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Outcomes in Young Patients After Respiratory Extracorporeal Membrane Oxygenation—Youth Is Not Always Protective*

KEYWORDS: acute respiratory distress syndrome; adult; extracorporeal life support; pediatric

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Extracorporeal membrane oxygenation (ECMO) has been used as rescue therapy in neonatal and pediatric patients with refractory respiratory failure for several decades. In contrast, it was used infrequently in adult patients until 2009, when publication of a landmark trial (1) coincided with the influenza A(H1N1) pandemic (2) and led to rapid escalation in the use of ECMO in adult patients with respiratory failure, overtaking the annual number of children supported by ECMO within 5 years (3).

***See also p. 11.**

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The distinction in medical care between late adolescence and adulthood varies between jurisdictions. For example, a 17-year-old with acute respiratory distress syndrome (ARDS) could reasonably be treated in a PICU or an adult ICU, depending on the circumstances of hospital admission, local infrastructure, previous medical care, and other factors. Whether outcomes differ between these two settings is unknown. In fact, differences in outcomes as patients transition from their teenaged years into early adulthood have been largely unexplored. While older age is a generally accepted risk factor for poorer outcomes after ECMO support, these subgroups—teenagers and young adults—might not be expected to reveal such a trend, given similarities in comorbidities and frailty. However, outcomes may diverge due to factors not based on biology alone because these subpopulations are often managed in different hospitals by different clinicians with overlapping but distinct protocols and practices.

In this issue of *Critical Care Medicine*, Brown et al (4) present a study attempting to establish whether outcomes differ between patients supported with ECMO for respiratory failure in their late teens and those in early adulthood. The impetus for this investigation was a nationwide study from Germany, which unexpectedly found that survival after respiratory ECMO was lower in patients 10–20 years old than those between 20 and 30 years old (5). Unadjusted comparisons in outcomes between individual centers or countries can be misleading or challenging (6), however, so Brown et al (4) chose to use the International Registry of the Extracorporeal Life Support Organization (ELSO) as their data source. All patients between 16 and 30 years old cannulated for respiratory failure from 1990 to 2020 were included. A total of 5751 patients were analyzed and divided into two groups, teenagers (16–19 yr old) and young adults (20–30 yr old). The primary outcome was survival to hospital discharge, which was higher in young adults than teenagers (69% vs. 63%; $p < 0.001$).

There were some clear differences between the groups, both in terms of pre-ECMO factors and management during ECMO. First, the teenagers had lower Pao_2/Fio_2 ratios (59 vs. 63; $p < 0.001$) and more frequent hypotension (48% vs. 42%; $p < 0.001$) immediately prior to cannulation, so it is possible that they had greater severity-of-illness and were at risk of worse outcomes from this alone. Conversely, it is also possible that these pathologic derangements were due to delays in cannulation while other, less invasive strategies were unsuccessfully attempted.

Second, the teenager group was treated more frequently with high-frequency oscillatory ventilation (HFOV) (13% vs. 4%; $p < 0.001$). HFOV has been largely abandoned in adult patients following the publication of two large, randomized trials demonstrating either no difference or worse outcomes in the HFOV group (7, 8). Whether HFOV is associated with worse outcomes in adolescence is unknown but an ongoing trial of prone positioning and HFOV in children may help clarify this (ClinicalTrials.gov identifier NCT03896763). Mechanical ventilation treatment recommendations also differ between adults (9) and children (10).

Third, the use of prone positioning was extremely sparse in both groups, but significantly lower in the teenager group (4% vs. 6%; $p < 0.001$). Although this may reflect the fact that the benefits of prone positioning in adult patients (11) were not evident throughout much of the time period analyzed by Brown et al (4), other recent studies of ARDS have also demonstrated that prone positioning may be underused in both adult and pediatric medicine (12, 13).

Fourth, venoarterial ECMO was more frequently used in the teenager group than the young adult group (15% vs. 7%; $p < 0.001$). While it is possible that concomitant circulatory failure or other issues related to severity-of-illness underlaid this observation, it may also have reflected the preferences of the cannulating doctor. Although most clinicians caring for adult patients would assume that venovenous ECMO should almost always be used for isolated respiratory failure, this is not necessarily the case in pediatrics, where venoarterial ECMO is still commonly used (14). The higher proportion of venoarterial ECMO use in the teenager group may have been due to a predilection for it among pediatric clinicians. However, venoarterial ECMO is consistently associated with higher mortality than venovenous ECMO (3, 15), and it is possible that this affected outcomes (4).

Last, it was noteworthy that the teenager group was at greater risk of hemorrhagic (23% vs. 17%; $p < 0.001$) and mechanical ECMO complications (18% vs. 15%; $p = 0.006$). Differences in management strategies during ECMO, such as anticoagulation protocols and

blood product transfusion thresholds, might have contributed to the risks of hemorrhage. Pediatric ECMO centers have to care for a very heterogeneous group of patients from newborns to adolescents, yet many will use the same anticoagulation protocol irrespective of age. Older patients generally need less anticoagulation because of greater net ECMO blood flow rates. The reported increase in mechanical complications also raises the question about center experience. ECMO in children tends to be concentrated in high volume, tertiary centers and such centralization of this highly specialized care is well-founded (16). Nonetheless, many adult centers now have far greater annual ECMO volumes than even the world's busiest pediatric programs, and there is some evidence supporting the existence of a volume-outcome relationship for ECMO (17). This may mitigate or help prevent ECMO-related complications.

A multivariable logistic regression analysis conducted by the authors controlled for many of these variables, yet the apparent differences between the two groups persisted. While these may have been due to unmeasured confounders, there were also some methodological limitations in the study which are worth highlighting. Many of these were acknowledged by the authors, including the lack of detail concerning important variables, such as plateau pressure, validated severity-of-illness scores, the effectiveness of treatment of the underlying disease, and medical comorbidities. The study included patients managed over 3 decades, during which time there were many changes in management strategies before and during ECMO which were difficult to control for. There were also changes in the indications for ECMO, with an increasing tendency to cannulate patients with conditions previously regarded as contraindications, such as septic shock and respiratory failure following hematopoietic cell transplantation (18–21). This may have paradoxically worsened outcomes in recent years. Additionally, the age classifications were treated dichotomously rather than as a continuous variable, which might not be the optimal approach (22).

There has been a tacit assumption thus far that all teenagers were managed in PICUs and the young adults were managed in adult ICUs. However, the ELSO registry does not provide this level of granularity, and it is unclear to what extent this is true. The study by Brown et al (4) should not be regarded as some crude comparison between managing young patients in PICU or adult ICU, although it is likely that practice differences between the two did influence the authors' results. Adult clinicians have become adept at respiratory ECMO over a short period of time by the sheer volume of cases, generally managing patients with respiratory failure (especially ARDS) in a relatively consistent manner (23). There is also considerably more data from randomized trials to help guide or standardize practice (1, 11, 24, 25). Pediatric clinicians must care for a much more heterogeneous group of patients, with different disease states and, to some degree, different physiology, yet without the same evidence framework. Indeed, the heterogeneity of these patients is one of the principal reasons that there is less evidence in children because it is much more difficult to conduct randomized trials. Consequently, pediatric clinicians have to adopt a more flexible management approach and adapt rapidly to different situations. The approaches of adult and pediatric clinicians both have strengths and weaknesses. The study by Brown et al (4) reminds us that communication between the two strengthens both and will hopefully spur more prospective research of the optimal management strategies in these vulnerable patients.

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