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RECOMMENDATIONS AND GUIDELINES

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

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Background and rationale

Although pulmonary embolism (PE) is still considered to be a 'rare' disease in the context of a population-based incidence of ≈ 0.5 per 10 000 children per year [1], it is nevertheless an important and increasingly recognized condition in pediatrics, with substantial 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 our knowledge about pediatric PE, the Pediatric and Neonatal Thrombosis and Hemostasis Subcommittee of the ISTH established, in 2012, a pediatric PE Working Group, whose specific tasks were to: systematically review the existing literature on pediatric PE; identify instances of heterogeneity in the definitions employed across studies; assess gaps in knowledge; and make recommendations for standardization of definitions and key objectives for future research.

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The Working Group and collaborators have recently published a systematic review of pediatric PE, including studies from 1946 to 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, so it was difficult to quantify increased susceptibility to PE or its adverse outcomes in relation to laboratory markers.
4 The diagnosis of thromboembolic PE was frequently delayed (probably because of a low index of suspicion in pediatrics), with a mean lag time from symptom onset to definitive diagnosis of ≈ 7 days (range 1–11 days) [2,5–9].
5 Given the frequency of diagnosis at autopsy, the reported incidence of pediatric PE is probably underestimated [8].

6 Two pediatric-specific PE clinical prediction models have been developed from retrospective cohort studies [10,11], but neither has yet been validated in an independent cohort or prospectively.
7 PE was diagnosed via computed tomographic pulmonary angiography (CTPA) in three-quarters 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 months to 6 months [3].
9 The use of thrombolytic and thrombectomy approaches (including surgical thrombectomy) was highly prevalent among published studies, being 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 from 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 Working Group was composed 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 probably accelerate the initiation of treatment, potentially improving outcomes. However, physicians must remain mindful that judicious use of CTPA is important, owing 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-term and long-term outcomes*. These are likely to be prospective studies with subcategorizations such as age, the presence or absence of provoking factors for thrombosis, and the 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, and elevation of cardiac enzymes (Table 1), may allow risk stratification, which, in turn, may predict the need for more aggressive initial therapy, e.g. thrombolytic therapy, in the case of high-risk presentations, or the potential for outpatient management of low-risk presentations.
- *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 radiologic, bearing in mind that the optimal duration of therapy may be other than 3 months

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

Demographic features
Age
Gender
Provoking factors
CVL-related versus non-CVL-related
Short-term risk factor versus persistent risk factor
Presence of malignancy
Hormone-related versus non-hormone-related
Anatomic distribution of thrombus
Segmental versus subsegmental
Details of diagnosis
Time from onset of symptoms to diagnosis/treatment
Presenting features
Symptomatic* versus asymptomatic/subclinical
Hemodynamic compromise
ECG 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; ECG, electrocardiogram; ECHO, echocardiogram. *Dyspnea, hypoxemia, pleuritic chest pain, and unexplained tachycardia [2]. †ST/T segment changes, S1Q3T3, and voltage criteria for right ventricular hypertrophy. ‡Tricuspid regurgitation, septal flattening, and 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

CTEPH, chronic thromboembolic pulmonary hypertension.

[13]. Key areas of research will include the role of thrombolysis and 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 (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 pretest probability and therefore do not require imaging*. These should be specific to pediatrics, and should be prospectively studied with both clinical and cost-economic analyses. This may require subgroup analysis, e.g. inpatient versus 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-based methods, taking into consideration radiation dose and the ability to detect subsegmental 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 multicenter prospective data collection by use of 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 the presenting features and outcomes of pediatric PE from multicenter, international studies.

Discussion

There is a significant burden associated with pediatric PE in terms of mortality and of morbidity, which can be both physical and psychosocial. Given the increasing prevalence of pediatric VTE, 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 on 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 that 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 one 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 two or more of the following risk factors: immobilization; hypercoagulable state; excess estrogen state; indwelling CVL; and 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 attributable 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 resulting in overestimation of mortality. It is therefore important to assess long-term outcomes (as shown in Table 2) 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 regarding enhancement of the quality and quantity of research in pediatric PE, in order to advance our 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 Conflict of Interests

M. Rajpurkar reports receiving grants and personal fees from Pfizer and Bristol Myers Squibb, and personal fees from Shire and Novo Nordisk, outside the submitted work. The other authors state that they have no conflict of interest.

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