CHEST

Acute Management of High-Risk and Intermediate-Risk Pulmonary Embolism in Children

A Review

Catherine Ross, MD; Riten Kumar, MD; Marie-Claude Pelland-Marcotte, MD; Shivani Mehta, BA; Monica E. Kleinman, MD; Ravi R. Thiagarajan, MBBS, MPH; Muhammad B. Ghbeis, MD; Christina J. VanderPluym, MD; Kevin G. Friedman, MD; Diego Porras, MD; Francis Fynn-Thompson, MD; Samuel Z. Goldhaber, MD; and Leonardo R. Brandão, MD

Severe forms of pulmonary embolism (PE) in children, althought rare, cause significant morbidity and mortality. We review the pathophysiologic features of severe (high-risk and intermediate-risk) PE and suggest novel pediatric-specific risk stratifications and an acute treatment algorithm to expedite emergent decision-making. We defined pediatric high-risk PE as causing cardiopulmonary arrest, sustained hypotension, or normotension with signs or symptoms of shock. Rapid primary reperfusion should be pursued with either surgical embolectomy or systemic thrombolysis in conjunction with a heparin infusion and supportive care as appropriate. We defined pediatric intermediate-risk PE as a lack of systemic hypotension or compensated shock, but with evidence of right ventricular strain by imaging, myocardial necrosis by elevated cardiac troponin levels, or both. The decision to pursue primary reperfusion in this group is complex and should be reserved for patients with more severe disease; anticoagulation alone also may be appropriate in these patients. If primary reperfusion is pursued, catheter-based therapies may be beneficial. Acute management of severe PE in children may include systemic thrombolysis, surgical embolectomy, catheter-based therapies, or anticoagulation alone and may depend on patient and institutional factors. Pediatric emergency and intensive care physicians should be familiar with the risks and benefits of each therapy to expedite care. PE response teams also may have added benefit in streamlining care during these critical events.

CHEST 2022; 161(3):791-802

KEY WORDS: anticoagulation; pediatric pulmonary embolism; surgical embolectomy; thrombolysis

Pediatric high-risk and intermediate-risk pulmonary embolism (PE) are associated with significant morbidity and mortality,[1-5] yet data are limited to case reports and single-center experiences.[6-10] Additionally, rates of PE in hospitalized children have been on the rise, with recent reports of six per 10,000 hospital discharges.[11] Current recommendations for acute management of severe PE in children mirror adult guidelines[12-17]; however, given that the cause and comorbidities associated with PE in children seem to differ from those in adults,[6,7,10] pediatric-specific circumstances must be considered.

ABBREVIATIONS: CBT = catheter-based therapy; CTEPH = chronic thromboembolic pulmonary hypertension; ECMO = extracorporeal membrane oxygenation; ESC = European Society of Cardiology; LV = left ventricle; NO = nitric oxide; PA = pulmonary artery; PE = pulmonary embolism; RV = right ventricle; SE = surgical embolectomy

AFFILIATIONS: From the Division of Medical Critical Care (C. Ross), Department of Pediatrics, the Division of Critical Care Medicine (M. E. Kleinman), Department of Anesthesiology, Critical Care and Pain Medicine, the Division of Cardiovascular Critical Care (R. R. Thiagarajan, M. B. Ghbeis, and C. J. VanderPluym), the Division of

We performed a narrative review of the management of high-risk and intermediate-risk PE. Based on the available data, our multidisciplinary expert panel discussed key definitions and decision points in the management of pediatric acute PE until consensus was met. Herein, we review the presentation and pathophysiologic features of shock resulting from PE, suggest pediatric-specific definitions for high-risk and intermediate-risk PE, and propose a pediatric-specific treatment algorithm that currently is the hospital-wide (inpatient and ED) guideline at Boston Children's Hospital.

Presentation

Children with acute PE most often demonstrate the classic symptoms of dyspnea and chest pain, with a minority of patients demonstrating hypoxemia, hemoptysis, shock, or cardiac arrest.[7] Many children with PE experience delays in diagnosis, with an average of 7 days after symptom onset,[18] likely because of the nonspecific symptomatology of PE, diagnostic challenges in nonverbal patients, and unreliable screening tools including D-dimer and Wells criteria, which do not perform as well in children.[19,20] Therefore, a high index of suspicion is required in children, especially those with risk factors for severe forms of PE, including use of oral contraceptives, presence of central venous catheter, obesity, and thrombophilia, among others.[6,7] It is also important to differentiate isolated acute PE from an acute PE on the background of chronic thromboembolic pulmonary hypertension (CTEPH), which may present with milder symptoms over the preceding weeks to months and requires an alternative management strategy.[21]

Pathophysiologic Features

Acute, severe forms of PE are characterized by varying degrees of pulmonary artery (PA) obstruction, PA hypertension, and acute right heart dysfunction or failure, with the most severe forms subsequently progressing to left heart failure, obstructive shock, and cardiac arrest (Fig 1). As PA pressures rise, the right ventricle (RV) dilates, and myocardial oxygen demand increases to preserve RV output. Severe dilation of the RV may cause stretching of the tricuspid annulus and consequent tricuspid regurgitation, further exacerbating systemic venous hypertension. If RV pressures are elevated beyond those of the systemic circulation, the interventricular septum will bow into the left ventricle (LV). This, in combination with limited pulmonary blood flow from the obstructed PA (and hence, limited pulmonary venous return to the LV), can lead to severely compromised LV preload and systemic shock. Systemic hypotension leads to impairment of oxygen delivery to the myocardium, which further contributes to RV failure, and a vicious cycle ensues. In the most severe cases, the combination of low systemic driving pressures and elevated downstream RV pressures results in impairment of coronary blood flow and subsequent cardiac arrest.[22]

Definitions

Classifications of acute PE in adults are based on the risk of early mortality.[14] However, given the paucity of data in children, similar risk stratification has not been described. We believe that, as in the adult population, the relative risk for early mortality in children is related to the degree of RV dysfunction or failure. Therefore, we propose the following definitions for pediatric PE adapted from the European Society of Cardiology (ESC) adult definitions.[14]

High-Risk (Massive) PE

High-risk (massive) PE was defined as acute PE causing cardiopulmonary arrest, sustained hypotension (systolic BP $<$ 5th percentile by age for at least 15 min or requiring vasoactive support), or normotension with signs or symptoms of shock (Fig 2). Note that the current adult guidelines from the ESC do not include the latter category in their definition of high-risk PE. However, because children in shock are known to compensate more often with increased systemic vascular resistance as compared with adults,[23] systemic pressures often are preserved, and hypotension generally is

Invasive Cardiology (D. Porras), Department of Cardiology, the Department of Pediatric Cardiology (K. G. Friedman), and the Department of Cardiac Surgery (F. Fynn-Thompson), Boston Children's Hospital, the Harvard Medical School (C. Ross, R. Kumar, M. E. Kleinman, R. R. Thiagarajan, M. B. Ghbeis, C. J. VanderPluym, K. G. Friedman, D. Porras, F. Fynn-Thompson, and S. Z. Goldhaber), the Center for Resuscitation Science (C. Ross and S. Mehta), Department of Emergency Medicine, Beth Israel Deaconess Medical Center, the Department of Pediatrics (R. Kumar), Dana-Farber/Boston Children's Cancer and Blood Disorders Center, and the Division of Cardiovascular Medicine (S. Z. Goldhaber), Department of Medicine, Brigham and Women's Hospital, Boston, MA; the College of Osteopathic Medicine (S. Mehta), New York Institute of Technology, Old Westbury, NY; the Division of Hematology/Oncology (M.-C. Pelland-Marcotte), Department of Pediatrics, CHU de Québec—Centre Mère Enfant-Soleil, Québec City, QC, the Department of Paediatrics (L. R. Brandão), Haematology/Oncology Division, The Hospital for Sick Children, and the Dalla Lana School of Public Health (L. R. Brandão), University of Toronto, Toronto, ON, Canada.

FUNDING/SUPPORT: C. R. was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health [Grant K23HL148312].

CORRESPONDENCE TO: Catherine Ross, MD; email: Catherine.ross@childrens.harvard.edu

DOI: https://doi.org/10.1016/j.chest.2021.09.019

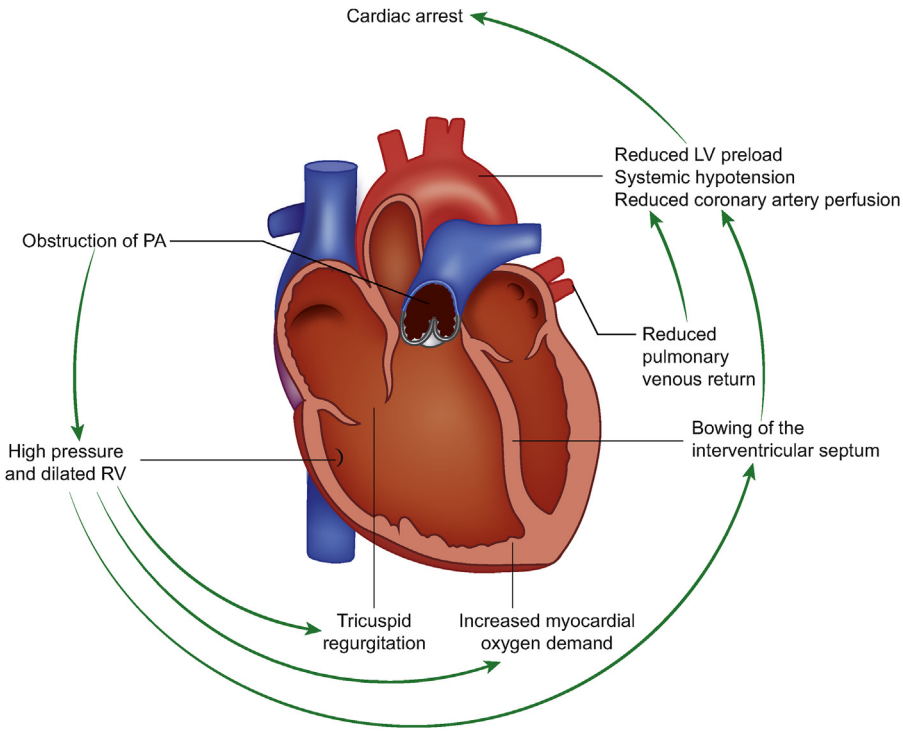

Figure 1 – *Diagram showing the pathophysiologic features of shock in severe pulmonary embolism. LV = left ventricle; PA = pulmonary artery; RV = right ventricle.*

thought of as a late sign of pediatric shock.[24] Therefore, we believe children with compensated (normotensive) shock as described by the American Heart Association's Pediatric Advanced Life Support Provider Manual should be included in the high-risk PE category.[24]

Intermediate-Risk (Submassive) PE

Intermediate-risk (submassive) PE was defined as acute PE without hypotension or compensated shock, but with evidence of RV strain by imaging, myocardial necrosis by elevated cardiac troponin levels, or both. It should be noted that the ESC's criteria for intermediate-risk PE is divided further into intermediate-high-risk PE (RV strain on imaging and elevated troponin levels) and intermediate-low-risk PE (RV strain on imaging or elevated troponin levels or other risk factors).[14] However, it is unclear whether further subdivision of patients in this cohort would warrant a meaningful change in management. Therefore, we suggest the steps detailed in Figure 2 to determine intermediate-risk vs low-risk PE classification. We emphasize that in the absence of RV enlargement on CT angiography, echocardiography should be performed to evaluate for RV strain if the PE is located centrally within the pulmonary vasculature or if the patient's vital signs remain abnormal. Although echocardiography is highly preferred in diagnosing RV strain in children, evidence of myocardial necrosis by elevated serum troponin levels also would indicate intermediate-risk PE if an echocardiogram cannot be obtained readily.

Low-Risk PE

Low-risk PE was defined as acute PE not meeting criteria for high-risk or intermediate-risk PE.

RV Strain: Criteria for diagnosing RV strain by echocardiography in adult PE have not been standardized, and pediatric data lack clear objective criteria for RV strain in pulmonary hypertension.[25] Therefore, we are unable to provide a comprehensive quantitative definition for RV strain in children. Interpretation of echocardiography by an experienced pediatric cardiologist is key in determining RV strain in pediatric PE. Features of RV strain with adult cutoffs and pediatric normal values are listed in Table 1.[26-29] On CT angiography, the diagnosis of RV strain primarily is based on the size of the RV relative to the LV, but absence of RV enlargement on CT angiography should not exclude the diagnosis of RV strain.

Primary Reperfusion: Primary reperfusion was defined as removal or disintegration of PE resulting in restored pulmonary blood flow.

Anticoagulation

Patients with high- or intermediate-risk PE should receive parenteral anticoagulation as soon as possible. At Boston Children's Hospital, a heparin infusion is used to

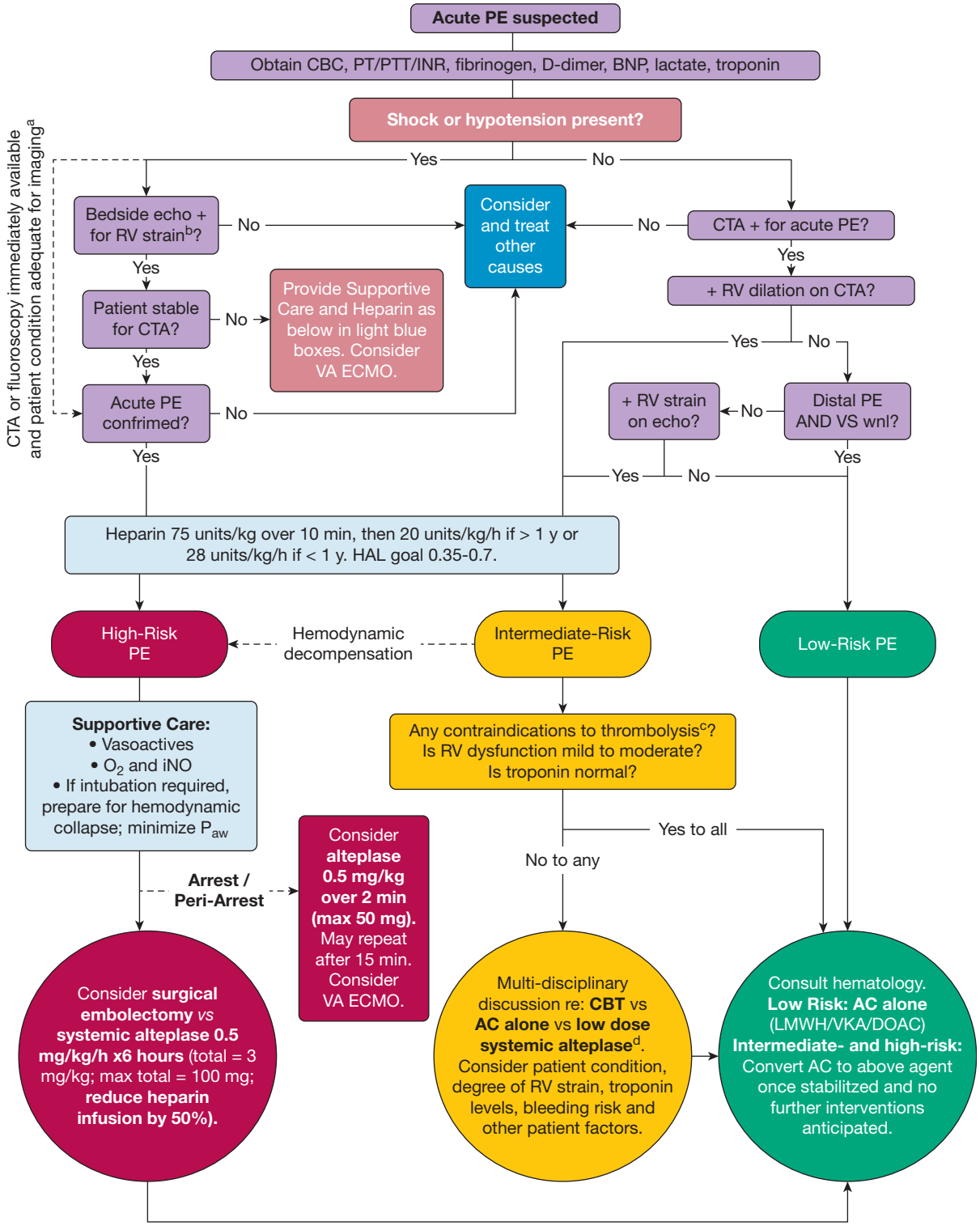

Figure 2 – *Suggested management algorithm for suspected acute PE in children younger than 18 years. AC = anticoagulation; BNP = brain natriuretic peptide; CBT = catheter-based therapy; CTA = CT angiogram; DOAC = direct oral anticoagulant; ESC = European Society of Cardiology; HAL = heparin activity level; iNO = inhaled nitric oxide; INR = international normalized ratio; IR = interventional radiology; LMWH = low-molecular-weight heparin; O_2 = oxygen; P_{aw} = mean airway pressure; PE = pulmonary embolism; PT = prothrombin time; PTT = partial thromboplastin time; RV = right ventricle; VA ECMO = venoarterial extracorporeal membrane oxygenation; VKA = vitamin K agonist; VS = vital signs; WNL = within normal limits.*

Considerations for High-Risk PE:
ICU LEVEL CARE

Favor surgical embolectomy for:
• Suspected tumor embolus (patients with Wilms Tumor, Ewings Sarcoma, osteosarcoma) or other non-thrombotic sources
• Patients with contraindications to thrombolysis[c]
• Patients with concomitant intracardiac thrombus
• Patients with intracardiac communications on echo
• Patients on ECMO

Favor thrombolysis for:
• Thrombi extending distally which are not amenable to surgical embolectomy
• Patients with comorbidities that confer additional surgical or anesthetic risk
• Patients in whom surgical embolectomy is not readily available (within 2 hours from diagnosis of PE)

Alternatives:
• CDT in the cardiac cath lab may be considered as an alternative means of diagnosis and treatment in certain scenarios. Pursuit of CDT should not delay life saving therapy.

Considerations for Intermediate-Risk PE:
ICU LEVEL CARE

CBT in the Cardiac Cath Lab is preferred for most patients with intermediate-risk PE *who require primary reperfusion.*

If CDT is unavailable or patient is a poor candidate, **AC ALONE is often preferred over systemic thrombolysis** given associated risks and lack of evidence supporting benefits in adult patients with intermediate-risk PE.

[d]**If systemic thrombolysis is used, low-dose alteplase may be used** to mitigate bleeding risks. Low-dose alteplase = 0.1 to 0.3 mg/kg/h x6 hours (total = 0.6 to 1.8 mg/kg; max dose = 50 mg).

Diagnostic Guidance in Critically Ill Patients:
[a]Rarely, definitive imaging may be immediately available and performed safely and more rapidly than echo in a patient with shock (in the ED, IR or cardiac cath lab). **If acute PE is confirmed and the patient remains in shock, obtaining an echo should not delay life saving therapy**

[b]Echo cannot rule out all PE, especially small distal PE that are not hemodynamically significant. However, in a patient with ongoing undifferentiated shock, lack of RV strain by echo should prompt consideration and treatment of other causes of shock.

[c]Contraindications to thrombolysis as per ESC 2019 guidelines:
Absolute contraindications: • Hemorrhagic stroke or stroke of unknown origin at any time • Ischemic stroke in the preceding 6 months • Central nervous system neoplasms • Recent major trauma/surgery/head injury in the preceding 3 weeks • Bleeding diathesis • Active bleeding
Relative contraindications • Transient ischemic attack in the preceding 6 months • Oral anticoagulant therapy • Pregnancy, or within one week postpartum • Non-compressible puncture site • Traumatic resuscitation • Refractory hypertension • Advanced liver disease • Infective endocarditis
Additional contraindications per BCH policy:
Prematurity with corrected gestational age < 37 weeks · Severe asphyxial event within 7 days · GI bleed within 2 months · Intracranial neoplasm, arteriovenous malformation, or aneurysm · Uncorrected bleeding diathesis · Specific catheterization-related contraindications including (but not limited to) significant aneurysm or intimal injury in a systemic artery (aorta, femoral artery), arterial access obtained above the inguinal ligament, large sheath size (especially arterial)
Absolute contraindications to thrombolysis might become relative in a patient with immediately life-threatening high-risk PE.

Figure 2 – *Continued.*

allow for rapid titration in the event that primary reperfusion is needed . Even if primary reperfusion is not pursued initially, we often continue heparin for up to 24 to 48 h in anticipation of possible intervention.[30] Bivalirudin also may be considered in institutions with experience with this agent.[31]

After initial treatment (or if initial presentation is low-risk PE), patients may convert to other anticoagulant agents such as low-molecular-weight heparins, vitamin K antagonists, or direct oral anticoagulants. Although the most recent pediatric guidelines from the American Society of Hematology have not recommended direct oral anticoagulants as potential therapeutic agents,[17] recent randomized controlled trials have shown noninferiority of rivaroxaban (direct anti-Xa inhibitor) and dabigatran (direct thrombin inhibitor) compared with standard of care regarding thrombosis-free survival, thrombosis resolution, and bleeding.[32,33] Therefore, the Food and Drug Administration has

TABLE 1] Findings Supporting Diagnosis PE of on Echocardiography in Children

Qualitative Echocardiography Findings		
Thrombus in right atrium, RV, main or proximal branch PA		
Flattened interventricular septum		
Paradoxical septal motion		
McConnell sign: hypokinesis of the RV free wall		
Qualitatively depressed RV function		
Quantitative or Objective Echocardiography Findings		
Finding	Adult Diagnostic Cutoff [a]	Pediatric Reference Range (Healthy Children)
Evidence of RV dilation by RV to LV ratio	> 1	≤ 0.66[26]
Tricuspid valve regurgitation with elevated jet velocity estimating elevated RV pressure	RV pressure > 40 mm Hg[27]	RV pressure < half systolic BP
Decreased TAPSE	< 16 mm	Range from 9.1 ± 1.6 mm in neonates to 24.3 ± 2.8 mm in 18-year-olds[28] (consensus guidelines recommend using a cutoff of < 10 mm in children[26])
Decreased peak systolic velocity of tricuspid annulus	< 9.5 cm/s	12.6 ± 1.8 cm/s[29]

PA = pulmonary artery; PE = pulmonary embolism; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion.
[a]Values refer to 2019 European Society of Cardiology Guidelines unless otherwise indicated.[14]

approved dabigatran for both acute management and secondary prophylaxis of pediatric thrombosis, including PE. We anticipate that the use of direct oral anticoagulants for management of pediatric PE will increase and recommend that a pediatric hematologist guide agent selection, monitoring, and duration of anticoagulation.

Management of Pediatric High-Risk PE

Primary Reperfusion

The ESC, the American Society of Hematology, and the American College of Chest Physicians adult guidelines endorse primary reperfusion with systemic thrombolysis for high-risk PE.[13,14,16] In a meta-analysis of 29 systematic reviews and 26 randomized controlled trials comparing thrombolysis with anticoagulation alone in adults with high-risk and intermediate-risk PE (n = 2,787), thrombolysis was associated with reduced mortality (relative risk, 0.61; 95% CI, 0.40-0.94) and risk of recurrent PE (RR, 0.56; 95% CI, 0.35-0.91), supporting thrombolysis as first-line therapy in the high-risk PE population.[16]

Published treatment algorithms for children also recommend thrombolysis for high-risk PE; surgical embolectomy (SE) or catheter-based therapies (CBTs) have been recommended as alternative treatments.[12,15,17,34] Of these treatment options, it remains unclear which is superior for the treatment of high-risk PE in children.[6,7,10] Given the relative lack of data on CBT for pediatric patients with high-risk PE,[35] our discussion focuses on thrombolysis and SE.

Retrospective adult studies have reported contemporary rates of in-hospital or 30-day mortality following thrombolysis (13%-37%[36-41]) and SE (4%-27%[39-43]), although inclusion criteria for these studies were variable, and some studies did not differentiate between high- and intermediate-risk PE. In a retrospective comparison, Lee et al[39] described thrombolysis (n = 1,854) vs SE (n = 257) in adult patients with acute PE. They showed equivalent 30-day and long-term mortality from all causes between the groups; however, the thrombolysis group experienced more stroke (1.9% vs 0.8%; OR, 4.70; 95% CI, 1.08-20.42), need for reintervention (3.8% vs 1.2%; OR, 7.16; 95% CI, 2.17-23.62), and recurrence requiring hospitalization (7.9% vs 2.8%; HR, 3.38; 95% CI, 1.48-7.73), but a lower risk of major bleeding (3.6% vs 9.0%; OR, 0.53; 95% CI, 0.31-0.92), compared with the SE group. Smaller retrospective studies have made similar observations.[36,37,41] Additionally, Aymard et al[36] showed

that patients who required rescue SE after failed thrombolysis achieved worse outcomes than those who received thrombolysis or embolectomy alone, indicating that attempted thrombolysis delayed definitive therapy, increased operative risks, or both for patients who ultimately required surgery. This is important because failure rates of thrombolysis for high-risk and intermediate-risk PE in adults (defined as ongoing clinical instability and RV strain on echo after 48 h) have been reported as high as 8% to 21%.[36,44] Note that the safety and efficacy of thrombolysis vs SE have never been compared in a head-to-head randomized clinical trial.

Outcomes after catheter-directed thrombolysis (the most common CBT) in adults were reported in a meta-analysis.[35] The 30-day mortality estimate was 8.0% (95% CI, 3.2%-14.0%) in the 210 adults with high-risk PE. Clinical success, defined as the reversal of decompensation, was 81.3% (95% CI, 72.5%-89.1%). Pooled rates for major bleeding and stroke were 6.7% (95% CI, 1.0%-15.3%) and 0% (95% CI, 0.000-0.007), respectively.

Until 2019, pediatric data on outcomes after high-risk PE were limited to case reports or series. Two retrospective studies were published recently by Ross et al[6] and Pelland-Marcotte et al[7] that describe consecutive cases of pediatric high-risk and intermediate-risk PE. Using pooled data from two studies, 46 children who demonstrated high-risk PE were reported in total. Outcomes by initial reperfusion therapy are reported in Table 2,[45,46] and the definitions used for outcomes are listed in e-Table 1. Caution should be used when interpreting these data given the high risk for confounding by indication bias in these studies (ie, risk of bleeding seems to be similar or increased with SE or anticoagulation alone compared with thrombolysis; however, clinicians likely avoided thrombolysis in patients who were more prone to bleeding).

Given the lack of evidence and based on our collective experience, we propose that primary reperfusion for pediatric high-risk PE be either thrombolysis or SE (Fig 2). Many regimens for systemic thrombolysis have been proposed.[47-50] Boston Children's Hospital currently uses alteplase 0.5 mg/kg/h over 6 h for a total of 3 mg/kg with a maximum of 100 mg. Patients may receive one to two additional doses of alteplase in cases of ongoing instability. Most pediatric centers reduce the heparin infusion rate by 50% during the alteplase infusion (Fig 2).

Major considerations for the decision to perform SE vs thrombolysis include the availability of an experienced pediatric cardiac surgeon and cardiac anesthesia team, anticipated delays for either therapy, relative or absolute contraindications for either approach, and surgical accessibility to the emboli (ie, more extensive distal emboli may not be amenable to SE). Another important consideration that may favor SE is suspicion for large tumor embolism, which may be clinically indistinguishable from thromboembolism, but would not be susceptible to thrombolysis (several of which have been reported, including Wilms tumor, Ewings sarcoma, and osteosarcoma).[5,6,8,10,51-53] Finally, patients who already are receiving extracorporeal membrane oxygenation (ECMO) may have better outcomes after SE rather than thrombolysis.[37] We consider CBT (at an experienced center) as an alternative therapy in the high-risk population given the paucity of data, reports of variable outcomes in high-risk PE,[35,54-56] and variable availability during off hours.

Supportive Care

Hemodynamic Support: Pediatric patients with high-risk PE likely will require intensive therapies in parallel with or while awaiting reperfusion therapy. Hypotension should be managed with vasoactive infusions. The ESC endorses use of norepinephrine in adults, which can improve "ventricular systolic interaction and coronary perfusion, without causing a change in [pulmonary vascular resistance]."[14] In our experience, epinephrine also may be helpful in supporting biventricular failure found in pediatric high-risk PE. A modest fluid resuscitation also may be attempted; however, excessive fluid administration may exacerbate RV failure.

Respiratory Support: Hypoxia is found commonly in patients with PE and should be supported with supplemental oxygen. Noninvasive ventilation may be used for enhanced oxygen delivery and may mitigate the risks of attempting intubation. Although intubation sometimes is necessary in patients with high-risk PE, extreme caution should be taken in this situation given the high risk of cardiac arrest in acute right heart failure. IV fluids, vasoactive infusions, resuscitation medications, equipment, and appropriate personnel should be present at the bedside. Induction medications with favorable hemodynamic profiles should be used (in our practice, ketamine and fentanyl are used with a rapid-onset paralytic). Great care also should be taken to

TABLE 2] Pooled Outcome Data for 46 Patients Who Demonstrated High-Risk PE by Initial Therapy From Ross et al[6] and Pelland-Marcotte et al[7]

Variable	Systemic Thrombolysis (n = 9)	Surgical Embolectomy (n = 13)	Catheter-Based Therapies (n = 5)	Anticoagulation Only or None[a] (n = 19)
All-cause hospital mortality	3 (33)	4 (31)	2 (40)	9 (47)
PE-related mortality[b]	2 (22)	2 (15)	1 (20)	6 (32)
Fatal PE	2/2 (100)	2/2 (100)	1/1 (100)	6/6 (100)
Fatal hemorrhage	0/2 (0)	0/2 (0)	0/1 (0)	0/6 (0)
Nonfatal major hemorrhage[c]	1 (11)	5 (38)	0 (0)	6 (32)
Required reintervention	3 (33)	3 (23)	1 (20)	1 (5)
Other procedural or anesthetic complication requiring early termination of procedure	N/A	0 (0)	1 (20)	N/A
CTEPH	2 (22)	0 (0)	0 (0)	0 (0)

Data presented as No. (%). CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism.
[a]Includes patients with unrecognized PE (diagnosed after death) and patients with limitations on medical interventions.
[b]Definition as per Girard et al.[45]
[c]Definitions as per International Society on Thrombosis and Haemostasis.[46]

minimize hypoxia during intubation by taking measures such as preoxygenation and apneic oxygenation. After intubatation, mechanical ventilation should be titrated to the minimal mean airway pressure necessary to minimize detrimental effects of positive pressure on RV filling.

Pulmonary Vasodilation: In addition to supplemental oxygen, pulmonary vasodilation with inhaled nitric oxide (NO) theoretically may improve hemodynamics and oxygenation by reducing pulmonary arterial pressure and decreasing RV afterload. Additionally, thrombus-related hemolysis produces free hemoglobin that scavenges intrinsic NO[57]; therefore, inhaled NO may replete this deficit and aid in promoting pulmonary vasodilation and endothelial function. However, robust data on efficacy and safety of inhaled NO in PE are lacking.[58]

ECMO: Patients with suspected or confirmed high-risk PE who remain hemodynamically unstable, who experience cardiac arrest, or both should be considered for emergent venoarterial ECMO cannulation (see Special Circumstances: *Cardiac Arrest*).

Bleeding: Hemorrhage is a common cause for hemodynamic decompensation in patients being treated for severe PE,[59] and reported rates of major bleeding range from 0.0% to 21.8% in pediatric patients.[1,6,7,60] Therefore, we consider correcting severe thrombocytopenia and coagulopathy in conjunction with antithrombotic therapy. We typically maintain a platelet count of $\geq 100 \times 10^9$/L and a fibrinogen level of ≥ 100 mg/dL in patients receiving lytic therapy.[49,50]

Special Circumstances

Cardiac Arrest: If cardiac arrest occurs before confirmation of PE, standard CPR should be administered according to Pediatric Advanced Life Support guidelines.[61] Empiric thrombolysis is not recommended for undifferentiated pediatric cardiac arrest; however, if the clinical scenario is highly compelling for PE-related cardiac arrest (ie, a patient with known DVT and sudden arrest not otherwise explained), intra-arrest thrombolysis may be considered (Fig 2). In institutions with rapid-response ECMO teams, ECMO should be considered for patients suspected of having high-risk PE, but who lack imaging to confirm the diagnosis.

If cardiac arrest occurs after confirmation of high-risk PE, standard CPR should be administered with early consideration for intra-arrest thrombolysis, venoarterial ECMO, or both.[62] Little is known about outcomes after intra-arrest thrombolysis or ECMO in cardiac arrest resulting from PE,[63-65] and the optimal approach for pediatric patients may differ based on the institution's experience and infrastructure. Importantly, the administration of alteplase during resuscitation may not negate ECMO candidacy given the drug's short half-life.[66-68] A recent meta-analysis showed that systemic thrombolysis preceding venoarterial ECMO did not confer increased mortality in adults with PE-related cardiac arrest.[62] However, this approach has not been studied in children and should be approached with extreme caution.

Published intra-arrest alteplase dosing strategies in adults are variable in the time over which a bolus is

administered, but seem to agree on a bolus dose of 50 mg of alteplase.[14,63,64] Lower bolus doses followed by alteplase infusions also have been reported in children with some success.[5] To approximate adult dosing, we administer a bolus of alteplase 0.5 mg/kg (maximum, 50 mg) over 2 min.

Neonates: Neonates have quantitative and qualitative differences in plasma contents relative to older children that result in lower circulating plasminogen levels. Therefore, if thrombolysis is attempted, we recommend transfusing fresh frozen plasma (10-20 mL/kg) before or concurrently with alteplase.

Management of Pediatric Intermediate-Risk PE

Primary Reperfusion

Adult guidelines recommend against the routine use of thrombolysis (or other reperfusion therapies) in adults with intermediate-risk PE (class III, level B).[13,14,16] The rationale for this recommendation is primarily based on results from the Pulmonary Embolism Thrombolysis trial in which adults with intermediate-high-risk PE were randomized to either thrombolysis and anticoagulation or anticoagulation alone.[30] Although a reduction in the composite outcome of early death and hemodynamic decompensation was observed in the thrombolysis group compared with the placebo group (2.6% vs 5.6%, respectively; OR, 0.44; $P = .02$), the increased risk of major bleeding (6.3% vs 1.2%, respectively; $P < .001$) and stroke (2.4% vs 0.2%, respectively; $P = 0.003$) seemed to outweigh the benefits of thrombolysis in this group. A recent meta-analyses by the American Society of Hematology supports these findings.[16]

Few observational studies report outcomes for SE in adult intermediate-risk PE. Although the reported mortality with surgical intervention is low (0%-7%),[40,43,69] it is generally avoided in intermediate-risk PE.[14]

In a meta-analysis of CBT, outcomes were reported for 945 adults with intermediate-risk PE with a clinical success rate (defined as prevention of decompensation) of 97.5% (95% CI, 95.3%-99.1%) and 30-day mortality rate of 0% (95% CI, 0%-0.5%); major bleeding and strokes were rare.[35] Small pediatric case series also have reported favorable outcomes for CBT in intermediate-risk PE.[54-56,70]

In addition to short-term outcomes, therapies used in the acute phase may reduce morbidities subsequent to PE such as CTEPH. For example, presence and size of residual perfusion defects after acute PE treatment have been shown to be associated with development of CTEPH,[71] suggesting that effective thrombus resolution may be protective. To this end, Sharifi et al[72] randomized adult patients with intermediate-risk PE to receive "safe dose" alteplase (approximately half of standard dosing) and anticoagulation vs anticoagulation alone. The results showed a significant reduction in the rate of elevated PA pressures in the thrombolysis group, and no bleeding complications occurred in any patients.

TABLE 3] Pooled Outcome Data for 36 Patients Who Demonstrated Intermediate-Risk PE[a] by Initial Therapy From Ross et al[6] and Pelland-Marcotte et al[7]

Variable	Systemic Thrombolysis (n = 13)	Surgical Embolectomy (n = 1)	Catheter-Based Therapies (n = 2)	Anticoagulation Only or None[b] (n = 20)
All-cause hospital mortality	0 (0)	0 (0)	0 (0)	4 (20)
PE-related mortality[c]	0 (0)	0 (0)	0 (0)	2 (10)
Fatal PE	0 (0)	0 (0)	0 (0)	1/2 (50)
Fatal hemorrhage	0 (0)	0 (0)	0 (0)	1/2 (50)
Nonfatal major hemorrhage[d]	0 (0)	0 (0)	0 (0)	0 (0)
Progression to high-risk PE requiring additional therapy	0 (0)	0 (0)	1 (50)	1 (5)
Other procedural or anesthetic complication requiring early termination of procedure	N/A	0 (0)	2 (100)	N/A
CTEPH	0 (0)	0 (0)	0 (0)	2 (10)

Data presented as No. (%). NA = not applicable; PE = pulmmonary embolisum; TEPH = chronic thromboembolic pulmonary hypertension.
[a]Includes patients who initially demonstrated intermediate-risk PE, but later progressed to high-risk PE.
[b]Includes patients with limitations on medical interventions.
[c]Definition as per Girard et al.[45]
[d]Definition as per International Society on Thrombosis and Haemostasis.[46]

However, the clinical relevance of this is unknown because the rates of elevated PA pressure were much higher than the current estimates of symptomatic CTEPH after PE.[73-75] In contrast, long-term follow-up studies from the Pulmonary Embolism Thrombolysis trial showed no difference in all-cause mortality or development of CTEPH between patients who received thrombolysis and those who received anticoagulation alone.[73,75]

Despite conflicting evidence for primary reperfusion reducing the risk of CTEPH in adults, pediatric providers may consider a more aggressive approach given the medical, financial, and psychosocial consequences of a chronic debilitating condition occurring in childhood. The prevalence of CTEPH in survivors of pediatric high-risk and intermediate-risk PE is unknown; however, the pooled incidence from Ross et al[6] and Pelland-Marcotte et al[7] was 3.6%, which approximates the incidence reported in adults (Table 3).[45,46,74]

The decision to pursue primary reperfusion vs anticoagulation alone should be addressed on a case-by-case basis by a multidisciplinary team. The team must weigh the benefits of primary reperfusion (reduction of early death or decompensation and possibly CTEPH) against the risks of these therapies (major bleeding, stroke, and anesthetic or procedural risks). Important considerations include the patient's overall clinical condition, degree of RV strain, presence of elevated troponin levels, anticipated bleeding risk, and available local expertise (Fig 2). Importantly, patient and family preferences also should be taken into account in light of these factors. If primary reperfusion is pursued, we prefer CBT, given the low rate of complications reported in adults with intermediate-risk PE. We generally avoid SE for intermediate-risk PE and reserve systemic thrombolysis for patients believed to be at high risk for decompensation and low risk for bleeding if CBT is not feasible. If thrombolysis is attempted in a child with intermediate-risk PE, we prefer a lower dose of thrombolysis potentially to mitigate the risks of bleeding (Fig 2).[72] In patients receiving anticoagulation alone, we suggest close monitoring for 48 to 72 h after the start of treatment, given that the median time to hemodynamic decompensation in the Pulmonary Embolism Thrombolysis trial was 1.79 ± 1.61 days for this group.[30]

Limitations

The guidance provided in this review should be viewed within the context of several limitations. Primarily, our proposed strategies rely heavily on adult literature and expert opinions within the author group, and therefore do not represent definitive evidence-based recommendations for management of high-risk and intermediate-risk PE in children.

Conclusions

High-risk and intermediate-risk PE are potentially fatal in children, and algorithms extracted from adult data may not account for differences seen in these populations. We propose pediatric-specific definitions of high-risk and intermediate-risk PE and provide a pediatric treatment algorithm. Given the extreme rarity of these events, we suggest that collaborative efforts across pediatric institutions to share best practices and outcomes are critical in further guiding acute management. Additionally, exploration of PE response teams in pediatric centers (including a pediatric intensivist or cardiac intensivist, a pediatric cardiothoracic surgeon, and a pediatric hematologist, if available) may be especially helpful in centralizing complex decision-making and streamlining care.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

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