



Blood products other than packed red blood cells in extracorporeal membrane oxygenation: guidelines, local protocols, and outcomes – a narrative review

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Background and Objective: Blood Product transfusion is often required during extracorporeal membrane oxygenation (ECMO) support for several reasons. Most of the available data and literature have assessed packed red blood cells (PRBCs) transfusion during extracorporeal support, however it is key to define the threshold for the variability of other blood products available for transfusion. This review aims to highlight published data supporting blood product transfusion, other than PRBCs, in patients on ECMO support, including guidelines, local protocols, and patient outcomes.

Methods: PubMed and Google Scholar were primarily used to access the targeted literature published until December 2022. We have also used authoritative text, published guidelines, and expert consensus. The literature on platelets, fresh frozen plasma (FFP), cryoprecipitate, albumin, and activated recombinant factor VII (rFVIIa) was summarized separately.

Key Content and Findings: Platelets, FFP, and cryoprecipitate, were discussed in detail with their guidelines and recommended dosage, while albumin and rFVIIa are discussed briefly, primarily due to lack of literature. The relevance of viscoelastic clotting tests to blood product transfusion were also reviewed. In emergency setting, ECMO circuits can be primed with crystalloid while cross-matching blood is being prepared. Albumin can be used as an additive to the primes as it increases the circuit life and prevents protein loss by adding oncotic pressure to the prime. The average platelet units transfused directly correlated with the type of ECMO. Platelet transfusion increases the platelet count by 30,000–100,000/ μ L. If the international normalized ratio (INR) is greater than 1.5–2.0 or if there is significant bleeding, FFP can be given in aliquots of 10 mL/kg. Cryoprecipitate is given at a dose of 5 mL/kg of body weight if the fibrinogen level is less than 100–150 mg/dL and will increase the fibrinogen concentration by 50 mg/dL/10 kg of body weight. Thromboelastography (TEG), and thromboelastometry (TEM) reduce the requirement for blood product transfusion in bleeding patients.

Conclusions: This review has highlighted the lack of data available regarding non-PRBC blood product transfusions and the appropriate therapy practices and preventive measures in ECMO patients. Further research is warranted to define and guide blood product transfusion thresholds, management practices, and limitations in ECMO patients.

Keywords: Blood product; extracorporeal membrane oxygenation support (ECMO support); platelet; fresh frozen plasma (FFP)

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Introduction

To facilitate cardiac surgery, mechanical cardiopulmonary support is most frequently used intraoperatively (i.e., cardiopulmonary bypass). Although it is less frequent, cardiopulmonary support can also be given for a longer period in an intensive care unit (ICU) when it is called extracorporeal membrane oxygenation (ECMO), extracorporeal life support (ECLS), or extracorporeal lung assist.

ECMO is a useful tool to treat patients with life-threatening cardiac and pulmonary dysfunction that is refractory to conventional management or when cardiopulmonary resuscitation (CPR) measures are not successful in achieving the return of spontaneous circulation (ROSC). An ECMO machine consists of a pump with an oxygenator that replaces the function of the heart and lung, respectively. Venoarterial (VA) and venovenous (VV) ECMO are the two variants. Although both offer respiratory support, only VA ECMO offers hemodynamic support (1).

Patients with ECLS often require blood products for several reasons such as for the treatment of hemorrhagic complications, the restoration of oxygen-carrying capacity, circuit priming, and hemostatic balance (2). ECMO can lead to reduced red cells lifespan and deranged activation of coagulation pathways due to the exposure of blood volume to shear forces and artificial materials. As a result, patients on ECMO often require significant blood transfusion (3).

The main frailty of ECMO support is bleeding (4,5). This complication is the leading cause of mortality in ECMO patients and may occur regardless of the severity of coagulation parameters and trauma (4-6). The requirement of increased blood transfusion volumes and hemorrhagic complications are directly associated with mortality (7).

One of the key management practices of bleeding in ECMO patients is transfusion support (6), however, there is a lack of evidence to guide blood product transfusion threshold and therapy for patients on ECMO (8). Although there have been previous research and studies regarding packed red blood cells (PRBCs) transfusion in ECMO patients, a few have emphasized and taken other blood products into consideration.

The objective of this narrative review is to outline recent and historical transfusion practices, other than PRBCs, in patients requiring ECMO support. This review aims to cover data that has been published up to December 2022, related to the transfusion of the following five blood

products in patients on ECLS: platelet, fresh frozen plasma (FFP), cryoprecipitate, albumin, and activated recombinant factor VII (rFVIIa). In the end we have also discussed point of care (POC) viscoelastic tests (VETs) of hemostasis briefly due to their key emerging role in the coagulation management of the patients on ECMO support. We present this article in accordance with the Narrative Review reporting checklist (available at <https://aob.amegroups.com/article/view/10.21037/aob-21-82/rc>) (9).

Methods

Literature review and data collection were primarily done from research databases of PubMed (<https://pubmed.ncbi.nlm.nih.gov>) and Google Scholar (<https://scholar.google.com>). The literature search was divided into seven parts after selecting appropriate MeSH terms. Five parts of the literature search were pertaining to the individual blood products under discussion; one part was related to VETs; and the last part was a general online data search related to blood product transfusion, anticoagulation practices, and clinical guidelines for patients on ECLS. The relevant literature uncovered was including case reports, observation studies, cohort studies, randomized controlled trials (RCTs), expert panel reports, review articles, and guidelines from international societies, published up to December 2022. Moreover, the 5th edition of *Extracorporeal Life Support: The ELSO Red Book* was also reviewed to collect some of the literature (10).

A summary of our search strategy is mentioned in *Table 1*, while a detailed approach on PubMed has been outlined in *Table 2*.

Results

A total of 816 articles were retrieved after incorporating proper Syntax on PubMed as per our search strategy explained above in *Tables 1,2*. After screening them thoroughly, we included 45 articles to be discussed in this narrative review; 43 out of 45 studies were either observational, or reviewed based on observational data, or expert consensus. Only two experimental studies were found that tested the impact of transfusion practices on the outcome; a randomized pilot trial of 31 pediatric ECMO patients where scheduled FFP transfusion did not affect the overall circuit life or blood product transfusion (11); and an experimental study of two ECMO circuits, where albumin priming showed to prevent platelet activation and

Table 1 The search strategy summary

Items	Specification
Date of search	Initial search in 2021 and re-search during 15–25 January 2023
Databases and other sources searched	PubMed, Google Scholar, <i>The ELSO Red Book</i> , 5 th edition
MeSH and free text terms used	“Platelet transfusion”, “ECMO”, “ECLS”, “extracorporeal membrane oxygenation”, “extracorporeal life support”, “FFP transfusion”, “fresh frozen plasma transfusion”, “plasma transfusion”, “fibrinogen transfusion”, “cryoprecipitate transfusion”, “albumin”, “rFVIIa”, “recombinant FVIIa”, “recombinant factor VIIa”, “recombinant factor VIIa”, “eptacog alfa”, “rotational thromboelastometry”, “thromboelastography”, “thromboelastometry”, “ROTEM”, “TEG”, “TEM”
Timeframe	Up to December 31, 2022
Inclusion criteria	All study types published in English related to the topic in the given period were included in the review
Selection process	Four authors (HE, MAUR, AAS, and HA) independently screened databases. Discrepancies were resolved by discussion. The first author (HE) reviewed <i>ELSO Red Book</i> . AAH supervised the selection process

ELSO, Extracorporeal Life Support Organization; ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal life support; FFP, fresh frozen plasma; rFVIIa, activated recombinant factor VII; FVIIa, activated factor VII; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TEM, thromboelastometry.

Table 2 Detailed search strategy on PubMed database

Topic	Syntax used	Total retrieved articles	Screened articles (on basis of title and abstract)	Final articles included in the study
Platelets	(Platelet transfusion) AND (((ECMO) OR (ECLS)) OR (Extracorporeal membrane oxygenation)) OR (extracorporeal life support)	166	24	9
FFP	(((FFP transfusion) OR (Fresh frozen Plasma transfusion)) OR (Plasma transfusion)) AND (((ECMO) OR (ECLS)) OR (Extracorporeal membrane oxygenation)) OR (extracorporeal life support)	226	18	8
Cryoprecipitate	((fibrinogen transfusion) OR (cryoprecipitate transfusion)) AND (((extracorporeal membrane oxygenation) OR (extracorporeal life support)) OR (ECLS)) OR (ECMO)	68	17	6
Albumin	(Albumin) AND (((Extracorporeal life support) OR (Extracorporeal membrane oxygenation)) OR (ECLS)) OR (ECMO)	193	9	5
rFVIIa	(((rFVIIa) OR (recombinant FVIIa)) OR (recombinant factor VIIa)) OR (recombinant activated factor vii) OR (eptacog alfa) AND (((ECMO) OR (ECLS)) OR (Extracorporeal Life Support)) OR (Extracorporeal Membrane Oxygenation)	52	18	7
TEG/ROTEM	((((rotational thromboelastometry) OR (ROTEM)) OR (TEG)) OR (TEM)) OR (thromboelastography)) OR (thromboelastometry)) AND (((ECMO) OR (ECLS)) OR (extracorporeal life support)) OR (extracorporeal membrane oxygenation))	111	23	10

ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal life support; FFP, fresh frozen plasma; rFVIIa, activated recombinant factor VII; FVIIa, activated factor VII; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TEM, thromboelastometry.

Table 3 The relevant literature on platelets transfusion in the patients on ECLS

Author, reference	Year	Study type	Number of subjects/centers	Outcome	Quality of evidence (GRADE)
Chevuru, <i>et al.</i> (13)	2002	Multicenter cross-sectional observation study	234 (neonates)	Average transfusions per day in neonates on ECMO are higher on VA as compared to VV ECMO	Low
Ang, <i>et al.</i> (14)	2009	Retrospective observational study	41 (adults)	Recent antiplatelet agents, larger Hb decline and longer ECMO duration increase daily platelet requirements	Very low
Bembea, <i>et al.</i> (15)	2013	Cross-sectional observational study	121 centers	ECMO anticoagulation management policies vary widely by center. However, median platelet count warranting platelet transfusion was 100,000/ μ L	Moderate
Esper, <i>et al.</i> (16)	2017	Cross-sectional observational study	54 centers	Significant practice variation among institutions regarding anticoagulation and transfusion during adult ECMO support	Moderate
Balle, <i>et al.</i> (17)	2018	Systemic review	115 (7 studies)	There is suggested evidence of reduced platelet adhesion, decreased platelet activation, and reduced platelet aggregation in adult patients during ECMO treatment	Very low
Jiritano, <i>et al.</i> (18)	2020	Systemic review and meta-analysis	7,205 (21 studies)	The underlying mechanisms of thrombocytopenia in patients on ECMO are multifactorial	Moderate
Nellis, <i>et al.</i> (19)	2020	Subgroup analysis of prospective observational studies	138 (3 days to 16 years)	Children supported by ECMO receive large volumes of plasma and platelet transfusions with some institutional guidance in the form of protocols, but significant variation in practice	Very low
Keene, <i>et al.</i> (20)	2020	Retrospective observational study	110 (neonates)	RBC and PLT transfusion rates are associated with in-hospital mortality among neonates receiving ECMO	Very low
Cashen, <i>et al.</i> (21)	2020	Retrospective observational study	511 (less than 19 years)	Platelet transfusion volume was associated with increased risk of mortality, bleeding, and thrombosis	Low

ECLS, extracorporeal life support; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous; RBC, red blood cell; PLT, platelet.

reduction in the initial adherence of platelets to the foreign material of the circuit (12). None of the studies included in the review had *High* quality of evidence as per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) certainty rating. Most of the evidence was either of *Low* or *Very Low* certainty. Evidence with a *Moderate* level of certainty was mostly related to the difference in practices among ECMO centers or experts. A summary of the studies included in this review is tabulated below (Tables 3-7).

Discussion

Current recommendations for non-PRBC blood product transfusion are based on very limited evidence. Most of

the evidence is extracted from observational studies with only a few clinical trials available. The data available up to December 2022, is not conclusive of relying solely on specific laboratory threshold for non-PRBC blood product transfusion. The decision should be multifaceted, including the clinical context, laboratory values, and viscoelastic studies. In an observational pre- and post-implementation cohort study, the use of a context-responsive anticoagulation and transfusion guideline has been found to reduce major hemorrhagic as well as thrombotic complications (43). Table 8 summarizes guidelines and recommendations of laboratory thresholds for the three most important non-PRBC blood products (platelets, FFP, and cryoprecipitate).

Despite the lack of widespread institutional guidelines for different blood products transfusion especially non-PRBC

Table 4 The relevant literature on FFP transfusion in the patients on ECLS

Author, reference	Year	Study type	Number of subjects/experts/centers	Outcome	Quality of evidence (GRADE)
Karam, <i>et al.</i> (22)	2013	Systematic review	843 studies	This review highlights the lack of evidence that is available to guide plasma transfusions in critically ill patients	Moderate
Doussau, <i>et al.</i> (23)	2014	Prospective observational study	967 patients	No evidence of FFP transfusion related reduction in 30-day mortality in patients undergoing cardiopulmonary bypass cardiac surgery with excessive bleeding	Moderate
Mazzeffi, <i>et al.</i> (24)	2017	Retrospective analysis	452 patients	A high transfusion ratio may improve survival in patients undergoing cardiac operations with massive intraoperative transfusion	Low
Nellis, <i>et al.</i> (19)	2020	Subgroup analysis of prospective observational studies	138 patients	Children supported by ECMO receive large volumes of plasma and platelet transfusions with some institutional guidance in the form of protocols, but significant variation in practice	Very low
Singh, <i>et al.</i> (25)	2020	An expert consensus document by an online survey	12 centers	The routine use of FFP is not indicated to normalize PT INR in nonbleeding patients in VV ECMO	Very low
McMichael, <i>et al.</i> (11)	2021	Randomized pilot trial	31 patients	Scheduled FFP did not increase circuit life and here was no difference in blood product transfusion of platelets, PRBCs, and FFP between groups	Moderate
Nellis, <i>et al.</i> (26)	2022	Systematic review and consensus conference series	29 experts	Therapeutic FFP should only be used in case of massive hemorrhage in ECMO patients	Low
Luo, <i>et al.</i> (27)	2022	Retrospective observational study	116 patients	FFP transfusion is markedly associated with in-hospital mortality among patients receiving ECMO	Low

FFP, fresh frozen plasma; ECLS, extracorporeal life support; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; ECMO, extracorporeal membrane oxygenation; PT, prothrombin time; INR, international normalized ratio; VV, venovenous; PRBC, packed red blood cell.

blood products, some ECMO centers have implemented some anticoagulation guidelines. A retrospective review of a single-centered university hospital demonstrated that a commitment to strict standardization can significantly mitigate some of the neurologic and hematologic complications (45).

Due to the nature of body size and the longer duration of ECMO in adult patients, transfusion requirements are higher in adults compared to Neonates (14). Henríquez-Henríquez *et al.* (46) found that the transfusion requirements were lower in pediatric patients on ECMO due to respiratory diseases than those due to cardiac disease or congenital diaphragmatic hernia. Literature evidence shows that restrictive transfusion strategies significantly decreased patient mortality (47).

The volume of transfusion received by patients on

ECMO is shown to be associated with the duration of ECMO (13,14) and it is therefore advisable to shorten that duration. Minimizing daily samples is also part of a strategy for lowering transfusion requirements (48). A prospectively collected data of 509 patients showed that VA ECMO patients have a greater transfusion burden than VV ECMO patients. Moreover, mortality is greater in the case of extreme transfusion requirements (49).

Circuit priming

Circuit priming needs to be carried out with meticulous attention to sterility, proper connections, and an air-free prime. Two types of primes are being used for circuit priming: blood prime and crystalloid prime. The volume of prime ranges from 80–250 mL, depending upon the

Table 5 The relevant literature on cryoprecipitate transfusion in the patients on ECLS

Author, reference	Year	Study type	Number of subjects/experts/centers	Outcome	Quality of evidence (GRADE)
Bembea, <i>et al.</i> (15)	2013	Cross-sectional observational study	121 centers	Median fibrinogen threshold being used for FFP or cryoprecipitate transfusion was 150 and 145 mg/dL for pediatric and adult (pediatric/adult mixed) ECMO centers, respectively	Moderate
Esper, <i>et al.</i> (16)	2017	Cross-sectional observational study	54 centers	Target fibrinogen level in ECMO patients were ranging from <150 to >250 mg/dL	Low
Thomas, <i>et al.</i> (28)	2018	Review article	–	The etiology of bleeding and thrombosis in ECMO patients is multifactorial. Low fibrinogen levels should be corrected by cryoprecipitate transfusion or fibrinogen concentrate infusion. Expert clinician in coagulation should be involved in the management	Low
Fang, <i>et al.</i> (29)	2020	Review article	–	Balancing the risks and benefits of management is important when managing bleeding or preventing clotting on patients on ECMO	Very low
Fong, <i>et al.</i> (30)	2021	Retrospective observational study	130 (adults)	Hypofibrinogenemia is an independent risk factor for bleeding events in adult ECMO patients	Moderate
Drop, <i>et al.</i> (31)	2022	Systemic review	107 studies	There is widespread lack of standardization of several parameters in coagulation research of pediatric ECMO patients	Moderate

ECLS, extracorporeal life support; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; FFP, fresh frozen plasma; ECMO, extracorporeal membrane oxygenation.

Table 6 The relevant literature on Albumin administration in the patients on ECLS

Author, reference	Year	Study type	Number of subjects/experts	Outcome	Quality of evidence (GRADE)
Adrian, <i>et al.</i> (12)	1998	Experimental study	2 ECMO circuits	Albumin priming appears to prevent platelet activation and might even reduce the initial adherence of platelets to the foreign material of the circuit	Very low
Aronson, <i>et al.</i> (32)	2017	Cross-sectional survey	127 HCPs	Equal preference of 5% albumin and crystalloids as a choice of intravenous fluids in ECMO patients among HCPs	Moderate
Wengenmayer, <i>et al.</i> (33)	2018	Retrospective observational study	283 patients	VA-ECMO patients who received albumin fluid resuscitation had significantly better hospital survival rates	Low
Acharya, <i>et al.</i> (34)	2020	Retrospective observational study	157 patients	A high FAR (>125) within the first 24 hours of VA-ECMO placement is associated with higher risk of subsequent ischemic stroke	Very low
Roth, <i>et al.</i> (35)	2021	Retrospective observational study	344 patients	A baseline FAR is independently associated with in-hospital thromboembolic events in patients undergoing VA-ECMO	Low

ECLS, extracorporeal life support; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; ECMO, extracorporeal membrane oxygenation; HCP, healthcare partitioner; VA, venoarterial; FAR, fibrinogen-albumin ratio.

Table 7 The relevant literature on rFVIIa administration in the patients on ECLS

Author, reference	Year	Study type	Number of subjects	Outcome	Quality of evidence (GRADE)
Wittenstein, <i>et al.</i> (36)	2005	Retrospective observational study	4 patients	rFVIIa is effective to achieve control of refractory hemorrhage in patients on ECMO support	Very low
Veldman, <i>et al.</i> (37)	2007	Retrospective observational study	7 patients	No statistically significant reduction in chest tube output or blood product transfusion seen in patients receiving rFVIIa on ECMO support as compared to their historic controls	Very low
Niebler, <i>et al.</i> (38)	2010	Retrospective observational study	17 patients	rFVIIa administration during ECMO support was associated with a decrease in bleeding severity and was not associated with increased thromboembolic events	Very low
McQuilten, <i>et al.</i> (39)	2012	Retrospective observational study	388 patients	There was a significant reduction in blood product administration after rFVIIa, however, there was higher rate of thromboembolic event in patients who were on ECMO while receiving rFVIIa	Low
Repešé, <i>et al.</i> (40)	2013	Retrospective observational study	15 patients	rFVIIa use for intractable hemorrhaging in patients receiving ECMO controlled bleeding, without major thrombotic events	Very low
Long, <i>et al.</i> (41)	2014	Retrospective observational study	7 patients	There is limited efficacy for rFVIIa use for refractory hemorrhage in pediatric patients on ECMO support	Very low
Anselmi, <i>et al.</i> (42)	2016	Retrospective observational study	30 patients	In case of life-threatening bleeding refractory to all conventional therapies, rFVIIa presents an acceptable safety profile in patients under ECMO support	Very low

rFVIIa, activated recombinant factor VII; ECLS, extracorporeal life support; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; ECMO, extracorporeal membrane oxygenation.

patient's size and the ECMO circuit used. The latest Extracorporeal Life Support Organization (ELSO) Adult and Pediatric ECMO Circuits guidelines recommend using blood prime for small pediatric patients <10–15 kg while ECMO circuits of patients >10–15 kg should be primed with crystalloid solutions (50). As it takes time to properly prime the circuits, some centers also use pre-primed ECMO circuits on standby, where circuits are filled with crystalloid solutions, and additives are added when it is needed. It is safe to maintain primed circuits for up to 30 days or more if we used crystalloid prime with the addition of albumin and the absence of glucose-containing solutions (9). Sodium bicarbonate, calcium chloride, heparin, FFP, and 25% albumin are often used as additives to the primes, mostly in blood-primed circuits (50).

Platelet

Thrombocytopenia is commonly found in critically ill patients and occurs in up to 20–50% of ICU patients (51–55). In patients on ECLS, not only does the platelet count

decrease but also the function of the platelet is also affected. Causes of thrombocytopenia in ECMO patients were found to be multifactorial such as contact with foreign surfaces, platelet activation, inflammatory and coagulative cascade activation, sepsis, medications, surgery, bleeding, and intravascular devices (18). The platelet function is altered in terms of reduced platelet adhesion, decreased platelet activation, and reduced platelet aggregation. The causes of platelet dysfunction and its association with reduced count still need to be investigated (17).

A 2013 international survey for ECMO registered centers found that the median threshold for platelet transfusion, in uncomplicated ECMO, for pediatric as well as mixed adult/pediatric programs was 100,000/ μ L with slight variation in the range (15). A more recent international survey of transfusion practices observed that platelet count triggers for ECMO are variable between institutions varying from less than 20,000 to 100,000/ μ L (16). According to the 2021 ELSO guidelines, bleeding patients with a platelet count of \geq 100,000/ μ L and non-bleeding patients with a platelet count between 50,000 to 100,000/ μ L should receive a

Table 8 Representation of highlighted guidelines and recommendations for transfusion of platelet, FFP, and cryoprecipitate [the information highlighted in this table is based on and adapted from the context of the ELSO Red Book (10) and AABB standards (44)]

Product	Description	Guideline	Dosage	Recommended lab schedule
Platelets	There are 2 types: apheresis platelets derived from single donor (most commonly used), 1 unit: 200–300 mL; pooled platelets from multiple donors, 4 to 6 units must be pooled to make a therapeutic dose	Platelet transfusion to maintain >80,000 to 100,000 μ L	10 mL/kg. Adults: dose will increase platelet count by 30,000–60,000/ μ L; neonates & pediatrics: increase 50,000 to 100,000/ μ L	Check platelet count every 12 hours
Fresh frozen plasma	1 unit (200–250 mL) contains: 70–100% of each clotting factor/mL; 1 to 2 grams of fibrinogen	FFP transfusion to maintain INR <2.0	10 to 15 mL/kg. Dose will increase clotting factor activity by 30% approximately	Check INR every 12 hours
Cryoprecipitate	Usually given in 10-unit dose. 1 unit contains: 150 mg fibrinogen, 80 IU of factor VII, vWF, factor XIII, fibronectin	To maintain fibrinogen >100 mg/dL or >150 mg/dL if bleeding or prior surgical intervention	1 unit (15 mL) will increase fibrinogen by 50 mg/dL per 10 kg of body weight	Check fibrinogen every 12 to 24 hours

FFP, fresh frozen plasma; ELSO, Extracorporeal Life Support Organization; AABB, Association for the Advancement of Blood & Biotherapies; INR, international normalized ratio; vWF, von Willebrand factor.

platelet transfusion of 10 mL/kg (7).

Apheresis platelet transfusion increases the platelet count by 30,000–60,000/ μ L in adult patients, while a 10 mL/kg dose of platelet transfusion in neonates increases platelet count by 50,000–100,000/ μ L (10). The most common cause of platelet transfusion in children from 3 days to 16 years of age was prophylaxis (79%), followed by major (12%), and minor bleeding (9%) in a subgroup analysis of two prospective, observational studies (19). Although we couldn't find any established guideline for platelet transfusion in ECMO patients, Vlaar *et al.* proposed a clinical practice guideline systemic review for prophylactic transfusion in thrombocytopenic critically ill patients. It recommends not using platelet transfusion to treat those patients unless the patient's platelet count drops below 10,000/ μ L. For the patients undergoing invasive procedures, they support not giving prophylactic platelet transfusion prior to invasive procedures for platelet counts above 100,000/ μ L. The guideline also suggests not giving prophylactic platelet transfusion prior to percutaneous tracheostomy or central line insertion for platelet counts between 50,000–100,000/ μ L; however, there is no recommendation for patients with severe thrombocytopenia, with platelet counts between 10,000 and 50,000/ μ L, as they suggest that further research is required to assess the required prophylactic platelet transfusion (56).

According to a multicenter analysis of platelet transfusion usage among neonates on ECMO, the average number of

platelet blood transfusion units received by patients per day directly correlated with the type of ECMO used as they found that patients who were on VV ECMO required less platelet transfusion than those on VA ECMO (13). A retrospective analysis of blood transfusion requirements predictors looked at the amount of blood products received by 41 adults during ECMO, and concluded that the use of antiplatelet within one week of initiating ECMO was an independent predictor of increased average daily platelet transfusion (14). Retrospective studies of pediatrics on ECMO found that platelet transfusion rate was associated with mortality risk, therefore further investigation is warranted to define the platelet transfusion threshold and determine whether platelet count or other indicating factors should be used as the optimal parameter for platelet transfusion (20,21).

Fresh frozen plasma

FFP transfusion is used in a range of clinical scenarios as a therapeutic intervention including the reversal of coagulopathy in bleeding patients as well as prophylactic use prior to procedures (57). The use of FFP comes with a range of side effects that need to be considered prior to administering (58). A recent retrospective observational study showed the association of FFP transfusion with in-hospital mortality among patients receiving ECMO in the form of a positive correlation (27).

Literature on critically ill patients (but not on ECLS) shows minimal improvement in prothrombin time/international normalized ratio (PT/INR) after FFP transfusion if there is only mild coagulopathy (59–61). That is why, multiple recent studies are emphasizing on judicious use of FFP to correct coagulopathy in the patients on EMCO. One of the expert consensus documents, which is supported by the Canadian Cardiovascular Critical Care (CANCCARE) Society and the Canadian Society of Cardiac Surgeons (CSCS) suggests against the routine use of FFP to normalize PT/INR in nonbleeding patients especially on VV-ECMO (25). Similarly, Transfusion and Anemia Expertise Initiative-Control/Avoidance of Bleeding (TAXI-CAB) systematic review and consensus conference series involving multidisciplinary international experts in hemostasis, and plasma/platelet transfusion in critically ill infants and children on ECMO support also suggests the use of therapeutic FFP transfusion only in case of massive hemorrhage; while clinical judgment is advised to be used in minimal, moderate, and severe bleeding (26). The 2021 ELSO guideline marks the goal of keeping INR <1.5 in bleeding and <3 in non-bleeding patients. To achieve this target, it also recommends FFP to be transfused at the rate of 10 mL/kg (up to 2 doses) (7).

A survey of 35 pediatric ECMO centers showed that 60% of them had institutional plasma transfusion protocols. Plasma transfusion was guided by INR in 67%, fibrinogen in 57%, PT in 48%, activated partial thromboplastin time (aPTT) in 33%, activated clotting time (ACT) in 29% and antithrombin also in 29% of the ECMO centers. Only a handful of institutes were using thromboelastography (TEG) R-time and rotational thromboelastometry (ROTEM) for plasma transfusion (19). A randomized pilot trial on 31 pediatric ECMO patients was done to determine whether transfusion of coagulation factors using FFP increased ECMO circuit life and decreased blood product transfusion as compared to the usual care. No statistically significant difference was observed in this study (11). Similarly, a multicenter prospective study found that there was no benefit of FFP on 30-day mortality between the patients who received FFP while on ECMO and those who did not (23).

On the other hand, mortality benefit has been observed in a retrospective analysis in cardiac surgical patients who were massively transfused (≥ 8 units of PRBCs) during the surgery. The patients who received high ratios of FFP/red blood cell (RBC) transfusion had lower mortality less renal failure and less re-operation for bleeding. However, they

had prolonged mechanical lung ventilation time and more atrial fibrillation incidents as compared to the patients who received low ratios of FFP/RBC (24). A systematic review of plasma transfusion strategies for critically ill patients highlights the need for further research and evidence to guide plasma transfusion in critically ill patients (22).

Cryoprecipitate

Cryoprecipitate, originally named cryoprecipitate antihemophilic factor (AHF), was developed as a therapy for patients with AHF deficiency, or hemophilia A. However, cryoprecipitate is now most frequently used to restore fibrinogen levels in patients with acquired coagulopathy, especially in clinical settings with hemorrhage, such as cardiac surgery, trauma, liver transplantation, or obstetric hemorrhage, and is no longer administered for its original purpose (62). Contrary to popular belief, cryoprecipitate only contains about 32% of the fibrinogen found in plasma; the rest remains in the cryosupernatant, also known as cryoprecipitate-reduced plasma (63). However, because cryoprecipitate is re-suspended in a relatively small volume, it contains fibrinogen at a higher concentration than in plasma. Due to differences in donors' levels of fibrinogen and institution-specific procedures, the actual concentration of fibrinogen in cryoprecipitate varies greatly (between 3 and 30 g/L). Nascimento *et al.* outlined the variability of cryoprecipitate pool content and volume among 22 different centers. Fibrinogen content in almost all cryoprecipitate centers was mostly ≥ 150 mg/U (62).

Due to the continuous thrombin formation and fibrinogen consumption during ECMO, fibrinogen levels may decrease. In a retrospective observational study on 130 adult patients on ECMO, hypofibrinogenemia was an independent risk factor for bleeding events (30). Low fibrinogen levels should be corrected by cryoprecipitate transfusion or fibrinogen concentrate infusion in the patients on ECMO (28,29). Due to a lack of studies in this particular area, we are mostly relying on expert opinion and commonly used practices. A survey of 187 international ECMO centers by Bembea *et al.* found that the median fibrinogen threshold being used for FFP or cryoprecipitate transfusion was 150 mg/dL (range, 60–200 mg/dL) for pediatric ECMO centers, while in adult only and adult/pediatric mixed ECMO centers, it was 145 mg/dL (range, 50–200 mg/dL) (15). A more recent international survey targeting ECMO centers showed a wider target fibrinogen level in ECMO patients ranging from <150 to >250 mg/dL (26).

Drop *et al.*'s systemic review of 107 records highlighted that only 20% described target fibrinogen ranges. Most of them were above 100 mg/dL (n=7) or 150 mg/dL (n=8) (31).

2021 ELSO adult and pediatric cryoprecipitate transfusion recommendations also rely on clinical experiences and local center guidelines. It recommends maintaining fibrinogen concentration >100 mg/dL in non-bleeding patients, and >150 mg/dL in bleeding patients or before any surgical intervention (7). The suggested dose is 1 unit/5 kg of cryoprecipitate, with a maximum of 6 units (7). The increase in plasma fibrinogen from 1 unit of Cryoprecipitate per 10 kg body weight is expected to be approximately 50 mg/dL.

A multicenter prospective cohort study on 1,175 trauma patients presented with hemorrhagic shock showed that cryoprecipitate transfusion is associated with decreased risk of multiorgan failure (64). However, cryoprecipitate has a risk of potential transmission of pathogens. This is why it has been withdrawn from use by various European countries (65,66).

Albumin

Human albumin (HA) is the major protein of the blood with a molecular weight of 69,000 Da. It is a negative acute phase reactant (67), having a robust, independent association with cardiovascular disease (CVD) at low levels (68). It is available for prescription as a colloid solution derived from the plasma of volunteer donors that have been pooled and heated at 60 °C for inactivation of pathogen inactivation (69). It is available commercially as an iso-oncotic (5%) or hyper-oncotic (20%) solution (69). HA solution can be prescribed in an ICU setting for first-line resuscitation of hypovolemia or hypovolemic shock. However, physicians often recommend its use in patients who have limited to no response to crystalloid solutions, or patients with low albumin levels related to hypovolemic shock (70). A cross-sectional survey of 124 healthcare partitioners (including cardiothoracic surgeons, cardiovascular anesthesiologists, and perfusionists) showed that although anesthesiologists prefer 5% albumin over crystalloids as the first choice of IV fluid in the patients on ECMO, there was no overall difference of preference among healthcare partitioner between the two fluid choices (32).

As albumin inhibits platelet function and thrombus formation (as compared to fibrinogen), a fibrinogen-albumin ratio (FAR) is often described as a marker of disease severity during prothrombotic conditions. A single-

center, retrospective observational study on 157 patients in the United States showed that the high FAR (>125) within the first 24 hours of VA-ECMO placement is associated with a higher risk of subsequent ischemic stroke (34). Later on, a similar study on a bigger sample in Germany revealed that a baseline FAR is independently associated with in-hospital thromboembolic events in patients undergoing VA-ECMO (35). This underscores the importance of maintaining a normal level of albumin in patients on ECMO. A retrospective registry study including 283 patients performed to evaluate albumin versus crystalloid fluid resuscitation in VA-ECMO patients found that patients that received albumin fluid resuscitation while on VA-ECMO had significantly better hospital survival rates (33). As a result of limited evidence supporting the guidelines of albumin in ECMO patients, albumin administration is based on physician experience and patient status.

Blood-primed ECMO circuits often use 25% albumin as an additive (50). It not only increases the pre-primed ECMO circuit life but also reduces the adsorption of plasma proteins to the ECMO circuit, and thus thrombus formation, by potentially adding the oncotic pressure (10). Evidence found that when primed with albumin ECMO circuits showed lower platelet destruction and platelet activation (12).

rFVIIa

rFVIIa is a vitamin-K-dependent glycoprotein structurally similar to human factor VII. In pharmacologic doses, rFVIIa promotes hemostasis at the site of injury without significant systemic activation of the clotting cascade (71). It is a treatment for refractory bleeding in patients on ECMO, and perioperative management in both adult and pediatric patients undergoing open heart surgeries including cardiopulmonary bypass (10).

There are multiple case reports (72-75) and case series (36,38,40) reporting a significant decrease in bleeding severity and markedly reduced blood product transfusion requirements in patients on ECMO. A retrospective analysis of 30 patients that received rFVIIa during ECMO support, found that rFVIIa was 93.3% effective in stopping bleeding (42). Contrary to that, a retrospective chart review of seven pediatric patients on ECMO in two different studies did not show any statistically significant difference in blood loss, or blood product transfusions before or after rFVIIa administration (37,41).

The dose of rFVIIa varies among different ECMO centers

ranging from 40–90 µg/kg (40,42). Some centers use even a lower range of 25–50 µg/kg (76) due to some reported cases of fatal thrombosis (77–80) because of rFVIIa (80–90 µg/kg) administered to patients of ECLS. A retrospective analysis of 388 pediatric patients receiving rFVIIa, showed a higher rate of thromboembolic events in patients who were on ECMO while receiving rFVIIa as compared to the ones who were not (19% *vs.* 4%, $P=0.009$) (39).

The 2014 ELSO anticoagulation guidelines (76) suggested the above-mentioned varying doses of rFVIIa in patients on ECMO, while 2021 guidelines only mention it as a reversal agent for direct thrombin inhibitor (7) where it having proven benefits (81).

TEG/ROTEM

TEG technology was originally described by Hartert in 1948 (82). It provides a visual assessment of clot formation and subsequent lysis under low-shear conditions like those present in the vena cava. ROTEM is a modern modification of the TEG technology. Both are a POC VETs of hemostasis in whole blood, which allow measurement of global clot formation and dissolution in real time (83).

Due to the possible risks of life-threatening bleeding or fatal thrombosis in patients on ECLS, timely knowledge of their coagulation status is of paramount importance for proper management. These viscoelastic POC tests are used commonly to monitor hemostasis in patients on ECMO as two retrospective observational studies showed that TEG/ROTEM correlates well with standard coagulation tests (84,85). Studies also revealed the benefit of VETs in detecting subtle changes in coagulation status (86) and more reliability over routine coagulation tests in detecting thromboembolic events (87).

Although multiple studies mention no statistically significant clinical benefit of using VETs over traditional coagulation tests (84,88) a multicenter, RCT shows that TEG-based anticoagulation management during ECMO was associated with the administration of lower heparin doses compared to an aPTT-based protocol (89). Similarly, a retrospective chart review of 261 patients on ECLS demonstrated an association between an ECMO anticoagulation laboratory protocol using anti-factor Xa assays, TEG, and antithrombin measurements and a decrease in blood product transfusion, a decrease in

hemorrhagic complications, and an increase in circuit life (90). Contrary to that, a pilot RCT of 16 patients on ECMO support did not show any statistically significant reduction in the amount of blood products transfused, the occurrence of bleeding, or thrombotic complications using TEM measurements (91). Another prospective observational study on 57 patients revealed that bleeding events cannot be predicted by means of specific ROTEM results (92), while the risks of thrombosis have been found to be associated with lower maximum clot firmness of intrinsic and extrinsic ROTEM in a Retrospective Cohort study on 73 patients with 623 ECMO days (93).

Figure 1 illustrates our recommendation on approaches to abnormalities observed with TEG and TEM, performed with heparinase for patients on anticoagulation with unfractionated heparin, derived from the ELSO Red Book (10) and the TEM Protocol in ECLS Study (TEMPEST) (91). However, there still remains a lack of evidence to support the effect of TEG and TEM in guiding blood product transfusion protocols in ECMO patients. Further research is required to assess the efficiency of using them as a quick bedside tool to guide blood product transfusion in this specific population.

Summary

This article not only highlights the scarcity of literature guiding non-PRBC blood product transfusion in patients on ECLS but also demonstrates that the quality of the available evidence is mostly low. This is the main reason for the significant variation among institutional practices in different ECMO centers. Establishing guidelines and protocols for transfusion practice in ECMO patients is essential to minimize the variability in the outcome noticed in the literature. Based on the available literature, we can safely summarize that the decision of non-PRBC blood transfusion in ECMO patients should be based upon three factors: (I) clinical context; (II) laboratory values; and (III) viscoelastic studies. Moreover, it is also evident from this review that multiple opportunities are there for future investigations including optimal transfusion threshold, optimal timing of transfusion to minimize the risk of complication, and a risk-benefit analysis associated with transfusing these blood products in ECMO patients. Hopefully, this article will stimulate the required research to fill the gaps in the area.

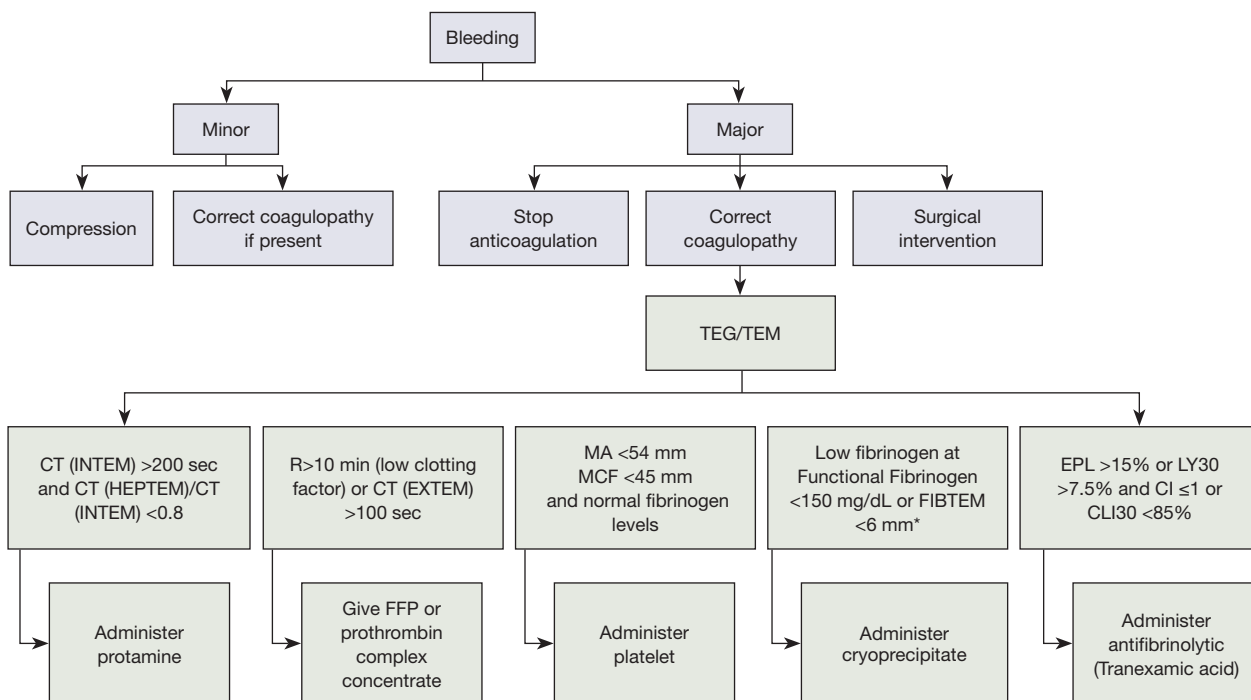


Figure 1 Illustrates our recommendation on approaches to abnormalities observed with TEG and TEM, performed with heparinase for patients on anticoagulation with unfractionated heparin, derived from 2021 ELSO guidelines (7). *, usually associated with prolonged R time. Treat prolonged R time with FFP first and if angle is still low, administer cryoprecipitate as above. TEG, thromboelastography; TEM, thromboelastometry; INTEM, intrinsically activated thromboelastometry; EXTEM, extrinsically activated thromboelastometry; CT, clotting time; HEPTEM, intem with addition of heparinase, used to assess heparin-related coagulation disturbances; R, reaction time; MA, maximum amplitude; MCF, maximum clot firmness; FIBTEM, EXTEM with the addition of cytochalasin D, used to assess fibrinogen-related coagulation disturbances; EPL, estimated percent lysis; LY30, lysis index at 30 minutes; CI, coagulation index; CLI30, clot lysis index at 30 minutes; FFP, fresh frozen plasma; ELSO, Extracorporeal Life Support Organization.

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