JACC: ADVANCES VOL. 3, NO. 4, 2024

EDITORIAL COMMENT

Childhood Pulmonary Embolism

Characterizing a Critical and Challenging Diagnosis*

Mary P. Mullen, MD, PhD[a,b]

Pulmonary embolism (PE) is a rare and likely under-recognized diagnosis in hospitalized children. There is an increasing incidence of PE in the pediatric population owing to evolving pediatric disease complexity, a growing number of patients with chronic conditions, and an expanded use of central lines for parenteral nutrition, hemodynamic management, hemodialysis, cancer treatment, and other infusion therapies.[1] Although causing significant mortality and long-term morbidity in the form of chronic thromboembolic disease, pediatric PE differs substantially from adult pulmonary thromboembolism in etiology, presentation, and associated medical conditions. This recognition has led to the development of recent guidelines for the diagnosis and management of PE that are targeted at the pediatric age range.[2,3] Yet, there remains much to be learned about the clinical characteristics and appropriate management of PE in children.

In this issue of *JACC: Advances*, Rastogi et al[4] report a retrospective multicenter observational study of children with PE treated at a US-based primary pediatric hospital over a 6-year span (2015-2021). They draw data from the Pediatric Health Information Systems Database (PHIS), which contains information from 49 American not-for-profit tertiary care pediatric hospitals affiliated with the Children's Hospital Association. This breadth and scale give them powerful numbers and experiences, but they may not be typical of pediatric patients admitted to nonspecialty hospitals or community centers. They charted PE when identified by the International Classification of Disease-Version 10 code at any point during hospitalization. The investigators describe the general characteristics of the cohort, treatment strategies, trends in treatment over time, and associations of treatment with outcome.

Their results showed that, of the 3,237,752 admissions to PHIS hospitals during the study period, 0.1% had a diagnosis of PE. After excluding repeat admissions and missing data, the study cohort included 3,136 patients (69% age ≥12 years, 46% male, 59% white), of whom 62% were diagnosed with at least 1 comorbid condition (20% congenital heart disease, 14% oncologic diagnoses, and 10% thrombophilia). Therapeutic choices were informative: 88% of patients were treated solely with anticoagulation, 7% with systemic thrombolysis, and 5% with directed therapy (site-directed thrombolysis or transcatheter/operative thrombectomy). There was significant variation in the use of systemic thrombolysis and directed therapies among individual hospitals. Rates of treatment choice were constant but anticoagulant choice differed with less warfarin and increased direct oral anticoagulant or direct thrombin inhibitor over the study time, reflecting emerging data for use of these newer approaches in the pediatric population. Patients treated with directed therapy were younger and more likely to have congenital heart disease than patients treated with anticoagulation alone. In-hospital mortality for the group overall was 7.5%, median length of stay was 10 days, and the median cost for hospitalization was $54,143. Directed therapy was associated with lower mortality than treatment with anticoagulation alone, while systemic thrombolysis had no difference in mortality compared to anticoagulation alone. Mortality was greater among patients with more profound illnesses, including those with at least 1 comorbidity,

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

From the [a]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, USA; and the [b]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.100896

congenital heart disease, oncologic disease, prematurity, intensive care unit admission, or extracorporeal membrane oxygenation course.

This large, multicenter experience describes and benchmarks the current state of the art for managing PE in children. Though rare, PE still carries substantial mortality, particularly among patients with cardiovascular or oncological diagnoses or major concurrent illnesses. As has been seen in the adult population, there is growing use of nonwarfarin oral treatments, reflecting recent pediatric trials of these agents and United States Food and Drug Administration approval for use in children. In contrast to growing practice in adult populations, there was more limited use of directed therapy to resolve the thrombosis, though the lower risk of mortality for the use of directed therapy may speak to judicious use of this intervention. Specific reports looking at the indications and outcomes for catheter-based intervention will be important. Interestingly, systemic thrombolysis was not associated with better outcomes than systemic anticoagulation alone. Again, it will be valuable to explore why patients in the aggregate did not seem to benefit from thrombolysis.

As with any diagnosis-based large data analysis, there are gaps in understanding the full medical details of individual patients. Limitations of the PHIS dataset include the inability to determine 2 well-known risk stratification factors: right heart strain or the presence of hemodynamic decompensation. These measures of cardiac dysfunction following PE are important in current pediatric PE management algorithms.[3] Similarly, it will be important to learn more about comorbid risk factors such as obesity, travel history, tobacco exposure, or oral contraceptive use. The presence of central venous catheter as a risk factor for PE, as opposed to a therapeutic intervention for PE, could not be ascertained, and therefore this well-known risk factor for PE could not be used as a prognostic variable in the study. Finally, PE can be part of yet-less-common, complex health concerns such as chronic thromboembolic pulmonary hypertension; however, this may be difficult to diagnose. In an academic, multicenter pediatric pulmonary hypertension registry, World Symposium on Pulmonary Hypertension Group 4 PH (chronic thromboembolic pulmonary hypertension) was identified in only 8 of 1,475 cases of PH.[5] Follow-up beyond inpatient diagnosis will be critical for understanding the true impact of PE on longer-term health for these children.

Timing of the study overlaps with COVID pandemic in 2020 and 2021. Early experience with COVID suggested an increased risk of PE and other thrombotic events in children. It will be critical to continue to monitor these data to see if COVID-era PE carries different risk factors and outcomes than historically have been seen.[6]

Even in large pediatric tertiary hospitals, it can be challenging to adequately characterize rare events and complications. The investigators have demonstrated the power of a vast pooled clinical database to identify the 0.1% of children diagnosed with PE. They have established a benchmark for outcomes in this disorder and identified important areas for ongoing quality of care analysis and newly needed interventions.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Mary P. Mullen, Department of Cardiology, Boston Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115, USA. E-mail: mary.mullen@cardio.chboston.org.

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KEY WORDS pediatrics, pulmonary embolism, thrombosis