Chapter 15
ECMO Use in the Pediatric Immunocompromised Hematology/ Oncology Patient

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Introduction

Any discussion of the use of extracorporeal membrane oxygenation (ECMO) in the pediatric immunocompromised hematology/oncology population must begin with a description of what ECMO is, what the mechanics/circuitry consist of, indications for ECMO, and procedure-associated complications.

A Brief History of ECMO

ECMO was developed out of the operating room as an extension of the use of cardiopulmonary bypass (CPB) and was initially used for surgical patients who did not tolerate separation from CPB [1]. The first successful report of prolonged use of what would now be termed venoarterial (VA) ECMO was in a victim of a traumatic aortic rupture by Hill et al. in 1972 [2]. Dr. Robert H. Bartlett is credited with expanding the use of ECMO to neonates with medically refractory respiratory failure in the early 1980s [3]. Dr. Bartlett further spearheaded an international collaboration of ECMO providers with the initiation of an annual meeting in 1982 and the organization of the Extracorporeal Life Support Organization (ELSO) in 1989. In addition to supporting regular scientific meetings and publishing several editions of

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textbooks (aimed at guiding providers in the use of ECMO and the training of bedside personal), ESLO has also organized and supported a database of ECMO patients. This database contains data on 87,366 patients with a survival to hospital discharge rate of 55% as of July 2017 [4].

ECMO Physiology/Circuit Composition

The general principle of ECMO is the drainage of deoxygenated blood from the venous circulation through a pumping device which then pumps blood through an oxygenator and warmer before returning to either the arterial side as in VA ECMO or the venous side as in venovenous (VV) ECMO. Modern ECMO circuitry consists of cannulas, tubing, a pump, and an oxygenator.

Cannulas come in varying sizes and lengths depending on the vessel being cannulated and the type of ECMO support employed. Basic circuitry requires at least one lumen for the blood to flow out of the body into the ECMO circuit and one lumen for the blood to be delivered back to the body. VV ECMO can be accomplished with one double-lumen cannula in one vein, while VA ECMO requires separate cannulation of a vein to remove the blood from the body and an artery to deliver the blood from the circuit back to the body. The tubing diameter and total length of tubing are generally of low enough resistance that the flow-limiting factor through the circuit is the resistance within the smaller-diameter cannula(s). A larger-bore inflow cannula is necessary as the pressure is lower on the venous side of the circuit, while the arterial (the outflow side on a VV circuit) side can be smaller in diameter secondary to the higher pressures after the pump. Cannula selection is thus based on the size of the vessel being cannulated and calculated flow necessary to support the patient needs.

Roller head pumps and centrifugal pumps comprise the clear majority of current ECMO pumps. More traditional roller head technology consists of an area of tubing that is sequentially compressed by two rollers 180 degrees apart such that as one of the rollers loses contact with the tubing, the other comes into contact. The amount of blood propelled forward is proportional to the revolutions per minute (RPM) of the roller heads and the volume of blood pushed forward with each revolution. Roller head pumps typically operate between 60 and 120 RPM. Centrifugal pumps consist of a spinning rotor which converts rotational kinetic energy to the energy of blood flow. The blood enters the pump head near the center and is accelerated by the impeller flowing radially outward toward the exit. Centrifugal pumps rotate at thousands of RPMs, and the blood flow generated is dependent of the pump preload, RPM, and pump afterload.

Roller head pumps have the advantage of providing a guaranteed output for any given RPM provided a constant preload. Roller head pumps are not sensitive to afterload but are preload dependent and have the ability to create considerable negative pressure within the venous cannula if proper precautions are not undertaken. High negative pressure within the venous cannula has the potential of causing suction injury at the point of contact with the vessel or right atrium or causing cavitation resulting in

bubble formation. In addition, the area of tubing compressed by the roller heads (the raceway) undergoes repeated stress and is at risk for rupture with prolonged ECMO support. Centrifugal pumps have the advantage of being more compact and are both preload and afterload sensitive, with varying outputs depending on the venous pressure supplying the pump and the pressure within the arterial cannula at the entrance into the bloodstream. As centrifugal pumps generally run in thousands of RPMs, there is a risk of heat generation near the rotor which resulted in hemolysis in older-generation pumps. Current-generation centrifugal pumps are magnetically levitated to prevent friction and limit the generation of heat, thus decreasing the damage to the blood cells traveling through the pump. Many programs have transitioned from the use of roller pumps to centrifugal pumps despite evidence of increased rates of complications including hemolysis and kidney injury [5, 6].

Modern oxygenator technology has evolved to be more compact, require a lower priming volume, and generate less resistance [7] while maintaining excellent gas exchange of carbon dioxide and oxygen. Carbon dioxide removal is accomplished by flowing a gas mixture (termed the "sweep gas," generally without carbon dioxide) countercurrent to the blood flow in the membrane. The gradient for removal is highest at the beginning and drops as carbon dioxide diffuses from the blood into the sweep gas, thus making the removal of carbon dioxide most dependent on the flow rate of the sweep gas. Oxygen diffusion is generally more efficient, and the concentration of oxygen in the blood and sweep gas equilibrates rapidly. This makes the effluent partial pressure of oxygen in the ECMO circuit more dependent on the partial pressure of oxygen contained within the sweep gas than the rate of the sweep gas flow.

VV Versus VA ECMO

The fundamental difference between VA and VV ECMO is the reliance on the function of the patient's heart for the entire cardiac output in VV ECMO as opposed to the hemodynamic energy delivered to the circulatory system by the ECMO pump in addition to any native cardiac output in VA ECMO. If direct cardiovascular support is required, VA ECMO must be employed.

While VV ECMO does not provide any direct circulatory energy to the patient, there are benefits to VV ECMO to the patient's cardiovascular system. Patients with severe respiratory failure being considered for ECMO generally require significant positive-pressure ventilation. This results in an increase intrathoracic pressure with a resultant decrease in right ventricular preload and increase in right ventricular afterload. Upon initiation of VV ECMO, the patient's gas exchange no longer depends on lung perfusion/ventilation, and the high positive-pressure ventilation settings can be decreased significantly. This decrease in intrathoracic pressure can provide relief to a right ventricle that may have been performing poorly under adverse loading conditions. Secondly, the VV ECMO circuit adds oxygen into the blood stream prior to the right ventricle, thereby increasing the oxygen content of pulmonary artery blood flow. Increased oxygen tension decreases pulmonary vascu-

lar resistance, thus decreasing right ventricular afterload. Finally, coronary blood flow is derived from the blood at the aortic root at the end of systole. As VV ECMO effectively increases the oxygen tension of the pulmonary artery blood, this also effectively increases the oxygen content of the pulmonary venous blood which returns to the left ventricle and is ejected into the aortic root to be perfused down the coronaries. On the contrary, during VA ECMO support, it is important to maintain some oxygenation to the lungs as coronary perfusion is derived from native left ventricular output when there is any native output from the aortic valve [8, 9].

The advantages of VV ECMO over VA ECMO include the possibility for single-vessel cannulation and removal of a source of systemic embolization. Dual-lumen cannulas are available in various sizes that can provide sufficient flow to support a VV ECMO circuit for patients as small as newborns through adulthood. Pediatric centers generally favor surgical cutdown implantation, but it is now common for adult institutions to place cannulas percutaneously by modified Seldinger techniques. As VV ECMO only delivers blood back to the venous side of the circulation, in the absence of a right-to-left intracardiac shunt, any embolus (air, particle, thrombus, etc.) produced by the circuit would not be delivered to the systemic circulation as it is in VA ECMO.

ECMO Indications

ECMO is a supportive, not curative, therapy. It can provide time for diagnosis and treatment of the underlying condition that led to the cardiopulmonary failure by supporting the function of the lungs and/or heart while those systems recover sufficiently to function without ECMO. In general, ECMO support is limited to weeks. Longer support times are generally associated with higher mortality [10]; as complications tend to occur, the longer ECMO support is necessary, and patients requiring longer support times likely have increased severity of cardiopulmonary failure [11]. Pediatric immunocompromised hematology/oncology patients are most likely to require ECMO support for sepsis, acute respiratory distress syndrome (ARDS), or sudden cardiac arrest (E-CPR).

Sepsis

Severe sepsis in a pediatric patient can lead to the need for ECMO support secondary to severe cardiac dysfunction, pulmonary dysfunction, or more commonly a combination of the two. Differentiation of the primary organ dysfunction can be difficult to discern in the acute situation leading many patients to be supported with VA ECMO when VV ECMO may be sufficient. Local practice, the individual practitioner's experience, and the patient's current condition are all reasonable factors to consider when deciding between support modalities.

ECMO is a valid support mechanism in sepsis as the underlying cause is generally time limited related to infection/inflammation. Sepsis is a multisystem disease by definition though, and supporting the heart and/or lungs with ECMO may not be sufficient to allow for recovery. Sepsis has been identified as a risk factor for survival in patients supported on ECMO, and survival rates are reported to be 36.8–82.4% [12–15]. The acute inflammatory milieu of sepsis results in impaired utilization of oxygen, disseminated intravascular coagulation (DIC), hepatic dysfunction, and renal dysfunction; all of which are not directly supported by ECMO. In particular, impaired utilization of oxygen is a problem frequently encountered in a patient with sepsis, and just supplying more cardiac output and oxygen via ECMO may not overcome this barrier. The group from Melbourne has theorized and shown some positive results with providing supraphysiologic cardiac output via central cannulation (cannulas placed directly in the right atrium and aorta via sternotomy) for ECMO [13, 14]. This technique allows for larger cannulas with shorter tubing lengths to decrease the resistance in the circuit, thereby allowing for higher flows. While central cannulation may allow for higher flows, others have been hesitant to pursue it given the additive hematologic impact of sepsis and ECMO with the need for anticoagulation and fears of increasing the high rate of hemorrhagic complications associated with ECMO with an open sternotomy.

ARDS

ARDS and other forms of acute respiratory failure have been the most successful applications of ECMO. Single organ system dysfunction which is mechanically supported by ECMO and can recover when allowed to rest (without further damage from aggressive positive-pressure ventilation) is the perfect disease state for ECMO to support. The ELSO database results bear this to be true as results for ECMO for pulmonary support are uniformly better than that for cardiac and E-CPR indications across all age groups [4].

As ARDS generally results in severe pulmonary dysfunction, VV ECMO is generally sufficient to support patients. Even patients requiring significant inotropic/vasopressor infusions prior to cannulation can be successfully managed with VV ECMO [16]. An initial trial in adult ARDS patients in 1979 did not show a significant survival benefit [17], but this trial has since been criticized by poor subject selection and poor management of ECMO in centers with very little experience prior to starting the trial. A more recent randomized trial in adult patients in the United Kingdom did show a survival and economic benefit which has reinvigorated the use of ECMO in the adult population [18]. While no equivalent randomized trial of ECMO vs. non-ECMO support has been or is likely to be done in pediatric age groups, current research efforts focus on when ECMO should be considered in an attempt to answer the questions of: (1) Does earlier ECMO initiation preserve lung function? and (2) When is consideration for ECMO support too late/futile?

E-CPR

ELSO defines E-CPR as the initiation of ECMO during an active cardiac or respiratory arrest. Most commonly this means ECMO is initiated during active chest compressions as the patient has failed conventional resuscitative efforts. Survival to discharge following E-CPR is generally reported around 40% [4, 19, 20]. Duration of cardiopulmonary resuscitation (CPR) prior to ECMO initiation would seem to be an intuitive determinant of outcome, but this has not been reliably shown [21]. Patients with good neurological outcomes have been reported with CPR durations as long as 280 min in extreme cases [22]. Neurological injury remains the paramount concern. Some neurological injury is identifiable in 22% of patients following E-CPR and accounts for the majority of the mortality [23]. In patients who survive to discharge following E-CPR, either no deficit or only mild dysfunction is seen in 79% [21]. All of these reports focus on in-hospital arrest and many specifically in patients with underlying cardiac disease. A recent review of the ELSO database attempted to look at patients without congenital heart disease receiving E-CPR and found a survival rate of 32% with a threefold increase in mortality in patients with sepsis [24].

Anticoagulation and Bleeding Complications

ECMO support requires the blood to travel outside the body and across the artificial surfaces of the pump and oxygenator. The blood interacts with these surfaces resulting in a consumptive coagulopathy [25]. Platelets and coagulation factors are activated and consumed. Anticoagulation during ECMO attempts to limit this consumption by preventing the coagulation system from interacting with the artificial surfaces. Modifications to ECMO circuits with bonding of heparin and albumin to plastic have been developed in an effort to limit the interaction [26, 27], but no clinical human study has shown this to be effective, and some have questioned the utility of these coatings [28]. While both coagulation factors and platelets are affected, traditionally only anticoagulants are used with few centers using platelet inhibitors [29]. Thromboembolic complications from clots within the circuit, particularly in VA ECMO, and thrombosis of the circuit with acute disruption of ECMO support are the primary complications resulting from inadequate anticoagulation.

The ideal anticoagulant would be fast acting, easy to monitor and titrate, and readily reversible in the event of bleeding. Unfractionated heparin (UFH) fits many of these characteristics and has been the mainstay of anticoagulation during ECMO. As UFH acts by enhancing the anticoagulant properties of antithrombin, antithrombin deficiency should be considered in patients unresponsive to standard doses of UFH. Some centers have advocated for more routine measurement and replacement of antithrombin [30, 31]. While most centers still use UFH primarily, there has been recent interest in the more routine use of direct thrombin inhibitors (argatroban, bivalirudin, and lepirudin) [29].

A whole blood activated clotting time (ACT) is the traditional method to monitor the level of anticoagulation. The ACT is a convenient test as it requires a small blood sample and can be done quickly at the bedside [32]. More recently, some centers have reported alternative anticoagulation strategies to include anti-Xa levels or thromboelastography [30, 31, 33, 34], but ACT monitoring remains the most utilized test [29].

Bleeding on ECMO is the most common patient complication. Transfusion support is the primary treatment to replace consumed platelets and coagulation factors. Each institution individualizes transfusion protocols to maintain adequate platelet numbers, coagulation factors (based traditionally on prothrombin times), and fibrinogen. Thromboelastography has been used by some centers to aid in the assessment of platelet and factor function [30, 35]. No hemostatic agent has been shown to reliably treat bleeding complications of ECMO. Several reports on the use of recombinant activated factor VII (rFVIIa) have shown some promise as a hemostatic agent, but thrombosis within the patient and circuit has also been reported [36, 37]. A general strategy for bleeding is (1) transfusion to correct coagulopathy and thrombocytopenia, (2) decrease or holding of anticoagulant infusion with lower anticoagulation test goals, (3) local control with consideration for surgical exploration and topical hemostatic agents, and (4) finally careful consideration for alternative therapies such as rFVIIIa.

Neurologic Complications and Monitoring

Neurologic complications including seizures, ischemic stroke from thromboembolism, and intracranial hemorrhage remain common and are potentially devastating complications of ECMO support [38–40]. The incidence of neurologic complications varies by age and definition of the complication. While VV ECMO may mitigate the risk of thromboembolic events and non-adjusted rates of neurologic injuries are greater in VA ECMO [38], no report has shown a risk-adjusted reduction in neurologic complications in VV ECMO. Not surprisingly, mortality and long-term morbidity are more common in patients with neurologic complications [38, 40, 41].

Monitoring of neurologic complications during ECMO varies by institution with no general consensus beyond the use of head ultrasound studies in infants with an open anterior fontanelle during the first few days of support [42, 43]. Real-time monitoring techniques including electroencephalograms, cerebral near-infrared spectroscopy, and transcranial Doppler ultrasound have been reported by single centers with a mixed ability to detect changes at the time of an event and poor correlation with more definitive neuroimaging techniques after ECMO support is completed [44]. With a high incidence in complications and lack of consensus regarding the best monitoring technique, the individual practitioner is left to decide what best techniques within any individual patient to employ. Monitoring should not place the patient at undue risk, but it is important to have a high index of suspicion as neurologic complications are common and have a profound effect on the outcome of ECMO support.

ECMO in Immunocompromised Hematology/Oncology Patients

The literature on patients receiving ECMO in the setting of an underlying malignancy comes from three large studies and multiple case reports. In 2010, Gow [45] reported the ELSO outcomes for 72 adult patients with solid tumors or hematologic malignancies (HM) receiving ECMO between 1992 and 2008. 39% of patients survived the ECMO run, and 32% survived to hospital discharge. Risk factors for mortality included requiring support for pulmonary versus cardiac failure and worse impairment of lung function prior to ECMO initiation. In 2014 the group from Vienna reported on fourteen adult HM patients requiring ECMO for ARDS [46]. Interestingly, the diagnosis of malignancy was made in four patients and five patients recieved their first chemotherapy while on ECMO support in this report. Survival to ICU and hospital discharge was 50%, and all survivors were alive at a median of 3 years of follow-up. The International ECMO Network (ECMONet) recently conducted a retrospective multicenter study and reported data from ten ICUs in seven countries on 203 immunocompromised patients greater than 15 years of age who underwent ECMO from 2008 to 2015 for severe ARDS [47]. 49% of patients had a HM or a solid tumor. In the entire cohort, 30% were alive at 6 months and 24%/20% in the HM/solid tumor subset, respectively, whereas 40% of solid organ transplant recipients were alive. A matched cohort analysis was performed between the entire group of immunocompromised patients and 94 non-immunocompromised patients receiving ECMO for ARDS. Six-month mortality was significantly higher (70 vs. 26%) in the immunocompromised patients. In an attempt to control for pre-ECMO severity of illness, 80 cases and controls were matched by PRESERVE mortality risk score; patients with an immunodeficiency diagnosis had an odds ratio of 5.7 for mortality when compared to the controls.

There is a paucity of data regarding outcomes of ECMO specifically in the pediatric oncology population. What literature exists is limited by small numbers and long reporting periods. Fourteen pediatric patients with malignancy received ECMO in Melbourne between 1993 and 2014, 9 of whom were neutropenic at the time of cannulation. Four children survived to discharge, and two (22%) from the most recent decade (2005–2014) are long-term survivors [48]. There are scattered recent individual case reports [49, 50] of successful short-term ECMO therapy for children with very specific indications: tumor lysis syndrome or support during induction chemotherapy to shrink a lymphoma-associated large mediastinal mass.

ECMO in Hematopoietic Stem Cell Transplant Patients

Whatever increased vulnerability exists for patients with malignancies in terms of ECMO candidacy would be expected to be even greater in patients undergoing hematopoietic stem cell transplantation (HSCT). Ablative conditioning, usually

used in transplants for malignant diseases, involves the administration of extremely high doses of chemotherapy with or without radiation therapy. Children transplanted for nonmalignant conditions often receive reduced intensity approaches that rely on intense immunosuppression which delays robust immune reconstitution. Candidates for HSCT often have multiple preexisting comorbidities related to the underlying disease process. Examples include the end organ damage (cerebrovascular disease or pulmonary hypertension) seen in sickle cell disease or the incompletely controlled viral infections in patients with immunodeficiency disorders. Immune reconstitution is a process that generally takes months to accomplish and can be delayed even longer in the presence of graft versus host disease (GVHD), graft failure, relapse of malignancy, or uncontrolled infection.

The first series of pediatric HSCT patients receiving ECMO was reported by Gow in 2006 based on ELSO registry data spanning 1991–2004 [51]. In this cohort of 19 children, ECMO was initiated for pulmonary support in the majority (17/19). 79% died during the ECMO run, and only 1 of the 19 survived to hospital discharge. This dismal outcome led the HSCT/ICU community to question the role of ECMO in the treatment of HSCT patients. Di Nardo [52] updated this data to include 29 patients treated between 1991 and 2012. Notably 21% in this group were placed on ECMO for cardiac compromise in comparison to the primarily pulmonary indication in the earlier series. 21% were decannulated, and three patients (10%) survived to hospital discharge. Oxygenation index was the strongest predictor of survival. An oxygenation index (OI) less than 38 had 75% sensitivity and 81% specificity in differentiating survivors from non-survivors. In general, outcomes for children undergoing HSCT are superior to those in adults including in the subset of patients requiring ICU level care. There is insufficient data to know if this is true for the much smaller group of patients receiving ECMO. Wohlfarth reported the European experience in adult HSCT patients with ARDS from twelve ICUs between 2010 and 2015 [53]. 19% of the 37-patient cohort survived to hospital discharge, and all of these early survivors were alive in remission at a median of 18 months later. Interestingly this is the only group that assessed time post-HSCT as a predictor of outcome. Patients more than 240 days after HSCT had a survival of 46% vs. 4% (1 of 24 patients) for those less than 240 days after transplant. The authors hypothesize that in the early post-HSCT phase, patients have very poor immune function and are also at greater risk of developing multiple organ dysfunction syndrome, a known predictor of poor outcome in all critical patients. Despite the low likelihood of short- and long-term survival, there are, as in the oncology population, anecdotal reports describing novel indications and some successes. One child was placed on ECMO for respiratory support in the setting of fulminant adenoviral pneumonia; he ultimately recovered after receiving adenoviral-specific cytotoxic T lymphocytes, a recent advance in the therapy of severe viral infections [54]. ECMO was used as a bridge therapy to allow allogeneic HSCT in an infant with immunodeficiency syndrome who received conditioning and donor stem cells while on the circuit. He ultimately was removed from ECMO and expired in the setting of therapy refractory CMV pneumonia [55].

How Should We Decide?

It is impossible to draw firm evidence-based conclusions about the efficacy or toxicity of ECMO in the immunocompromised pediatric population from the existing literature. The combination of selection bias in terms of what patients are offered on ECMO and the reporting bias in terms of which cases are submitted for publication eventually published colors of any interpretation of the small body of literature that exists.

Given the medical intensity involved in initiating and continuing ECMO as well as the inherent risks associated with the procedure, there is understandable concern about the use of this modality in those receiving cancer therapy or undergoing HSCT. There is great heterogeneity in this group of patients, however, in terms of both the predicted efficacy and toxicity of ECMO therapy and in the ultimate prognosis. Thus, it may be helpful to have a standardized assessment tool for pediatric immunocompromised hematology/oncology/HSCT patients failing conventional support for whom ECMO is being considered (Fig. 15.1).

The first question, applicable to all ECMO candidates, is whether the cause of cardiorespiratory failure is treatable and potentially recoverable within the time that ECMO can provide heart/lung support. The next major consideration is the patient's status with regard to the underlying oncologic/HSCT diagnosis. In oncology patients,

Is Cause of Cardiorespiratory Failure Treatable/Recoverable?	
Oncology Population	**Hematopoietic Stem Cell Transplant Population**
Underlying Malignancy • Remission Status • Prognosis	**Underlying Disease** Malignant Non Malignant Disorder* • Remission Status/Disease Control • Prognosis
Place in therapy regimen	Time post-HSCT
	Presence of graft vs. host disease
Previous Organ Damage/Infections	
Current Comorbidities • Marrow function • Active infections • Other organ dysfunction	
Input from parents, primary team, ICU, ECMO team	

*Nonmalignant Disorders: Hemoglobinopathies, Bone Marrow Failure disorders, Immune Deficiencies

Fig. 15.1 Assessment tool when considering extracorporeal membrane oxygenation in immunocompromised/oncology/hematopoietic stem cell transplant pediatric patients

it is important to know the specific diagnosis and stage of disease, where the child is in the planned treatment course, whether the disease is currently responding to therapy, and the expected disease-free survival for this diagnosis. For example, a child with metastatic osteosarcoma who has not responded to initial therapy has a very different predicted outcome from a child with standard risk acute lymphoblastic leukemia (ALL) currently in complete remission. HSCT is rarely offered to patients for whom long -term survival is not possible. For these patients it is essential to know the underlying disease for which transplant was performed and whether the transplant has achieved the planned objective of cure. This would manifest as remission in children transplanted for malignant diseases and as good donor engraftment in those transplanted for bone marrow failure syndromes, hemoglobinopathies, and other nonmalignant conditions. A child several weeks after HSCT for high-risk leukemia not in remission at the time of transplant has a very different health status than a child transplanted 6 months previously for an underlying immunodeficiency disorder and who now has full donor engraftment. It is also important to know where the child is in the post-HSCT trajectory. Immediately following HSCT, patients have impairment in all hematopoietic lineages. They are neutropenic as well as platelet and red cell transfusion dependent. Neutrophil, platelet, and red cell counts usually improve 3–4 weeks following transplant, but lymphocyte function remains abnormal for months particularly in the setting of graft manipulation (T-cell depletion) or active GVHD. The information that must be obtained for all oncology/HSCT children includes previous infections/organ toxicities from the disease or treatment-related complications as well as current comorbidities. In all situations the goals of the parents and the primary medical team will be instrumental in the decision-making process and in delivering optimal care to these critically ill patients.

The existing data certainly suggests that oncology/HSCT patients requiring ECMO support have poorer outcomes as a group when compared to other populations receiving ECMO for similar indications. Schmidt et al. nicely reviewed some of the contributing factors, including underlying impairment in immune function increasing the risk of nosocomial infections, bleeding complications, and altered drug pharmacokinetics in a population receiving a myriad of medications [56]. However, it is also clear that ECMO can offer short- and long-term survival to some proportion of these vulnerable patients, approximately 30% of oncology and 5–20% of HSCT group. Notably, the majority of patients who are discharged from the ICU following ECMO are long-term survivors indicating that if ECMO can be successfully navigated, there is no unique long-term toxicity in these patients. Because of statistical limitations, most reports do not focus on the identification of risk factors that would allow candidate selection enriched for those predicted to gain the most benefit. The mortality score recently developed for children undergoing ECMO for respiratory failure [57] and based on ELSO data from 2001 to 2013 is a first step. In this cohort pre-ECMO factors shown to be predictive of outcome included the length of ventilation, severity of pulmonary disease, and presence of other organ dysfunction. Interestingly 4% of this group carried a cancer diagnosis as a comorbid condition, and this conferred two times the odds ratio of hospital mortality. This scoring system should be validated in immunocompromised children to ascertain

whether the previously identified factors remain significant and to attempt to identify factors unique to this population (time from diagnosis or transplant, expected prognosis from underlying disease). Then a concerted effort must be made to develop consensus patient selection guidelines even in the absence of statistically robust data. This will allow the ICU/oncology/HSCT community to begin to determine whether the current poor survival is related to unique vulnerabilities in this population or reflects selection bias with ECMO only offered as a last resort to patients beyond the point where recovery is not feasible regardless of the intervention. A perspective piece from 2005 discusses the ethical dilemmas that arise when insufficient data exist yet decisions need to be made. They propose a possible approach in the context of describing the case of a 13-year-old autologous HSCT patient who required ECMO in the setting of neutropenic sepsis and was ultimately successfully weaned from ECMO with count recovery [58]. They raise many relevant issues including whether regulatory oversight and IRB approval are necessary and the difficulties in obtaining truly informed consent in this situation. They do not discuss other possible issues including resource utilization and staff discomfort when an intense procedure is predicted to fail more often than to succeed.

In conclusion the data that exists is not robust but does suggest across multiple studies in adult and pediatric populations that immunocompromised hematology/oncology/HSCT patients have an increased risk of ECMO failure compared to immunocompetent patients. The results seem to be improving in more recent eras, which mirrors the successes seen in outcomes for both immunocompromised patient populations in general and in other types of patients requiring ICU or ECMO support. Moving forward a reasonable goal would be to create and validate a predictive model for outcome in this specific population and to incorporate this into the development of consensus guidelines. Input from stakeholders caring for both pediatric immunocompromised hematology/oncology/HSCT patients and pediatric ICU patients is essential to address the combination of challenges presented by this heterogeneous critically ill patient population.

References

1. Baffes TG, Fridman JL, Bicoff JP, Whitehill JL. Extracorporeal circulation for support of palliative cardiac surgery in infants. Ann Thorac Surg. 1970;10(4):354–63.
2. Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ, Gerbode F. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med. 1972;286(12):629–34.
3. Bartlett RH, Andrews AF, Toomasian JM, Haiduc NJ, Gazzaniga AB. Extracorporeal membrane oxygenation for newborn respiratory failure: forty-five cases. Surgery. 1982;92(2):425–33.
4. Extracorporeal Life Support Organization. ECLS registry report-international summary. 2017.
5. Barrett CS, Jaggers JJ, Cook EF, Graham DA, Yarlagadda VV, Teele SA, Almond CS, Bratton SL, Seeger JD, Dalton HJ, Rycus PT, Laussen PC, Thiagarajan RR. Pediatric ECMO outcomes: comparison of centrifugal versus roller blood pumps using propensity score matching. ASAIO J. 2013;59(2):145–51.

6. O'Brien C, Monteagudo J, Schad C, Cheung E, Middlesworth W. Centrifugal pumps and hemolysis in pediatric extracorporeal membrane oxygenation (ECMO) patients: an analysis of extracorporeal life support organization (ELSO) registry data. J Pediatr Surg. 2017;52(6):975–8.
7. Stanzel RD, Henderson M. Clinical evaluation of contemporary oxygenators. Perfusion. 2016;31(1):15–25.
8. Kinsella JP, Gerstmann DR, Rosenberg AA. The effect of extracorporeal membrane oxygenation on coronary perfusion and regional blood flow distribution. Pediatr Res. 1992;31(1):80–4.
9. Secker-Walker JS, Edmonds JF, Spratt EH, Conn AW. The source of coronary perfusion during partial bypass for extracorporeal membrane oxygenation (ECMO). Ann Thorac Surg. 1976;21(2):138–43.
10. Gupta P, Robertson MJ, Beam B, Gossett JM, Schmitz ML, Carroll CL, Edwards JD, Fortenberry JD, Butt W. Relationship of ECMO duration with outcomes after pediatric cardiac surgery: a multi-institutional analysis. Minerva Anestesiol. 2015;81(6):619–27.
11. Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, Hodgson C, Scheinkestel C, Cooper DJ, Thiagarajan RR, Brodie D, Pellegrino V, Pilcher D. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J. 2015;36(33):2246–56.
12. Meyer DM, Jessen ME. Results of extracorporeal membrane oxygenation in children with sepsis. The extracorporeal life support organization. Ann Thorac Surg. 1997;63(3):756–61.
13. Maclaren G, Butt W, Best D, Donath S, Taylor A. Extracorporeal membrane oxygenation for refractory septic shock in children: one institution's experience. Pediatr Crit Care Med. 2007;8(5):447–51.
14. MacLaren G, Butt W, Best D, Donath S. Central extracorporeal membrane oxygenation for refractory pediatric septic shock. Pediatr Crit Care Med. 2011;12(2):133–6.
15. Smalley N, MacLaren G, Best D, Paul E, Butt W. Outcomes in children with refractory pneumonia supported with extracorporeal membrane oxygenation. Intensive Care Med. 2012;38(6):1001–7.
16. Roberts N, Westrope C, Pooboni SK, Mulla H, Peek GJ, Sosnowski AW, Firmin RK. Venovenous extracorporeal membrane oxygenation for respiratory failure in inotrope dependent neonates. ASAIO J. 2003;49(5):568–71.
17. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC 2nd, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, Miller RG Jr. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA. 1979;242(20):2193–6.
18. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D. CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351–63.
19. Tajik M, Cardarelli MG. Extracorporeal membrane oxygenation after cardiac arrest in children: what do we know? Eur J Cardiothorac Surg. 2008;33(3):409–17.
20. Thiagarajan RR, Laussen PC, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. Circulation. 2007;116(15):1693–700.
21. Joffe AR, Lequier L, Robertson CM. Pediatric outcomes after extracorporeal membrane oxygenation for cardiac disease and for cardiac arrest: a review. ASAIO J. 2012;58(4):297–310.
22. Yu HY, Yeh HL, Wang SS, Tsai MK, Chen YS, Ko WJ, Lin FY. Ultra long cardiopulmonary resuscitation with intact cerebral performance for an asystolic patient with acute myocarditis. Resuscitation. 2007;73(2):307–8.
23. Barrett CS, Bratton SL, Salvin JW, Laussen PC, Rycus PT, Thiagarajan RR. Neurological injury after extracorporeal membrane oxygenation use to aid pediatric cardiopulmonary resuscitation. Pediatr Crit Care Med. 2009;10(4):445–51.

24. Conrad SJ, Bridges BC, Kalra Y, Pietsch JB, Smith AH. Extracorporeal cardiopulmonary resuscitation among patients with structurally normal hearts. ASAIO J. 2017;63(6):781–6.
25. Muntean W. Coagulation and anticoagulation in extracorporeal membrane oxygenation. Artif Organs. 1999;23(11):979–83.
26. Palmer K, Ehren H, Benz R, Frenckner B. Carmeda surface heparinization in neonatal ECMO systems: long-term experiments in a sheep model. Perfusion. 1995;10(5):307–13.
27. Urlesberger B, Zobel G, Rodl S, Dacar D, Friehs I, Leschnik B, Muntean W. Activation of the clotting system: heparin-coated versus non coated systems for extracorporeal circulation. Int J Artif Organs. 1997;20(12):708–12.
28. Silvetti S, Koster A, Pappalardo F. Do we need heparin coating for extracorporeal membrane oxygenation? New concepts and controversial positions about coating surfaces of extracorporeal circuits. Artif Organs. 2015;39(2):176–9.
29. Bembea MM, Annich G, Rycus P, Oldenburg G, Berkowitz I, Pronovost P. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey. Pediatr Crit Care Med. 2013;14(2):e77–84. PMCID: PMC3567253.
30. Agati S, Ciccarello G, Salvo D, Turla G, Undar A, Mignosa C. Use of a novel anticoagulation strategy during ECMO in a pediatric population: single-center experience. ASAIO J. 2006;52(5):513–6.
31. Urlesberger B, Zobel G, Zenz W, Kuttnig-Haim M, Maurer U, Reiterer F, Riccabona M, Dacar D, Gallisti S, Leschnik B, Muntean W. Activation of the clotting system during extracorporeal membrane oxygenation in term newborn infants. J Pediatr. 1996;129(2):264–8.
32. Green TP, Isham-Schopf B, Steinhorn RH, Smith C, Irmiter RJ. Whole blood activated clotting time in infants during extracorporeal membrane oxygenation. Crit Care Med. 1990;18(5):494–8.
33. Baird CW, Zurakowski D, Robinson B, Gandhi S, Burdis-Koch L, Tamblyn J, Munoz R, Fortich K, Pigula FA. Anticoagulation and pediatric extracorporeal membrane oxygenation: impact of activated clotting time and heparin dose on survival. Ann Thorac Surg. 2007;83(3):912–9; discussion 919–20.
34. O'Meara LC, Alten JA, Goldberg KG, Timpa JG, Phillips J, Laney D, Borasino S. Anti-Xa directed protocol for anticoagulation management in children supported with extracorporeal membrane oxygenation. ASAIO J. 2015;61(3):339–44.
35. Oliver WC. Anticoagulation and coagulation management for ECMO. Semin Cardiothorac Vasc Anesth. 2009;13(3):154–75.
36. Niebler RA, Punzalan RC, Marchan M, Lankiewicz MW. Activated recombinant factor VII for refractory bleeding during extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2010;11(1):98–102.
37. Warren OJ, Rogers PL, Watret AL, de Wit KL, Darzi AW, Gill R, Athanasiou T. Defining the role of recombinant activated factor VII in pediatric cardiac surgery: where should we go from here? Pediatr Crit Care Med. 2009;10(5):572–82.
38. Cengiz P, Seidel K, Rycus PT, Brogan TV, Roberts JS. Central nervous system complications during pediatric extracorporeal life support: incidence and risk factors. Crit Care Med. 2005;33(12):2817–24.
39. Luyt CE, Brechot N, Demondion P, Jovanovic T, Hekimian G, Lebreton G, Nieszkowska A, Schmidt M, Trouillet JL, Leprince P, Chastre J, Combes A. Brain injury during venovenous extracorporeal membrane oxygenation. Intensive Care Med. 2016;42(5):897–907.
40. Nasr DM, Rabinstein AA. Neurologic complications of extracorporeal membrane oxygenation. J Clin Neurol. 2015;11(4):383–9. PMCID: PMC4596114.
41. Lorusso R, Gelsomino S, Parise O, Di Mauro M, Barili F, Geskes G, Vizzardi E, Rycus PT, Muellenbach R, Mueller T, Pesenti A, Combes A, Peek G, Frenckner B, Di Nardo M, Swol J, Maessen J, Thiagarajan RR. Neurologic injury in adults supported with veno-venous extracorporeal membrane oxygenation for respiratory failure: findings from the extracorporeal life support organization database. Crit Care Med. 2017;45(8):1389–97.

42. Heard ML, Clark RH, Pettignano R, Dykes FD. Daily cranial ultrasounds during ECMO: a quality review/cost analysis project. J Pediatr Surg. 1997;32(8):1260–1.
43. Khan AM, Shabarek FM, Zwischenberger JB, Warner BW, Cheu HW, Jaksic T, Goretsky MJ, Meyer TA, Doski J, Lally KP. Utility of daily head ultrasonography for infants on extracorporeal membrane oxygenation. J Pediatr Surg. 1998;33(8):1229–32.
44. Bembea MM, Felling R, Anton B, Salorio CF, Johnston MV. Neuromonitoring during extracorporeal membrane oxygenation: a systematic review of the literature. Pediatr Crit Care Med. 2015;16(6):558–64.
45. Gow KW, Lao OB, Leong T, Fortenberry JD. Extracorporeal life support for adults with malignancy and respiratory or cardiac failure: the extracorporeal life support experience. Am J Surg. 2010;199(5):669–75.
46. Wohlfarth P, Ullrich R, Staudinger T, Bojic A, Robak O, Hermann A, Lubsczyk B, Worel N, Fuhrmann V, Schoder M, Funovics M, Rabitsch W, Knoebl P, Laczika K, Locker GJ, Sperr WR, Schellongowski P. Arbeitsgruppe fur hamato-onkologische Intensivmedizin der Osterreichischen Gesellschaft fur Internistische und Allgemeine Intensivmedizin und Notfallmedizin (OGIAIN). Extracorporeal membrane oxygenation in adult patients with hematologic malignancies and severe acute respiratory failure. Crit Care. 2014;18(1):R20. PMCID: PMC4055976
47. Schmidt M, Schellongowski P, Patroniti N, Taccone FS, Reis Miranda D, Reuter J, Prodanovic H, Pierrot M, Dorget A, Park S, Balik M, Demoule A, Crippa IA, Mercat A, Wohlfarth P, Sonneville R, Combes A, International ECMO Network (ECMONet), the REVA Research Network and the IDEA Study Group. Six-month outcome of immunocompromised severe ARDS patients rescued by ECMO. An international multicenter retrospective study. Am J Respir Crit Care Med. 2018 Jan 3.
48. Smith S, Butt W, Best D, MacLaren G. Long-term survival after extracorporeal life support in children with neutropenic sepsis. Intensive Care Med. 2016;42(5):942–3.
49. Huang M, Owen E, Myers S, Raj A. Cardiopulmonary failure requiring ECMO bypass resulting from leukemia cell lysis in a patient with childhood acute myelomonocytic leukemia. Case Rep Hematol. 2015;2015:640528. PMCID: PMC4466370.
50. Lueck C, Kuehn C, Hoeper MM, Ganser A, Eder M, Beutel G. Successful use of extracorporeal membrane oxygenation during induction chemotherapy in a patient with mediastinal tumor mass of a T lymphoblastic lymphoma. Ann Hematol. 2016;95(10):1719–21.
51. Gow KW, Wulkan ML, Heiss KF, Haight AE, Heard ML, Rycus P, Fortenberry JD. Extracorporeal membrane oxygenation for support of children after hematopoietic stem cell transplantation: the extracorporeal life support organization experience. J Pediatr Surg. 2006;41(4):662–7.
52. Di Nardo M, Locatelli F, Palmer K, Amodeo A, Lorusso R, Belliato M, Cecchetti C, Perrotta D, Picardo S, Bertaina A, Rutella S, Rycus P, Di Ciommo V, Holzgraefe B. Extracorporeal membrane oxygenation in pediatric recipients of hematopoietic stem cell transplantation: an updated analysis of the extracorporeal life support organization experience. Intensive Care Med. 2014;40(5):754–6.
53. Wohlfarth P, Beutel G, Lebiedz P, Stemmler HJ, Staudinger T, Schmidt M, Kochanek M, Liebregts T, Taccone FS, Azoulay E, Demoule A, Kluge S, Svalebjorg M, Lueck C, Tischer J, Combes A, Boll B, Rabitsch W, Schellongowski P. Intensive Care in Hematologic and Oncologic Patients (iCHOP), Caring for critically ill immunocompromised patients Multinational Network (NINE-I). Characteristics and outcome of patients after allogeneic hematopoietic stem cell transplantation treated with extracorporeal membrane oxygenation for acute respiratory distress syndrome. Crit Care Med. 2017;45(5):e500–7.
54. Di Nardo M, Li Pira G, Amodeo A, Cecchetti C, Giorda E, Ceccarelli S, Brescia LP, Pirozzi N, Rutella S, Locatelli F, Bertaina A. Adoptive immunotherapy with antigen-specific T cells during extracorporeal membrane oxygenation (ECMO) for adenovirus-related respiratory failure in a child given haploidentical stem cell transplantation. Pediatr Blood Cancer. 2014;61(2):376–9.

55. Di Nardo M, Locatelli F, Di Florio F, Cecchetti C, Amodeo A, Rutella S, Bertaina A. Extracorporeal membrane oxygenation as a bridge to allogeneic T-cell depleted hematopoietic stem cell transplantation in infants with severe combined immune deficiency: is it feasible? Intensive Care Med. 2014;40(10):1600–1.
56. Schmidt M, Brodie D, Combes A. Patients with hematologic malignancies have many reasons to die during extracorporeal membrane oxygenation. Crit Care. 2014; 18(5): 522-014-0522-0. PMCID: PMC4163603.
57. Bailly DK, Reeder RW, Zabrocki LA, Hubbard AM, Wilkes J, Bratton SL, Thiagarajan RR. Extracorporeal life support organization member centers. Development and validation of a score to predict mortality in children undergoing extracorporeal membrane oxygenation for respiratory failure: pediatric pulmonary rescue with extracorporeal membrane oxygenation prediction score. Crit Care Med. 2017;45(1):e58–66. PMCID: PMC5532876.
58. Wolfson RK, Kahana MD, Nachman JB, Lantos J. Extracorporeal membrane oxygenation after stem cell transplant: clinical decision-making in the absence of evidence. Pediatr Crit Care Med. 2005;6(2):200–3.