Review Article

Transfusion of blood products during extracorporeal membrane oxygenation: a narrative review of rationale, indications, impact on immune function and outcome

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Abstract: The use of extracorporeal membrane oxygenation (ECMO) support poses several risks, particularly thrombosis and bleeding. As a result, transfusion of blood components is frequent during extracorporeal support. In this review we aim to describe the rationale and indications of blood products transfusions, and their impact on the immune function and outcome. The red blood cells (RBC) transfusion threshold is very debated, because of awareness of transfusion-associated adverse events due to liberal strategies. To date, no specific recommendations exist but a comprehensive physiologic approach appears feasible to evaluate the need for RBC transfusion. For patients without bleeding, the guidelines of the Extracorporeal Life Support Organization (ELSO) suggest fresh frozen plasma (FFP) administration if the prothrombin time (PT) ratio is higher than 1.5–2.0 and/or there is significant bleeding. Conversely, for bleeding patient indications often refer to trauma guidelines, where it is recommended to use a 1:1 ratio of RBC and FFP in massive transfusion situations. The indications for antithrombin supplementation are unknown and large inhomogeneity exists between different ECMO centers and between pediatric and adult patients. Supplementation of fibrinogen is considered only for bleeding patients and/or with fibrinogen level below 100 or 150 mg/dL. ELSO guidelines suggest 25–50 IU/kg of prothrombin complex concentrate as an alternative to FFP for patients with active bleeding and a prolonged PT. Recombinant activated factor VII might be a potential therapeutic option for intractable bleeding despite conventional treatment but may cause life-threatening thrombotic complications. Platelet transfusions might be limited to cases of severe thrombocytopenia accompanied by bleeding. ELSO guidelines recommend a target of at least 80×10^9/L platelets. Liberal platelets transfusion thresholds may be reasonable in case of intracranial hemorrhage. Albeit rare, multiple adverse events of blood products transfusion are described. There is no evidence of transfusion-related acute lung injury during ECMO support, likely because of the difficulty to distinguish the cause of clinical worsening in patients with severe respiratory failure. Infections represent a major contributor on morbidity and mortality in ECMO patients. However, as of today, no literature has explored the impact of transfusions on immune function of ECMO patients. Currently, there are no specific guidelines for transfusions in ECMO patients and the management is highly variable among centers. Further research is warranted on this topic.

Keywords: Extracorporeal membrane oxygenation (ECMO); transfusion; blood products; red blood cells (RBCs); platelets; plasma

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Introduction

In recent years, extracorporeal membrane oxygenation (ECMO) has been increasingly used in critically ill patients with respiratory and/or cardiac failure (1). Despite its widespread use, ECMO is still associated with a high rate of complications. Among these, bleeding and thrombotic events are reported in up to 12% and 3% of adult patients receiving ECMO, respectively (2). During extracorporeal support, blood comes into contact with artificial surfaces (e.g., tubing, blood pump and exchange membrane), which determine the activation of the inflammatory and the coagulative response. Indeed, as soon as blood is exposed to the extracorporeal circuit, the contact and complement systems, the intrinsic and extrinsic coagulation pathways, together with leukocytes, platelets and endothelial cells are activated (3,4). All these systems are highly intertwined and this interplay, along with other mechanisms (e.g., shear stress, patient proinflammatory status), produces multiple hemostasis alterations that are either responsible for thrombotic complications or increased bleeding tendency (4). The risk of bleeding is further raised by continuous anticoagulation, which is necessary to reduce the incidence of thromboembolic events (5).

In the last decades, technological improvements, such as heparin-coated circuits and centrifugal pumps, allowed the reduction of hemostasis perturbations, hemolysis and anticoagulation requirements (6,7). However, hemorrhagic and thrombotic episodes still represent a major contributor to mortality during ECMO support. Indeed, 64% and 78% of patients with hemorrhage and ischemia, respectively, died, according to the 2019 Extracorporeal Life Support Organization (ELSO) complications report (2).

Transfusions are common among ECMO patients. Indeed, a recent international survey found up to 56% of patients on ECMO received 3–5 units of red blood cells (RBC) and 69% of patients received 1–2 units of fresh frozen plasma (FFP). However, transfusion triggers were highly heterogenous among institutions and no clear guidelines exist on this topic (8). Moreover, transfusions are associated to both infectious and noninfectious adverse events. For these reasons, optimization of the transfusion strategy is crucial for an adequate management and to potentially improve outcomes. This review aims to discuss the rationale and indications to blood component transfusions during ECMO and their impact on outcome. Moreover, how they affect immune response and the associated noninfectious adverse events is reviewed. The infective risk of transfusions is extremely low and will not be discussed in this review (9). We present the following article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.com/article/view/10.21037/aob-21-32/rc).

Methods

We conducted two literature searches in December 2020 and March 2021, using MEDLINE through the PubMed search engine with the MeSH terms: (I) blood transfusion, critical care and (II) blood transfusion, ECMO, immune function. We included articles published in English after the year 1970 up to February 2021, about blood transfusion in critical patients, patients on ECMO and about its impact on immune function.

Rationale of transfusions in ECMO patients

ECMO patients may receive transfusions for bleeding, to increase oxygenation or to treat coagulopathy. In the case of active bleeding, although no specific guidelines on ECMO patients exist, usually clinicians refer to common practice for trauma patients (10). Therefore, all blood components are transfused and aim to restore the lost homeostasis. However, ECMO patients receive blood components also when there is no active and life-threating bleeding. In this situation RBC transfusions are expected to increase the available amount of oxygen for tissues. Thus, the benefit of high hemoglobin (Hb) concentrations must be weighed against the risks of transfusions. Indeed, in critically ill patients an association between transfusions and poorer outcomes has been identified by different clinical studies (11,12). In addition, the multicenter Transfusion Requirements in Critical Care (TRICC) trial showed a restrictive transfusion strategy (Hb threshold for transfusion <7 g/dL) is as effective as a liberal strategy (Hb threshold for transfusion <10 g/dL). Moreover, a survival benefit has been observed in the restrictive policy group in patients younger than 55 years and less critically ill (Apache score ≤20) (13). However, no similar randomized controlled trial investigated this endpoint in the subset of ECMO patients.

As for other blood components (e.g., plasma, platelets and specific plasma derivatives), these are commonly used to treat coagulopathy. However, transfusion thresholds and triggers remain debated and evidence is scarce.

In the following sections, we will address the different blood components, discussing indications and, when

available, the relevant studies regarding their use in ECMO patients. The main findings of the present review are summarized in *Table 1*.

RBC transfusion

RBC transfusion is one of the most debated aspect in the management of patients treated with ECMO. Bleeding episodes, and thus transfusion requirements, are higher in ECMO patients than in other critically ill patients. This is due to the anticoagulation therapy (14) and to the alterations of hemostasis caused by the exposure of blood to artificial surfaces, as previously discussed (15).

Hb concentration plays a pivotal role in oxygen transport, as the majority of the arterial oxygen content is bound to Hb. Therefore, increasing Hb increases the oxygen carrier in the blood and consequently, augments the amount of oxygen upload at the oxygenator. This results in improved oxygen delivery to the peripheral tissue, possibly reducing hypoxia and, in case of patients with respiratory failure on veno-venous (V-V) ECMO support, in a better arterial Hb saturation (16,17). On the other hand, the oxygen delivery during ECMO can be also improved by increasing the extracorporeal blood flow (18). Thus, despite the physiologic rationale for increasing Hb concentration in ECMO patients, increasing awareness of transfusion-associated adverse events has questioned the practice of liberal transfusion strategies. Randomized controlled trials (13,19) showed that restrictive strategies result in similar outcomes and reduced transfusion requirements compared to liberal strategies. Therefore, a low Hb transfusion threshold (i.e., 7 g/dL) and maintaining a Hb concentration between 7 and 9 g/dL are currently recommended in critically ill patients to reduce the risk of transfusion-associated adverse events.

To date, no specific recommendations exist for RBC transfusion in patients treated with ECMO due to the low quality of the available evidence (20).

A prospective observational study found that pre-ECMO hematocrit (P=0.04), platelets nadir (P=0.02), antithrombin (AT) (P<0.01) and renal failure (P=0.09) were associated with RBC transfusion. The authors also found a lower survival rate in patients who received more RBC units (>150 mL/d) than patients who received less RBC units (62.7% *vs.* 89.9%, log-rank P<0.01) (21).

Other preliminary evidence suggests that a restrictive strategy could be used in ECMO patients without any impact on clinical outcomes (22). Doyle *et al.* compared outcomes of patients before and after changing from a liberal transfusion policy (Hb target 10–12 g/dL) to a restrictive one (Hb target 8–9 g/dL). The median Hb concentration decreased from 9.7 to 8.7 g/dL (P<0.001) and the average number of RBC units transfused decreased from 0.66 RBC units per ECMO to 0.44 (P<0.001) without any negative impact on outcome (6-months survival 72.9% *vs.* 74.2%, P=0.914) (23).

A systematic review and meta-analysis (24) that included 1,070 patients on ECMO from observational studies and randomized controlled trials showed that a lower transfusion threshold was associated with a lower risk of mortality, a lower risk of renal failure and a lower transfusion rate. However, due to the low quality of included studies and the high heterogeneity, these findings should be interpreted with caution.

The TRAIN-ECMO survey showed that only 46% of centers considered the Hb level as the only transfusion trigger. However, the average Hb level was higher in V-V ECMO patients than in other critical patients (9.1±1.8 *vs.* 8.3±1.7 g/dL, P<0.01). In addition to Hb level, other variables were occasionally considered as indicators for transfusion: mixed venous saturation (18.2% of cases), arterial saturation (6.4%), oxygen delivery (6.1%), ongoing bleeding (7.5%) and tissue perfusion parameters (lactates 7.9%, clinical signs of hypoperfusion 3.9%) (25).

The RBC transfusion strategy in patients supported by ECMO remains a matter of debate. A restrictive policy appears feasible, but clinicians are expected to apply a comprehensive physiologic approach to evaluate the need for RBC transfusion, always considering the risk-benefit balance.

Plasma and coagulation factors

Plasma

Plasma is the portion of whole blood that remains after the cellular elements (i.e., red and white blood cells) and platelets have been removed by centrifugation. It includes coagulation factors. Plasma is stored as FFP and it is thawed when needed for transfusion. Once unfrozen, the plasma must be transfused within 24 hours, otherwise the concentrations of factors V and VIII begin to decline (26). In clinical practice, FFP has been used during ECMO support to correct elevated prothrombin time (PT) and to supplement AT in heparin-resistant patients (27). Indications for FFP during ECMO support differ for patients with or without active bleeding. For patients who are not bleeding,

Table 1 Summary of findings of the review

Blood components	Rationale	Indications	Non-infectious adverse events	Immune response	Adverse outcome
RBC	Bleeding episodes are more common in ECMO patients	No specific evidence	Febrile non-hemolytic transfusion reactions (0.1%), mild-moderate allergic reactions (0.08%), delayed serological transfusion reactions (0.01%), TRALI: acute respiratory failure developed after blood	TRIM: immunosuppressive effect due to allogenic RBCs themselves or to the by-products derived by alterations occurring during storage, due to increased infectious risk	Higher rates of transfusions are associated with lower survival
	Increasing Hb results in improved oxygen delivery, which is crucial in severe hypoxic patients	Comprehensive physiologic approach	Immune or non-immune acute hemolytic		
FFP	Loss of clotting factors due to dilution from circuit priming and coagulopathy induced by contact with artificial surface	Active bleeding: 1:1 ratio of RBC and FFP	Transfusion reactions		–
	Antithrombin supplementation in heparin resistant patients	Non-active bleeding: depending on PT ratio (higher than 1.5/2.0)	Fluid overload		
AT	Correct levels of AT are crucial to obtain an effective anticoagulation with UFH during ECMO	Maintain AT activity between 80–120%	–		Increased risk of bleeding
	AT consumption can be a consequence of circuit-related inflammation				
Fibrinogen	Involved in platelets aggregation and clot formation	Bleeding patient and/or with fibrinogen level <100–150 mg/dL;	–		–
		Pediatric population with qualitative deficiencies in fibrinogen function			
PCC	Supplementation of coagulation factors in bleeding patients	25–50 IU/kg of PCC as an alternative to FFP for patients with active bleeding and a prolonged PT	–		–
Recombinant FVIIa	Compassionate use for refractory bleeding	–	–		Fatal thrombosis, emboli, clotting circuits
Platelets	Thrombocytopenia in patients undergoing ECMO is multifactorial and common and increases bleeding risk, blood products transfusion requirements and mortality	Thresholds: severe thrombocytopenia: under 20×10^9/L; active bleeding: $50–80\times10^9$/L; liberal in intracranial hemorrhage	–		Volume of platelets transfusion associated with higher risk of death

RBC, red blood cells; FFP, fresh frozen plasma; AT, antithrombin; PCC, prothrombin complex concentrate; ECMO, extracorporeal membrane oxygenation; Hb, hemoglobin; UFH, unfractionated heparin; PT, prothrombin time; TRALI, transfusion-related acute lung injury; TRIM, transfusion related immunomodulation.

the degree of PT elevation which mandates correction is unclear. ELSO guidelines (28) suggest FFP administration if the PT ratio is higher than 1.5/2.0 and/or there is significant bleeding. Singh *et al.*, in a consensus paper, suggest FFP transfusion in peculiar situations, like invasive maneuvers, but do not indicate the routine use of FFP, due to its well-known risks (e.g., fluid overload, transfusion related acute lung injury and immunologic reactions) (27). Instead, for bleeding patients on ECMO, indications for the transfusion of FFP are undefined, and practitioners often refer to other literature and guidelines, such as those regarding trauma. In the trauma literature, it is recommended to use a 1:1 ratio of RBC and FFP in massive transfusion situations (29,30). This would maintain an adequate concentration of coagulation factors, reduce organ dysfunction and improve survival (30-32). ECMO patients also suffer from a decrease in clotting factors below normal values for at least 24 hours after initiation of ECMO support, due to the dilution from the circuit prime and coagulopathy induced by blood contact with artificial surfaces (33,34). This decrease is more pronounced in pediatric patients due to their smaller circulating blood volume and lower levels of coagulation factors, as compared to adults. Because of this, some pediatric ECMO centers include FFP in the ECMO priming solution to attenuate this loss of clotting factors (35,36). In addition, balancing pro- and anticoagulation factors through FFP administration may decrease overall circuit clot formation, thereby decreasing need for circuit change, which currently occurs in approximately 20% of ECMO patients (37). In a study aimed to resolve this issue, however, scheduled FFP did not increase the circuit life. Moreover, both the intervention and the control group had similar rate of bleeding and thrombosis (38). To date, indications for FFP transfusion are still unclear and represent an open field of research.

AT

AT (previously called AT III) is a natural anticoagulant. It inhibits thrombin (factor IIa), factor Xa, and other serine proteases in the coagulation cascade, such as factor IXa (39). During ECMO support, the use of unfractionated heparin is a conventional anti-coagulation strategy (40). Following the administration of unfractionated heparin, AT activity is dramatically accelerated due to a conformational change leading to enhanced exposure of the AT reactive center induced by heparin binding. This conformational change converts AT from a slow inactivator of coagulation factors to a rapid inactivator (41). The AT testing measures the activity (function) and the amount (quantity) of plasmatic AT. Replacement of AT can be accomplished more effectively by administering an AT product rather than FFP, as FFP has a low AT concentration (1 unit/mL). In clinical practice, the therapeutic effect of heparin might be difficult to achieve when AT level is less than 50% (42,43). Moreover, mild AT deficiency is associated with an increased risk of venous thromboembolism (44). During ECMO support or cardiopulmonary bypass, an accelerated AT consumption has been described as a consequence of complex inflammatory responses (45). This may result in ineffective anticoagulation with heparin (46). For this reason, AT supplementation is a common practice in neonates, children (36,47) and adults treated with ECMO (40). On the contrary, AT supplementation may increase the risk of bleeding because of its anticoagulant property. Protti *et al.* in a survey analyzed 273 unique responses from different ECMO centers and found that AT is routinely monitored in 49% and routinely prescribed in 38% of ECMO centers. These percentages rise to 81% and 66% respectively in pediatric centers. Supplementation triggers vary and frequent indications are a difficult achievement of the anticoagulation target (in 51% of centers) or a plasmatic AT activity below a certain target (i.e., 60% to 80%, in 49.0% of centers) (40). More recently, Panigada *et al.* randomized V-V ECMO patients treated with unfractionated heparin to AT supplementation to maintain plasmatic AT activity between 80% and 120% or no supplementation. No difference was found between groups in the primary outcome (heparin dosage) or in secondary outcomes (i.e., anti-Xa levels; bleeding and thrombosis events; ECMO circuit clotting) (48). Considering the results of their study together with previous literature (42-44), Panigada *et al.* do not recommend AT supplementation in patients with an AT level above 60% (48). In conclusion, to date, the indications for AT supplementation are unknown and large inhomogeneity exists between ECMO centers. Therefore, further research is needed to clarify which patients would benefit from AT supplementation.

Fibrinogen, cryoprecipitate, prothrombin complex concentrate (PCC) and recombinant activated factor VII

Fibrinogen is a plasma glycoprotein synthesized by the liver, with numerous functional interactions and pivotal role in hemostatic balance (49). It is primarily involved in platelet aggregation and establishment of fibrin network for clot formation (50). Fibrinogen is available as fibrinogen

concentrate or cryoprecipitate. Fibrinogen concentrate is a purified form of fibrinogen derived from pooled human plasma, which undergoes a pasteurization process to minimize the risk of immunologic and allergic reactions. Cryoprecipitate is a plasma-derived blood product for transfusion containing fibrinogen, factor VIII, factor XIII, von Willebrand factor (VWF), and fibronectin. Supplementation of fibrinogen, as a concentrate or cryoprecipitate, is considered only for bleeding patient and/or with fibrinogen level <100–150 mg/dL (28). In particular, pediatric patients have an immature hemostatic system and demonstrate qualitative deficiencies in fibrinogen function (51,52). Downey *et al.* demonstrated that fibrinogen concentrate administration reduced intraoperative allogenic blood transfusions when compared to cryoprecipitate in infants requiring cardiac surgery (53).

PCCs are concentrates of coagulation factors and anticoagulants purified from plasma. They contain high levels of three to four coagulation factors (II, IX, and X in 3 factor PCCs; II, VII, IX, and X in 4 factor PCCs), along with proteins C and S. Use of PCC during ECMO support is limited to bleeding events. ELSO guidelines (28) suggest 25–50 IU/kg of PCC as an alternative to FFP for patients with active bleeding and a prolonged PT. Different reports, in adult and pediatric patients, described the use of recombinant activated factor VII as a compassionate treatment for refractory bleeding (54-56) during extracorporeal support. However, cases of fatal thrombosis after administration of recombinant activated factor VII (rFVIIa) during ECMO support have been reported (57-59). rFVIIa might be a last therapeutic option for patients receiving ECMO with intractable bleeding, but clinicians must be aware of possible life-threatening systemic thrombosis, emboli, or circuit clotting (55).

Platelets

Thrombocytopenia is a frequent acquired condition among critically ill adult patients, commonly associated with sepsis and disseminated intravascular coagulation. It is usually defined as a platelet count lower than 150×10^9/L. Its prevalence at the time of intensive care unit (ICU) admission ranges from 8.3% to 67.7%, whereas its incidence during ICU stay ranges from 14% to 44% (60). An analysis on 3,721 ICU patients from the PROTECT study (61,62), a large RCT comparing two anticoagulation regimens on deep vein thrombosis prevention, found a prevalence of thrombocytopenia of 26%.

Thrombocytopenia is associated with a higher risk of bleeding, with an increased blood product transfusion requirement and a significantly higher ICU and hospital mortality (60,62,63).

Five major mechanisms can result in thrombocytopenia. The most common in ICU patients are hemodilution, due to dilution caused by other blood products, crystalloid or colloid solutions, and increased platelet consumption. This consumption can be due to bleeding, sepsis, intravascular coagulopathy and extracorporeal circuits, which are the main topic of our discussion. Less common mechanisms are decreased platelet production, increased platelet sequestration and increased platelet destruction by immune mechanisms (64,65).

As mentioned above, the exposure of blood to non-biological artificial surfaces and the shear forces and turbulences associated with the extracorporeal circulation result in the activation of a systemic inflammatory response and the activation of the coagulation cascade (66,67).

Platelets are a major mediator of this inflammatory process (66,68). The shear stress causes cell damage with release of VWF and collagen exposure: this results in platelet adhesion via glycoprotein Ib and subsequent expression of glycoprotein IIb/IIIa receptors that bind to fibrinogen, promoting platelets aggregation. This causes platelet consumption and disfunction of the remaining platelets, which underwent some degree of activation and degranulation, thus increasing bleeding risk in these patients (66,69,70). This results in the development of thrombocytopenia (71,72) and consequently in a clinically relevant increased risk of bleeding (65).

A systematic review and meta-analysis by Jiritano *et al.* regarding platelet function during ECMO showed a prevalence of thrombocytopenia reaching 21% in patients on ECMO. The cause of the decrease in platelet count was multifactorial, including not only the contact with foreign surfaces, but also other contributing factors (e.g., sepsis, medications, surgery, bleeding, intravascular devices, and blood transfusions) (73). Dzierba and coworkers retrospectively compared platelets levels between ECMO and non-ECMO acute respiratory distress syndrome (ARDS) patients. A multivariate analysis, adjusted for potential confounders, showed no significant association between the use of ECMO and severe thrombocytopenia (74). Another recent retrospective cohort study of 100 adults who received ECMO for acute respiratory failure found that decline of platelet count

over time was not associated with the duration of ECMO use. The results of these studies suggest that the perceived association between ECMO and the development of thrombocytopenia is best explained by the initial severity of critical illness and the development of multi-organ failure while on ECMO, rather than by the presence of the extracorporeal circuit itself (71).

As discussed above, hemorrhagic events represent a main threat in ECMO patients. Despite several studies assert bleeding is a clinical implication of thrombocytopenia in patients undergoing ECMO (73,75), the association between hemorrhagic events and decrease in platelets count must be better characterized (71). In a study on 164 patients on ECMO, low platelets levels were not a significant risk factor for hemorrhagic complications (which occurred in 45% of patients). Contrarily, a high activated partial thromboplastin time (aPTT) value was an independent predictor of bleeding events, reaffirming the difficulty of achieving a balance between anticoagulation and hemorrhagic risk in ECMO patients (67).

Most platelets transfusions in critically ill and surgical populations are based on prophylactic, rather than therapeutic indications. Different thresholds have been proposed, based on the patient's bleeding risk, on the presence of active bleeding and on antiplatelet medications or disorders affecting platelet function. In the setting of acute traumatic hemorrhage, it is recommended to maintain a platelet count above 50×10^9/L, and above 75–100 $\times10^9$/L in case of central nervous system injury. In the setting of active bleeding, a threshold of 50×10^9/L is commonly employed as a trigger for platelet transfusion (100×10^9/L if the bleeding involves the central nervous system, the eyes or the lung) (65,76). Thresholds for platelets transfusion are mainly based on expert opinions (77) and no randomized trials on transfusions strategies in thrombocytopenic ICU patients have been conducted so far (78). Future research should aim to solve this issue, because platelet transfusion may be associated with harm, including nosocomial infections, transfusion-related lung injury, transfusion-associated circulatory overload and increased ICU morbidity and mortality (65,67,78-83). In particular, platelet volume requirement was independently associated with a higher risk of death in V-V ECMO patients (82).

Recommendations for platelets transfusion in ECMO patients vary considerably (84), and literature on this topic is scarce. Transfusions might be limited to cases of severe thrombocytopenia accompanied by bleeding (85). ELSO guidelines recommend a target of at least 80×10^9/L platelets in patients on ECMO (28). However, different studies reported the indication of maintaining a platelet count above 20×10^9/L (50×10^9/L in presence of active bleeding) (67,71,86,87). In ECMO patients who developed intracranial hemorrhage, as reported in a study by Cavayas and coworkers, liberal platelets transfusion thresholds even in absence of bleeding may be reasonable, until more data are available (88). Standardized triggers have not been established yet (89).

Noninfectious transfusion-associated adverse events

Even though the transfusion of blood components in critical care patients is commonly performed and, sometimes, is a lifesaving resource, it is not a harmless treatment.

Of note, a recent retrospective study evaluated the association between blood products administration and clinical outcomes in ECMO patients. The multivariate analysis showed a 1% mortality increase and a 1% increase in thrombotic events for each blood component unit transfused (90).

Over the past decades, adequate donor and recipient patients screening greatly reduced the infectious risk to fewer than 1 per 2 million transfusions (9). Nevertheless, awareness about noninfectious transfusion-associated adverse events has recently increased. These adverse events are attributable to the contaminants of the blood products and the alterations of RBCs during the storage (reduced deformability, increased fragility and more risk of hemolysis and microvascular disfunction). The most common adverse events are febrile non-hemolytic transfusion reactions (0.1% of transfusions), mild-moderate allergic reactions (0.08% of transfusions) and delayed serological transfusion reactions with mild or no consequence (0.01% of transfusions) (9). Other transfusion-associated adverse events, like acute hemolytic transfusion reactions and transfusion-related acute lung injury (TRALI), although rarer, can have serious consequences in critical patients and be life-threatening.

Acute hemolytic transfusion reactions typically occur after RBC transfusion in patients with preexisting antibodies, but can also occur with a non-immune-mediated mechanism (9,91). Moreover, during extracorporeal circulation, hemolysis is a common complication due to mechanical reasons (i.e., shear stress), and acute hemolytic transfusion reactions could worsen an already present condition.

TRALI is defined as an acute respiratory failure developed after blood transfusion in a patient with no other risk factor for acute lung injury and no pulmonary oedema. It has an immune-related pathogenesis, and it is considered as the first cause of transfusion-related death (81). It is believed TRALI is determined by the premorbid inflammatory status of the patient, which activates the pulmonary endothelium and sequesters the polymorphonucleates in the lungs. The exposure of the polymorphonucleates to antibodies present in the stored blood products generates a hyperactive inflammatory response of the polymorphonucleates which causes the lung damage (92). There is no evidence on the incidence of TRALI during ECMO support, likely because it is very difficult to distinguish the cause of clinical worsening in patients with very severe respiratory failure. Nevertheless, many conditions frequently found in ECMO patients, such as mechanical ventilation, sepsis and extracorporeal circulation in cardiopulmonary bypass for cardiac surgery have been identified as risk factors for TRALI (81). Moreover, TRALI itself could determine the need of ECMO to provide time to recover to the injured lungs (93).

Prevention and management of adverse events

The best strategy to prevent transfusion-associated adverse events is avoiding any unnecessary transfusion. This aim could be reached by developing patient blood management programs based on transfusion guidelines and high-quality evidence (9). This approach aims to avoid unnecessary transfusions adopting, whenever possible, a restrictive strategy that appears feasible in patients on ECMO, as previously described. In addition, patient blood management programs promote other tools such as the use of viscoelastic point-of-care tests to guide transfusion decisions and antifibrinolytics to correct coagulopathy (9). The use of viscoelastic tests would allow to transfuse only the specific blood component needed by the patient, reducing the exposure to all the contaminants of stored blood.

In case of adverse event, transfusions must be interrupted, a supplemental blood sample should be collected to repeat type and the transfusion service should be warned (9). Moreover, supportive treatment must be established immediately, paying attention to the development of potentially fatal adverse events.

Transfusion impact on the immune function

Blood transfusions can affect the immune function of the recipient. This concept emerged in 1978, when Opelz and colleagues observed renal transplant recipients survived more if transfused with RBC. This suggested an immunosuppressive effect of allogeneic RBC transfusion (94). This effect was defined as transfusion-related immunomodulation (TRIM), which is mainly considered as an immunosuppressive effect of RBC transfusions and seems associated to both RBCs themselves and the by-products derived from storage lesions of stored RBCs (9,95). From a pathophysiological point of view, RBC transfusions may alter the innate immune response. Immediately after the transfusion, there is some extent of phagocytosis of the transfused RBCs by macrophages and monocytes. These release inflammatory cytokines and non-transferrin bound iron, which, in turn, causes an immunosuppressive status. The subsequent activity of phagocyte function is inhibited, and the iron substrate is available for bacterial growth. This could raise the incidence of nosocomial infections. In addition, it has been observed that heme and Hb may alter the phenotype of macrophages towards an anti-inflammatory status, which could undermine the response to pathogens and the immunosurveillance of neoplasms. Chronically, monocytes and macrophages may exhibit memory. Once the innate immune response cells are exposed to transfused RBC they may be unable to respond to a subsequent noxious stimulus. However, the clinical impact of TRIM remains debated. TRIM has been studied in cancer patients and transfusions have been associated to an increased risk of cancer recurrence in some clinical trials (96). Moreover, a meta-analysis showed a risk ratio of healthcare-associated infections of 0.82 (95% confidence interval, 0.72–0.95) for a restrictive RBC transfusion strategy compared to a restrictive strategy (97). Therefore, TRIM could explain the increased risk of infections in patients receiving RBC transfusion.

Immunomodulation is an issue of concern in patients supported by ECMO who are at increased risk of infection as a result of various mechanisms: longer duration of ECMO treatment, higher number of catheters, possible colonization of cannulae and oxygenator and alteration of inflammatory system (98). Furthermore, infections represent a major contributor on morbidity and mortality in ECMO patients (99,100). However, no literature has

explored specifically the impact of transfusions on immune function of ECMO patients yet.

Conclusions

Transfusions are common in patients on ECMO to treat bleeding complications, improve oxygen delivery or treat coagulopathy induced by the activation of the coagulation and inflammatory cascade caused by the extracorporeal support. Currently, there are no specific guidelines for transfusions in ECMO patients and their management is highly variable among centers. The risk-benefit ratio of transfusions must be considered, as liberal strategies carry detrimental transfusion-related adverse events, which could be immediate, like in TRALI, but also delayed, as the immunosuppression induced by RBC transfusion. Research efforts are required to provide evidence of the effect of blood components transfusion and to determine whether they affect outcome.

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