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Transfusion Thresholds for Adult Respiratory Extracorporeal Life Support: An Expert Consensus Document*

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ABSTRACT

Severe acute respiratory distress syndrome (ARDS) can complicate novel pandemic coronavirus disease (COVID-19). Extracorporeal life support (ECLS) represents the final possible rescue strategy. Variations in practice, combined with a paucity of rigourous guidelines, may complicate blood-product resource availability and allocation during a pandemic. We conducted a literature review around venovenous extracorporeal membrane oxygenation (VV-ECMO) transfusion practices for platelets, packed red blood cells, fresh frozen plasma, prothrombin complex concentrate, and antithrombin. Pertinent society

RÉSUMÉ

La nouvelle maladie à coronavirus pandémique (COVID-19) peut se compliquer d'un syndrome de détresse respiratoire aiguë (SDRA) grave. Dans un tel cas, l'assistance vitale extracorporelle constitue la dernière stratégie de secours possible. Les divergences dans les pratiques, combinées à un manque de lignes directrices rigoureuses, peuvent compliquer l'accessibilité et la répartition des ressources relatives aux produits sanguins en situation de pandémie. Nous avons passé en revue les publications s'intéressant aux pratiques en matière de transfusion de plaquettes, de concentré de globules rouges, de

All who drink of this remedy recover in a short time except those whom it does not help, who all die.

—Aelius Galenus (Claudius Galenus)

Severe acute respiratory distress syndrome (ARDS) may complicate pandemic novel coronavirus disease (COVID-19) in approximately 12% of cases. Extracorporeal life support (ECLS), in the form of venovenous extracorporeal membrane oxygenation (VV-ECMO), can be successful for severe ARDS support in adults. The World Health Organization (WHO)

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guidelines were examined, and the practice of Canadian ECLS experts was sampled through an environmental scan. This paper represents a synthesis of these explorations, combined with input from the Canadian Cardiovascular Critical Care (CANCARE) Society, Canadian Society of Cardiac Surgeons, and the Canadian Critical Care Society. We offer a pragmatic guidance document for restrictive transfusion thresholds in nonbleeding patients on VV-ECMO, which may attenuate transfusion-related complications and simultaneously shield national blood product inventory from strain during pandemic-induced activation of the National Plan for the Management of Shortages of Labile Blood Components.

plasma frais congelé, de concentré de complexe prothrombinique et d'antithrombine à des patients sous oxygénation par membrane extracorporelle (ECMO pour *extracorporeal membrane oxygenation*) veinoveineuse. Nous avons notamment examiné les lignes directrices pertinentes de différentes associations et analysé la situation à partir d'un échantillon des pratiques adoptées par des spécialistes canadiens en assistance vitale extracorporelle. L'article qui suit constitue une synthèse de ces examens et des commentaires recueillis auprès de la Société canadienne pour les soins intensifs cardiovasculaires, de la Société canadienne des chirurgiens cardiaques et de la Société canadienne de soins intensifs. Ce document d'orientation pragmatique pour l'établissement de seuils de transfusion restrictifs chez les patients sous ECMO veinoveineuse qui ne présentent pas d'hémorragie a été créé afin d'atténuer les complications liées à la transfusion et d'éviter des pressions indues sur les stocks nationaux de produits sanguins en cas de pandémie nécessitant l'exécution du Plan national de gestion en cas de pénuries de composants sanguins labiles.

recommended ECLS consideration in experienced centres for COVID-19—induced severe ARDS. Many jurisdictions planned for increasing demand and application of VV-ECMO during COVID-19.[1]

ECLS, although an effective rescue therapy, is resource intensive. Of particular concern is blood- product transfusion needs during extracorporeal support and implications on dwindling or depleted national inventory during a pandemic. Knowledge of COVID-19 vascular effects and coagulation implications is evolving, which may influence blood-product transfusion thresholds.

Several drivers exist for the use of blood products during ECLS. Both bleeding and thrombosis are potential patient and circuit complications. The antagonism of bleeding diatheses and circuit thrombosis necessitates a balanced approach between administration of blood products and anticoagulation. Furthermore, one of the physiological goals of ECLS includes increasing oxygen delivery to overcome profound tissue hypoxia. As oxygen delivery is influenced by oxygen saturation and hemoglobin (in addition to cardiac output), clinicians traditionally transfused to higher hemoglobin targets to augment delivery of oxygen.

Galen's admonition on the value of a remedy may be reflected in blood product utility in the critically ill. Recently, several studies outside of ECLS have questioned this practice and have suggested that more restrictive blood-product transfusion may be the preferred strategy. Rigourous evidence for transfusion practice in the ECLS population is lacking. Moreover, the potential demand for ECLS during the COVID-19 pandemic may be much greater, leading to additional blood-product consumption. This prompted a request by the National Emergency Blood Management Committee (NEBMC), National Advisory Committee on Blood and Blood Products (NAC), and Canadian Blood Services for suitable transfusion thresholds during activation of the National Plan for the Management of Shortages of Labile Blood Components.[2]

An environmental scan of Canadian ECLS programs was performed: 17 Canadian ECLS centres were contacted through e-mail, with 12 centres answering, representing a 70.6% response rate. All geographic regions were represented. A semistructured telephone interview was conducted to gather data regarding transfusion policies, protocols, and practices.

The purpose of this document is to provide guidance for nonbleeding patients on VV-ECMO around packed red blood cell, platelet, and fresh frozen plasma (FFP) transfusion, along with prothrombin complex concentrate (PCC) and antithrombin administration, within the Canadian context. An expanded version with full reference list is available in the Supplementary Material.

This document is supported by the Canadian Cardiovascular Critical Care (CANCARE) Society and the Canadian Society of Cardiac Surgeons (CSCS). Although societal endorsement is reserved for clinical practice guidelines developed through comprehensive guideline methodology, the Canadian Critical Care Society (CCCS) recognizes the importance of guidance offered in this document to Canadian ECMO practitioners nationwide.

Packed Red Blood Cells

Optimized oxygen delivery during ECLS support is predicated upon adequate blood flow rates and hemoglobin concentration. Extracorporeal Life Support Organization (ELSO) guidelines suggest considering hemoglobin up to 150 g/L to permit lower ECMO flow rates. More recent pandemic-specific ELSO interim guidelines suggest a transfusion threshold of 70 to 80 g/L.[3]

To assist the National Emergency Blood Management Committee in determining ongoing transfusion needs, an environmental scan of Canadian ECLS centres was performed. The majority of Canadian centres use a restrictive transfusion threshold strategy (Supplemental Table S1).

In adult critical care units, more restrictive transfusion triggers are standard: typically, < 70 g/L.[4] In addition, correction of anemia in septic patients may not improve oxygen use or outcomes.

Specific to adult cardiac surgical patients, a restrictive packed red cell transfusion (< 75 g/L) was noninferior to

liberal transfusion (< 95 g/L), in a moderate to high-risk cohort. However, this did not include patients on ECLS.

A retrospective study of a blood conservation protocol incorporating a restrictive transfusion strategy (transfusion trigger <70 g/L) in patients on VV-ECMO described survival and end-organ recovery similar to historical reports.[5]

In patients persistently hypoxemic despite ECLS, the physiological tendency to amplify oxygen delivery with a higher hemoglobin threshold is controversial. It is unclear whether the potential benefit of oxygen delivery augmentation through the allogeneic blood transfusion outweighs the risks. This may only be apparent at a severely restrictive threshold, when it is plausible that further reduction in oxygen-carrying capacity could be deleterious.

Expert consensus statements

Based on limited evidence and expert consensus, we suggest the following for nonbleeding patients who are supportable with adequate ECMO flow rates to achieve the ECLS consultant's physiological goals, provided that inventory is adequate: In stable nonbleeding patients for whom clinical goals are attainable, a hemoglobin transfusion threshold of 75 g/L, and as low as 70 g/L, is reasonable, based on the ECLS consultant's clinical judgement.

Platelets

Hemorrhagic complications are major contributors to mortality during ECLS. Thrombocytopenia is common in critical illness and multifactorial in origin; consumption and disseminated intravascular coagulation caused by underlying disease process, pharmacologic agents and platelet adhesion and aggregation due to artificial biosurface interactions are all implicated. In addition, platelets may also be dysfunctional. The incidence of intracranial hemorrhage, with associated poor outcomes, has led some to recommend liberal platelet transfusion.

Danish investigators, using impedance aggregometry and cytometry, found impaired platelet aggregation with reduced activation upon initiation of ECMO. When adjusted for thrombocytopenia, however, platelet aggregation was not impaired. The authors concluded that impaired aggregation during ECMO is a consequence of thrombocytopenia.

It has also been reported that thrombocytopenia is not related to the duration of time on VV-ECMO; rather, illness acuity (**A**cute **P**hysiology and **C**hronic **H**ealth **E**valuation **II** [APACHE II] score) and platelet count at ECLS cannulation predict developing thrombocytopenia < 50 000/μL.

Of note, adequate anticoagulation is vital to prevent platelet consumption on the membrane. Inadequate anticoagulation may paradoxically lead to worsening thrombocytopenia and hemorrhage.

Current practice at several high-volume Canadian centres is to maintain platelet counts > 50 000/μL (Supplemental Appendix S1). Many Canadian centres, however, adhere to established ELSO Adult Respiratory Failure Guidelines (August 2017), using a platelet transfusion trigger for < 80 000/μL.[3] More recent interim pandemic-specific ELSO guidelines suggest platelets > 50 000/μL, or even lower, in the absence of bleeding.

Expert consensus statements

No randomized clinical trials are available to affect guidance. Based on limited, low-quality evidence and expert consensus, we suggest the following for nonbleeding patients, provided that the inventory is adequate:

- A platelet transfusion threshold of 50,000/μL is reasonable.
- Routine platelet transfusion for assumed platelet dysfunction in the absence of thrombocytopenia should not be undertaken without objective evidence of platelet dysfunction (eg, aggregrometry and cytometry).
- For patients undergoing cannulation or decannulation, high-risk procedures with a history of associated bleeding, or deemed to be at higher risk of bleeding by the ECLS physician, consideration may be given to transfusion to a higher platelet threshold.

Antifibrinolytics

There are no data to guide routine administration of antifibrinolytic agents during respiratory ECMO. ELSO cautions against routine use because of observational reports of hypercoaguability in COVID-19.

Previous ELSO guidelines recommended daily fibrinogen-level monitoring and correction with FFP or fibrinogen.[3] This is not standard practice in many adult ECLS centres across Canada.

Expert consensus statements

Owing to a paucity of data and based on expert consensus, we suggest that routine use of antifibrinolytic agents is not indicated and may pose a potential for harm in certain pathophysiologic states. Also, routine fibrinogen-level monitoring and correction is not supported by robust data, but replacement may be considered when fibrinogen levels are low (eg, <1.00 g/L) or if active bleeding is present.

Fresh Frozen Plasma, Prothrombin Concentrate Complex, Antithrombin

Fresh frozen plasma (FFP) has been used during ECMO to correct elevated prothrombin time international normalized ratio (PT INR), and to provide supplemental antithrombin in heparin-resistant patients. Depletion of endogenous antithrombin can occur during cardiopulmonary bypass (CPB), and recombinant antithrombin or FFP use to replenish antithrombin levels is routine.

It is unclear what degree of elevation in PT INR mandates correction in nonbleeding patients on VV-ECMO. ELSO guidelines suggest a FFP administration "if the INR is >1.5 to 2.0 and/or there is significant bleeding."

Prothrombin concentrate complex (PCC) contains factors II, VII, IX, X, and may also contain proteins C and S. Administration of PCC should be considered in

Table 1. Suggested blood-product transfusion thresholds for nonbleeding patients on VV-ECMO

Product	PRBC	Platelets	FFP
Suggested transfusion threshold	70-75 g/L	50,000/μL	• No routine transfusion threshold • FFP or AT3 for heparin resistance

AT3, antithrombin III; FFP, fresh frozen plasma; PRBC, packed red blood cells; VV-ECMO, venovenous extracorporeal membrane oxygenation.

hemorrhaging patients only, as there are no strong data to support use for routine PT INR correction, and use of PCC could be associated with significant harm.

No current consensus exists among ECLS centres regarding antithrombin monitoring or repletion. Some programs elect to replace antithrombin when heparin resistance is a clinical concern: that is, suboptimal anticoagulation targets; low activated partial thromboplastin time (aPTT); activated clotting time; or anti-Xa levels, despite escalation of unfractionated heparin dosing. To restore antithrombin levels, FFP, cryoprecipitate, or recombinant antithrombin are suggested by ELSO.

Expert consensus statements

In the absence of data, and owing to practice variability among ECLS centres, we suggest the following:

- Routine use of FFP is not indicated to normalize PT INR in nonbleeding patients on VV-ECMO.
- Routine use of PCC is not indicated to normalize PT INR in nonbleeding patients on VV-ECMO and may be harmful in certain physiological states.
- Transfusion of FFP can be considered for PT INR > 2.0 but should be done following a trial of intravenous vitamin K replacement (10 mg intravenously for 3 days).
- For cannulation, decannulation, and other invasive procedures, FFP transfusion to target PT INR of 1.5 may be considered, based on clinician preference.
- For evolving heparin resistance, antithrombin replenishment with recombinant antithrombin, or—alternatively—FFP, may be considered. Consultation with the local transfusion medicine physician or hematologist is strongly advised.

Conclusions

VV-ECMO is often a viable rescue therapy for severe ARDS. Unfortunately, there are a paucity of robust data to guide blood product transfusion practices in this population. In a pandemic context, the potential exists for exhaustion of blood-product supply.

We propose that a restrictive approach to transfusion for stable, nonbleeding patients on VV-ECMO can be safely applied, summarized in Table 1. Such a strategy may prevent unnecessary transfusions, with the known associated harm, and also mitigate consumption of essential blood-product inventory.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2020.06.014.