almost 10% with exposure to CRRT. Using a power calculation based on this mortality difference, if $\alpha = 0.05$ and power = 0.8, the sample size needed to demonstrate this difference is 432 per treatment group, which is about 10-fold larger than available for analysis. The 43 subjects per group was sufficiently large to find a significant difference if mortality in the CRRT group increased to 66% compared to 35% for alpha = 0.05 and power = 0.8. (15). Like many pediatric ECMO studies, the current study is hampered by insufficient power to draw firm conclusions.

The report by Lou et al (4) is provocative and attempts to address a common problem among a high-risk, high-cost patient population in an era of limited resources. Ultimately, the question as to how, when, and who (if anyone) will benefit from CRRT during ECMO appears to require the adoption of similar consensus definitions, standards, technologies, and system-based practices that effectively changed the course of ARDS (3) and sepsis (2) nearly 20 years ago.

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Complications During Extracorporeal Membrane Oxygenation: Why Collaboration Is Key*

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Anticoagulation during extracorporeal membrane oxygenation (ECMO) and complications of hemorrhage and thrombosis are difficult issues, daunting to the most seasoned ECMO clinicians, and difficult to study due to heterogeneity of ECMO indications, patient ages, preexisting comorbidities, etc. As shown in a recent survey of members of the Extracorporeal Life Support Organization (ELSO), there is wide variability in the way anticoagulation is monitored and achieved during ECMO (1). First, among ECMO centers, monitoring ranges from minimalist to very involved approaches: activated clotting time (ACT)-only to multiple-test monitoring, including antithrombin levels, anti-factor Xa activity, or thromboelastography. Second, a number of products are being used that have not been rigorously studied in ECMO, including antifibrinolytics, direct thrombin inhibitors, serine protease inhibitors, antiplatelet agents, etc (1). Third, there are no accepted or validated definitions for hemorrhage, thrombosis, or disseminated intravascular coagulation (DIC) during ECMO. These terms are being used widely in the literature but will oftentimes be defined differently, making it impossible to compare results among studies. For example, DIC during

*See also p. 167.

Key Words: anticoagulation; extracorporeal; extracorporeal membrane oxygenation; hemorrhage; thrombosis

Dr. Bembea received support for article research and manuscript preparation from the National Institutes of Health (NIH) (NIH/National Institute of Neurological Disorders and Stroke [NINDS] K23NS076674). She and her institution received grant support from the NIH/NINDS.

DOI: 10.1097/PCC.0000000000000328

extracorporeal support cannot be defined using validated scores such as the DIC score of the International Society on Thrombosis and Haemostasis (2). In the absence of ECMO-specific, validated scores, DIC is therefore defined variably or reported without a clear definition, for example, a composite of thrombocytopenia unresponsive to transfusion, prolonged ACT despite lower heparin infusion rates, prothrombin time higher than three times normal, and evidence of clinical bleeding from surgical and/or other sites, versus D-dimer more than 10,000 U/L and fibrinogen less than 150 mg/dL, versus no definition provided (3–6). Similarly variable definitions are used for hemorrhagic complications (6–9).

In this issue of *Pediatric Critical Care Medicine*, Dalton et al (10) present a retrospective analysis of all neonatal and pediatric ECMO-related hemorrhagic and thrombotic complications in eight centers that were part of the second funding cycle of The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN), using data extracted from the ELSO Registry at each of the centers (10). Patients were separated by presence or absence of a diagnosis of congenital diaphragmatic hernia (CDH), given the known higher rate of overall complications in neonates with CDH on ECMO (7). In this highly selected group of children's hospitals with large ICUs and ECMO programs, the authors found that hemorrhagic and thrombotic complications were frequent in both the CDH and non-CDH populations: 45% and 60%, respectively, in 263 patients with CDH and 38% and 31%, respectively, in 1,773 patients without CDH. After adjusting for potential confounders, such as indication for ECMO, ECMO mode, or ECMO duration, hemorrhage and thrombosis were associated with decreased survival (10).

The authors used the results of this study as baseline preparatory data for a now ongoing prospective observational study of hemorrhagic and thrombotic complications in newborns and children on ECMO, conducted at CPCCRN centers. Studies of such complications have been mostly limited to single-center reports spanning several years and inevitably influenced by local practices, patient selection, and historical bias. This ongoing CPCCRN study will be the first to systematically address hemorrhagic and thrombotic complications during ECMO in multiple centers, using strict data definitions, with detailed dynamic data on the timing of abnormal laboratory results, interventions related to anticoagulation and blood product administration, and onset of complications, and adequate sample size and power. There are several similar projects ongoing in North America, such as the Registry of ECMO Anticoagulation in Pediatrics initiated by the Pediatric Critical Care Blood Research Network, a subgroup of Pediatric Acute Lung Injury and Sepsis Investigators, and a Canadian U.S. collaborative funded by the ELSO, between the Stollery Children's Hospital, University of Alberta, Edmonton, Canada, and the C.S. Mott Children's Hospital at the University of Michigan, Ann Arbor, MI. The most important task of investigators pursuing this line of research will be to establish strong collaborations to ensure adequate sample size, diversity of centers that allows generalizability, and standardized data collection forms and definitions. Also, basic science and industry partnerships will be needed to further elucidate the complicated and poorly-understood pathophysiology of coagulation during ECMO. Translational studies will be needed to better inform the use of pharmacologic and blood product therapies in ECMO patients, especially in view of the fast-paced development of new, more biocompatible, circuit-blood interfaces.

This study has the limitations of a retrospective review and lack of standardization of hemorrhagic and thrombotic outcomes definitions. Some of the findings in the study, for example, lower survival rate from 2010 to 2011 in pediatric ECMO patients, are difficult to interpret due to the inability to adjust for confounders such as severity of illness. There are no data on dosing of unfractionated heparin infusions, the use of direct thrombin inhibitors, the use of blood products, or the type(s) of tests used to monitor anticoagulation. Finally, there are no data that could help assess for selection bias such as preexisting comorbid conditions and no data on missingness (e.g., for rarely-measured laboratory values such as free plasma hemoglobin).

The findings of the Dalton et al (10) study point to the important and common problem of hemorrhagic and thrombotic complications in ECMO patients and provide a first step for more rigorously conducted prospective studies. Future studies will need to tackle the myriad issues surrounding coagulation disturbances and anticoagulation during ECMO, such as circuit-blood interactions (e.g., inflammatory response and activation of coagulation), adequacy of tests to assess the status of the coagulation system (e.g., global vs partial measures of coagulation and measures of drug activity such as anti-factor Xa), outcome measures (e.g., bleeding score and thromboembolic burden score), and pharmacokinetics and pharmacodynamics of anticoagulant medications, all of these taking into account the influence of age and developmental hemostasis, preexisting diagnoses, and presence of new or progressive multisystem organ failure (11).

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Opioid and Benzodiazepine Withdrawal Syndrome: Can We Predict and Prevent It?*

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Why some children may be more vulnerable to develop iatrogenic withdrawal syndrome (IWS) than others is not well known. In this issue of *Pediatric Critical Care Medicine*, Best et al (1) present a systematic review of the literature in which they collected possible risk factors associated with the development of IWS. They evaluated 34 articles and classified the identified risk factors into three categories: patient-level (e.g., age, severity of illness, duration of therapy, and cumulative dose), process-level (e.g., withdrawal assessment and sedation/weaning protocols), and system-level factors (such as PICU bed availability and protocol compliance). These categories were synthesized into a conceptual framework of IWS risk in critically ill children which might serve as a basis for further research.

Regarding patient-level variables, not surprisingly duration of opioid and/or benzodiazepine therapy and cumulative doses are associated with the occurrence of withdrawal symptoms (1). From the prospective studies, it was calculated that the onset of IWS was always after 5 days of opioids treatment and mostly after 10 days of benzodiazepine treatment (1). We have to realize, however, that in the evaluated studies, dosing of both morphine and benzodiazepines was not based on population pharmacokinetic-pharmacodynamic modeling and simulation (2). The cumulative doses might have resulted in overdosing therefore. Another proposed patient-level factor is criticality or severity of illness. The authors of the review suggest that severity of illness, and particularly brain injury or ischemia, contributes to a higher prevalence of IWS. However, the brain injury itself can induce symptoms such as irritability and restlessness that overlap with symptoms of IWS. So what is the chicken and what is the egg in these patients? On top of that, severity-of-illness scores such as Pediatric Index of Mortality and Pediatric Risk of Mortality score never been validated optimal for patients with severe brain injuries. The scores have been validated for the first 24 hours of admission only, not accounting for the reality that patients may deteriorate afterward.

The authors mention pharmacogenetics as a possible explanation for why patients vary in opioid requirements. With respect to pharmacogenetics and IWS, two promising polymorphisms are of interest: μ-opioid receptor, and catechol-o-methyltransferase (COMT). Wachman et al (3) found that of 86 infants with neonatal abstinence syndrome those with 118A>G AG/GG genotypes and those with COMT 158A>G AG/GG required less treatment and had shorter length of stay than those without one of these polymorphisms. To further study the relevance of these polymorphisms, we would need DNA samples from large studies of children with and without IWS who received opioids and benzodiazepines by protocol including validated and appropriated assessment tools.

With respect to process-level factors, the evidence of the effectiveness of sedation and weaning protocols was inconclusive. Protocolized weaning of sedatives and opioids in the PICU setting is not easy in view of the heterogeneity of the PICU patient population with respect to age, underlying diagnoses, and amount of illness. Protocol violations may be justified because individual patients' needs cannot always be covered by

*See also p. 175.

Key Words: opioid and benzodiazepine withdrawal; opioids; pediatric intensive care unit; sedation

The authors have disclosed that they do not have any potential conflicts of interest.

DOI: 10.1097/PCC.0000000000000327