Review Article

Transfusion management during extracorporeal membrane oxygenation for extended indications: a narrative review

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Background and Objective: Extracorporeal membrane oxygenation (ECMO) support is associated with a high rate of blood product transfusions, but the amount of transfusions is associated with increased mortality rate. Thus, judicious transfusion strategies should be put in place. However, there is no homogeneous transfusion practice among centres and there is a lack of consensus about transfusion triggers during ECMO. This is enhanced for the special clinical situation in which ECMO is performed. We aimed to verify if there is a common approach to hemocomponent transfusion and if there is a consensus about transfusion thresholds among studies, especially in those who investigate ECMO support for special circumstances such as bridge-to-transplant treatment, sepsis, trauma, or shock during pregnancy. The main scope of this review is to summarize previously published findings about transfusion protocols and practice during ECMO, focusing on extended indications.

Methods: The PubMed database was used to identify articles we were interested in. All these papers were written in the English language and were published between 1990 and 2022.

Key Content and Findings: We found heterogeneity in transfusion strategy during ECMO support. Amongst the papers analyzed, few studies identify transfusion thresholds and protocols during ECMO for special conditions.

Conclusions: We endorse the need for further observational studies to clarify current transfusion strategies in ECMO patients among different centres before starting new trials on this topic.

Keywords: Extracorporeal membrane oxygenation (ECMO); blood transfusion; blood transfusion triggers; extended indications for ECMO; ECMO for special circumstances

Received: 30 November 2021; Accepted: 14 October 2022; Published online: 02 November 2022.
doi: 10.21037/aob-21-81
View this article at: https://dx.doi.org/10.21037/aob-21-81

Introduction

Establishing a transfusion threshold can be a challenge in critically ill patients undergoing extracorporeal membrane oxygenation (ECMO) support. Extracorporeal Life Support Organization (ELSO) recommends maintaining Hb levels to achieve an optimal oxygen delivery (for most ECMO centres this level is between 7–12 g/dL) (1) but these data are not yet supported by solid scientific evidence.

Table 1 Emerging indications for ECMO

New ECMO indications
Bridge to heart or lung transplantation
Trauma-related respiratory failure
Sepsis-related respiratory failure
Pulmonary hypertension
Shock state during pregnancy

ECMO, extracorporeal membrane oxygenation.

There are several reasons why clinicians may decide to transfuse a patient with ECMO support: to counteract the haemodilution resulting from circuit priming, to improve oxygen delivery, to restore the haemostatic balance and to compensate for blood losses due to hemolysis and, frequently, for haemorrhagic complications. For each of these scenarios, it is unsurprising that patients on ECMO support have a higher transfusion requirement (2).

What complicates the determination of the transfusion threshold is the variability of blood component requirements for different clinical conditions. For example, both adult and paediatric venovenous (VV) ECMO patients with respiratory failure are shown to be less need of transfusions than venoarterial (VA) ECMO patients mainly because of hemolysis and haemorrhagic complications which often occur during VA ECMO configuration. The longer ECMO circuit and duration performed in adult patients compared to paediatric patients can partially explain why the former has greater transfusion requirements (3).

However, modern ECMO circuits are shorter, more biocompatible and heparin-coated, and have smaller oxygenators resulting in less haemolysis and ultimately a lower haemorrhagic risk. The shorter circuit and less haemodilution by priming with crystalloid (<1 L) ultimately means a lower transfusion requirement for all patients (4).

New ECMO indications

Upcoming technological advances are boosting the implementation of ECMO in several forms of cardiorespiratory support. The major indications for ECMO support are both hypoxemic and hypercapnic respiratory failure (5) and cardiac/circulatory failure [including refractory cardiogenic shock (6,7) and cardiac arrest (8)]. Along with these "conventional" indications, the positive outcomes, have resulted in a recent resurgent interest also for other clinical conditions (*Table 1*) (9,10).

As stated above, evidence-based transfusion thresholds for haemocomponents during ECMO support do not exist in the literature. One reason for this is that blood transfusions are associated with adverse events, such as volume overload, transfusion-associated acute lung injury (11), immunomodulation, human leukocyte antigen (HLA) sensitization, red blood cell (RBC) antigen sensitization, and transfusion-transmitted infection. As a result, it is necessary to perform a careful risk-benefit analysis (12) before deciding on transfusion. Studies report that stored RBCs have a lower concentration of 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) leading to a reduced O_2-binding capacity. In addition, during storage, RBCs are prone to increased membrane stiffness and osmotic fragility, and once transfused, they might activate the inflammation system resulting in an increased risk of thrombosis (13). ECMO blood flow is an important determinant of oxygen delivery to the tissues, and RBC transfusion is found to increase oxygen content, resulting in augmented delivery even at lower ECMO blood flow rates (14).

Aim of the review

This review aims to examine the different transfusion strategies present in the literature, focusing on the circumstances in which liberal protocols are adopted, with a particular interest in emerging indications. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.com/article/view/10.21037/aob-21-81/rc).

Methods

We conducted our search on the electronic database PubMed. The search was limited for articles in English languages and published from 1999 to 2022. Keywords used for the search were: "extracorporeal membrane oxygenation", "blood transfusion", "blood transfusion triggers (or thresholds)", "extended (or broadened) indications for ECMO", "ECMO for special circumstances". Of the 30 results, we counted only ten articles (shown in *Table 2*) in which authors established laboratory parameters as transfusion triggers.

Table 2 The search strategy summary

Items	Specification
Date of search	10.10.2021
Databases and other sources searched	PubMed
Search terms used	"Extracorporeal membrane oxygenation", "blood transfusion", "blood transfusion triggers (or thresholds)", "extended (or broadened) indications for ECMO", "ECMO for special circumstances"
Timeframe	1990–2022
Inclusion criteria	English language
Selection process	The selection was conducted independently by two investigators (ST and CV) and then revised by two senior investigators (FS and GM)

Discussion: conventional *vs.* unconventional uses of ECMO

Conventional indications: *liberal vs. restrictive transfusion strategy*

There are several retrospective studies showing the safety of the restrictive strategy (14). Despite the conventional haemoglobin threshold to define restrictive strategy being 7 g/dL, in ECMO the current practice is to consider the restrictive strategy with a higher threshold (15). There is a meta-analysis that demonstrates that the higher the haemoglobin transfusion threshold the higher the mortality rate (16). A recently published multicentre, prospective, cohort study including 604 adult patients on VV-ECMO for ARDS enrolled between 1 December 2021 and 22 February 2022, identified 7 g/dL as the only PRBC transfusion threshold associated with lower mortality rate (17).

In a retrospective study (18), including 402 patients treated with VV ECMO between 2011 and 2017, different strategies were compared. In 2014, after switching from a liberal to a restrictive transfusion protocol (with a haemoglobin transfusion threshold below 8 g/dL), investigators described the outcomes, complications related to transfusions and costs of patients treated with a liberal *vs.* restrictive strategy. Mortality rates were comparable between the two groups and to those of the ELSO registry. When a restrictive transfusion strategy was used, the average number of units transfused fell by 0.2 RBC units per ECMO day. This could result in significant cost-sparing effect and prevent unnecessary use of blood products. Moreover, with restrictive transfusion, there was a decrease in the extracorporeal blood flow of 0.5 L/min. However, non-survivors on VV ECMO had higher RBC transfusion requirements following a shift in transfusion practice.

In another study (19), 415 transfused acute respiratory distress syndrome (ARDS) patients were divided into two main groups: 128 with a 10 g/dL transfusion threshold and 240 patients at 8 g/dL (47 patients were excluded for incomplete data sets) The latter group was analyzed with 1:1 propensity score matching; 99 patients were placed on ECMO and 70 were not. During the first 28 days from ARDS onset, authors found that patients in the lower-threshold group were more difficult to wean from mechanical ventilation than higher-threshold group patients, while among patients who underwent ECMO support, those in the higher-threshold group had comparable rates of ECMO weaning than the lower-threshold group.

Unconventional indications

ECMO and transplantation

Today, patients with respiratory and cardiac failure for end-stage disease can benefit from ECMO support as a bridge treatment for transplantation (20,21). However, we found few studies in which transfusion triggers were clearly defined.

VV ECMO, acting as a valid substitute for maximal ventilatory support, can avoid ventilatory-induced lung injury and deep sedation and ultimately attenuate cardiorespiratory, musculoskeletal, and metabolic deconditioning. One study (22) investigated patients listed for lung transplantation who developed acute respiratory failure and compared the outcomes between those who received ECMO support as bridging treatment (15 patients) to those who did not (10 patients). In this study, the main triggers to PRBC transfusion were: active bleeding, hypoxemia, and haematocrit below 25%. Among the ECMO group, 9 patients survived to hospital discharge.

Of these patients, seven were transplanted. The amount of RBCs transfused was significantly higher in non-survivors (3.3 *vs.* 18.5 U, P=0.003).

Similarly, VA ECMO is a fundamental mechanical circulatory support for patients with heart failure awaiting heart transplantation. In a retrospective single-centre observational study (23) that included 64 children undergoing mechanical circulatory support for at least 2 days, over a period of approximately 12 years (January 1990 to July 2002), the authors compared outcomes of interest among those on ECMO support (34 patients) and those who were on a pulsatile flow (paracorporal and pneumatically driven) mechanical support device called Berlin heart (30 patients). Of the 64 children with terminal heart disease, nearly half (31 patients) were on the list for heart transplantation: 23 received Berlin heart support and 9 received ECMO as a bridge to transplant treatment. The local transfusion protocol was to transfuse PRBC, fresh frozen plasma, and platelets when haemoglobin was below 9 g/dL, fibrinogen was below 180 mg/dL, and platelets were below 70,000/mm^3. In general, children on ECMO support had a significantly higher daily transfusion requirement (mL/kg bw/day) of RBCs (60.32±17.18 *vs.* 17.18±2.2, P<0.001), fresh frozen plasma (46.96±21.01 *vs.* 8.50±3.98, P<0.001) and platelets (24.63±6.26 *vs.* 4.32±0.98, P<0.001) than those on Berlin heart support. These results suggest that the decision-making process to transfuse the patients should take into account not only the levels of haemoglobin but also the circuit management and the ECMO configuration.

Regarding ECMO support during liver transplantation, applying a restrictive strategy to transfusion is imperative due to the higher risk of bleeding. We are aware of a case report (24) in which VA ECMO was used as a rescue option in the case of portopulmonary hypertension recognized intraoperatively. The authors emphasize the temporary nature of this support because of the well-known higher risk of bleeding and infection typically observed in patients who undergo liver transplantation.

ECMO and sepsis

ECMO has also shown benefits as a rescue treatment in patients with sepsis-related respiratory failure. Since the lung is the most common source of sepsis (25), successful treatment of respiratory failure can reduce the mortality rate in patients with sepsis. However, choosing the right timing and transfusion threshold in the septic patient can be a challenge due to the increased oxygen consumption typically observed in this cluster of patients. In a large multicentre observational study (26), data from 3,195 patients with severe sepsis or septic shock admitted to 42 ICUs from 40 institutions across Japan were retrospectively analyzed. Among patients diagnosed with severe respiratory failure, those who received ECMO support (n=40) were matched with those who did not (n=150), and the outcomes were compared between the two groups. The transfusion strategy in ECMO patients complied with ELSO's recommendations to maintain haemoglobin levels between 12 and 14 g/dL. Although there was no statistically significant difference in mortality between the two groups, the ECMO group received significantly more transfusions of RBCs {6 [0–14] *vs.* 0 [0–4], P=0.000}, fresh frozen plasma {0 [0–4] *vs.* 0 [0–10], P=0.019} and platelets {10 [0–30] *vs.* 0 [0–15], P=0.001} than the control group.

In a case series (27), the outcomes of six adult patients with respiratory failure and a mean SOFA score of 9.6 who underwent VV ECMO between 30 March 2001 and 30 April 2001 were retrospectively analyzed. Only two patients required transfusion of fresh frozen plasma. Fibrinogen was maintained between 1.4 and 6 g/dL and no patient required cryoprecipitate. Platelets were transfused to maintain platelet counts above 65,000. To maintain haemoglobin levels above 14 g/dL, the average daily requirement for RBCs was 11.8 units. All patients survived. Moreover, when sepsis accompanies other conditions in which ECMO is indicated (for example, pulmonary hypertension) (28) it is evident that the average platelet transfusion requirement increases. This can also be explained by the fact that the patients with sepsis had significantly longer runs of ECMO than the other groups.

ECMO and pulmonary hypertension

Another extended indication for ECMO support is pulmonary hypertension. In a multicentre historical cohort study (28) of 234 infants needed ECMO support, the cut-off for platelet administration was between 110,000/mm^3 (centre A) and 100,000/mm^3 (centres B and C). For patients with pulmonary hypertension, the mean daily platelet transfusion requirement was 1.4±0.6 units with a mean duration of ECMO therapy of 6.9±4.2 days.

ECMO and trauma

In the last case-series cited, two of the six patients had trauma-related respiratory failure. Indeed, ECMO support is increasingly better performing also in trauma-related cardiorespiratory failure. In another case series (29), 24 polytrauma patients with respiratory failure unresponsive to

conventional ventilation therapy were treated with ECMO. Triggers to transfuse RBCs, fresh frozen plasma, and platelets show further variability: haematocrit >40–45%, fibrinogen >200 mg/dL, platelets >100,000/mm^3 (>150,000 if active bleeding was ongoing). The most frequent complication was bleeding (75%) and the survival rate was 63%.

In a retrospective study (30), mortality among 81 patients receiving ECMO via subgroup analyses of trauma and non-trauma patients was analyzed. During the study period, significantly increased mortality in the group with a haematocrit greater than 31% [relative risk (RR): 1.73 with a 95% CI: 1.134–2.639] was identified. The targeted values of the restrictive protocol were haemoglobin 8–9.5 g/dL, fibrinogen >250 mg/dL and platelet count >50,000/mm^3. The more blood products transfused, the higher the mortality rate observed both in the overall population and in the trauma group (26).

A further multicentre retrospective cohort study (31) evaluated records of adult trauma patients between 16 and 55 years of age treated for acute hypoxemic respiratory failure between January 2001 and December 2009. The authors reported that in many instances transfusions were given to maintain haemoglobin above 10 g/dL and platelet counts above 75,000/mm^3 (27).

ECMO and pregnancy

ECMO support was successfully adopted also in pregnant (32,33) despite the well-known higher risks of haemolysis. In one case series (34), blood transfusions were given to four pregnant patients on ECMO support for respiratory failure to maintain hematocrit above 28%. In another case series, the authors defined a transfusion threshold of 7 g/dL of haemoglobin in seven pregnant patients on VA ECMO support for cardiogenic shock, unless there was evidence of dysoxia despite optimization of circuit support (35).

As shown in *Table 3*, we collected ten articles in which was explicated clear transfusion triggers. All are observational studies (mainly case series and retrospective studies). The main population investigated was adults but two studies investigated their endpoints among paediatric patients and

Table 3 Characteristics of studies included and summary of results

References	Extended indication	Design	ECMO population (number of patients)	ECMO configuration	Transfusion thresholds/triggers	Results
Yanagida *et al.* (22)	Bridge to lung transplantation	Retrospective observational	Adult patients (n=25): 15 ECMO *vs.* 10 no-ECMO group	VV; 3 patients required conversion to VA ECMO	Hct <25%	Among ECMO group, non-survivors (6/15) required higher amount of PRBC transfused. Among patients who survived to hospital discharge (9/15), seven were transplanted
Stiller *et al.* (23)	Bridge to heart transplantation	Retrospective observational	Paediatric patients (n=32): 9 ECMO *vs.* 23 Berlin heart	VA	Hb <9 g/dL; fibrinogen <180 mg/dL; Platelet count <70,000/μL	Lower mortality in Berlin heart group. Higher daily transfusion requirement for children on ECMO support
Takauji *et al.* (26)	Sepsis-related respiratory failure	Retrospective observational	Adult patients (n=190): 40 ECMO *vs.* 150 no-ECMO	VV	Hb <12 g/dL (range, 12–14 g/dL)	No statistically significant difference in mortality between the two groups. Higher amount of blood component transfused in ECMO group
Chevuru *et al.* (28)	Sepsis-related respiratory failure	Multicentre historical cohort	Paediatric patients (n=234)	VV (n=81); VA (n=138); 15 patients required conversion from VV to VA ECMO	Platelet counts <110,000/μL (centre A) and <100,000/μL (centres B and C)	Patients who were on VA ECMO had higher mortality and required more platelet transfusions per day than patients who were on VV ECMO

Table 3 (*continued*)

Table 3 (*continued*)

References	Extended indication	Design	ECMO population (number of patients)	ECMO configuration	Transfusion thresholds/triggers	Results
Peek *et al.* (27)	Sepsis-related respiratory failure	Case series	Adult patients (n=6)	VV	Hb <14 g/dL; fibrinogen <1.4 g/dL (range, 1.4–6 g/dL); platelet counts <65.000/μL (range, 65.000–300.000/μL)	All six patients survived. Two of the six patients required respectively transfusions of fresh frozen plasma and platelets. No cryoprecipitate was needed. Mean red cell requirement during the ECLS course was 11.8 units
Michaels *et al.* (29)	Trauma-related respiratory failure	Case series	Adult patients (n=24)	VV	Hct <40–45%; fibrinogen <200 mg/dL; platelet counts <100,000/μL	17 patients (56.7%) wean from ECLS and 50% survived to discharge. Bleeding complications (requiring transfusion) occurred in 58.6% of patients and were not associated with mortality
Swol *et al.* (30)	Trauma-related respiratory failure	Retrospective observational study	Adult patients (n=81)	VV	Hb <8 g/dL (range, 8–9.5 g/dL); fibrinogen <250 mg/dL; platelet counts <50,000/μL	Significantly increased mortality was observed in the group with a hematocrit greater than 31%. A significant increase in mortality was observed as the average number of transfusions per day in the hospital increased
Guirand *et al.* (31)	Trauma-related respiratory failure	Multicentre retrospective cohort study	Adult patients (n=102): 26 ECMO *vs.* 76 mechanical ventilation group	VV	Hb <10 g/dL; platelet counts <75.000/μL	Adjusted survival rate was greater in the ECLS group. ECLS patients received more blood transfusions and had more bleeding complications
Sharma *et al.* (34)	Cardiorespiratory support during pregnancy	Case series	Pregnant patients (n=4)	VV	Hct <28%	All patients survived hospitalization and were discharged without significant morbidity. Fetal survival was 75%
Desai *et al.* (35)	Cardiorespiratory support during pregnancy	Case series	Pregnant patients (n=7)	VA	Hb <7 g/dL	Maternal and fetal survival rate to discharge was 80%. One patient was successfully delivered on VA ECMO

ECMO, extracorporeal membrane oxygenation; VV, venovenous; VA, venoarterial; Hb, haemoglobin; Hct, haematocrit; PRBC, packed red blood cell; ECLS, European College for Liberal Studies.

two among pregnant patients. The most frequent ECMO configuration was VV; only two studies investigate their endpoints in VA ECMO support populations and two studies reported the VV to VA configuration changing. Most of these studies considered laboratory levels of haemoglobin as PRBC transfusion trigger but in three

studies the clinical decision to transfuse PRBC was based on the haematocrit percentage threshold. Among the studies considered, only the case series of Desai respect the criteria of restrictive transfusion strategy (haemoglobin threshold of 7 g/dL).

Summary

Though it is currently possible to explore haemoglobin thresholds for transfusion in "conventional" indications for ECMO support, like ARDS due to bacterial or viral pneumonia (36), there is still too much heterogeneity among studies considering the recently advanced indications for ECMO. The main issues are the cases when the patient has a very high risk of bleeding like in trauma or perioperative periods, or the case of high risk of fluid shift like in burn injuries. Haemoglobin and vascular mass are fundamental to achieving adequate blood flow during ECMO support for reaching higher oxygen delivery, and the administration of PRBC should always be balanced with the patient's needs, O_2 availability and blood flow determined by the clinical situation.

The analysis of several studies with specific indications confirmed the high heterogeneity but the tendency of reducing the transfusions is evident. Moreover, the important step-up for research would compare the different strategies for transfusions in homogenous groups according to indications for ECMO and configuration. Before starting new trials on this topic, broader observational studies, unbiased due to long enrolment periods, should be attempted to understand the current evolving practice and to propose changes to improve management, costs, and outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Blood* for the series "Blood Transfusion Practice in ECMO Patients". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://aob.amegroups.com/article/view/10.21037/aob-21-81/rc

Peer Review File: Available at https://aob.amegroups.com/article/view/10.21037/aob-21-81/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-21-81/coif). The series "Blood Transfusion Practice in ECMO Patients" was commissioned by the editorial office without any funding or sponsorship. GM served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aob-21-81
Cite this article as: Tigano S, Vitiello C, D'Alesio MV, Sanfilippo F, Astuto M, Arcadipane A, Martucci G. Transfusion management during extracorporeal membrane oxygenation for extended indications: a narrative review. Ann Blood 2023;8:17.