrated up while on alteplase. Recommendations for modification of the UFH infusion may be made at the discretion of the hematology consultant, based on individual patient risk factors for bleeding and thrombosis.



Intermediate Risk with high and low risk of decompensation

High risk: For intermediate risk with high risk of decompensation, CDT along with low-dose systemic thrombolysis is the preferred approach for primary reperfusion. If there is an absolute contraindication for the use of systemic thrombolysis, CDT alone is preferred. If there are relative contraindications only (and no absolute contraindications), low dose systemic alteplase may be used in conjunction with CDT. Prior to CDT, patients should be initiated on UFH at 10units/kg/hr and IV low-dose alteplase at a fixed dose of 0.03-0.06mg/kg/hour (max 2mg/hr). Of note, UFH should not be titrated up while on alteplase. Recommendations for modification of the UFH infusion may be made at the discretion of the hematology consultant, based on individual patient risk factors for bleeding and thrombosis.

Low risk: For intermediate risk PE with low risk of decompensation, anticoagulation alone with UFH is recommended. For these individuals, close monitoring is advised for 48-72 hours after the start of treatment since the median time to hemodynamic decompensation in this category of patients is approximately 2 days.

Low Risk

Patients with pulmonary embolism who are hemodynamically stable, have no evidence of right heart strain, and have normal cardiac biomarkers are considered to have low-risk pulmonary embolism. At Phoenix Children's, the preferred initial anticoagulant is UFH. In general, low-risk patients can be transitioned to low molecular weight heparin (LWMH) or direct oral anticoagulants after 24-48 hours of UFH in discussion with hematology. The duration of AC therapy in PE has not been defined and treatment duration varies from 3 months to 6 months in absence of ongoing risk of thrombosis. At Phoenix Children's, the ultimate decision regarding need for additional interventions, timing to transition from UFH to LWMH or a direct oral anticoagulant, length of therapy and follow-up care is guided by Hematology. The total duration of AC therapy in PE has not been defined and treatment duration varies from 3 months to 6 months in absence of ongoing risk of thrombosis.

Supportive Care

Hemodynamics/RV dysfunction

If volume resuscitation is required, close observation of hemodynamics including heart rate, blood pressure, NIRs, and CVP (if available) is suggested as volume overloading the RV can lead to decreased cardiac output. Hypotension should be recognized early and treated with inotropic and vasoactive support including epinephrine or norepinephrine infusions to improve RV contractility and systemic blood pressure. In addition, right ventricular support may be improved with use of lusitropic agents (if blood pressure allows), inhaled nitric oxide and titration of mechanical ventilatory support to optimize pulmonary vascular resistance if the patient is intubated.

Hypoxemia/acute respiratory failure management

Hypoxemia should be aggressively treated with supplemental oxygen with low flow nasal cannula, high flow oxygen delivery systems, or non-invasive support as needed. Given the risk of cardiovascular collapse with sedation and positive pressure ventilation, intubation should be attempted only for refractory hypoxemia and/or hypercarbia/acidosis. Intubation should be performed by a skilled provider with preparation beforehand for a cardiac arrest including optimization (as able) of hemodynamics. Consideration of ECMO on standby should be discussed for all high-risk and intermediate with high risk for decompensation patients.

Mechanical support

Discussion of the need for ECMO should include all patients with high-risk PE and individuals with intermediate risk at high risk for decompensation. This discussion should occur early and immediately following risk stratification and prior to the implementation of a definitive therapy and/or procedures requiring sedation. For patients with high-risk PE or intermediate risk at high risk of decompensation undergoing a procedure, the ECMO primer and Surgery team (CT or general) should be notified of the patient prior to the procedure and a discussion of candidacy, cannulation strategies, and need for ECMO on standby for OR or IR procedures should occur. For ECMO on standby, a primed circuit should be available outside the operating room/interventional radiology suite. The presence of the ECMO primer may be requested in the OR/IR suite at time of induction especially if patient not already intubated. Their presence will be decided on a case-by-case basis. If there are issues during the procedure, a code and/or ECPR should be called per current procedure.

Cardiac arrest

If a patient with known PE has a cardiac arrest, systemic thrombolysis may be considered with administration of systemic alteplase in addition to administration of high-quality CPR following PALS guidelines. If the patient is a candidate for ECPR, the ECMO team should be notified immediately. VA-ECMO is the modality of choice for individuals with PE and refractory shock/hypoxemia. Importantly, administration of systemic alteplase is NOT a contraindication for ECMO.

Medication Recommendations

Anticoagulation

Anticoagulation with UFH should be started on every patient with suspected intermediate or high-risk PE until a definitive plan for further intervention is decided. Patients should receive a loading dose followed immediately by an infusion. Heparin is typically continued for 24-48 hours in anticipation of possible intervention.

Table 6. Recommendations for the use of Unfractionated Heparin in PE			
Age	Loading Dose	Initial Infusion Rate**,***	Monitoring Parameters
Neonates & Infants < 1 year	75 units/kg IV (max 7500units)	28 units/kg/hour	Obtain anti-Xa (*OR aPTT) 6 hours after loading dose
Children ≥ 1 year and < 16 years		20 units/kg/hour	
≥ 16 years		15 units/kg/hour	
*aPTT should be used if anti-Xa is unreliable due to interfering laboratory parameters (plasma free hemoglobin >300 mg/dL; bilirubin >20 mg/dL; triglycerides >800 mg/dL) **If alteplase is used, decrease UFH dose to 10units/kg/hour ***Maximum dose 1500unit/hour			

Monitoring while on UFH:

- Baseline: CBC, PT/INR, aPTT, platelets, fibrinogen, hematocrit, hemoglobin, serum creatinine
- Daily: fibrinogen, hemoglobin, hematocrit, platelets, CBC
- More frequent monitoring recommended if:
  - Platelets < 100,000 per mcl and/or fibrinogen < 100 mg/dL, or
  - Patient has increased risk of thrombocytopenia or decreased fibrinogen
- Goal anti-Xa 0.3-0.7 units/mL
- Goal aPTT 70 – 123 seconds

Table 7. Unfractionated Heparin Adjustments based on Anti-Xa and aPTT Monitoring					
Anti-Xa (Units/mL)	aPTT* (sec)	Bolus (Units/kg)	Hold (minutes)	Rate Change	Repeat UFH anti-Xa OR aPTT (Hours)
≤ 0.1**	< 40	50	Do not hold	Increase 20%	6 hours
0.11 – 0.29	40 – 69	No Bolus		Increase 10%	6 hours
0.3 – 0.7	70 - 123			No change	6 hours; then Q24 hours once two consecutive values in therapeutic range
0.71 – 0.99	124 – 164			Decrease 10%	6 hours
1 – 1.19	> 164		30 minutes	Decrease 20%	6 hours
≥ 1.2***	> 164***		Minimum 60 minutes; continue to hold until anti-Xa < 1 OR aPTT <111	Decrease 30%	Q1 hour until anti-Xa < 1 Or aPTT < 164 sec; then Q6 hours once drip restarted

*aPTT should be used if anti-Xa is unreliable due to interfering laboratory parameters (plasma free hemoglobin >300 mg/dL; bilirubin >20 mg/dL; triglycerides >800 mg/dL)
**Confirm that specimen was not drawn from same line as intralipid infusion
***Confirm that specimen was not drawn from heparinized line or same extremity as site of heparin infusion

Systemic Thrombolysis

*For patients who are receiving systemic thrombolysis, UFH dose should be decreased to 10 units/kg/hour.

Table 8. Systemic Thrombolysis Indications	
Absolute Indications (must meet at least one of the below criteria)	Potential Indications (may consider systemic thrombolysis)
• High risk PE leading to cardiopulmonary arrest • High risk PE with hemodynamic instability (hypotension with sustained SBP < 5th percentile by age for at least 15 minutes or requiring vasoactive support or normotension with signs of shock) • Intermediate risk PE with high risk of decompensation (with ECHO/CT findings of both RH strain and elevated biomarkers). A low dose alteplase is preferred in these individuals and in combination with CDT • PE with associated proximal limb deep vein thrombosis (DVT) with concern for acute limb ischemia • PE with associated extremity completely veno-occlusive DVT with factor VIII greater than/equal to 150 units/dL and D-dimer greater than/equal to 0.5 mcg/mL	• Severe hypoxemia • Large perfusion defect on ventilation-perfusion scan • Extensive embolic burden on computed tomography • Free-floating type A right atrial or ventricular thrombus • Patent foramen ovale

Table 9. Contraindications to Thrombolysis		
Absolute*	Relative	Special Precautions
• Hemorrhagic stroke or stroke of unknown origin at any time • Ischemic stroke in the preceding 6 months • Central Nervous System (CNS) neoplasms • Recent major trauma/surgery/head injury in the preceding 3 weeks • Bleeding diathesis • Active bleeding	• Transient ischemic attack in the preceding 6 months • Oral anticoagulant therapy • Pregnancy, or within 1 week postpartum • Non compressible puncture site • Traumatic resuscitation • Refractory hypertension • Advanced liver disease • Infective Endocarditis	• Prematurity with corrected gestational age <37 weeks • Severe asphyxia event within 7 days • GI bleed within 2 months • Intracranial neoplasm, arteriovenous malformation or aneurysm • Specific catheterization-related contraindications including significant aneurysmal or intimal injury in a systemic artery (aorta, femoral artery), arterial access obtained above the inguinal ligament, large sheath size (especially arterial) • Inability to maintain platelet >50,000mm3, fibrinogen >100mg/dL, INR < 1.7 despite transfusion • Lumbar puncture in preceding 72 hours • History of anaphylaxis to alteplase

*Absolute contraindications to alteplase may become relative if using low dose alteplase (0.03-0.06mg/kg/hr).

Table 10. Alteplase Dosing
High Dose Alteplase
• < 60kg: 0.5mg/kg/hr run continuously for 6 hours (total 3 mg/kg, max 100 mg) • ≥ 60 kg: 100 mg total dose run continuously over 2 hours (50mg/hr) *Patients may receive 1-2 additional doses in cases of ongoing instability
Low Dose Alteplase (to use prior to CDTs in both high-risk PE with high risk of bleeding and intermediate risk PE with high risk of decompensation)
• Fixed dose of 0.03 mg/kg/hour – 0.06 mg/kg/hour (max 2 mg/hour) for 12-48 hours • If poor clinical or radiological response determined by ECHO changes and/or clinical worsening with persistent elevation in biomarkers may consider increasing dose by 0.03 mg/kg/hour every 6 hours to a max of 2 mg/hour • Systemic thrombolysis will be discontinued following completion of CDT
Rescue Alteplase for Cardiac Arrest
• < 60 kg: 0.5 mg/kg over 2 minutes • > 60 kg: 50 mg over 2 minutes (max 50mg) • If ROSC not achieved within 15 minutes, then repeat dose • If ROSC is achieved, repeat dose, but infuse over 1 hour and initiate heparin drip (no bolus)

Monitoring while receiving alteplase:

- UFH should be decreased to 10units/kg/hour (max 2000units/hr) for all patients while on alteplase at low or high dose and the UFH dose should not titrated. Recommendations for modification of the UFH infusion may be made at the discretion of the hematology consultant, based on individual patient risk factors for bleeding and thrombosis. Anti-factor Xa and/or aPTT should not be used to titrate UFH while on alteplase. Once alteplase is discontinued, resume monitoring UFH as per UFH protocol above.
- Patient should be on continuous cardiorespiratory monitoring with frequent or continuous blood pressure measurements for at least 24 hours after administration is completed.
- Assess invasive catheters hourly for bleeding.
- Consider transfusion of FFP before starting alteplase and daily while on alteplase to replete plasminogen.
- Laboratory assessment and goals:
    - Check CBC and DIC panel every 6 hours
    - Maintain fibrinogen > 100 mg/dL, platelet count > 100, and prothrombin time (PT) within 3 seconds of upper limit of normal

Surgical Embolectomy

- Surgical embolectomy (SE) should be reserved for selected individuals with an acute PE and proximal pulmonary artery occlusion.
- Patients to be considered for surgical embolectomy include those with:

  1) High risk PE patients with refractory cardiogenic shock

  2) High risk PE patients who cannot receive systemic thrombolysis and/or CDT, or remain unstable after its administration

  3) Intermediate risk PE patients for whom CDT and/or thrombolysis is contraindicated or have failed

  4) Patients with right heart thrombi located close or straddling through a patent foramen ovale (PFO), associated intracardiac thrombus or intracardiac communication, tumor embolus, and

  5) Patients supported on ECMO
- Discuss eligibility for SE early with CT surgery in ALL individuals with high-risk PE regardless of which initial management strategy is decided. This allows the CT surgical team to evaluate candidacy, surgical accessibility of the emboli and potential contraindications. It will also facilitate early conversations with cardiac anesthesia and ECMO teams.

Special Populations

RV failure secondary to PE

The primary management of RV failure should focus on treating the underlying mechanism leading to increased RV afterload, aka the pulmonary embolus. In the meantime, hemodynamic support with epinephrine or norepinephrine should be considered in patients who are hemodynamically unstable. In addition, the use of inhaled nitric oxide (iNO) may help decrease RV afterload and improve hemodynamics via pulmonary vasodilation.

RA thrombus

The presence of central venous catheters or other vascular devices increases the risk of RA thrombus development. There are two types of RA thrombi, Type A which is freely mobile and Type B which is fixed to the right atrial wall. Minimal data exist in pediatrics describing management of concomitant RA thrombus and PE. Currently there is limited data to support a definitive therapy. At our institution, the preferred approach for PE associated with intracardiac thrombus is surgical embolectomy. However, an individualized approach balancing the size of clot, presence of a PDA, hemodynamic stability of the patient, and risk of patient bleeding is necessary. A multidisciplinary discussion with cardiovascular surgery, hematology, and IR is recommended to discuss the different therapeutic options.

Non-thrombotic PE

Different cell types can cause non-thrombotic embolization, including adipocytes, hematopoietic, tumor cells, etc. In addition, bacteria, fungi, parasites, foreign materials, and gas can lead to PE. Symptoms are similar to those of acute VTE and include dyspnea, tachycardia, chest pain, cough, and occasionally hemoptysis, cyanosis, and syncope. Diagnosis of non-thrombotic PE can be challenging. Given the rarity of this disease, evidence-based treatment strategies are limited and based mainly on small case series.

Septic embolism

Septic embolism to the pulmonary circulation is a relatively rare clinical event and is commonly associated with right-sided endocarditis, septic thrombophlebitis, osteomyelitis, soft tissue infections, or urinary tract infections. Septic embolism usually manifests as multiple pulmonary nodules, infiltrates, or abscesses in the setting of an infection. Septic embolism is usually not associated with pulmonary

hypertension. The diagnosis is based on identifying the source of septic emboli, positive blood culture tests and chest X-ray or CT findings in the right clinical context. Although Staphylococcus aureus is the most common bacterial pathogen, the increasing number of immunocompromised patients—and those with indwelling catheters and vascular prostheses—has led to a rise in the incidence of anaerobic Gram-positive and Gram-negative bacteria, bacterioidae species, and fungi. Specific treatment of the responsible bacterial or fungal microorganism is necessary.

Foreign-material pulmonary embolism

The increasing use of interventional techniques in modern medicine has drastically increased the incidence of foreign-material PE. Examples of foreign material include silicone, broken catheters, guide wires, vena cava filters, coils for embolization, cement from vertebroplasty, and endovascular stent components. If possible, intravascular foreign objects should be removed as the material may cause further thrombosis and sepsis.

Fat embolism

Fat embolism (FE) is common after both traumatic and nontraumatic events in children; however, identifying the source of the embolic is difficult to determine. FE can also occur during lipid and propofol infusion, intraosseous infusion, bone marrow harvest and in sickle cell disease, pancreatitis and fatty liver disease. The pathophysiology behind the source of these emboli as well as the physiologic ramifications of their presence remains unclear. The classical triad of fat embolization is characterized by altered mental status, respiratory distress, and petechial rash occurring typically 12–36 hours after injury. In most cases, the condition is self-limiting. Treatment should be supportive. Although the successful use of high doses of systemic corticosteroids has been reported in humans, there is no evidence that these drugs alter the course of the disease and/or affect outcomes.

Air embolism

Although air embolism can occur in both the venous and arterial systems, venous emboli are more common. Venous air embolization is a serious complication of endovascular procedures resulting in significant morbidity and mortality. It occurs as a result of a pressure gradient that allows air to enter the bloodstream, which can subsequently occlude blood flow. This complication can arise in a range of clinical situations including interventional radiology (IR) procedures, trauma, barotrauma, central line placement and removal, and certain types of surgical interventions such as cardiac and neurosurgery. In contrast, arterial air embolism occurs following direct instillation of air into the arterial tree (i.e., angiography) or paradoxically, through a septal defect or patent foramen ovale (PFO). Though the higher intravascular pressure in the arterial system is somewhat protective, arterial air embolism has the potential to produce ischemia or infarction in any organ with limited collateral blood supply, even when the volume of air is small. Symptoms and signs associated with serious air embolism are non-specific and can be difficult to diagnose. Clinical symptoms include dyspnea, cough and chest pain. Neurological symptoms include seizures, loss of consciousness, altered mental status, and hemiparesis/hemiplegia. In many cases, patients may exhibit sudden onset of a combination of signs and symptoms. Although much of the literature discusses arterial infarcts as a result of air embolism, it is worth noting that intravascular air can also cause venous infarcts. Although the diagnosis can be made by X-ray or echocardiography, CT scanning may be the most sensitive diagnostic test, showing a unique picture of round or mirror-shaped densities localized ventrally in the supine patient. Treatment is primarily supportive including maintenance of circulation, the prevention of further entry of gas, oxygen therapy/mechanical ventilation, and volume expansion. The patient should be placed in the left lateral decubitus position to prevent RV outflow obstruction by airlock. In the case of large amounts of central air, aspiration via the use of a central venous catheter might be an option.

Tumor embolism

Pulmonary tumor embolism is characterized by emboli in the pulmonary arterial system consisting of tumor cells without fibrocellular intimal proliferation and not contiguous with the metastatic foci. It is a rare event in the late stages of malignancy that carries a poor prognosis. Occlusion of the pulmonary microvasculature by tumor cells and associated thrombi may mimic thromboembolic disease. Detection of tumor cells in pulmonary vessels within the lung specimens is the only means to establish diagnosis. Unfortunately, pulmonary tumor embolism is rarely recognized before death since 1) the clinical features of pulmonary tumor embolism are quite similar to those of thrombotic pulmonary embolism; 2) the difference between thrombotic and metastatic pulmonary embolism is not easily differentiated on radiographic studies, making radiological diagnosis difficult; and 3) Positron Emission Tomography (PET)/CT is not sensitive enough to differentiate tumor embolism from thrombotic embolism. Therefore, pulmonary tumor embolism cases are often identified primarily by autopsy. Treatment should target the underlying malignant disease. In high-risk pulmonary tumor embolism, SE is preferred over systemic thrombolysis. Anticoagulant treatment is often prescribed in this context as well because tumor embolism and VTE are difficult to distinguish.

Inferior Vena Cava (IVC) filters

Currently, there are no data to support prophylactic IVC filter placement as mechanical and pharmacologic prophylaxis is preferred for children with VTE. Indications for filter placement in children should follow adult evidence-based guidelines until pediatric guidelines become available. IVC filters have been used historically in children with PE weighing more than 10 kg with contraindication to anticoagulation and associated proximal lower extremity deep venous thrombosis (DVT), recurrent DVTs and high risk of VTE. Current adult 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. IVC filters should be used with caution, however, as complication rates are high including new clot formation, migration of filter, and vascular damage.

Chronic Anticoagulation and Prevention of Recurrence

The aim of anticoagulation after acute PE is to complete the treatment of the acute episode and prevent recurrence of VTE. Most of the randomized studies focusing on long-term anticoagulation for VTE in adults have included patients with DVT, with or without PE. Only two randomized studies have specifically focused on patients with PE. There is little data on long-term AC for VTE in children. The incidence of recurrent VTE does not appear to depend on the clinical manifestation of the first event. However, in patients who have had a PE, VTE more frequently recurs as PE, while in patients who have had a DVT, it tends to recur more frequently as DVT. Therefore, the case fatality rate of recurrent VTE in patients who have previously had a PE is twice as high as that of VTE recurrence after DVT.

The vast majority of pediatric VTE are provoked, and evidence on duration of anticoagulation for pediatric VTE is highly limited but suggests that a maximum duration of 3 months is reasonable for most patients with provoked VTE, whereas longer duration is likely appropriate for unprovoked VTE. Whether shorter duration than 3 months is optimal for pediatric provoked VTE is as yet unclear.

Significant advances have been made in the understanding of pediatric thrombosis, yet many of the current pediatric recommendations are based on adult data. This is suboptimal, as there are several important differences between pediatric and adult VTE patients including: types of comorbidities; distribution of common anatomic locations of VTE; profile of provoked versus unprovoked VTE; and rates of mortality and morbidities associated with VTE. In addition, the hemostatic system in children changes from birth to adulthood, and anticoagulant pharmacokinetics are age dependent.

Four anticoagulant drugs are most commonly used in pediatrics: UFH given as an intravenous infusion, used in inpatient settings particularly among critically ill children whose lability in clinical status warrants the use of a short-acting agent; LMWH by twice-daily subcutaneous injection, used as subacute therapy in the majority of children, given that >90% of VTE in children are provoked; oral vitamin K antagonists, used particularly in children who have unprovoked VTE or significant chronic risk factors for recurrent VTE; and DOACs. The pharmacokinetics, pharmacodynamics, doses and need for frequent drug monitoring for all anticoagulant drugs can vary greatly in children compared to adults.

In general terms, an anticoagulant duration of 3 months is recommended for provoked VTE (including cerebral sinovenous thrombosis) in which the provoking factors have resolved, of 6–12 months for a first unprovoked VTE, and of indefinite duration for recurrent unprovoked VTE. Consideration should be given to neonates for the use of shorter duration of anticoagulation, typically between 6 weeks-3 months.

Long-Term Sequelae and Follow-Up

The patency of the pulmonary arterial bed is restored in the majority of PE survivors within the first few months following the acute episode; therefore, no routine follow-up CTA Chest imaging is needed in such patients treated for PE. However, in other patients, thrombi become persistent and organized, which in rare cases may result in Chronic Thromboembolic Pulmonary Hypertension (CTEPH), a rare and life-threatening condition that can result in progressive right-sided heart failure and death. It occurs as a result of unresolved thrombi obstructing the pulmonary arteries. The following criteria are used to make the diagnosis after 3 months of anticoagulant therapy: (1) mean pulmonary artery pressure >25 mmHg with a pulmonary capillary wedge pressure ≤ 15 mmHg, and (2) at least one (segmental) perfusion defect detected by lung scan, CTA Chest, or pulmonary angiography.

Because there are no pathognomonic signs or symptoms for CTEPH, the diagnosis is often delayed or missed. Patients may present with exertional dyspnea, exercise intolerance, and non-specific abnormalities on physical examination. As the disease progresses, there is a high risk of developing right heart failure. While the natural history of acute pulmonary embolism is near-complete resolution of emboli within 3–6 months, the persistence of any signs or symptoms after this duration of antithrombotic therapy warrants further investigation.

Most pediatric patients with chronic thromboembolic disease exhibit an underlying hypercoagulable state. Lupus anticoagulant, anticardiolipin antibodies, and protein C deficiency are some of the most common predisposing thrombophilic states in children. However, subjects with other prothrombotic states such as antithrombin III, factor V Leiden, or prothrombin gene mutations may also be at increased risk for CTEPH. In those without an underlying hypercoagulable disorder, a different thromboembolic risk factor (i.e., ventriculoarterial shunt, malignancy, indwelling catheters, hormonal therapy, obesity, etc.) is often present. Therefore, in children who have PE with an underlying hypercoagulable state and/or other thromboembolic risk factors, careful follow-up would be recommended to ensure complete resolution of the thrombus burden.

Diagnostic workup begins with chest radiography, pulmonary function studies, an ECG, and an echocardiogram. If CTEPH is suspected, a lung VQ scan should assess for subsegmental or larger unmatched perfusion defects. Given its high sensitivity, a normal lung VQ scan can effectively rule out the disease, while an abnormal test result prompts further evaluation with right heart catheterization, catheter-based pulmonary angiography, CTA chest, or MRI.

The first step in management is anticoagulant therapy (subcutaneous low molecular weight heparin, oral anticoagulant). Once the diagnosis is established, targeted PH therapy is also recommended.

Pulmonary thromboendarterectomy (PTE) is the treatment of choice for suitable individuals, and its success has been demonstrated in children. To be considered operable, a patient must have sufficient surgically accessible thromboembolic material without extensive distal disease. Balloon pulmonary angioplasty is an emerging option for inoperable CTEPH or patients with recurrent or persistent PH after PTE; however, this approach is rarely used in children and long-term results are lacking.

Persisting Symptoms and Functional Limitation after Pediatric Pulmonary Embolism

Persistent symptoms and abnormalities in cardiorespiratory function or echocardiography are commonly observed in adults following a diagnosis of PE; prevalence of similar signs and symptoms in pediatric PE patients are unknown. Post-PE syndrome (PPEI) encompasses a constellation of symptoms, physical findings as well as functional, radiographic and hemodynamic abnormalities following PE. The exact definition of what constitutes PPEI has not been agreed upon, but the definition is usually restricted only to patients with symptoms of reduced functional status who have measurable limitation in cardiopulmonary function. There is a paucity of data that exists regarding its diagnosis, pathogenesis and treatment for individuals who have this complication. The scarcity of data regarding PPEI in pediatrics is attributable to lack of guidelines and uniformity of post-PE assessments and inadequate long-term outcomes data. Given the rising rates of PPE, well-designed studies to examine long-term outcomes including PPEI are of priority.

Treatment of PPEI in adults is largely supportive, with no specific well-studied interventions for patients who do not meet criteria for CTEPH. Cardiopulmonary rehabilitation may improve symptoms and exercise tolerance.

Few high-quality, observational studies exist specifically regarding long-term outcomes for pediatric patients with PE. Long-term studies in adults with PE have shown that half of patients do not return to their previous level of functioning and continue to have reduced quality of life for years after the event. Nearly half of adults have exercise limitation one year following PE. Other studies in adults with PE have identified exertional dyspnea in 36%, and persistent perfusion defects in 28%. While comorbidities among adults and pediatric patients differ, there are unique pediatric pathologies including congenital heart disease that may also contribute to poor functional outcomes, but this needs further study.

Follow-Up

Evaluation of the patients 3–6 months after the acute PE episode is recommended to assess the persistence (or new onset) and severity of dyspnea or functional limitation, and to evaluate for possible signs of VTE recurrence, co-morbidities or bleeding complications of anticoagulation.

In patients complaining of persisting dyspnea and poor physical performance, trans-thoracic echocardiography (TTE) should be considered as the next step to assess the probability of (chronic) PH and thus possible CTEPH. Patients with a high echocardiographic probability of PH, or those with intermediate probability combined with elevated pro-BNP levels or risk factors/predisposing conditions for CTEPH should be considered for a V/Q scan or CTA chest.

If mismatched perfusion defects are found on the V/Q scan, further diagnostic workup is indicated. If, on the other hand, the V/Q scan is normal and the patient's symptoms remain unexplained, cardiopulmonary exercise testing (CPET) may be performed. By providing evidence of reduced maximal aerobic capacity, CPET supports the need for further follow-up visits and helps to identify candidates for pulmonary rehabilitation, exercise, or weight-reduction programs. CPET may also be helpful in patients with suspected CTEPH and coexisting left heart and/or respiratory disease; in such cases, it can help to establish the main limiting factor and thus set priorities for the treatment strategy.

For patients who report as free of dyspnea or functional limitation at 3–6-month follow-up after acute PE but have risk factors/predisposing conditions for CTEPH, further follow-up visits may be scheduled, and the patient must be advised to return if symptoms appear. Alternatively, TTE may be considered to assess the probability of PH.

Admission Criteria

1. All individuals with suspected PE based on risk factors and clinical presentation.
2. Individuals with confirmed PE based on imaging and laboratory findings.
3. Subjects with intermediate or high-risk PE should be admitted in the ICU for ongoing care, hemodynamic and respiratory monitoring and definitive therapy.

Discharge Criteria

1. Individuals with low-risk PE once cleared by Hematology. These individuals should continue outpatient AC therapy with close monitoring and follow-up care in Hematology clinic.
2. Individuals with intermediate and high-risk PE are safe to transition care to the general pediatric ward/Hematology once a definitive therapy is implemented (systemic thrombolysis, CDT, SE) and there is clear hemodynamic and respiratory improvement (improvement in systemic oxygenation, RV function and resolution of shock). Individuals can continue systemic AC under Hematology guidance.

Patient and Family Education/Discharge Planning

1. Prior to hospital discharge, patients and families should complete education on the use of LMWH or oral anticoagulants.
2. Patients should continue outpatient care in Hematology clinic.
3. In patients complaining of persisting dyspnea and poor physical performance in the outpatient setting, trans-thoracic echocardiography (TTE) should be considered as the next step to assess the probability of Chronic Pulmonary Hypertension and thus possible CTEPH.

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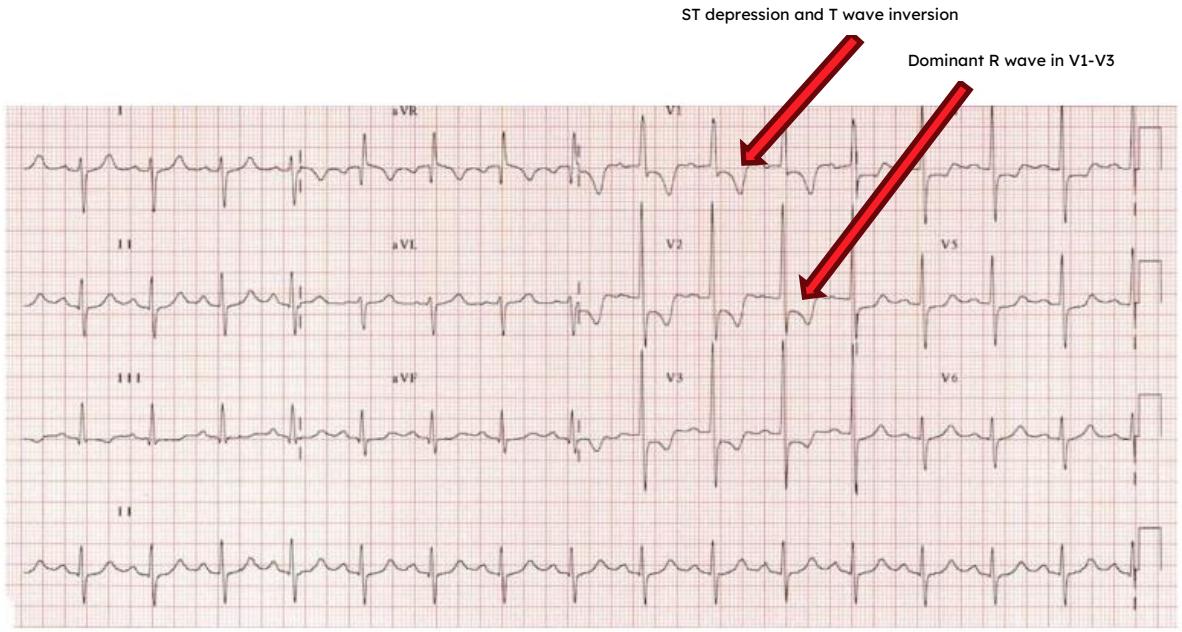
Appendix A

Right ventricular strain on ECG

Definition: RV strain is the name given to repolarization abnormality on an ECG which indicates either a significant right ventricular hypertrophy (RVH) or right ventricular dilation.
The main ECG features are:

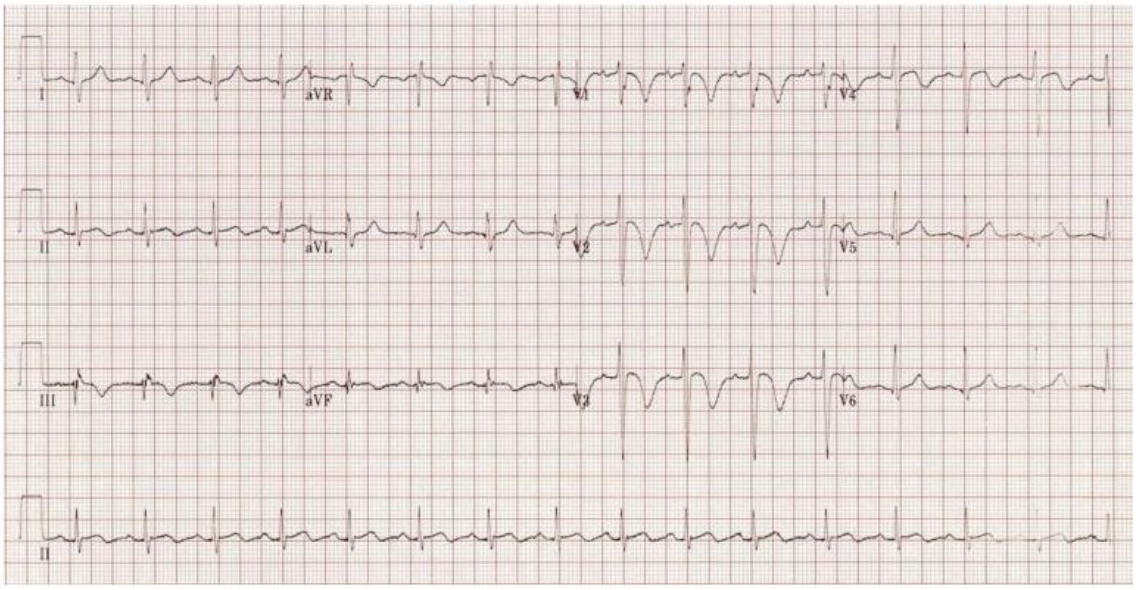
1. ST depression and T wave inversion in the RV leads (V1-V3, and inferior leads : II,III, aVF)
2. Other features may include:
    a. Right axis deviation
    b. Dominant R wave in V1 and dominant S wave in V5/V6

Examples:



Right ventricular strain pattern due to RVH:

Example of acute right ventricular dilation due to a massive PE



-T waves are prominently inverted in leads V1, V2, V3 and in leads III, aVF