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Extracorporeal membrane oxygenation in children receiving haematopoietic cell transplantation and immune effector cell therapy: an international and multidisciplinary consensus statement

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Use of extracorporeal membrane oxygenation (ECMO) in children receiving haematopoietic cell transplantation (HCT) and immune effector cell therapy is controversial and evidence-based guidelines have not been established. Remarkable advancements in HCT and immune effector cell therapies have changed expectations around reversibility of organ dysfunction and survival for affected patients. Herein, members of the Extracorporeal Life Support Organization (ELSO), Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (HCT and cancer immunotherapy subgroup), the Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT), the supportive care committee of the Pediatric Transplantation and Cellular Therapy Consortium (PTCTC), and the Pediatric Intensive Care Oncology Kids in Europe Research (POKER) group of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) provide consensus recommendations on the use of ECMO in children receiving HCT and immune effector cell therapy. These are the first international, multidisciplinary consensus-based recommendations on the use of ECMO in this patient population. This Review provides a clinical decision support tool for paediatric haematologists, oncologists, and critical care physicians during the difficult decision-making process of ECMO candidacy and management. These recommendations can represent a base for future research studies focused on ECMO selection criteria and bedside management.

Introduction

Haematopoietic cell transplantation (HCT) is a possible curative strategy for children with selected malignant and non-malignant disorders.[1] Advances in HCT have led to expanding indications and eligibility, with good overall survival and disease-free outcomes.[2–5] Immune effector cell therapies—for example, chimeric antigen receptor T-cells directed against antigens such as CD-19—have been associated with remarkable remission rates of more than 90% among patients with relapsed or refractory acute lymphoblastic leukaemia, who previously had no other curative options.[6–8] Nonetheless, 10–40% of children receiving these therapies might require support in the paediatric intensive care unit (PICU).[2]

Combined advancements in the fields of paediatric critical care, HCT, and immune effector cell therapy have been associated with substantial improvements in survival,[2,9–13] which have steadily improved to 48–75% for paediatric patients receiving HCT.[2,3,12] Such improvements have led to renewed interest in the consideration of advanced life support modalities, such as extracorporeal membrane oxygenation (ECMO), which were previously judged inappropriate for these patients.[14–16]

Aside from improving survival in the PICU among paediatric patients receiving HCT or immune effector cell therapies, several other factors have contributed to increased consideration of ECMO in this population. Improvements in ECMO technology have made it safer and more easily available at the bedside.[17–19] There are reports of the successful use of this technology among other populations previously considered to have relative contraindications (eg, premature infants, patients infected by *Bordetella pertussis*, and patients who received solid organ transplantation).[16,17,20,21] There are also increasing reports of improvements in ECMO survival among paediatric patients who have received HCT.[22–27] Randomised trials to determine the efficacy of potentially life-saving interventions such as ECMO are complex to develop and the small number of cases available pose a statistical and ethical challenge around randomisation of these therapies. Yet, judicious candidate selection for advanced life support is important to ensure appropriate resource use and equitable access to care, and to manage patient and caregiver expectations. Thus, we convened an international collaborative group to provide consensus recommendations on the use of ECMO in paediatric patients receiving HCT or immune effector cell therapy.

Methods

We convened a four-member Steering Committee (KMM, MDN, AHA, and PM), who conducted an electronic literature search in PubMed, Embase and Scopus (from Jan 1, 1995, to March 15, 2021) using a combination of key medical terms related to ECMO, neonatal and paediatric

Key messages

- Combined advancements in the fields of paediatric critical care, haematopoietic cell transplantation (HCT), and immune effector cell therapy have been associated with substantial improvements in survival
- Advanced life support technologies, such as extracorporeal membrane oxygenation (ECMO), can be considered in paediatric patients receiving HCT or immune effector cell therapy
- Decisions around ECMO candidacy should be made by a multidisciplinary team (as long-term survival expectations after HCT and immune effector cell therapy continue to evolve rapidly), in conjunction with the patient and family
- Decisions around ECMO candidacy should be guided by the patient's chances of recovery from critical illness in a reasonable amount of time
- ECMO can be used in patients receiving HCT with non-malignant diseases or with malignancies at low risk of recurrence with a reasonable disease-free survival estimation (>30% disease-free survival at 1-year post-HCT)

HCT, and neonatal and paediatric immune effector cell therapies (appendix p 1). Panelists were selected from eight diverse disciplines and the membership and leadership of: (1) the Extracorporeal Life Support Organization (ELSO); (2) Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (HCT and cancer immunotherapy subgroup); (3) the Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT); (4) the supportive care committee of the Pediatric Transplantation and Cellular Therapy Consortium (PTCTC); and (5) the Pediatric Intensive Care Oncology Kids in Europe Research (POKER) group of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC). Recommendations were developed via a Quaker-based consensus technique (figure 1),[28,29] and prepared according to the Appraisal of Guidelines, Research and Evaluation reporting checklist (see appendix for more details).[30]

Recommendations and evidence base

Approach to ECMO candidacy for patients undergoing paediatric HCT or immune effector cell therapy is summarised in figure 2. 36 consensus recommendations are listed in the table.

ECMO indications have increased in the past 10 years and vary according to the patient's age and the centre's experience;[17,20] however, indications are largely determined by the inability to provide adequate gas exchange and adequate end-organ perfusion.

The use of ECMO for neonatal respiratory failure has decreased over the past decade with the advent of high-frequency oscillatory ventilation, surfactant therapy, and inhaled nitric oxide.[17] Yet, its use in paediatric patients has rapidly increased over time.[19]

In children, parenchymal lung diseases (eg, viral and bacterial pneumonia, and aspiration) are the most common respiratory diseases, whereas congenital heart diseases are the most common cardiac indications, followed by septic shock, myocarditis, cardiomyopathies, and cardiac arrest.[20,31] ECMO criteria are well defined for neonatal respiratory failure.[32,33] However, criteria for paediatric respiratory failure are not well defined, vary among centres, and are often guided by derangements of physiological parameters, such as sustained PaO_2 and FiO_2 less than 60–80, sustained elevation of oxygenation index, elevated ventilator pressure (peak airway pressure of more than 28 cmH_2O on conventional mechanical ventilation, or higher than 30 cmH_2O on high-frequency oscillatory ventilation), and evidence of iatrogenic barotrauma on chest radiograph.[17,34] ECMO criteria for

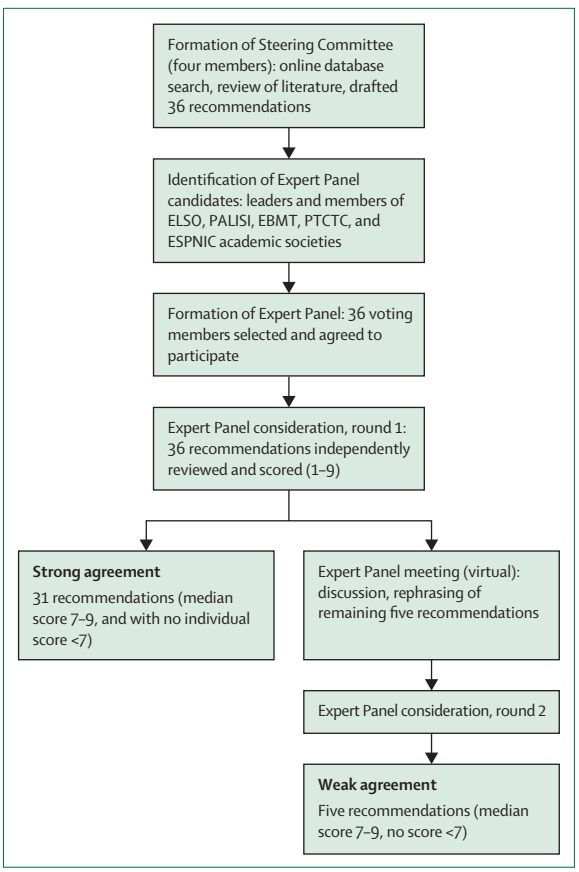

Figure 1: **Flow chart of the method used in the development of consensus recommendations**
Steering Committee members developed recommendations following Quaker-based consensus technique, which were then anonymously voted on by Expert Panel members using the Research and Development/University of California Los Angeles Appropriateness Method Scale EBMT=European Society for Blood and Marrow Transplantation. ELSO=Extracorporeal Life Support Organization. ESPNIC=European Society of Pediatric and Neonatal Intensive Care. PALISI=Pediatric Acute Lung Injury and Sepsis Investigators. PTCTC=Pediatric Transplantation and Cellular Therapy Consortium.

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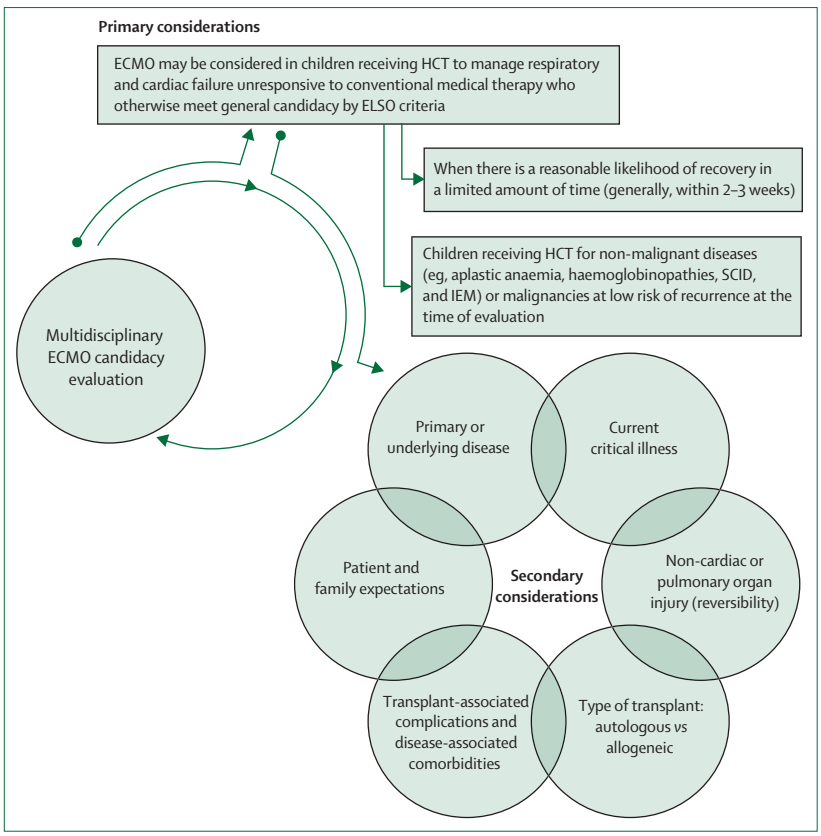

Figure 2: **The approach to evaluating ECMO candidacy in paediatric recipients of HCT and IEC therapy based on the adopted consensus recommendations**
ECMO candidacy of paediatric patients receiving HCT and IEC therapy should be discussed by a multidisciplinary team. Primary considerations should include general ELSO candidacy criteria, primary disease for which they have received HCT or IEC therapy, and anticipated duration of ECMO requirement. Comprehensive secondary considerations should be evaluated on a case-by-case basis ECMO=extracorporeal membrane oxygenation. ELSO=Extracorporeal Life Support Organization. HCT=haematopoietic cell transplantation. IEM: inborn errors of metabolism. SCID=severe combined immune deficiency.

MI, USA; Department of Pediatrics, Division of Pediatric Nephrology, McGovern Medical School, The University of Texas Health Science Center, Houston, TX, USA (Prof R Swinford MD); **Pediatric Critical Care, Children's Healthcare of Atlanta, and Emory University School of Medicine, Atlanta, GA, USA** (Prof M Paden MD, Prof J D Fortenberry MD); **Congenital Heart Center, University of Florida, Gainesville, FL, USA** (Prof G Peek MD); **Division of Pediatric Intensive Care and Neonatal Medicine, Paris South University Hospital, Le Kremlin-Bicetre, France** (Prof P Tissieres MD); **Institute of Integrative Biology of the Cell, CNRS, CEA, Univ. Paris Sud, Paris Saclay University, Paris, France** (Prof P Tissieres);

neonatal and paediatric cardiac failure are similar and are used in patients with persistent poor end-organ perfusion (eg, rising lactate and reduced urinary output) despite maximal medical therapy.[31,33,35,36]

ECMO contraindications can be absolute (eg, lethal chromosomal disorder or other lethal anomaly, severe brain damage, and uncontrolled bleeding) or relative (eg, long duration of mechanical ventilation for more than 14 days, primary pulmonary hypertension, end-stage hepatic or renal failure, pre-existing chronic illness with poor long-term prognosis, or HCT).[17] Relative contraindications have progressively declined, given the positive results observed with the use of ECMO in selected populations previously considered ineligible.[24,37–40]

General considerations for ECMO candidacy among paediatric recipients of HCT

The use of ECMO in patients with reversible respiratory and cardiac diseases has increased and outcomes have improved.[19,34,35,41–42] This positive trend is coupled with a decline in many relative contraindications of ECMO.[37,38] In paediatric patients undergoing HCT, data on ECMO use showed a progressive increase in survival over time compared with previous reports; therefore, the role of ECMO continues to be re-evaluated in selected patients in this population.[22–27,43,44] However, evaluation of ECMO candidacy in this population is challenging and dedicated evidence-based guidelines have not been established. ECMO candidacy and management of this select population is based on feedback from retrospective studies, case series, and case reports.

Malignant and non-malignant diseases are associated with different early and long-term outcomes;[45] therefore, understanding of the primary underlying disease is crucial to evaluate ECMO candidacy and could affect survival. Further, patients with non-malignant diseases can present with multiorgan dysfunction (eg, from iron overload and toxicity),[46] whereas patients with malignant diseases can present with less baseline organ dysfunction, but a higher risk of disease relapse.[47] Based on these considerations, the panel strongly agrees that ECMO may be considered for patients undergoing HCT with non-malignant diseases or with malignancies at low risk of recurrence with a reasonable disease-free survival estimation (>30% disease-free survival at 1 year post-HCT).[48] A disease risk index validated in paediatric patients with acute lymphoblastic leukaemia or acute myeloid leukaemia could help the multidisciplinary team in assessing extracorporeal membrane oxygenation candidacy.[49]

The panel also had strong agreement that current critical illness, its time course, and potential reversibility in a reasonable timeframe may affect ECMO survival.[50–53] Respiratory and cardiac failure after HCT could be due to infectious and non-infectious causes (eg, inflammatory, myocardial injury after chemotherapy, and total body irradiation);[51,54–57] these causes might require different treatments and their reversibility could depend on several factors including the type of transplantation (autologous *vs* allogeneic), the causative agent (eg, multidrug-resistant organisms), response to treatment (eg, anti-inflammatory drugs in hyperinflammatory conditions), and the patient's state of immune reconstitution.[51,52,55] Reversibility of the critical illness in a reasonable amount of time is another important aspect to consider. The risk of mortality due to ECMO complications increases by 1–3% per day of ECMO support.[58–60] Thus, there was strong agreement that ECMO should be considered only when chances of recovery from critical illness are high and expected in a limited time frame (2–3 weeks).[61] Longer periods could place patients at risk of severe, irreversible complications.

Panelists also strongly agreed that the assessment of organ reserve prior to ECMO (eg, duration of mechanical ventilation, chronic heart failure, and presence of liver and kidney dysfunction) is essential for the decision-making process of ECMO candidacy. Data from the general paediatric population suggest that longer duration of mechanical ventilation and the presence of liver or

	Level of agreement
General considerations for ECMO candidacy among paediatric recipients of HCT	
ECMO may be considered in children receiving HCT to manage respiratory and cardiac failure that is unresponsive to conventional medical therapy and who otherwise meet general candidacy by ELSO criteria:	
only when there is a reasonable likelihood of recovery in a limited amount of time (generally, within 2–3 weeks)	Strong agreement (75% agreement)
in children receiving HCT for non-malignant diseases (eg, aplastic anaemia, severe combined immune deficiency, haemoglobinopathies, and inborn errors of metabolism) or malignancies at low risk of recurrence at the time of the evaluation	Strong agreement (88·90% agreement)
in children with refractory thrombocytopenia, ECMO may be considered with extreme caution; reversibility of thrombocytopenia might guide decision-making	Weak agreement
We do not recommend the use of ECMO in paediatric patients receiving HCT who have a disease relapse after more than two HCT	Weak agreement
We do not recommend the use of ECMO in paediatric patients receiving HCT who have a likelihood of disease-free survival of less than 30% at 1-year post-HCT	Weak agreement
Evaluation of ECMO candidacy at bedside	
When evaluating ECMO candidacy in children receiving HCT, clinicians must critically evaluate:	
the underlying primary disease	Strong agreement (97·22% agreement)
the current critical illness, its therapeutic course, and its likelihood of recovery with specific treatments	Strong agreement (100% agreement)
the number of injured organs other than the lung and heart	Strong agreement (97·22% agreement)
the type of HCT (autologous *vs* allogeneic)	Weak agreement
the presence of relapse, disease-associated co-morbidities, or other HCT-specific complications	Strong agreement (97·22% agreement)
the patients' and families' goals of care and expectations	Strong agreement (94·44% agreement)
Use of ECMO relative to neutrophil recovery and engraftment	
ECMO may be considered with extreme caution before neutrophil recovery and engraftment in children receiving autologous or allogeneic HCT with respiratory or cardiac failure due to potentially treatable pathogens (eg, bacterial infections)	Strong agreement (86·11% agreement)
ECMO may be considered in paediatric HCT patients following neutrophil recovery and engraftment only in patients with respiratory failure in whom the likelihood of recovery is high (eg, when available specific therapeutic interventions, such as laboratory-proven effective anti-infectious therapy, adoptive immunotherapy, and anti-TNFα inhibitors may aid recovery)	Strong agreement (95% agreement)
ECMO may be considered in paediatric HCT patients following neutrophil recovery and engraftment only to manage reversible cardiac toxicities (eg, life-threating arrhythmias, cytokine release syndrome, and chemotherapy-induced or viral myocarditis)	Strong agreement (97·22% agreement)
Use of ECMO in patients with primary HCT poor graft function	
ECMO candidacy among paediatric patients receiving HCT with primary graft failure or rejection should be made on a selective case-by-case basis	Strong agreement (86·11% agreement)
If the patient is clinically eligible for HCT boost and re-transplantation (with, for example, no active uncontrolled infection and no active graft-versus-host-disease) and this is reasonably expected to reverse organ dysfunction within a defined period, ECMO may be considered as a bridge to definitive therapy	Strong agreement (80·55% agreement)
Use of ECMO in patients with specific HCT complications	
There are insufficient data to recommend the use of ECMO to manage respiratory or cardiac failure in children with sinusoidal obstruction syndrome or transplant-associated thrombotic microangiopathy	Strong agreement (75% agreement)
Use of ECMO in paediatric long-term survivors after HCT	
ECMO may be considered among long-term survivors (>2 years post-HCT) who are in remission of their primary disease and who have not developed secondary malignancies or have active chronic graft-versus-host-disease	Strong agreement (77·79% agreement)
ECMO may be considered as a bridge to lung transplantation for patients with lung fibrosis (bronchiolitis obliterans) who are at least 2 years cancer-free following HCT and who otherwise qualify for lung transplantation	Strong agreement (75% agreement)
General principles of ECMO management in paediatric patients receiving HCT	
Once ECMO candidacy has been established, we recommend prompt initiation to avoid the progression of multiorgan failure in patients with potentially reversible causes	Strong agreement (91·66% agreement)
We recommend maintenance of high ECMO blood flow rates to reduce the levels of anticoagulation (activated clotting time between 160–180 s)	Strong agreement (75% agreement)
We recommend the use of coated ECMO circuits and oxygenators with a limited number of connectors	Strong agreement (72·22% agreement)
We recommend high vigilance for infection	Strong agreement (97·22% agreement)
We recommend targeting a platelet count of ≥40 000/μL during ECMO	Strong agreement (91·66% agreement)
We recommend maintaining antithrombin-III activity within normal range (80–100%) and fibrinogen levels (>200 mg/dL) with supplementation as needed	Strong agreement (75% agreement)
We recommend the use of renal replacement therapy in the following clinical scenarios: (a) acute kidney injury during ECMO (Kidney Disease Improving Global Outcomes >stage 2, cystatin C estimated glomerular filtration rate <50% baseline, or neutrophil gelatinase-associated lipocalin >150 ng/mL); (b) fluid overload more than 10% and refractory to diuretics; (c) electrolyte abnormalities (including uraemia) unresponsive to optimal medical therapy; and (d) hyperammonaemia (ammonia blood level >250 mmol/L despite maximal medical therapy)	Strong agreement (88·90% agreement)
We recommend lung rest ventilatory settings	Strong agreement (86·40% agreement)
Ancillary respiratory therapies (such as prone positioning and surfactant supplementation) during ECMO should be considered on a case-by-case basis	Weak agreement

(Table continues on next page)

	Level of agreement
(Continued from previous page)	
Use of ECMO in paediatric patients receiving immune effector cell therapy	
ECMO may be considered as a bridge to IEC therapy in paediatric patients on a case-by case-basis	Strong agreement (75% agreement)
ECMO may be considered on a case-by-case basis for paediatric patients receiving IEC therapies	Strong agreement (83·33% agreement)
ECMO may be considered in children with cardio-respiratory failure due to cytokine release syndrome after IEC therapy based on expected reversibility with treatment	Strong agreement (75% agreement)
ECMO may be considered in paediatric patients with IEC-associated haemophagocytic lymphohistiocytosis	Strong agreement (75% agreement)
General framework for multidisciplinary ECMO assessment and management of paediatric patients undergoing HCT and IEC therapy	
Adjudication of ECMO candidacy of paediatric HCT—IEC patients should be conducted by a multidisciplinary team that includes, but is not limited to: ECMO providers, HCT—IEC physicians, palliative and supportive care, social work, pharmacy, nursing, infectious disease, nephrology, patient and their guardians	Strong agreement (88·90% agreement)
Daily management of ECMO in paediatric HCT—IEC patients should be coordinated by a multidisciplinary team with daily rounds and open communication	Strong agreement (94·44% agreement)
Decisions regarding cessation of ECMO in paediatric HCT—IEC patients for futility should be made by a multidisciplinary team and consider pivotal timepoints for evaluation that were established before its initiation	Strong agreement (100% agreement)
Importance of registry reporting of ECMO patients	
Paediatric HCT—IEC patients who are supported with ECMO should be reported to dedicated data registries	Strong agreement (100% agreement)

ELSO=Extracorporeal Life Support Organization.

Table: **Summary of international and multidisciplinary consensus-based recommendations on the use of extracorporeal membrane oxygenation (ECMO) in paediatric patients receiving haematopoietic cell transplantation (HCT) or immune effector cell (IEC) therapy**

Division of Pediatrics, Transportation and Neonatal Critical Care Medicine, APHP, Paris Saclay University Hospital, "A.Beclere" Medical Center and Physiopathology and Therapeutic Innovation Unit-INSERM-U999, Paris Saclay University, Paris, France (Prof D De Luca MD); **Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University of Regensburg, Regensburg, Germany** (Prof S Corbacioglu MD); **Division of Pediatric Critical Care Medicine, Department of Pediatrics, Beatrix Children's Hospital Groningen** (Prof M Kneyber MD), **and Critical Care, Anesthesiology, Peri-Operative and Emergency Medicine (CAPE)** (Prof M Kneyber), **University Medical Centre Groningen, University of Groningen, Groningen, Netherlands; Pediatric Intensive Care Unit, Imperial College Healthcare NHS Trust, London, UK** (Prof S Nadel MD); **Interdisciplinary Pediatric Intensive Care Unit, Universitäetsklinikum Tuebingen, Tuebingen, Germany** (Prof M Kumpf MD); **Department of Pediatric Intensive Care, University Medical Center Utrecht/ Wilhelmina Children's Hospital, Utrecht, Netherlands**

kidney failure before ECMO are associated with increased mortality.[62,63]

Bleeding is an important complication of ECMO that often limits its potential benefits; therefore, strict haemostatic balance should be achieved.[64,65] Generally, according to the ELSO criteria,[65,66] platelet counts should be maintained between 80 000/μL and 100 000/μL to reduce the risk of bleeding during ECMO; however, this target could be infeasible in patients receiving HCT because of their haematological status.[25] Therefore, clinical situations of refractory thrombocytopenia should be evaluated with extreme caution before considering ECMO (weak recommendation).[67] Potential reversibility of thrombocytopenia (eg, with pending platelet engraftment or resolution of consumptive coagulopathy) might guide the decision making.

The panel reached weak agreement regarding the importance of considering the type of HCT during the ECMO candidacy process. Data show no difference in terms of ECMO survival between patients receiving autologous versus allogeneic HCT;[26] however, it is well known that both are associated with different transplant-related mortality, which is lower (≤5%) in autologous than in allogeneic HCT (up to 10–20%).[4,49,68,69] Further, the type of HCT and the preparative regimen (myeloablative *vs* reduced-intensity conditioning) could affect post-transplant outcomes,[45,52] contribute to organ toxicity (eg, sinusoidal obstructive syndrome), transplant-related mortality (eg, infections and acute graft-versus-host-disease), and immune reconstitution.[23,25,48,52]

Impaired immune reconstitution following myeloablative allogeneic HCT could alter T-lymphocyte and B-lymphocyte counts and function with associated susceptibility to viral and fungal infections. Graft characteristics (eg, donor source, cell dose, graft manipulation for T-cell depletion, and HLA matching) could also affect HCT outcomes;[52] however, although immune reconstitution is a key variable influencing outcomes after HCT,[2] improvements in HLA-matching techniques, availability of adoptive cell therapy for infectious complications, early detection and management of sinusoidal obstructive syndrome, and graft-versus-host-disease have rendered graft characteristics of less importance when evaluating ECMO candidacy at bedside.[44,53,67,70,71]

The rapid advancements in HCT and immunotherapies, (eg, anti-CD19 chimeric antigen receptor T-cells and bispecific T-cell engager blinatumomab) continue to change survival expectations and have made the establishment of ECMO contraindications in paediatric patients receiving HCT particularly challenging. Low likelihood of recovery after disease recurrence and progression is difficult to ascertain or predict with the dynamic treatment options available in the cellular and immunotherapy fields. Despite this, patients who have disease relapse after more than two HCTs and a low likelihood of recovery (disease-free survival <30% at 1 year post-HCT) should be considered as absolute contra-indications for ECMO (weak agreement).[16,65,72] Thus, it is very important to encourage an open and multidisciplinary discussion, including the patient and family members, to individualise ECMO indications and discuss in advance when to stop ECMO in cases of irreversible complications (strong agreement).[73,74] The best measures of success for ECMO are unclear. The panel extrapolated expected survival benchmarks for other high-risk groups considered eligible for ECMO, with a disease-free survival assessment point that is standardly available in HCT. For example, in-hospital survival of young infants with

disseminated herpes simplex virus or *Bordetella pertussis* pneumonia is approximately 25–30% with ECMO, and disease-free survival among patients receiving HCT is usually assessed at 1 year.[16]

In summary, decisions around ECMO candidacy should be made by a multidisciplinary team in conjunction with the patient and family, and should be guided by chances of recovery from critical illness in a reasonable amount of time (generally 2–3 weeks).

Use of ECMO before neutrophil recovery and engraftment

The panel strongly agreed that ECMO may be considered with extreme caution before neutrophil recovery and engraftment in children receiving autologous or allogeneic HCT with respiratory or cardiac failure due to potentially treatable pathogens. Use of ECMO before neutrophil recovery and engraftment in this population has been historically considered an absolute contraindication; however, a new report suggest that among patients undergoing HCT who develop acute respiratory failure and require advanced therapeutic support, neutrophil recovery at time of respiratory failure and presence of a respiratory pathogen should not be used as determining factors when counselling families about survival.[75] Anecdotal reports of long-term survival (up to 1 year) have emerged among patients receiving HCT who received ECMO support before neutrophil recovery in the setting of bacterial infection.[38,74,76] Further, the successful use of granulocyte transfusions as a bridge to neutrophil recovery and newer antibiotic regimens suggest that the presence of a bacterial infection in an HCT recipient before neutrophil recovery should not be the sole basis for exclusion from ECMO candidacy.[77]

Early viral and fungal infections following HCT, in particular before white blood cell recovery in the allogeneic setting, are challenging and further complicated by impaired T-cell and B-cell immune reconstitution.[48] With these types of infections, ECMO candidacy should be considered with extreme caution. Available antiviral and antifungal therapies have insufficient efficacy in the absence of functional lymphocytes, which is common in the early phases after HCT;[78–80] further, the time to robust immune reconstitution is dependent on the preparative regimen used, graft source and processing, presence of graft-versus-host-disease, and specific graft-versus-host-disease prophylaxis and management, and infusion of donor or third-party allogeneic cytotoxic lymphocytes is generally avoided before neutrophil recovery and engraftment.

Use of ECMO following neutrophil recovery and engraftment

The panel strongly agreed that ECMO may be considered in paediatric HCT patients following neutrophil recovery and engraftment only in patients with respiratory or cardiac failure, or both in whom the likelihood of recovery of the critical illness is high (expected ECMO survival >30%).

Immune deficits could persist for more than 1 year following HCT.[81] Poor immune reconstitution could reduce the potential for recovery from infectious causes of respiratory and cardiac failure; therefore, ECMO should be considered only when the expected survival is more than 30%, or when specific therapies to treat refractory infections are available.[48] The emergence of surveillance strategies for early detection of infectious reactivation (eg, next-generation sequencing assays)[82] and advancements in adoptive immunotherapies (such as the availability of donor third-party cytotoxic lymphocytes directed, but not limited to, viral pathogens—eg, cytomegalovirus, adenovirus, BK and JC virus, Epstein-Barr virus, SARS-CoV-2) could allow for effective treatment when immune reconstitution is still impaired.[44,83] These therapies have also been successfully used during ECMO.[44]

Idiopathic pneumonia syndrome is a major cause of non-infectious mortality after allogeneic HCT, and tumour necrosis factor-α is a driving effector molecule in this process.[39,84] A tumour necrosis factor-α inhibitor, etanercept, in conjunction with corticosteroids has been associated with favourable outcomes for idiopathic pneumonia syndrome. Response rates of 50–70% in early-onset idiopathic pneumonia syndrome (≤100 days after HCT) have been observed. Among patients with late-onset idiopathic pneumonia syndrome (>100 days after HCT), up to 43% have shown complete clinical responses with a durable survival benefit at 2-year follow-up.[85] Therefore, patients with the most severe forms of idiopathic pneumonia syndrome could benefit from ECMO support while awaiting the effects of etanercept and corticosteroids.[39]

Myocarditis associated with allogeneic immune reactions could have a poor prognosis, including sudden cardiac death, but the response to immunosuppressive therapy is generally good.[55,56] Considering the reversibility of these abnormalities after immunosuppressive therapy, it is reasonable to consider ECMO as a bridge to recovery. Similarly, arrhythmias and other serious cardiac dysfunction that could be seen in cytokine release syndrome following related haploidentical HCT and immune effector cell therapies are generally reversible with appropriate interventions and could benefit from ECMO.[35,86]

Use of ECMO in patients with poor graft function

Poor graft function is defined as bilinear or trilinear severe cytopenia (ie, persistent thrombocytopenia $<20\times10^3$/μL and haemoglobin <70 g/L, and neutropenia $<0\cdot5\times10^3$/μL) after engraftment, with hypocellular bone marrow, without graft-versus-host-disease or disease relapse.[87] Historically, the outcome of poor graft function has been poor. However, changes in indications for HCT,

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transplantation regimens, and graft manipulation have modified the landscape for these patients, and some could benefit from a second transplant in these scenarios. Rescue transplants have been associated with successful engraftment and long-term survival.[88–90] Stem cell boosts administered without further chemotherapy or radiation have also been associated with good outcomes.[88]

Therefore, the panelists strongly agreed that ECMO candidacy among paediatric HCT patients with poor graft function should be evaluated on a case-by-case basis and with a multidisciplinary team. Quality of life and patients' goals of care after HCT should also be re-evaluated during the multidisciplinary meeting. The panel agreed that ECMO candidacy for these selected cases should consider: medical eligibility for rescue HCT, stem cell boost, presence or absence of complications including relapse, refractory thrombocytopenia, sinusoidal obstructive syndrome, graft-versus-host-disease, active and uncontrolled infection, and potential chances of survival with a rescue HCT procedure (strong agreement).

Use of ECMO in patients with specific HCT complications

The panel strongly agreed that there are insufficient data to recommend the use of ECMO to manage respiratory or cardiac failure in children with sinusoidal obstruction syndrome or transplant-associated thrombotic microangiopathy; thus, decisions regarding ECMO candidacy in patients with these complications should be made on a case-by-case basis with a multidisciplinary team discussion evaluating benefits and risks. Non-infectious causes of acute and chronic respiratory failure include pulmonary oedema, pulmonary toxicity syndrome (eg, following cyclophosphamide, bleomycin, and methotrexate), sinusoidal obstructive syndrome, diffuse alveolar haemorrhage, idiopathic pneumonia syndrome, and pulmonary manifestations of graft-versus-host disease such as bronchiolitis obliterans. These causes all require different treatments with reported variable outcomes. In such cases, the use of ECMO should warrant a case-by-case consideration supported by the fact that anecdotal case reports suggest a survival benefit in specific circumstances, such as peri-engraftment syndrome,[91] diffuse alveolar haemorrhage,[92–94] idiopathic pneumonia syndrome,[39,76] chronic graft-versus-host-disease, and bronchiolitis obliterans.[95]

Use of ECMO in paediatric long-term survivors

Important factors affecting long-term survival are: disease recurrence, organ failure, and secondary cancers.[96] Chronic graft-versus-host-disease is another important factor associated with late mortality in recipients of allogeneic HCT.[96] Outcome studies show that children in remission for 2–5 years after transplantation have a high probability of long-term survival.[49] Poor immune status is a well known risk factor for ECMO mortality, which improves over time with a reduction of immunosuppressive therapies, and new therapies to prevent and treat graft-versus-host-disease have shown promising results.[97] Taken together, the panel strongly agreed that ECMO may be considered among paediatric long-term survivors (>2 years post-HCT), who are in remission of their primary disease and who have not developed secondary malignancies or have active chronic graft-versus-host disease. Considerations for lung transplantation in paediatric patients receiving HCT with bronchiolitis obliterans is beyond the scope of this Review. In one case series, the median time between HCT and lung transplantation was 18 months.[98] Ideal candidates for lung transplantation are expected to have had prolonged survival after HCT.[99] Given that paediatric long-term survivors of HCT might be candidates for lung transplantation, the panel strongly agreed that ECMO may be used as a bridge to lung transplantation in long-term survivors with acute on chronic respiratory failure due to bronchiolitis obliterans".[100–104]

General principles of ECMO management in paediatric patients receiving HCT

The panel strongly agreed that ECMO should be initiated early,[22,23,91,105] as soon as general ELSO cardiac or respiratory criteria are met,[31,34] to avoid the development and progression of multiorgan failure in potentially curable children. Data suggest an increased risk of mortality in paediatric patients receiving HCT with high oxygenation index, high positive end-expiratory pressure, need for high doses of inotropic support, and long duration of mechanical ventilation before ECMO.[22,25,49,63] Further, the use of high peak inspiratory pressure (39 cmH_2O [IQR 30–45]) in paediatric patients receiving HCTs before extracorporeal membrane oxygenation was associated with reduced survival.[26] An oxygenation index of 38 or less before ECMO was associated with 75% sensitivity and 81·3% specificity in distinguishing survivors from non-survivors;[22] use of high positive end expiratory pressure (eg, >10 cmH_2O) before ECMO was more frequent in non-survivors, but this finding was not significant in all studies.[22,26] Currently established prediction scores (Ped-RESCUERS and P-PREP) for children receiving ECMO suggest that use of milrinone or long duration of mechanical ventilation (>14 days) before ECMO are associated with reduced survival.[50,63]

Delayed immune reconstitution and immunosuppressive treatments for control of bidirectional alloreactivity (ie, graft-versus-host disease and host-versus-graft effect, leading to graft rejection) increase the risk of opportunistic infections.[2] Despite these considerations, infections during ECMO were not associated with mortality in paediatric patients receiving HCT.[23,26] Still, the panel strongly recommends high-vigilance for infections in paediatric HCT patients receiving ECMO as typical signs and symptoms of sepsis such as fever could be absent and changes in vital signs (eg, fever) might be subtle while receiving organ support.

Children undergoing HCT could experience severe hyperinflammatory states (eg, sepsis, alloreactivity, and cytokine release syndrome), which can affect both primary (ie, platelet count and function) and secondary haemostasis (ie, the overall clotting and bleeding risk),[65] increasing the risk of bleeding. This risk could be further amplified during ECMO by the contact of blood with the foreign surfaces of the ECMO circuit and by the anticoagulation strategy used (eg, heparin and bivalirudin).[65,106,107] Historically, unfractionated heparin has been used for anticoagulation during ECMO; studies from the past 5 years show similar efficacy and safety (ie, risk of bleeding and thrombosis) with direct thrombin inhibitors (eg, bivalirudin and argatroban). Bivalirudin has been most frequently used in paediatric patients receiving ECMO as an alternative to heparin for its simplicity to titrate and non-dependency on antithrombin activity. Although bivalirudin can be considered as a good alternative to heparin for anticoagulation during ECMO, its superiority has not been shown; further, there are no data on bivalirudin anticoagulation in children supported with ECMO after HCT.[108,109]

Coagulation management among paediatric patients having HCT receiving ECMO is challenging compared with the general PICU population. Thus, the panel strongly agreed that anticoagulation during ECMO should be accurately tailored in patients receiving HCT, balancing both the risks of bleeding and thrombosis. The achievement of these goals is complex and requires a strict and individualised management of platelet count and all other clotting parameters (ie, activated clotting time, activated partial thromboplastin time, prothrombin time, anti-Factor Xa, fibrinogen concentration, and d-dimer concentration).[64,65] Unfortunately, data in neonatal and paediatric patients receiving ECMO suggest that laboratory measurements of anticoagulation such as activated clotting time, activated partial thromboplastin time, and anti-Factor Xa levels are unable to predict the risk of bleeding or thrombosis during ECMO; further, they correlated poorly with each other and with the dose of anticoagulant used (eg, heparin).[110] Thus, many clinicians are adopting viscoelastic tests such as rotational thromboelastometry or thromboelastography to stratify the risk of bleeding.[111–113] These tests allow bedside assessment of clotting time (eg, reaction time with thromboelastography or clotting time with rotational thromboelastometry) and help define the role of platelets, fibrinogen, and fibrinolysis on clot formation. In neonatal and paediatric patients receiving ECMO, maintaining a thromboelastography reaction time (evaluated kaolin) of more than 17 min could reduce the risk of thrombosis,[114] although values of reaction time that correlate with bleeding are undefined. Specific data on viscoelastic tests are scarce in patients having HCT receiving ECMO.

Patients having HCT generally receive prophylactic platelet transfusions when the platelet count is less than 10 000/μL.[115] During ECMO, the consumption of platelet and coagulation factors is amplified; thus, a higher platelet count should be maintained to reduce the risk of bleeding. Due to this precarious haemostatic equilibrium, the panel strongly agreed that a platelet count higher than 40 000/μL should be maintained to avoid bleeding during ECMO and that fibrinogen and antithrombin III should be supplemented with plasma-derived concentrate to maintain physiological levels (>200 mg/dL and 80–100%, respectively).[116,117] Plasma supplementation is not recommended for fibrinogen and antithrombin III supplementation and should be reserved only to correct deficits of coagulations factors due to consumption.[66] The trend of d-dimer concentrations can be of help to monitor progressive oxygenator failure due to clots.[64] Use of high ECMO blood flow and antithrombogenic coated circuits and oxygenators could help to reduce levels of anticoagulation (activated clotting time between 160–180 s),[118,119] even if robust data are inadequate supporting these practices (strong agreement).[105,120] Definition of high ECMO flow is challenging, is based on adult data, and could depend on the ECMO type (venoarterial *vs* venovenous). Data suggest that anticoagulation for venoarterial ECMO could be stopped as long as ECMO flows are maintained at a level that allows complete blood exchange in the circuit at least every 20 s (2 L/min).[121] In venovenous ECMO, anticoagulation could be stopped if ECMO blood flows are maintained at 3–3·5 L/min at the minimum.[118]

When bleeding is the major issue (eg, diffuse alveolar haemorrhage), and likelihood of survival is otherwise expected to be high, alternative strategies without anticoagulation can be considered.[121]

In general, we have insufficient data to support the use of a specific mode of mechanical ventilation or specific ventilator settings during ECMO. Therefore, for children who have HCT receiving ECMO, the panel strongly agreed to follow the current ELSO guidelines.[34] This means maintaining a low–normal peak inspiratory pressure of lower than 25 cmH_2O, a fraction of inspired oxygen lower than 50%, a positive end-expiratory pressure at 5–15 cmH_2O to avoid de-recruitment, and a low respiratory rate. Spontaneous breathing could be a reasonable option to reduce sedation, allow mobilisation, and enhance recovery; however, when applied, it should not prevent the maintenance of an adequate pump flow. Ancillary respiratory therapies did not have any survival benefit in paediatric acute respiratory distress syndrome; thus, their use during extracorporeal membrane oxygenation remain controversial and should be evaluated on a case-by-case basis (weak agreement).

Acute kidney injury in paediatric patients receiving HCT could occur as part of other organ dysfunction syndromes or as a cytokine-driven processes, which could first manifest clinically as fluid accumulation.[122] Paediatric patients requiring ECMO frequently develop acute kidney injury (ie, from the Kidney Disease: Improving Global Outcomes guideline of stage 2 or

more) as progression of multiorgan failure or secondary to renal ischaemia due to hypoperfusion from low cardiac output.[123] Additionally, the initiation of ECMO itself could predispose patients to the development of, or worsening of acute kidney injury via (1) hypoperfusion from non-pulsatile renal blood flow in venoarterial-ECMO, (2) blood exposure to artificial surfaces leading to systemic inflammation and hypercoagulability, and (3) haemolysis leading to haemoglobinuria, which can be further worsened by excessive negative pressure generated by ECMO pump management.[124] Cumulative fluid overload and failure to return to dry weight have been associated with higher mortality and longer duration of ECMO.[123,125] Thus, maintenance of strict fluid balance is essential during ECMO and can improve gas exchange.[34,123,125] The panel strongly agreed that renal replacement therapy should be considered when fluid overload is higher than 10% (from PICU admission or baseline weight) and refractory to diuretics.[126–130]

Use of ECMO in paediatric patients receiving immune effector cell therapy

Immune effector cell therapies have been associated with remarkable outcomes for patients with relapsed and refractory acute lymphoblastic leukaemia who previously had no curative options.[83] Eligibility for these therapies usually balances risks with whether immune effector cell therapy can reverse the potentially disqualifying comorbidities present. The panel strongly agreed that ECMO may be considered as a bridge to immune effector cell therapy in cases of acute respiratory or cardiac failure, or both, on a case-by case-basis.[131] Following immune effector cell therapy, extreme refractory hypoxaemia with cytokine release syndrome is rare; it is important to evaluate the differential diagnosis of cytokine release syndrome (eg, paediatric acute respiratory distress syndrome secondary to septic shock, pulmonary oedema, and diffuse alveolar haemorrhage). There are insufficient data to support the use of ECMO to manage complications such as cytokine release syndrome and immune effector cell-associated haemophagocytic lymphohistiocytosis. Thus, we recommended that ECMO be considered on a case-by-case basis, based on the expected reversibility of these complications (strong agreement).[83,132]

General framework for multidisciplinary ECMO assessment and management

The panel had strong agreement that multidisciplinary rounds and open communication between the health-care providers and families are essential for the successful management of these patients, especially when receiving advanced life-supportive therapies. Daily open communication is a pivotal strategy to reduce health-care staff resentment, moral distress, and build resilient behaviour among health-care staff working with these patients.[133–135] Health-care staff must consider the patients and families' goals of care and expectations while trying to balance the benefit of this invasive intervention versus the risk of futile care.[16,73,136] Intensivists, oncologists, and haematologists are not the sole arbiters to decide who should or should not receive ECMO; nursing staff, social workers, pharmacists, and caregivers should be involved in any decisional steps (strong agreement).[137] Team alignment around shared goals of care is important.[138] Ensuring that both health-care providers and the family understand why ECMO is used, the possible outcomes, and when and how it will be stopped in case of no response to treatment, will help the whole team to be prepared for the worst, while working for the best clinical outcomes.

Importance of registry reporting of ECMO in patients

Data analysis using national (eg, PEDECOR, PHISD, and PediECMO) and international (eg, ELSO) registries is foundational to understanding the role of ECMO in the management of paediatric patients receiving HCT or immune effector cell therapy. However, these registries present several limitations. Data entry is voluntary, which could limit the completeness and accuracy of available data sets. Registries for ECMO, HCT, and immune effector cell thearpy were not built to capture the complexity of these patients and comprehensive clinical information is often unavailable. Further, data coming from these disparate registries are difficult to combine (although not impossible).

The panelists strongly recommend that patients receiving HCT or immune effector cell therapy who are supported with ECMO should be reported to dedicated data registries. Although no existing registry is ideal, expansion of joint registry efforts could facilitate improved data capture in the future. This effort could soon refine the selection criteria and management of patients receiving HCT supported with ECMO. Adoption of clinical decision tools could facilitate more standardised practice from which we can better determine optimal candidate selection, ECMO timing, and best practice (eg, anticoagulation and management of fluid overload), and assess measures of success, including, survival, quality of life, and long-term neurodevelopmental outcomes.[65]

Limitations

The most important limitation is the lack of high-quality evidence available, which limits the consistency and the generalisability of our recommendations. Nevertheless, the panel believes that these consensus recommendations are based on a rigorous and standardised process that is useful in circumstances of inadequate published evidence.

These recommendations might not be appropriate for low-resource settings where some adjunctive therapies are not immediately available (eg, rapid availability of adoptive cellular therapies to treat specific infective agents and biological expertise in donor graft manipulation).

Regardless, these international and multidisciplinary recommendations across multiple academic societies are an important step forward.

Conclusions

Improved PICU survival of patients receiving HCT has encouraged critical care physicians to reconsider the use of extracorporeal life support intervention such as ECMO to manage refractory acute respiratory failure or cardiogenic shock in this patient population. There are no published guidelines regarding the use of ECMO in paediatric patients receiving HCT or immune effector cell therapy, and the published evidence is scarce. In this Review, we establish that these patients could be eligible for advanced life support therapies such as ECMO. We provide the first international and multidisciplinary consensus recommendations on the use of ECMO in children receiving HCT or immune effector cell therapy. These recommendations can serve as a clinical decision support tool during the difficult decision-making process regarding ECMO candidacy and during management of these patients with complex needs. Further, they establish a platform for future research in this field including, but not limited to, optimal ECMO candidate selection, time to ECMO initiation, and optimal management such as anticoagulation practices and fluid overload.

Contributors

KMM, MDN, AHA, and PM conceptualised the project and as Steering Committee members performed a literature review and drafted recommendations for voting by expert panel members. DDL and MKn served as methodologists for the project. BS, KM, BDB, MEM, AL, OG, DDL, and JB were non-voting members involved in the project, revised the manuscript, and provided feedback. All other authors served as voting panel members who reviewed the literature and participated in Quaker-based consensus development as described in the methods. All authors made meaningful contributions to the drafting and revising of the manuscript.

Declaration of interests

We declare no competing interests.

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