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Full Length Article

Results of a multinational survey of diagnostic and management practices of thromboembolic pulmonary embolism in children

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ABSTRACT

Introduction: The incidence of thromboembolic (TE)-pediatric pulmonary embolism (PPE) is increasing. We sought to evaluate current practice patterns and gaps in the management of TE-PPE.
Materials and methods: After Institutional Review Board approval, SurveyMonkey® questions were sent to members of the Pediatric/Neonatal Thrombosis and Hemostasis Subcommittee, of the International Society on Thrombosis and Haemostasis and the Hemostasis and Thrombosis Research Society.
Results: Of 442 members of the two groups, 134 (30%) responded, and 125 (28%) complete responses were analyzed. Eighty percent practiced at a pediatric facility, 88% at academic centers, and 59% in the USA. Computed tomography pulmonary angiography (CTPA) was the preferred diagnostic modality (89%). D-dimer testing was variably used; 22% used clinical diagnostic prediction models and 8% had specific clinical care pathways for TE-PPE management. Prognostic stratification models were used to guide therapy by 4%. Indications for thrombolytic therapy varied considerably; 40% had a standardized protocol for thrombolysis, employing various modalities (45% systemic, 25% catheter-directed, 19% pharmaco-mechanical) and tissue plasminogen activator dose intensities. Duration of anticoagulation was variable with 58% prescribing anticoagulation for duration of > 3 months–6 months; 61% followed for long-term adverse outcomes.
Conclusion: This multinational survey of thrombosis/hemostasis specialists mainly based at pediatric academic centers demonstrates that antithrombotic management of TE-PPE (including duration of anticoagulation and use/non-use of thrombolysis) varies considerably. Furthermore, standardized care pathways to facilitate acute evaluation and management decisions are in place in a minority of centers. These findings help to inform the design of future clinical trials in TE-PPE.

1. Introduction

Pulmonary embolism (PE) is an infrequent but potentially life threatening form of venous thromboembolism (VTE) [1]. The incidence of pediatric PE (PPE) has increased by 200% over the last 15 years but there is a significant paucity of information on the diagnosis and management of PPE [2]. Given that several gaps exist in this field, recently, the Pediatric/Neonatal Thrombosis and Hemostasis Subcommittee of the Scientific and Standardization committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) made specific recommendations for further research in the field [3]. A systematic review of the published literature on PPE revealed that there were two patterns of PPE [4]. One is the classic thromboembolic (TE) PE; the other, unique to children, occurred due to local causes such as congenital heart disease surgery, congenital anomalies of the pulmonary artery etc. and was deemed to be an “in-situ pulmonary artery

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thrombosis" (ISPAT). Published studies over the course of the last few decades have revealed that diagnostic and treatment modalities for TE-PPE are highly variable [4]. To understand contemporary practice patterns, we conducted a multinational survey of a group of pediatric thrombosis/hemostasis physicians.

2. Materials and methods

The Institutional Review Board of the Wayne State University (WSU) School of Medicine approved the study. Questions were developed in Survey Monkey® according to guidelines for reporting survey-based research [5] and were divided into specific sections: demographic information of the survey respondents; diagnosis of TE-PPE; acute management of TE-PPE with specific focus on early clot reduction techniques (ECRT); extended anticoagulation in TE-PPE; evaluation of thrombophilia and associated risk factors; follow-up for long-term outcomes after TE-PPE; and management of asymptomatic TE-PPE. To assess specific trends in management patterns, hypothetical case scenarios were also provided and results were analyzed descriptively.

Survey questions were primarily in multiple-choice format and some used branching logic with specific follow-up questions. Prior to implementation, the survey was pre-tested by the authors of this manuscript, members of the pediatric hematology oncology division at WSU ($n = 6$) and two external pediatric thrombosis /hemostasis experts (Dr. Ayesha Zia, University of Texas Southwestern and Dr. Leslie Raffini, Children's Hospital of Philadelphia). After incorporating changes suggested from the pre-review, the survey was sent via an online survey tool to the practitioners who had identified themselves to be pediatric thrombosis/hemostasis physicians in the membership rosters of the ISTH SSC's Pediatric/Neonatal Thrombosis and Hemostasis Subcommittee and the Hemostasis Thrombosis Research Society (HTRS, North America). An incentive of US $50 was offered as an electronic gift card for the first 125 participants who completed the survey.

At the initiation of the survey, the respondents were advised regarding the two types of PE in children (as mentioned in the previous section) and were asked to restrict their responses as pertaining specifically to TE-PPE in patients < 21 years of age. The respondents were also assured of the anonymous nature of responses and were asked to proceed only if they consented to participate voluntarily. A copy of the full survey is attached in the "Supplemental materials" section.

Responses were analyzed using SPSS statistical software (Version 24.0, IBM Inc.). Statistical analysis was descriptive and a non-parametric Fischer's Exact test was used to evaluate associations between responses to specific clinical scenarios. Additionally, to assess differences in management patterns, responses were dichotomized and analyzed according to professional experience (≤10 years versus > 10 after completion of hematology training), affiliation (academic vs. non-academic centers), country of practice (USA versus Non-USA), number of PE patients evaluated annually (≤5 versus > 5 PE patients per year) and existence of a clinical care pathway or pulmonary embolism response team (yes versus no).

3. Results

There were 342 members of the Pediatric/Neonatal Subcommittee of the ISTH SSC and 160 HTRS members who identified themselves as pediatric thrombosis/hemostasis physicians; 60 members belonged to both societies. The survey was therefore sent to a total of 442 unique individuals, of whom 134 (30%) responded; 2 did not consent to participate in the survey and 7 more revealed that they did not manage PE in children as previously defined. Thus, a total of 125 (28%) analyzable complete responses were obtained. Characteristics of the survey study population, with regard to years of experience, practice setting, and TE-PPE management experience, are summarized here: Among the respondents, 49% were within 10 years of training and 46% were > 10 years after training. A small minority (5%) was still in training. The majority (80%) practiced at a pediatric facility, while 6% practiced at a combined adult and pediatric facility; 88% were affiliated with an academic medical center, 9% with a community medical hospital and 3% with private medical center. Fifty nine percent of the respondents practiced in the United States while 41% were from other countries (8% Canada, 6% Saudi Arabia, 2% each Brazil, Australia, Switzerland, Czech Republic, Germany, United Kingdom, Israel, Singapore, Turkey, Thailand, 1% each Austria, Spain, Indonesia, Moldova, Mongolia, The Netherlands, New Zealand, Russia and Sweden). The majority of physicians (69%) evaluated 1–5, 21% evaluated 6–10, 8% evaluated 11–20 and 2% evaluated > 20 new children with PE annually.

3.1. Diagnostic evaluation

The physicians used a variety of modalities for the diagnosis of TE-PPE with computed tomography pulmonary angiography (CTPA) being the most common (89%). A D-dimer value was variably used by the physicians to determine further radiologic testing for the diagnosis of TE-PPE; 17% indicated that they "*always*" use, 24% "*often*" use, 38% "*occasionally*" use and 18% "*never*" use the D-dimer value to determine further radiologic testing. Twenty percent of respondents reported using a clinical diagnostic prediction model validated in adults, for the diagnosis of TE-PPE with the Wells criteria (original, modified or simplified) being most frequently used (92%), followed by the Pulmonary Embolism Rule-out Criteria (PERC) (12%). Furthermore, 8% of the respondents reported the existence of a specific pulmonary embolism response team (PERT) or a clinical care pathway for the rapid diagnosis and acute management of TE-PPE at their institutions. Within such teams, the composition consisted of a variety of subspecialists: 80% had pediatric intensive care physicians, 60% had pediatric cardiologists, 90% had pediatric hematologists, 60% had pediatric emergency care physicians, 10% had pediatric hospitalists/general pediatricians, 60% had pediatric radiologists, 50% had interventional radiologists and 30% had cardiovascular surgeons as part of the team. Overall, 80% responded that they would like to be involved in clinical research evaluating the impact of the PERT on outcomes of TE-PPE.

3.2. Acute management of TE-PPE

Among the respondents, 40% indicated that they had a specific management protocol for thrombolysis/thrombectomy while 60% did not have such a protocol; 33% of the physicians admitted all patients with TE-PPE to the ICU while 57% admitted to the ICU depending on the clinical condition of the patient. We also attempted to review the current practice of early risk categorization of TE-PPE among physicians: Four percent indicated that they use a prognostic risk score for classification of PE; 67% used the pulmonary embolism severity index (PESI) and 33% used the European Society of Cardiology (ESC) model. The survey results also showed that the physicians use a variety of methods to assess the severity of PE (Fig. 1a) and for the use of ECRT (Fig. 1b). As shown in Fig. 1a, 98% of physicians used clinical signs and symptoms to assess the severity of PE. A large proportion of physicians also used abnormalities on echocardiography (ECHO, 92%), electrocardiography (EKG, 69%), radiologic location of the thrombus (84%) and biomarkers such as elevated troponin (46%) and B-natriuretic peptide (BNP, 32%) to assess the severity of PE. With regard to situations in which they would use ECRT (Fig. 1b), 95% of physicians stated that prescribed thrombolytic therapy for patients with hemodynamic collapse, 50% prescribed thrombolytic therapy to hemodynamically stable patients who show evidence of cardiac dysfunction or cardiac strain and 24% of physicians stated that they prescribed thrombolytic therapy based solely on the site of the thrombus (i.e. main or right/left main pulmonary artery).

Tissue-type plasminogen activator (tPA) was the most preferred agent (98%) for use for thrombolysis. Furthermore, the survey revealed that the physicians used a variety of routes (45% used systemic

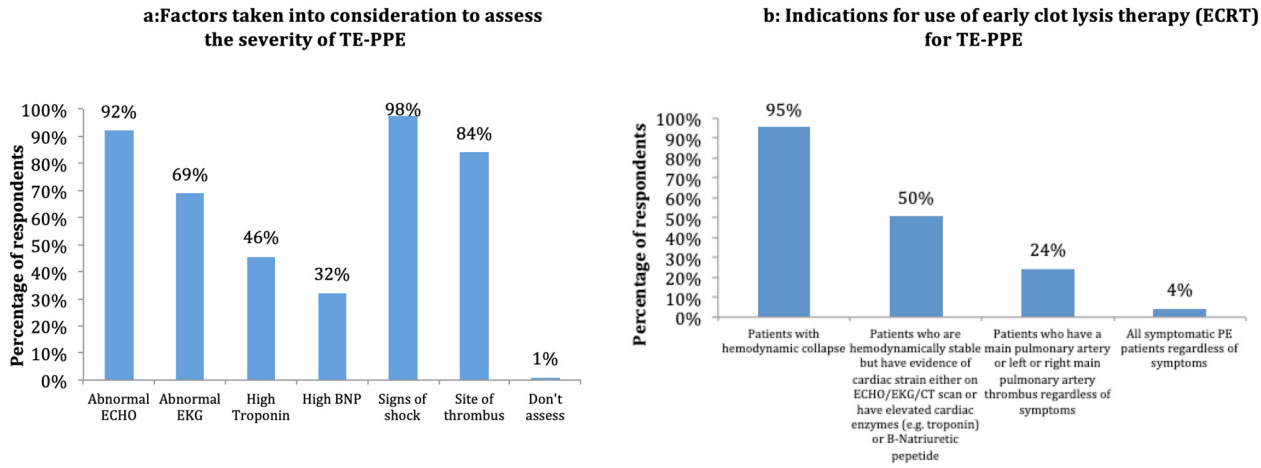

Fig. 1. a and b: Factors taken into consideration to assess the severity of TE-PPE and indications for use of early clot reduction techniques (ECRT).
ECHO: echocardiography; EKG: electrocardiography; BNP: brain natriuretic peptide; CT: computed tomography; PE: pulmonary embolism.

thrombolysis, 25% used catheter directed thrombolysis, 19% used pharmaco-mechanical thrombolysis, 3% performed surgical removal of the thrombus) and intensities for administering thrombolysis. When catheter-directed or pharmaco-mechanical thrombolysis was used, it was performed by interventional radiologists (66%), interventional cardiologists (21%), critical care/intensive care physicians (13%) and vascular surgeons (14%). The most frequent dose of tPA used for systemic thrombolysis was 0.1–0.5 mg/kg/h over 6 h (55%) followed by 0.01–0.06 mg/kg/h over 24–48 h (31%). For catheter–directed thrombolysis, the most common tPA dose was 1–2 mg/h administered through the catheter over 24 h (62%); 18% had an alternate dose for catheter directed thrombolysis and 18% did not perform catheter-directed thrombolysis at their center.

Adjunctive measures used during thrombolysis (Fig. 2a) and the practice of administering FFP to supplement plasminogen (Fig. 2b) vary considerably. In regards to duration of thrombolysis, 39% of physicians revealed that they continue thrombolysis for ≤ 48 h, 27% for 48–72 h, 9% for 72–96 h, 2% for > 96 h and 18% do not have a set maximal limit for administering thrombolytic therapy.

When questioned about screening for other sites of deep venous thrombosis (DVT), 74% responded that they screen for upper and lower extremity DVT for *all* patients while 21% screen if there are symptoms or signs of DVT; an additional 31% screen for intra-cardiac thrombosis in the presence of a central venous catheter (CVC). Evaluation of thrombophilia was also variable as indicated in Table 1.

3.3. Long-term choice of anticoagulants and duration of anticoagulation

To understand the practice patterns in prescription of anticoagulants (ACs), the respondents were advised to consider the age of the patient and to assume that there were no restrictions in terms of medication availability or insurance approval. As seen in Fig. 3, the choice of ACs was age-dependent. In neonates and infants < 1 year, 96% responded that low-molecular weight heparins (LMWH) were their AC of choice. For patients aged > 1–6 years, 74% preferred LMWH, 22% preferred a vitamin K antagonist (VKA) and 2% prescribed direct oral anticoagulants (DOACs). In children between 6 years of age and puberty, 60% preferred a LMWH, 34% preferred VKA and 4% prescribed DOACS. In post-pubertal children, 37% prescribed a LMWH, 32% VKA and 31% used DOACs for the long-term management of PE.

When questioned regarding duration of AC therapy for TE-PPE, 17% indicated that they treat for 6 weeks–3 months. On the other hand, 58% indicated that they treated TE-PPE for duration of > 3 months–6 months, 16% indicated that they prescribed AC for 6 months–1 year and 10% prescribed > 1 year or life-long anticoagulation. Furthermore, 17% believed that patients with non-central PE (segmental/non-segmental) needed shorter duration of therapy, while the majority (68%) of physicians did not differentiate between the two for the duration of therapy. The practice for evaluation of residual thrombosis (RT) at the end of AC therapy also varied with 60% indicating that they routinely re-imaged at the end of anticoagulant therapy while 40% did not. When questioned about the role of RT on

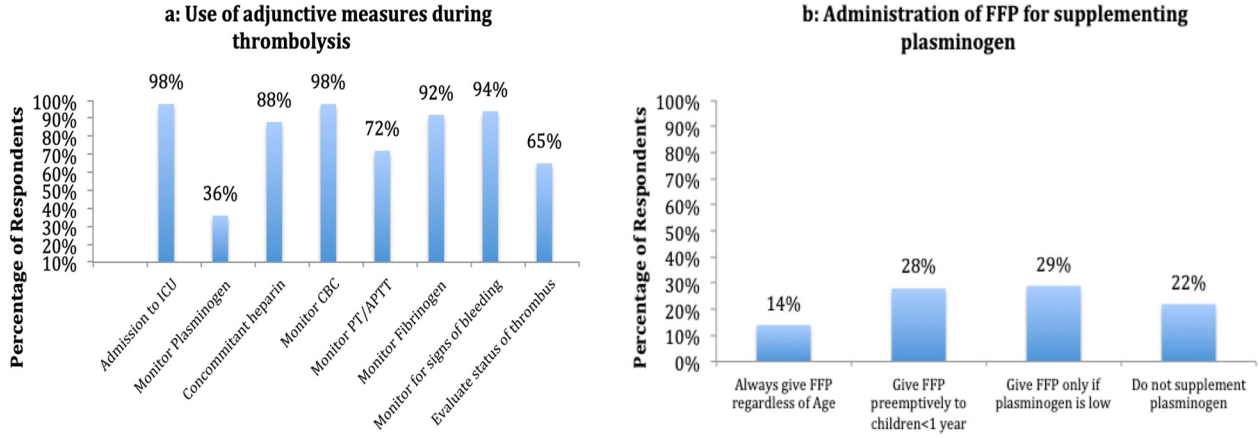

Fig. 2. a and b: Use of adjunctive measures during thrombolysis and administration of FFP to supplement plasminogen.
ICU: intensive care unit; CBC: complete blood count; PT/APTT: prothrombin time/activated partial thromboplastin time; FFP: fresh frozen plasma.

Table 1
Practice pattern for evaluation of thrombophilia in TE-PPE.

	Neonates- < 1 year	1 year-Puberty	Post-pubertal
Natural anticoagulant (Protein S, Protein C, Antithrombin III) deficiency			
Always test	50%	47%	47%
Evaluate only if family history or other reason	45%	47%	47%
Never test	6%	6%	6%
Genetic thrombophilia (Factor V Leiden mutation, prothrombin gene mutation)			
Always test	35%	39%	38%
Evaluate only if family history or other reason	48%	46%	50%
Never test	17%	15%	12%
Elevated levels of clotting factors (Factor VIII, Von Willebrand factor etc.)			
Always test	28%	33%	35%
Evaluate only if family history or other reason	37%	37%	36%
Never test	35%	30%	29%
Anti phospholipid antibody			
Always test	47%	54%	57%
Evaluate only if family history or other reason	37%	39%	40%
Never test	16%	6%	3%
Homocysteine level			
Always test	26%	31%	30%
Evaluate only if family history or other reason	34%	34%	35%
Never test	41%	35%	35%
Lipoprotein (a) level			
Always test	16%	23%	25%
Evaluate only if family history or other reason	34%	30%	34%
Never test	50%	46%	42%

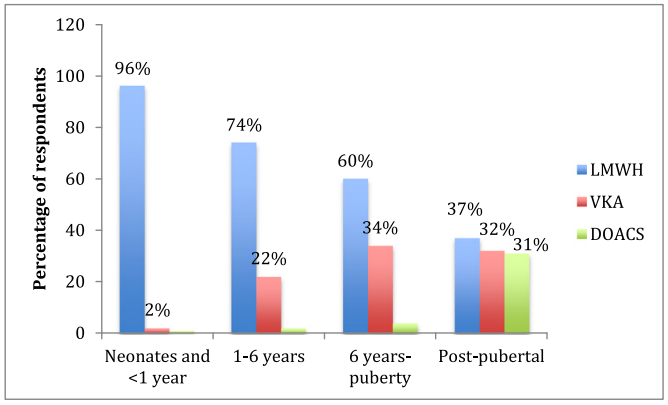

Fig. 3. Age-dependent differences in choice of prescribed anticoagulants for TE-PPE in children.
LMWH: low molecular weight heparin; VKA: vitamin K antagonist; DOACS: direct oral anticoagulants.

the duration of AC therapy, 13% of the respondents indicated that they increased the duration of therapy from 6 weeks to 3 months, 58% responded that they increased the duration of AC from 3 months to 6 months and 35% indicated that the presence of RT would not alter the duration of predetermined AC therapy.

3.4. Evaluation of long-term sequelae

Sixty-one percent of the respondents indicated that they regularly followed patients for evaluation of long-term adverse outcomes such as chronic thromboembolic pulmonary hypertension (CTEPH); 77% performed ECHO, 39% EKG, 49% evaluated objective or subjective

Table 2
Trends in practice according to sub-categorizations.

A. Respondents' affiliation with an academic versus non- academic center

- Respondents from non-academic centers tended to use the clinical diagnostic models such as the Wells criteria while those from academic centers did not
- Only a few centers had a clinical care pathway (or a PERT system), all belonged to academic centers
- Academic centers were more likely to have a specific management protocol for thrombolysis/thrombectomy
- Respondents from academic and non-academic centers were equally inclined to use systemic and catheter directed thrombolysis; The use of pharmaco-mechanical thrombolysis was generally seen in academic centers
- There was a tendency for use of high dose tPA for systemic thrombolysis in non-academic centers while academic centers used both high and low dose tPA
- An age-dependent increase in the use of vitamin K antagonists and DOACs (especially in the post-pubertal age) was seen with no differences in trends in academic versus non academic centers
- In regards to thrombophilia testing, there was tendency for academic centers to test for natural anticoagulant deficiency and genetic thrombophilia in all patients while non-academic centers are more likely to test when there was a positive family history, or if the clot was unprovoked. Antiphospholipid antibody (APA) testing was performed by both academic and non-academic centers while testing for homocysteine levels and lipoprotein (a) levels and elevated levels of clotting factors was very heterogeneous with no specific differences between academic and non-academic centers.
- There was no difference between academic and non-academic centers regarding duration of therapy with the majority of the respondents indicated
- Respondents from non-academic centers were less likely to re-image at the end of prescribed anticoagulant therapy, and likely to manage asymptomatic central PE with anticoagulation
- Respondents from academic centers were inclined to not differentiate between central and non-central PE

B. Respondents from US versus non-US countries

- There were no differences in the diagnostic tests, use of D-dimer, use of clinical prediction models, likelihood of having a clinical care pathway, or a specific pathway for thrombolysis/thrombectomy, likelihood of admission to the ICU, use of a prognostic risk prediction model between US and non-US countries. There was a greater tendency to use pharmaco-mechanical thrombolysis in the US; Non-US countries were less likely to use catheter directed thrombolysis.
- There was a tendency to give FFP in all or in patients < 1 year in non-US countries to supplement plasminogen while respondents from the US tend to give FFP when there is a low level of plasminogen or when there was no response seen after thrombolysis
- As regards anticoagulant use, although an age dependent increase was seen in the use of vitamin K antagonists and DOACS, low molecular weight heparin was the most common anticoagulant that was preferred by the US respondents. On the other hand after the neonatal period, VKA were the anticoagulants of choice. US respondents indicated that they were more likely to prescribe DOACs than VKA in the post pubertal age than the non-US respondents
- There were no differences in the thrombophilia testing patterns between the US and non-US respondents across all ages and tests
- There were no differences in the duration of therapy between US and non-US respondents.
- US respondents were less likely to image at the end of prescribed anticoagulation.
- Non-US countries were more likely to follow children with PE for long term adverse outcomes
- There was no difference in the prescribed anticoagulation duration between US and non-US countries for asymptomatic PE
- US respondents tended not to re-image at the end of therapy

C. Number of new TE-PPE patients seen annually by the respondents (≤5 versus > 5)

- Although the numbers were small, centers that evaluated > 5 TE_PE patients per year tend to have a clinical care pathway or PERT and a specific protocol for thrombolysis/thrombectomy
- In regards to anticoagulant use, although age dependent increase was seen in the use of vitamin K antagonists and DOACS, low molecular weight heparin was the most common anticoagulant that was preferred. In the 6 years-pubertal age group, there was a higher tendency to use VKA by respondents who evaluate > 5 TE-PPE patients per year than those who evaluate < 5 TE-PPE per year
- Respondents that evaluate > 5 TE-PPE patients tend to follow TE-PPE patients for long term adverse outcomes

D. Whether the respondent had a clinical pathway PERT at their center or not

- All respondents (100%) with a PERT tend to use CT pulmonary angiography for diagnosing TE-PPE

(*continued on next page*)

Table 2 (*continued*)

- Respondents with a PERT team tend to have specific protocols for thrombolysis/thrombectomy
- Respondents with a PERT team tend to use catheter directed and pharmaco-mechanical thrombolysis over systemic thrombolysis
- For systemic thrombolysis, respondents with PERT teams tend to use TPA 0.1–0.5 mg/kg/h rather than low dose TPA
- For catheter directed thrombolysis, respondents with PERT teams tend to use TPA 1–2 mg/h for 24 h rather than urokinase or other dosing
- Respondents with PERT teams tend to give thrombolysis for 48–72 h or longer as compared to < 48 h of thrombolysis
- Respondents with PERT teams tend to follow TE-PPE patients for long term adverse outcomes
- Respondents with PERT teams tend to treat asymptomatic PE like symptomatic PE as compared to those without PERT team

E. Respondents experience as reflected by number of years after training (≤10 years versus those > 10 years after training)

- Respondents with ≤10 years of training tend to use CT pulmonary angiography while respondents with > 10 years tend to also use other modalities such as MRI angiography/VQ scan and echocardiography
- Respondents with < 10 years experience tend to use thrombolysis as compared to respondents with > 10 years of experience
- Although LMWH was the most common anticoagulant of choice across all age groups with an age dependent increase in the use of vitamin K antagonists and DOACs, there was tendency for respondents with > 10 years experience to use vitamin K antagonists in the post neonatal age groups as compared to those with < 10 years of experience
- Respondents with > 10 years of experience tend not to test for elevation in FVIII and Lipoprotein a levels across all age groups

measures of exercise hypoxia, 48% performed pulmonary function testing and 6% performed a pulmonary angiography to evaluate for CTEPH.

3.5. Asymptomatic TE-PPE

When asked about practice patterns of management of asymptomatic TE-PPE, 58% indicated that they did not differentiate between symptomatic and asymptomatic TE-PPE and treated both in a similar manner; 25% indicated that in the case of asymptomatic PE, if the thrombus was centrally located, they managed like symptomatic TE-PPE. Furthermore, 55% revealed that they would re-image patients with asymptomatic TE-PPE to evaluate for resolution.

3.6. Analysis according to various categorizations

We stratified survey responses according to various categories mentioned previously in the “Materials and methods” subsection. Results (Table 2) are described descriptively (if considered relevant to the topic) with notation made on the trends (although statistical significance as deemed by a p-value of < 0.05 was not achieved).

Descriptive analysis of cases (please see Supplemental material for the exact wording of the questions).

The survey participants were provided an opportunity to respond to hypothetical case scenarios. There were two case scenarios per section, each designed to address a specific challenging issue regarding the management of TE-PPE. As seen in Table 3, question 1a assessed respondents' approach towards D-dimer testing. The results reveal that 33% of the respondents did not test a D-dimer routinely and 26% tested a D-dimer primarily for determining whether to prescribe AC therapy or for determining the duration of therapy. The reasons for not testing a D-dimer varied considerably (Question 1b). Question 2 addressed D-dimer testing in a variety of scenarios in order to evaluate the circumstances in which the respondents considered D-dimer testing to be potentially useful. The responses suggest that D-dimer testing was considered to be more useful in cases presenting to the emergency department than in inpatients, and in older children compared to younger children. Cases 3 and 4 primarily assessed the respondents approach to hemodynamically unstable and stable TE-PPE respectively. As can be seen by the responses, 47% of respondents preferred systemic thrombolysis in hemodynamically unstable TE-PPE and 66% preferred AC therapy for hemodynamically stable TE-PPE regardless of the site of thrombus. Cases 5 and 6 gauged the respondents' approach to duration of AC therapy for segmental/subsegmental and central TE-PPE. As is evident by the responses, most of the respondents prescribed anticoagulation for more than three months regardless of the location of the thrombus. Case 7 addressed the respondent's approach to patients with respiratory symptoms in setting of prior pulmonary embolism. The responses suggest some form of imaging was undertaken to investigate, with the most common modality being echocardiogram to assess for pulmonary hypertension. Question 8 assessed the duration of follow up for TE-PPE. As seen in Table 3, the follow-up period was variable.

4. Discussion

In the past, several surveys of experts in pediatric blood disorders have provided data regarding practice patterns of specific disease states in childhood [6–9]. We conducted a survey of a group of multinational pediatric thrombosis hemostasis experts, the results of which demonstrate a wide variation in management approaches between practitioners despite the existence of consensus-based recommendations for antithrombotic therapy in children with VTE [27,28].

As evident from the results, the vast majority of respondents (89%) indicated that they utilize CTPA as the preferred modality for the diagnosis of TE-PPE. Given the high usage of CTPA as indicated by this survey, there is a strong need for standardizing techniques of CTPA in children. Interestingly, there are specific variables that may affect the quality of CTPA results in children. As summarized by Lee et al., timing of the contrast bolus (bolus tracking versus empiric delay), type of CT images (axial versus multi-planar) and underlying diseases (e.g. sluggish flow in the pulmonary artery due to the Fontan procedure) may affect the diagnosis of PE on CTPA in children [10,11]. A recent survey of Society of Pediatric Radiology members revealed that there is considerable variation in the policies and practices of how CTPA is conducted in children, highlighting a critical need to determine the optimal technique for this practice [12].

This survey also revealed that the use of an elevated D-dimer to guide further radiologic evaluation of TE-PPE was highly variable. Thus far, the utility of an elevated D-dimer has only been evaluated in retrospective cohorts of PPE patients and findings from our survey likely reflect trends in practice patterns that emerge from the fact that although an elevated D-dimer value was shown to have a high sensitivity in PPE, the overall specificity is quite variable [13]. The survey further revealed that the majority of physicians do not systematically use a diagnostic clinical prediction model but among those who do use such a model, the Wells score was most common. Previous retrospective studies in pediatrics have revealed the sensitivity of the Wells score to be between 72 and 86% and the specificity to be 60%, for TE-PE [14,15]. Other studies evaluating scores such as the PERC criteria have yielded higher sensitivity (84–100%) and but a lower specificity (24–34.7%) [15,16], but as indicated by the survey results, it is rarely used. Patients with PE often present with confounding symptoms and in adults, diagnostic prediction models in combination with an elevated D-dimer value are often used to drive further radiologic testing. The survey results indicate, there is an urgent need to conduct prospective studies to evaluate the role of an elevated D-dimer and clinical decision making rules in TE-PPE.

Results from this survey indicate that a high proportion of physicians considered admission of TE-PPE patients to the ICU. Given that all patients with TE-PE do not present with cardiovascular instability, the appropriateness of healthcare utilization with its associated cost, warrants assessment. Importantly, the majority of physicians indicated that they do not have a clinical care pathway for the management of TE-PPE. Studies in adult PE patients have demonstrated that

Table 3
Hypothetical case scenario analysis.

Case number	Primary goal of case with brief description	Results (%)	
1a	Utility of D-dimer testing in a 15 year old on oral contraceptive pill presenting with shortness of breath, chest pain, flu-like symptoms, cough and productive sputum	I would request D-dimers with a decision not to proceed to imaging for pulmonary embolism if they were negative	16%
		I would request D-dimers if the Well's score (or another diagnostic prediction model) gave a low probability of pulmonary embolism with a decision not to proceed to imaging if they were negative	14%
		I would request D-dimers in order to decide whether to give anticoagulant therapy/determine duration of therapy prior to imaging but proceed to imaging whether the result was positive or negative	26%
		I would not request D-dimers	34%
		Other (please specify)	10%
1b	Follow up question for not testing D-dimer*	I would not request D-dimers as I have already made the decision to proceed to imaging for PE	45%
		I wouldn't request D-dimers as their negative predictive value is not known in this age group	47%
		I would not request D-dimers as I do not find them to be helpful in children and adolescents	20%
		Other	25%
2	Settings in which D-dimer testing is adopted by respondents	A 12-year-old pre-pubertal male with acute lymphoblastic leukemia and unexplained tachycardia during an inpatient stay for control of nausea and vomiting	12%
		A 14-year-old post-pubertal female presenting to the emergency department with tachypnea and hypoxia after a long haul flight	56%
		A 2-year-old male with nephritic syndrome presenting with breathlessness and tachycardia	34%
		A 9 -year-old female with stable ulcerative colitis presenting to the emergency department with shortness of breath and pleuritic chest pain	40%
		A 17-year-old female who has started a combined oral contraceptive pill 2 months back presenting to the emergency department with haemoptysis.	55%
		I don't rely on a D-dimer value for proceeding for testing for PE	49%
3	Management of hemodynamically unstable PE, with thrombus in the main PA	Start systemic thrombolysis using TPA/urokinase	47%
		Pharmaco-mechanical thrombolysis using EKOS or Angiojet with thrombolysis	17%
		Catheter directed thrombolysis	22%
		Heparin infusion/Low molecular weight heparin/Fondaparinux	9%
		Direct oral anticoagulants	0%
		Other (please specify)	6%
4	Management of hemodynamically stable PE, with thrombus in the main PA	Start systemic thrombolysis with TPA/Urokinase	14%
		Pharmaco-mechanical thrombolysis using EKOS/Angiojet with thrombolysis	8%
		Catheter directed thrombolysis	10%
		Heparin infusion/Low molecular weight heparin/fondaparinux	66%
		Direct oral anticoagulants (DOACs)	0%
		Other (please specify)	3%
5	Duration of anticoagulation in a 14-year-old boy with segmental and sub segmental PE where the risk factor has resolved and the clot has resolved thrombus.	Stop anticoagulation	6%
		Check a D-dimer level and if elevated, continue anticoagulant therapy	5%
		Continue anticoagulant therapy to complete 3 months of treatment	68%
		Continue anticoagulant therapy to complete 6 months of treatment	18%
		Continue anticoagulant therapy to complete one year of treatment	0.8%
		Other	2%
6	Duration of anticoagulation in a 14-year-old boy with central PE where the risk factor has resolved and the clot has resolved thrombus	Stop anticoagulation	5%
		Check a D-dimer level and if elevated, continue anticoagulant therapy	4%
		Continue anticoagulation to complete 3 months of therapy	55%
		Continue anticoagulation to complete 6 months of therapy	30%
		Continue anticoagulation to complete 1 year of therapy	2%
		Other	3%
7	Evaluation of dyspnea in a patient after PPE	Counsel regarding expected deconditioning following pulmonary embolism	41%
		Re-image for possible new pulmonary embolism	46.4%
		D-dimer, leg Doppler ultrasound if lung imaging negative	22%
		6 minute walk test	26%
		Cardiopulmonary exercise testing to determine peak oxygen uptake	47%
		Echocardiogram	83%
		Other (please specify)	17%
8	Duration of follow up of PE for CTEPH	6 months	2%
		1 year	18%
		2 years	29%
		5 years	10%
		Until adulthood	16%
		Refer back to primary practitioner for long-term follow-up	22%
		Other (please specify)	4%

multidisciplinary PERTs lead to rapid diagnosis of and improved outcomes after PE [17,18]. Whether the development of such teams for pediatric patients will result in similar outcomes is yet to seen.

Patients with PE exhibit a wide variation in clinical presentation and outcomes. The short-term mortality differs widely, ranging from < 2% in patients with clinically stable PE, approximately 30% in patients who present with shock, to > 65–95% in patients who experience cardiorespiratory arrest [19]. Therefore, prognostic risk

stratification drives early therapeutic interventions, differentiating patients who may benefit from aggressive ECRT (e.g. thrombolysis or thrombectomy) from those in whom conventional AC therapy appears most appropriate. In adults, a variety of risk prediction tools such as the PESI, simplified PESI (sPESI) and others have been developed and validated using a combination of clinical symptoms, presence of underlying risk factors and vital signs [20–24]. This survey indicated that the majority of pediatric thrombosis/hemostasis physicians do not systematically use a prognostic risk prediction model for risk stratification of TE-PPE but instead use a variety of parameters (such as ECHO, ECG, BNP, troponin) in assessing risk (Fig. 1). This likely reflects the fact that such prognostic risk prediction tools have not been consistently evaluated in predicting outcomes in TE-PPE. A recent (published after the completion of the survey) retrospective review of PPE patients has demonstrated that that while the sensitivity of sPESI was 100% and specificity was 30% in predicting 30-day mortality, area under the ROC curve was 0.76 (95% CI 0·64–0·87) [25]. Thus, there is a further need to develop and evaluate risk prediction models in TE-PPE.

The results also revealed the variability of practice patterns for using ECRT in TE-PPE. Although ECRT has shown to improve 30-day outcomes after PE, thrombolytic therapy clearly increases the risk of bleeding [4,26]. In adult PE patients, currently, thrombolytic therapy is reserved for those who present with hemodynamic collapse (shock) [27]. In the Pulmonary Embolism Thrombolysis (PEITHO) trial conducted in adult PE patients, the clinical efficacy and safety of thrombolytic therapy in intermediate-risk PE (patients who have evidence of cardiac dysfunction but do not present with shock) was evaluated and demonstrated a significant reduction in death and hemodynamic collapse in patients receiving thrombolytic therapy [28]. However, this was at the cost of a higher risk for hemorrhagic stroke and extra-cranial bleeding. Whether children and adolescents will have a similar bleeding risk is unknown. As shown by the survey results, significant differences also exist in the choice of ECRT likely dictated by the availability of local resources and lack of evidence of superiority of any specific therapy in TE-PPE. Although tPA was the agent of choice for thrombolysis, there was significant variability in the dose, route, concomitant supportive care (admission to ICU, supplementation of FFP etc.), monitoring and duration of thrombolysis. Given that thrombolytic therapy has a heightened risk of bleeding, these data demonstrate a clear need to standardize and evaluate thrombolytic regimens in terms of duration and dose of thrombolytic agents and also for monitoring of efficacy and safety of these risky therapeutic modalities in children.

This survey also revealed an interesting pattern in long-term management of TE-PPE. As anticipated, there was an age-dependent variation in the choice of anticoagulants with LMWH being the drugs of choice in younger children. Despite limited information on the efficacy and use of DOACs in children, it is interesting to note that approximately one third of physicians preferred to prescribe a DOAC in adolescent TE-PE patients. Safety and efficacy findings from randomized trials of DOACS for pediatric VTE treatment are eagerly awaited.

The duration of therapy for TE-PPE is highly variable. The majority of respondents prescribed AC therapy for > 3 months with no significant differentiation between central and segmental TE-PPE. Also, interestingly, 58% of survey respondents stated that they would increase the AC therapy duration if there was residual thrombosis at the end of three months of therapy reflecting their belief that it is a risk factor for recurrent VTE after PPE. Currently, guidelines for duration of AC in children do not differentiate between PE and non-PE VTE and recommend anticoagulation therapy for ≤ 3 months if the provoking factor has resolved [29,30]; however, expert opinions still vary [31]. Thus, there is ongoing ambiguity in defining the optimal duration of AC for TE-PPE and indeed, in the only ongoing RCT that aims to define duration of AC for pediatric VTE (Kids-DOTT), children with PE were not included until a recent amendment to include patients with non-proximal PE [32].

Our results also revealed that there is considerable variation in the concurrent evaluation for other sites of VTE and long-term follow-up for outcomes after TE-PPE. Similarly, there is a lack of consistent follow-up in terms of duration and the types of tests used to screen for post-TE-PPE consequences. Although there are some recommendations on the necessary follow up after PE [33], prospective studies are limited in children [34]. The authors are aware of one ongoing prospective study evaluating post-PE impairment (www.clinicaltrials.gov NCT03068923).

4.1. Limitations

Our study had a few limitations. As previously stated, the survey was sent to the membership rosters of two scientific societies, and likely reflects opinions of predominantly pediatric hematologists working in academic tertiary care centers. Thus, it is possible that these opinions are reflective of a minority of physicians as we had a 30% response rate. The management of TE-PPE may be different by physicians that are not members of either ISTH Pediatric/Neonatal Subcommittee or HTRS. The majority of the respondents were from the US with low participation by physicians from other countries and hence may not truly reflect practice patterns in non-US countries. Nonetheless, these limitations not withstanding, we believe this is the first survey that specifically has focused on evaluating practice patterns of hematologists on the management of TE-PPE. Our study is notable for demonstrating that TE-PPE is a rare disease at individual centers and there is considerable variability in management. These findings, while providing information about current practice patterns, will help to identify critical gaps in the management of TE-PPE and provide data for planning of future clinical trials in this field.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.08.002.

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