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Recommendations for future research in relation to pediatric pulmonary embolism: communication from the SSC of the ISTH

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Running Title: Pediatric pulmonary embolism

Background and Rationale

Although still considered a "rare" disease in the context of a population-based incidence of approximately 0.5 per 10,000 children per year [1], pulmonary embolism (PE) is nevertheless an important and increasingly recognized condition in pediatrics, with substantive risks of mortality and morbidity [2,3]. Unfortunately, these risks and numerous other critical factors regarding pediatric PE have historically been poorly characterized. In order to advance knowledge on pediatric PE, the Pediatric and Neonatal Thrombosis and Hemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) established a pediatric PE Working Group in 2012, whose specific tasks were to: systematically review the existing literature on pediatric PE; identify instances of heterogeneity in definitions employed across studies; assess gaps in knowledge; and make recommendations for standardization of definitions and key objectives for future research.

The Working Group and collaborators have recently published a systematic review of pediatric PE including studies from 1946-2013 [1], whose key findings are summarized below:

1. Two distinct patterns of pediatric PE were recognized:- thromboembolic PE and in-situ pulmonary artery thrombosis (ISPAT), the definition of which is '*in-situ thrombosis of the pulmonary artery due*

to local causes such as congenital heart disease, anomalies of the pulmonary artery and lung transplantation'. Most of the studies on risk factors, treatments, and outcomes included predominantly thromboembolic PE (where specified);

2. Frequently-reported risk factors among published studies were immobilization (present in 38% of cases), infection (31%), the presence of a central venous line (CVL) (23%), surgery/trauma (22%), malignancy (15%), hormonal contraception/pregnancy (15%) and obesity (13%) [2-7];

3. Thrombophilia testing in children with PE was variably reported between studies and, as such, it was difficult to quantify increased susceptibility to PE or its adverse outcomes in relation to laboratory markers;

4. Diagnosis of thromboembolic PE was frequently delayed (likely due to a low index of suspicion in pediatrics), with a mean lag time from symptoms onset to definitive diagnosis of approximately 7 days (range 1-11 days) [2,5-9];

5. Given the frequency of diagnosis at autopsy, the reported incidence of pediatric PE is likely underestimated [8];

6. Two pediatric-specific PE clinical prediction models have been developed from retrospective cohort studies [10,11], but neither has been validated as yet in an independent cohort nor prospectively;

7. PE was diagnosed via computed tomographic pulmonary angiography (CTPA) in three-fourths of pediatric cases among reported series [1], but direct comparisons of diagnostic performance among various imaging modalities have not been published;

8. Anticoagulant therapy duration generally ranged from 3-6 months [3];

9. The use of thrombolytic and thrombectomy approaches (including surgical thrombectomy) was highly prevalent among published studies, reported in 29%, possibly reflecting some reporting bias [12];

10. Data on long-term outcomes (in particular, functional measures and quality of life (QoL)) and predictors of outcome were sparse and few prospective longitudinal studies exist by which to generate hypotheses on

optimal management (to be subsequently tested in interventional trials) [3,6].

Methods

The recommendations that are given here are based on presentations at the Pediatric and Neonatal Thrombosis and Hemostasis Subcommittee meetings during the 2014, 2015 and the 2016 meetings of the ISTH. In addition, the Working Group further evaluated the available literature and agreed on consensus recommendations during face-to-face meetings and teleconferences. The pediatric PE Working Group was comprised of M.Rajpurkar and N.A.Goldenberg (Co-Leaders), T.T.Biss, A.K.C.Chan, C.H.van Ommen and S.Williams.

Major recommendations

- **Education and awareness campaigns should focus on facilitating the prompt investigation and diagnosis of PE in children.** This will require education to promote the importance of recognizing respiratory symptoms and signs, in combination with risk factor(s) for venous thromboembolism (VTE), as potentially indicating PE. Avoiding delay in diagnosis will likely accelerate initiation of treatment, potentially improving outcome. However, physicians must remain mindful that judicious use of CTPA is important due to the potential for unnecessary radiation exposure during investigation for a low incidence condition.
- **Institutions should develop protocols and strive to adopt a standardized approach to the management of PE in children. When they occur, variations from this approach should be explicit and well documented.** This will increase the value of the data collected from prospective and retrospective studies.
- **Future cohort studies should be designed with the aim of determining the factors that predict short- and long-term outcomes.** These are likely to be prospective studies with sub-categorization such as age, the presence or absence of provoking factors for thrombosis and anatomic distribution of

thrombus [Table 1]. Measures of clinical severity at presentation, e.g. respiratory and hemodynamic status, Echocardiogram or electrocardiogram evidence of right heart strain, elevation of cardiac enzymes, [Table 1] may allow risk stratification which in turn may predict the need for a more aggressive initial therapy, e.g. thrombolytic therapy, in the case of high risk presentation, or the potential for outpatient management of low risk presentation.

- **The optimal intensity, duration and modality of antithrombotic therapy, including mechanical and pharmacologic thrombolysis and surgical thrombectomy, for PE in children should be determined.** Rather than extrapolation from adult practice, this will require the conduct of well-designed, clinical trials that are adequately powered to determine differences in efficacy, safety and QoL. Measured outcomes should be both clinical and radiological, bearing in mind that the optimal duration of therapy may be other than 3 months [13]. Key areas of research will include the role of thrombolysis, thrombectomy and the duration of therapy required.
- **The optimal management of incidental/subclinical PE should be evaluated.** This will require the collection of outcome data, with a comparison between treated and untreated cases.
- **Further data are required to determine the long-term outcomes of pediatric PE.** These include recurrence, exercise capacity and chronic thromboembolic pulmonary hypertension (CTEPH; which should be clearly defined) and also PE-specific QoL and the psychosocial impact of a diagnosis of PE during childhood. Mortality should be reported as both PE-related and all cause mortality [Table 2].

Other recommendations

- **Clinical prediction models and D dimer measurement should undergo further evaluation as means of identifying children with suspected PE who have a low pre-test probability and therefore do not require imaging.** These should be specific to pediatrics and should be prospectively studied using both clinical and cost-economic analyses. This may require subgroup analysis, e.g.

inpatient vs. outpatient presentation, as the predictive value may vary between subgroups.

- **The most appropriate imaging modality should be determined in terms of sensitivity, specificity and acceptability within a pediatric population.** This should include the evaluation of CTPA, pulmonary angiography, perfusion scans and Magnetic Resonance Imaging (MRI)-based methods, taking into consideration radiation dose and the ability to detect sub-segmental PE.
- **The role of thrombophilia as a risk factor for initial presentation with PE and recurrent thrombosis should be investigated.** This is most likely to be achieved by multi-center prospective data collection using a standard set of investigations for inherited and acquired thrombophilia [2,6].

The authors suggest that an important first step is to collect high quality, standardized, prospective data on presenting features and outcomes of pediatric PE from multi-center, international studies.

Discussion

There is a significant burden associated with pediatric PE in terms of mortality in addition to morbidity that can be both physical and psychosocial. Given the increasing prevalence of pediatric venous thromboembolism it is likely that the incidence of pediatric PE will also continue to rise [14].

The recent systematic review and meta-analysis of the literature, coupled with these recommendations, have identified a need for large-scale, prospective, multicenter studies to evaluate aspects of pediatric PE [1]. Particular emphasis should be placed on the design and execution of high quality cohort studies as the challenges of conducting randomized clinical trials in rare pediatric disorders are well known. Several key points and recommendations from this work warrant emphasis and discussion. Standardization of definitions in relation to ISPAT, the severity of presentation, thrombophilia and outcomes is required. The development of clinical scores and the identification of biomarkers that

predict outcome are needed in order to derive and validate prognostic models which will inform risk stratification in future interventional trials.

Existing clinical prediction rules that were developed in adults lack sensitivity and specificity in a pediatric population [10,15,16]. The negative predictive value of D dimer estimation requires further evaluation in children presenting with suspected PE [2,10,11]. A pediatric-specific clinical prediction model developed by Hennelly et al requires the presence of 1 or more of hypoxia, tachycardia and oral contraceptive pill use to trigger a high-risk score [10]. A further model developed by Lee et al requires 2 or more of the following risk factors: immobilization; hypercoagulable state; excess estrogen state; indwelling CVL; prior PE and/or deep vein thrombosis [11]. These models have the potential to identify a low-likelihood cohort of children with respect to PE, who may not require diagnostic imaging for PE, thereby avoiding unnecessary exposure to radiation. However, both were derived from single center studies within tertiary care hospitals and included a small number of confirmed cases of PE [10,11]. They would therefore require evaluation in an independent cohort in addition to the standardization of definitions such as 'immobilization'.

Mortality rates are significant but many deaths are due to underlying disease states and thrombosis-related mortality occurs less often [1]. In addition, the preponderance of retrospective studies carries a real potential for reporting biases that overestimate mortality. Long-term outcomes (as shown in Table 2) are therefore important to assess in prospective cooperative studies. Although the psychosocial impact of PE occurring in childhood has been little studied, previous evaluation of QoL tools for children and adolescents receiving anticoagulant therapy suggest that there may be psychological, behavioral and social problems associated with this potentially life-threatening diagnosis, the burden of anticoagulant monitoring, the need for lifestyle modification and the physical symptoms of PE [17,18].

The recommendations presented here serve as a call-to-action for renewed focus and support toward enhancing the quality and quantity of research in pediatric

PE, in order to advance knowledge in the field and ultimately improve outcomes for these children. Further recommendations are likely to emerge from this future work.

Addendum

N. A. Goldenberg and M. Rajpurkar initiated the project and supervised all aspects of the manuscript writing. T. Biss was responsible for drafting the first version of the manuscript. All authors reviewed and revised the manuscript and were in agreement with the final version.

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Disclosure of Conflicts of Interests

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Table 1. Potential prognostic factors to be addressed in future studies of pediatric pulmonary embolism

Table 2. Important outcome measures for future observational and interventional studies of pediatric pulmonary embolism

Table 1. Potential prognostic factors to be addressed in future studies of pediatric pulmonary embolism

Demographic features	• Age • Gender
Provoking factors	• CVL related vs. non-CVL related • Short-term risk factor vs. persistent risk factor • Presence of malignancy • Hormone related vs. non-hormone related
Anatomic distribution of thrombus	• Segmental vs. sub-segmental
Details of diagnosis	• Time from onset of symptoms to diagnosis/treatment
Presenting features	• Symptomatic* vs. asymptomatic/subclinical • Hemodynamic compromise • EKG abnormalities indicating right heart strain † • ECHO abnormalities indicating right heart strain‡ • Elevation of cardiac enzymes • Elevated D-dimer, inflammatory markers, other indices of

	coagulation/fibrinolysis
Antithrombotic therapy	• Nature of antithrombotic therapy, including thrombolysis (systemic/catheter-directed) and mechanical thrombectomy • Intensity of anticoagulant therapy • Duration of anticoagulant therapy
Response to antithrombotic therapy	• Degree of thrombus resolution

CVL, central venous line; EKG, electrocardiogram; ECHO, echocardiogram; PE, pulmonary embolism

*Dyspnea, hypoxema, pleuritic chest pain, unexplained tachycardia [2]. † ST/T segment changes, S1Q3T3, voltage criteria for right ventricular hypertrophy. ‡Tricuspid regurgitation, septal flattening, right ventricular dilation [3]

Table 2. Important outcome measures for future observational and interventional studies of pediatric pulmonary embolism

Mortality	• All cause mortality • Thrombosis-related mortality • Bleed-related mortality

Morbidity	• Thrombus recurrence • Physical morbidity: - Exercise capacity - Pulmonary function - Presence of CTEPH* - Hemorrhagic events • Psychosocial and behavioral morbidity: - Quality of life

* Chronic thromboembolic pulmonary hypertension