Anticoagulation Therapy during Extracorporeal Membrane Oxygenator Support in Pediatric Patients

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Extracorporeal membrane oxygenation (ECMO) is a salvage therapy for critically ill patients. Although ECMO is becoming more common, hemorrhagic and thromboembolic complications remain the major causes of death in patients undergoing ECMO treatments. These complications commence upon blood contact with artificial surfaces of the circuit, blood pump, and oxygenator system. Therefore, anticoagulation therapy is required in most cases to prevent these problems. Anticoagulation is more complicated in pediatric patients than in adults, and the foreign surface of ECMO only increases the complexity of systemic anticoagulation. In this review, we discuss the pathophysiology of coagulation, anticoagulants, and monitoring tools in pediatric patients receiving ECMO.

Key Words: *Extracorporeal Membrane Oxygenation; Extracorporeal Life Support; Anticoagulation; Pediatrics*

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a life-saving salvage therapy for critically ill patients. ECMO use has increased over the past few decades, and according to the international summary of Extracorporeal Life Support Organization (ELSO) registry report in Jan 2017, patients on ECMO consist of 68% neonate and pediatric patients (Neonates: 44.8%, Pediatric: 24.1% and Adults: 31.1%).

While cardiopulmonary bypass (CPB) is used to assist patients undergoing open heart surgery, ECMO or extracorporeal life support (ECLS) provides a simplified version of CPB that is used temporarily to support refractory cardiac and respiratory failure. Depending on the cannulation type, it can assist both the cardiac and the pulmonary functions (venoarterial ECMO), or only the pulmonary function (venovenous ECMO). Regardless of this difference, an ECMO system is composed of a circuit, a pump, and an oxygenator.

Significant improvements in medical materials, components, and techniques over the past 50-60 years have allowed ECMO to be utilized not only in the operating room but also in the intensive care unit. A ventricular assist device (VAD) is an implantable mechanical device that pumps blood from the ventricles to the rest of the body without oxygenator. A VAD is usually used in patients with heart failure as a bridge to transplant or destination therapy. The characteristics of mechanical circulatory support systems are shown in Table 1.

Although ECMO is becoming more popular, hemorrhagic and thromboembolic complications remain the major threat of ECMO treatment, as they are the most frequent causes of death.[1] Recently, the Extracorporeal Life Support Organization (ELSO) registry has reported that thrombotic complications occur in up to 20% of patients with ECMO support.[2] These complications commence upon blood contact with artificial surfaces of the circuit, blood pump, and oxygenator system. Therefore, anticoagulation therapy is required in most cases to prevent these problems. Systemic anticoagulation therapy may aggravate a life-threatening hemorrhage, such as intracranial hemorrhage and infarction.[3] Here, we describe the blood-surface interactions and anticoagulation therapies in pediatric patients compared with those in adults.

TABLE 1. Characteristics of mechanical circulatory support systems

	CPB	ECMO	VADs
Duration of support	A few hours or less	Days to weeks	Months to years
Exposure of blood to artificial surface	All blood exposed to a large surface area	Some blood exposed to a large surface area	Some blood exposed to a relatively small surface area
Membrane oxygenator	Yes	Yes	No
Trauma to blood cells	Yes	Yes	Less
Mobilization of patient	No	Yes/No	Yes
Anticoagulation therapy requirement	High	Some	Less

CPB: cardiopulmonary bypass, ECMO: extracorporeal membrane oxygenation, VADs: ventricular assist devices.
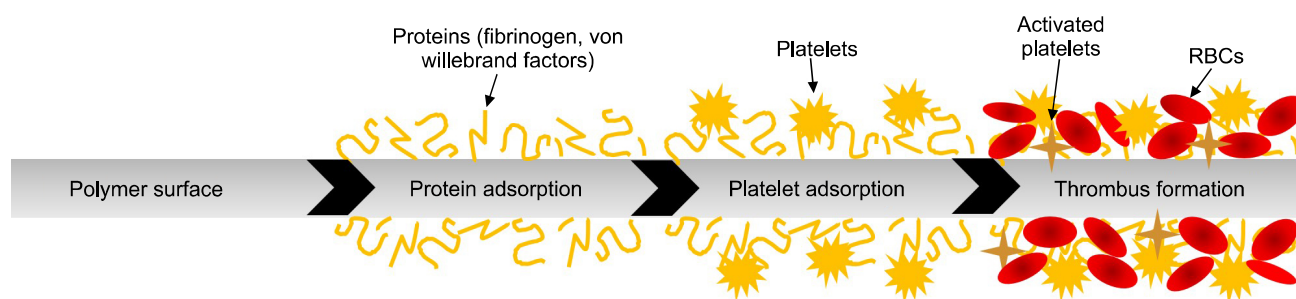
FIG. 1. Schema of blood-artificial surface interaction that leads to thrombus formation.

BLOOD INTERACTIONS WITH ARTIFICIAL SURFACES DURING ECMO

Because the blood is exposed to foreign non-endothelial materials (components of the circuit and oxygenator), all mechanical circulatory support systems can trigger acute inflammatory responses and coagulation (Fig. 1).[4] However, these interactions trigger inflammatory and coagulative reactions that cannot be completely controlled to this day. The severity of the action may depend on the duration of support, the anticoagulant used, individual patient characteristics, and the type of artificial material employed. Contact with artificial surfaces activates the complement system through an alternative pathway that releases the anaphylatoxins C3a (alternative pathway) and C5a (terminal pathway).[5] Activated complements induce the synthesis of cytokines, which belong to the subgroups of proinflammatory (interleukin-6 and interleukin-8, tumor necrosis factor-a) and anti-inflammatory (interleukin-10) cytokines.[6-8]

Shear stress induced by roller pumps induces red blood cell hemolysis. The recent development of centrifugal pumps has rendered hemolysis less problematic.[9] Blood cells are injured by contact with artificial materials and by shear stress, turbulence, cavitation, and osmotic forces, triggering very high hemolysis rates.[10] Plasma proteins and lipoproteins become progressively denatured during ECMO,[11,12] increasing plasma viscosity and reducing protein solubility. The levels of plasma immunoglobulins (Ig) G, A, and M as well as albumin decrease as well.[13]

HEMORRHAGIC AND THROMBOTIC COMPLICATIONS DURING ECMO

Hemorrhagic complications develop in 12%-52% of patients on ECMO.[2,3,9,13] A central nervous system (CNS) hemorrhage may be especially severe and is associated with high-levels of in-hospital mortality and morbidity. However, few studies have compared the prevalence of hemorrhage in neonates and infants. Some authors have grouped hemorrhagic complications in pediatric cardiac patients on ECMO according to age group and diagnostic category.[3] Pediatric ECMO patients who had undergone cardiac surgery were found to be more prone to surgical site and CNS bleeding than other pediatric ECMO patients; the mortality rate was double the usual rate seen in ECMO.[3] Thrombotic complications also occurred: clots in the circuit were reported in 15% of pediatric patients under ECMO, clots in the oxygenation system in 12%, and intracranial infarctions in 4%.[14] There are many contributors to the risks of bleeding and thromboembolic events. Important factors of pro-hemorrhagic conditions include excessive heparin use for systemic anticoagulation, consumption of coagulation factors, low fibrinogen levels, thrombocytopenia, platelet dysfunction, hyperfibrinolysis, and other coagulation disorders. On the other hand, pro-thrombotic factors indicate inadequate use of heparin for systemic anticoagulation, acquired thrombin deficiency, consumption of Protein C, S, consumption of tissue factor pathway inhibitor (TFPI), endothelial dysfunction, heparin-induced thrombocytopenia (HIT), and blood stasis in the cardiac chambers.[15]

BASELINE LABORATORY DATA AND TRANSFUSION STRATEGY

If a patient is considered to be a candidate for ECMO, baseline laboratory data is essential. These may already be available for critically ill patients, but clinicians must review any incident of coagulopathy prior to ECMO. The required baseline laboratory values include the complete blood count (CBC) including platelet count, the prothrombin time, the activated partial thromboplastin time (aPTT), the fibrinogen, d-dimer levels, the activated clotting time (ACT), the level of antithrombin activity, and thromboelastographic/ thromboelastometric data (if available).

The ELSO guidelines state that blood products such as platelets, frozen plasma, or cryoprecipitate can be administered if significant coagulopathy is evident prior to ECMO initiation.[13] Hemoglobin levels should be maintained at a minimum value of 8 g/dL, depending on the clinical situation. If the level is lower than 8 g/dL, packed red blood cells (PRBC) should be administered. The platelet count should be above 80,000 cells/mm^3; platelet concentrates are often needed, especially in patients who bleed actively or have a high risk of bleeding. Lower platelet counts (lower than normal but above 45,000 cells/mm^3) may be acceptable for patients with a low risk of bleeding.[16] Usually, fibrinogen progressively increases during ECMO; however, in postcardiotomy ECMO, within the first hours after ECMO implantation, the level of fibrinogen can be very low.[17] The values of fibrinogen should be at a minimal level of 100 g/dL. If the values are lower than that, fibrinogen concentrate is available in most centers for supplementation. If fibrinogen concentrate is unavailable, cryoprecipitates can be administered.[16]

PRIMING OF THE ECMO CIRCUIT

Various combinations of blood products are used to prepare priming solutions. For adults, many centers use only crystalloid-based solutions, most likely due to the lack of time when treating a critically ill patient. For children, combinations of banked blood and other colloid solutions are most commonly used.[13] Unfractionated heparin (UFH) 50-100 units per 1 unit of PRBC may also be added. In more urgent situations, priming can be performed with crystalloids while waiting for cross match results. Other blood products may be added when they become available. ECMO priming represents a massive transfusion especially for pediatric patients. To prevent cardiac arrest during this process, freshly irradiated and washed RBCs should be used in every new priming cycle.[18]

MANAGEMENT OF ANTICOAGULATION THERAPY

Anticoagulation therapy is an imperfect science, being especially difficult in neonates and children.[19] No definitive anticoagulation therapies for neonates and young children on ECMO have yet emerged. Anticoagulation is important to maintain a clot-free oxygenator circuit, and to stabilize the patient hemostatically. It is especially important for patients with cardiac failure who are on ECMO, because left ventricular (LV) stasis can trigger LV thrombosis followed by fatal intracranial infarction.[20] UFH is the most widely used and best-studied gold standard anticoagulant for pediatric patients; several other anticoagulants are also employed. The characteristics of the major anticoagulants are described in Table 2.

1. Unfractionated heparin

UFH is the anticoagulant most commonly used during ECMO in both adults and children. UFH interacts with antithrombin (AT) and the tissue factor pathway inhibitor (TFPI). The UFH-AT complex immediately inhibits coagulation.[21] Once bound together, the UFH-AT complex has much greater effects of inhibition on coagulatory protein activity compared with AT alone. The UFH-AT complex potentiates the inhibitory effects of activated proteins, factors Xa, IXa, XIa, XIIa, and IIa (thrombin). The throm-

TABLE 2. Characteristics of anticoagulants

	Unfractionated Heparin	Bivalirubin	Argatroban	Nafamostat mesilate
Metabolism	Hepatic	Intravascular proteolysis	Hepatic	Renal
Half life	90 min	15-18 min	39-51 min	8 min
Route	Intravenous	Intravenous	Intravenous	Intravenous
Dosage	50-100 units/kg bolus 20-50 units/kg/h continuously	Not established 0.125 mg/kg bolus infusion followed by 0.125 mg/kg/h continuously[34,35]	0.75 mcg/kg/min continuously[39]	Not established 0.48 mg/kg/h[48]
Monitoring methods	Anti factor Xa ACT, aPTT	Not established ACT, aPTT	Not established ACT, aPTT	Not established ACT, aPTT
Antidote	Protamine sulfate	Not established	Not established	Not established

ACT: activated clotting time; aPTT: activated partial thromboplastin time.

bin inhibition requires binding of both AT and thrombin to UFH, on the other hand, factor Xa inhibition requires that only AT binds to UFH. UFH inhibits thrombin only after its formation, and does not inhibit either thrombin formation or thrombin already bound to fibrin. UFH increases the effect of TFPI by increasing its affinity to factor Xa.[22,23] UFH has a short half-life and its action is reversible by protamine sulfate. The aPTT, ACT, and an anti-Xa assay are routinely used to monitor coagulation status. UFH is given as a bolus infusion (50-100 units/kg of body weight) to both adults and children after cannulation prior to initiation of ECMO. UFH is then infused continuously during ECMO support. Intermittent bolus infusions can be given depending on the clinical situation and the results of monitoring tests. In adults, lower doses may be appropriate; however, in neonates and pediatric patients, higher doses should be given when no hemorrhage is apparent.[13] The target ACT level of 180-220 is typically achieved with an infusion rate of 20-50 units/kg/h. However, this rate varies among most neonatal and pediatric patients because of greater complexity of their condition. Low molecular weight heparin (LMWH) can also be administered subcutaneously in adult patients during ECMO, but is used less commonly. There are limited reports on LMWH in pediatric patients on ECMO.

2. Antithrombin replacement

Antithrombin (AT) is an inhibitor of serine proteases produced by the liver. AT acts as an anticoagulant principally by inhibiting thrombin and factor Xa.[21] Although the optimal level of AT in ECMO patients is unknown, an AT deficiency should be suspected in neonates and children whose requirements for UFH increases to over 35-40 units/kg/h. A relative deficiency of AT contributes significantly to the increased UFH requirements of neonates and pediatric patients, and may render anticoagulation therapy inadequate. Neonates and infants have lower AT activities than older children and adults. Some centers prophylactically replace AT to the target ranges of 50%-100%.[24] On the other hand, some centers replace AT only when a reduced effect of UFH is evident.[23] Some authors recommend that the target AT level should be >50% in all patients; others prefer target levels of over 80% in neonates and over 100% in infants and children. AT concentrates (plasma-derived or recombinant) are commonly available and are given when AT activity falls below 30%-80%. AT replacement is preferred over infusion of frozen plasma treatments because frozen plasma contains only 1 U/mL AT and plasma would need to be given at over 20 mL/kg to reach an optimal level.[19] After AT infusion, the UFH dose can be decreased by up to 50%. The ACT should be calculated or an anti-Xa assay performed 30-60 min after AT infusion.[19]

3. Alternative anticoagulants

Alternative anticoagulants include direct thrombin inhibitors (e.g., bivalirudin), factor Xa inhibitors (e.g., rivar-oxaban, argatroban), factor XIIa inhibitors, and nafamostat mesilate. No large-scale studies on these alternatives have been performed in the pediatric population.

1) Direct thrombin inhibitors: Direct thrombin inhibitors (DTIs) inhibit both circulating and bound thrombin. DTIs are advantageous because they have a lower inter-individual variability as they bind directly to the thrombin, forming complexes. These effects are independent of AT as the levels are not predictable in pediatric population, especially in critically ill patients.[25] Additionally, DTIs have more predictable pharmacokinetics compared to heparin because they are independent of plasma proteins. DTIs can be used as an alternative anticoagulant in children with heparin-induced thrombocytopenia (HIT).[26,27] The significant limitation of DTIs is the lack of an antidote. Although several studies demonstrated that recombinant activated clotting factor VII,[28,29] further studies are needed. There are limited reports on the use of DTIs in pediatric populations, especially those on ECMO support where further studies are needed.

Major DITs are bivalirubin, argatroban, and leupirudin. In children, bivalirudin and argatroban are frequently used and lepirudin is reported to increase the bleeding risk.[30]

Bivalirudin is a potential DTI that can be used as an initial anticoagulant in ECMO patients but can also be secondarily used in patients with HIT or UFH resistance.[31,32] Since bivalirudin metabolizes through intravascular proteolysis, its use can be considered in critically ill patients with hepatic and renal insufficiencies. Very limited data is available for neonates and pediatric patients, particularly those on ECMO. In 2013, Nagle et al. reported on 12 patients with UFH resistance, UFH failure, or HIT who switched from heparin to bivalirudin where anticoagulation were successful.[33] Although pediatric dosages of bivalirudin have not yet been established, a pilot study demonstrated an effective and safe dose of 0.125 mg/kg bolus infusion followed continuously by 0.125 mg/kg/h.[34,35] The target therapeutic aPTT range is 1.5-2.0-times the normal value; a target of 1.5-2.5-times that of normal values is better when it is sought to maintain optimal circuit mechanics.[36] The extent of thromboembolic complications was also found to be similar in ECMO patients on heparin and bivalirudin.[36,37]

Argatroban is another synthetic DTI, derived from L-arginine, which binds reversibly to the thrombin active site. It is the first pediatric labeled anticoagulant in the United States for treatment of thrombosis in patients with HIT.[29] In general treatment of thrombosis in children (not ECMO patients), it is administered at 0.75 mcg/kg/min continuously and the target aPTT is maintained at 1.5-3 times that of normal levels, which should be checked 2 h after the bolus administration.[38] The dose can be titrated in step sizes of 0.25 mcg/kg/min according to the level of aPTT.[39] Dose reduction should be considered in critically ill patients with impaired hepatic function because argatroban is hepatically eliminated.[40] There were limited studies in-

cluding ECMO patients. In 2006, Hursting et al. reviewed 12 patients aged 1 week to 16 years who received argatroban simultaneously with ECMO or VAD. Argatroban was administered during circuit priming, and both the ACT and aPTT were monitored. An oxygenator clot developed in one patient, disseminated intravascular coagulation in another, and gastrointestinal bleeding in a third.[41,42]

2) Nafamostat mesilate: Nafamostat mesilate (NM) is a synthetic serine-protease inhibitor used for acute pancreatitis and shock. Recently, it has been used to reduce hemorrhagic complications of hemodialysis and plasmapheresis with its characteristics of a very short half-life. In several studies, NM has been reported to reduce urinary excretion of potassium and cause hyperkalemia. The drug and its metabolites inhibit amiloride-sensitive sodium conductance in the renal cortical collecting ducts leading to impaired urinary potassium excretion.[43,44]

The results of its use during ECMO application were controversial, although most reported results were limited to Asian countries, mostly from Korea and Japan. Lim et al. found that NM was associated with a higher risk of bleeding than heparin in ECMO patients.[45] In contrast, Park et al. and Han et al. reported that NM was a safe alternative anticoagulant for ECMO patients with a high risk of bleeding.[46,47] Nagaya et al. reported preliminary data on the use of NM in 12 neonates on ECMO who had a high risk of bleeding, and bleeding was well controlled in 8 of these 12 cases.[48] The average dose used was 0.48±0.22 mg/kg/h and were monitored by measuring the activated clotting time (ACT).[48] However, no large study of NM use has yet been reported, especially in the pediatric population. Even more, accurate dosage and titration method principles have not yet been established in the pediatric population and further studies are needed.

3) Other anticoagulants: Rivaroxaban is the first oral DTI that specifically inhibits Factor Xa and prevents thrombin formation. However, limited data on its use in pediatric patients are available.[19] Rivaroxaban is used for treatment and prevention of deep vein thrombosis or pulmonary embolism in adult patients.

Factor XIIa inhibitors are new anticoagulants evaluated only in animal models of ECMO. A recombinant human FXIIa-neutralizing antibody prevented thrombosis in the extracorporeal circuit without increasing the risk of bleeding.[49]

MONITORING THE HEMOSTATIC SYSTEM DURING ECMO

Several in vitro whole-blood and plasma tests are available to measure UFH or other anticoagulants, and each has certain limitations when employed during ECMO. A lack of test standardization is a major limitation, especially when used to evaluate neonatal and pediatric populations. During ECMO employing UFH, use of a single test is not acceptable, but the need to perform multiple tests, several times daily can easily confuse team members. Each center

must develop a monitoring method that works best in that center.

In addition, the ECMO circuit triggers more inflammation, in turn affecting cellular and plasma components in younger patients. Additionally, anticoagulation therapy and monitoring are more complicated in neonates and pediatric patients than in adults.

1. Activated clotting time (ACT)

The activated clotting time (ACT) is the most commonly used measure of UFH status during ECMO. This is an inexpensive, whole-blood bedside test. The ACT is the amount of time taken for blood to form a fibrin clot by adding various activators of coagulation (thus, the ACT is the time until the end of the clotting cascade).[13,19] However, the ACT does not only represent the effect of UFH, being affected by many factors including the platelet count, platelet functionality, levels of fibrinogen and coagulation factors, the patient's temperature, hemodilution status, and various technical parameters.[50]

A retrospective review of 600 pediatric ECMO patients given heparin revealed a modest correlation (r=0.48) between the ACT and the UFH dose, and concluded that the ACT did not accurately reflect UFH status.[50] Other studies reported various correlations (from none to higher levels) between UFH status and the ACT.[13,19] There are limited studies in correlation of ACT and other anticoagulants.

2. Activated partial thromboplastin time (aPTT)

The aPTT guidelines were developed based on data from adults. The data correlated poorly with UFH status in neonatal and pediatric patients. The aPTT is more reliable in adults given modest doses of UFH; many adult ECMO centers prefer to use the aPTT rather than the ACT when monitoring and adjusting UFH doses. However, in infants, the baseline aPTT is prolonged, rendering the aPTT less reliable as a monitoring test.[51] The UFH dose and the aPTT exhibit a linear relationship in normal pediatric subjects, but the aPTT varies unpredictably in those who are ill, limiting its utility when evaluating UFH status.[13,19] Compared with other monitoring tools, the aPTT correlated well with the anti-Xa activity levels in pediatric patients under cardiac catheterization and cardiac surgery.[52] In addition, several studies report that the aPTT reflected UFH status better than the ACT in pediatric ECMO patients.[53]

Monitoring methods for other anticoagulants, such as DTIs have not yet been established, but aPTTs are most commonly used for monitoring. Further studies on monitoring various anticoagulants in the pediatric population are needed.

3. Anti-Xa assays

Many clinicians use anti-Xa assays as substitutes for the aPTT or ACT. These are plasma-based tests that are not affected by platelet activities. The assays measure UFH-AT complex levels, not thrombin inhibition. In a single-cen-

ter study, the anti-Xa assay results correlated well with UFH status. Additional advantages of the assays include a reduced need for blood sampling, less transfusion of blood products, and fewer thrombotic/hemorrhagic complications.[16,17,54-56] However, anti-Xa assays are chromogenic. Thus, if the hemoglobin or bilirubin levels become elevated during ECMO, the assay may yield artificially low values; the data must thus be interpreted with caution.[57] Newall et al. prospectively compared UFH concentrations (measured via protamine titration) and the effects of UFH (using the aPTT, an anti-Xa assay, and the thrombin clotting time) in pediatric patients under cardiac catheterization.[58] No monitoring method yielded data that correlated well with protamine titration results. It was thus suggested that the current recommendations are inappropriate for pediatric populations; these require either a different monitoring test or an alternative anticoagulant.[58] Despite these concerns, most ECMO centers use anti-Xa assay data to guide anticoagulation therapy. Some centers recommend that the daily ACT target range should be based on anti-Xa assay data and AT activity levels.[59,60]

4. Viscoelastic testing

Viscoelastic tests (thromboelastography and rotational thromboelastometry) evaluate whole-blood coagulation and fibrinolysis. These are the only methods that evaluate clot strength, and can be performed bedside. They evaluate the time to initial fibrin formation, kinetics, clot establishment, the strength and stability of the clot, clot lysis, and the function of platelets.[61] However, the tests are not yet widely available. One retrospective pilot study on children on ECMO revealed that qualitative platelet dysfunction was both frequent and severe upon thromboelastographic testing.[62]

CONCLUSION

Anticoagulation therapy is important to maintain the circuit and a clot-free oxygenator, and to stabilize the patient hemostatically, but it is especially complex in neonates and children. No definitive anticoagulation therapies for neonates and young children on ECMO have yet been established. Most anticoagulation studies are based on adult populations, and very few studies on the pediatric population on ECMO were found. Additionally, monitoring the levels of anticoagulation is more complicated in pediatric patients as ECMO circuit adds more complexity. To find the most acceptable anticoagulants for pediatric patients on ECMO, an effective dosage and monitoring method should be established based on newer anticoagulants. The greatest limitation of ECMO research, especially on pediatric populations, is the variabilities of ECMO protocols and algorithms among centers and countries. Many centers worldwide use non-standardized equipment (cannulae and oxygenators) to treat children and follow in-house management algorithms. Although most ECMO patients, especially pediatric patients, have their specific

situation and individualized reasons for ECMO, following standardized algorithms is very important. Prospective, multicenter studies for newer anticoagulants in pediatric patients are urgently needed.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Bartlett RH, Gattinoni L. Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. Minerva Anestesiol 2010;76:534-40.

2. Thiagarajan RR, Barbaro RP, Rycus PT, McMullan DM, Conrad SA, Fortenberry JD, et al. Extracorporeal life support organization registry international report 2016. ASAIO J 2017;63:60-7.

3. Werho DK, Pasquali SK, Yu S, Donohue J, Annich GM, Thiagarajan RR, et al. Hemorrhagic complications in pediatric cardiac patients on extracorporeal membrane oxygenation: an analysis of the extracorporeal life support organization registry. Pediatr Crit Care Med 2015;16:276-88.

4. Wo Y, Brisbois EJ, Bartlett RH, Meyerhoff ME. Recent advances in thromboresistant and antimicrobial polymers for biomedical applications: just say yes to nitric oxide (NO). Biomater Sci 2016;4:1161-83.

5. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 1981;304:497-503.

6. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997;96: 3542-8.

7. Fischer WH, Jagels MA, Hugli TE. Regulation of IL-6 synthesis in human peripheral blood mononuclear cells by C3a and C3a(desArg). J Immunol 1999;162:453-9.

8. Donnelly RP, Freeman SL, Hayes MP. Inhibition of IL-10 expression by IFN-gamma up-regulates transcription of TNF-alpha in human monocytes. J Immunol 1995;155:1420-7.

9. Kawahito K, Nose Y. Hemolysis in different centrifugal pumps.

Artif Organs 1997;21:323-6.

10. Leverett LB, Hellums JD, Alfrey CP, Lynch EC. Red blood cell damage by shear stress. Biophys J 1972;12:257-73.

11. Hoffman M. A cell-based model of coagulation and the role of factor VIIa. Blood Rev 2003;17 Suppl 1:S1-5.

12. Becker RC. Cell-based models of coagulation: a paradigm in evolution. J Thromb Thrombolysis 2005;20:65-8.

13. Lequier LL, Massicotte P. Anticoagulation and bleeding during ECLS. In: Annich G, ed. ECMO: Extracorporeal Cardiopulmonary Support in Critical Care. 4th ed. Ann Arbor:Extracorporeal Life Support Organization,2012;157-70.

14. Dalton HJ, Garcia-Filion P, Holubkov R, Moler FW, Shanley T, Heidemann S, et al. Association of bleeding and thrombosis with outcome in extracorporeal life support. Pediatr Crit Care Med 2015;16:167-74.

15. Ranucci M. Coagulation, anticoagulation and inflammatory response. 1st ed. Milan:Springer,2014.

16. Bembea MM, Schwartz JM, Shah N, Colantuoni E, Lehmann CU, Kickler T, et al. Anticoagulation monitoring during pediatric extracorporeal membrane oxygenation. ASAIO J 2013;59:63-8.

17. Irby K, Swearingen C, Byrnes J, Bryant J, Prodhan P, Fiser R. Unfractionated heparin activity measured by anti-factor Xa levels is associated with the need for extracorporeal membrane oxygenation circuit/membrane oxygenator change: a retrospective pediatric study. Pediatr Crit Care Med 2014;15:e175-82.

18. Kim DW, Cheon KR, Cho D, Lee KS, Cho HJ, Jeong IS. Transfusion associated hyperkalemia and cardiac arrest in an infant after extracorporeal membrane oxygenation. Korean J Crit Care Med 2015;30:132-4.

19. Ryerson LM, Lequier LL. Anticoagulation management and monitoring during pediatric extracorporeal life support: a review of current issues. Front Pediatr 2016;4:67.

20. Cho HJ, Kim BY, Song ES, Oh SG, Oh BS, Jeong IS. Fatal left ventricular thrombosis in an infant receiving extracorporeal membrane oxygenation support: a case report. Korean J Crit Care Med 2013;28:123-6.

21. Pratt CW, Church FC. Antithrombin: structure and function. Semin Hematol 1991;28:3-9.

22. Boisclair MD, Lane DA, Philippou H, Esnouf MP, Sheikh S, Hunt B, et al. Mechanisms of thrombin generation during surgery and cardiopulmonary bypass. Blood 1993;82:3350-7.

23. Edmunds LH Jr, Colman RW. Thrombin during cardiopulmonary bypass. Ann Thorac Surg 2006;82:2315-22.

24. Stansfield BK, Wise L, Ham PB 3rd, Patel P, Parman M, Jin C, et al. Outcomes following routine antithrombin III replacement during neonatal extracorporeal membrane oxygenation. J Pediatr Surg 2017;52:609-13.

25. Bates SM, Weitz JI. The mechanism of action of thrombin inhibitors. J Invasive Cardiol 2000;12 Suppl F:27F-32.

26. Murdoch IA, Beattie RM, Silver DM. Heparin-induced thrombocytopenia in children. Acta Paediatr 1993;82:495-7.

27. Potter C, Gill JC, Scott JP, McFarland JG. Heparin-induced thrombocytopenia in a child. J Pediatr 1992;121:135-8.

28. Levi M, Bijsterveld NR, Keller TT. Recombinant factor VIIa as an antidote for anticoagulant treatment. Semin Hematol 2004;41(1 Suppl 1):65-9.

29. Young G, Yonekawa KE, Nakagawa PA, Blain RC, Lovejoy AE, Nugent DJ. Recombinant activated factor VII effectively reverses the anticoagulant effects of heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin ex vivo as measured using thromboelastography. Blood Coagul Fibrinolysis 2007;18:547-53.

30. Shantsila E, Lip GY, Chong BH. Heparin-induced thrombocytopenia. A contemporary clinical approach to diagnosis and management. Chest 2009;135:1651-64.

31. Sanfilippo F, Asmussen S, Maybauer DM, Santonocito C, Fraser JF, Erdoes G, et al. Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: a systematic review. J Intensive Care Med 2017;32:312-9.

32. Mirdamadi A. Dabigatran, a direct thrombin inhibitor, can be a life-saving treatment in heparin-induced thrombocytopenia. ARYA Atheroscler 2013;9:112-4.

33. Nagle EL, Dager WE, Duby JJ, Roberts AJ, Kenny LE, Murthy MS, et al. Bivalirudin in pediatric patients maintained on extracorporeal life support. Pediatr Crit Care Med 2013;14:e182-8.

34. Almond CS, Harrington J, Thiagarajan R, Duncan CN, LaPierre R, Halwick D, et al. Successful use of bivalirudin for cardiac transplantation in a child with heparin-induced thrombocytopenia. J Heart Lung Transplant 2006;25:1376-9.

35. Young G, Tarantino MD, Wohrley J, Weber LC, Belvedere M, Nugent DJ. Pilot dose-finding and safety study of bivalirudin in infants <6 months of age with thrombosis. J Thromb Haemost 2007;5:1654-9.

36. Pieri M, Agracheva N, Bonaveglio E, Greco T, De Bonis M, Covello RD, et al. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: a case-control study. J Cardiothorac Vasc Anesth 2013;27:30-4.

37. Ranucci M, Ballotta A, Kandil H, Isgro G, Carlucci C, Baryshnikova E, et al. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. Crit Care 2011;15:R275.

38. Lewis BE, Hursting MJ. Argatroban therapy in heparin-induced thrombocytopenia. In: Greinacher A, Warkentin TE, eds. Heparin-induced Thrombocytopenia. 3rd ed. New York:Marcel Dekker,2004.

39. Madabushi R, Cox DS, Hossain M, Boyle DA, Patel BR, Young G, et al. Pharmacokinetic and pharmacodynamic basis for effective argatroban dosing in pediatrics. J Clin Pharmacol 2011;51:19-28.

40. Swan SK, Hursting MJ. The pharmacokinetics and pharmacodynamics of argatroban: effects of age, gender, and hepatic or renal dysfunction. Pharmacotherapy 2000;20:318-29.

41. Kawada T, Kitagawa H, Hoson M, Okada Y, Shiomura J. Clinical application of argatroban as an alternative anticoagulant for extracorporeal circulation. Hematol Oncol Clin North Am 2000;14:445-57, x.

42. Hursting MJ, Dubb J, Verme-Gibboney CN. Argatroban anticoagulation in pediatric patients: a literature analysis. J Pediatr Hematol Oncol 2006;28:4-10.

43. Kitagawa H, Chang H, Fujita T. Hyperkalemia due to nafamostat mesylate. N Engl J Med 1995;332:687.

44. Muto S, Imai M, Asano Y. Mechanisms of hyperkalemia caused by nafamostat mesilate. Gen Pharmacol 1995;26:1627-32.

45. Lim JY, Kim JB, Choo SJ, Chung CH, Lee JW, Jung SH. Anticoagulation during extracorporeal membrane oxygenation; nafamostat mesilate versus heparin. Ann Thorac Surg 2016;102:

534-9.

46. Park JH, Her C, Min HK, Kim DK, Park SH, Jang HJ. Nafamostat mesilate as a regional anticoagulant in patients with bleeding complications during extracorporeal membrane oxygenation. Int J Artif Organs 2015;38:595-9.

47. Han SJ, Kim HS, Kim KI, Whang SM, Hong KS, Lee WK, et al. Use of nafamostat mesilate as an anticoagulant during extracorporeal membrane oxygenation. J Korean Med Sci 2011;26:945-50.

48. Nagaya M, Futamura M, Kato J, Niimi N, Fukuta S. Application of a new anticoagulant (Nafamostat Mesilate) to control hemorrhagic complications during extracorporeal membrane oxygenation--a preliminary report. J Pediatr Surg 1997;32:531-5.

49. Larsson M, Rayzman V, Nolte MW, Nickel KF, Bjorkqvist J, Jamsa A, et al. A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. Sci Transl Med 2014;6:222ra17.

50. Baird CW, Zurakowski D, Robinson B, Gandhi S, Burdis-Koch L, Tamblyn J, et al. Anticoagulation and pediatric extracorporeal membrane oxygenation: impact of activated clotting time and heparin dose on survival. Ann Thorac Surg 2007;83:912-9; discussion 919-20.

51. Kuhle S, Eulmesekian P, Kavanagh B, Massicotte P, Vegh P, Lau A, et al. Lack of correlation between heparin dose and standard clinical monitoring tests in treatment with unfractionated heparin in critically ill children. Haematologica 2007;92:554-7.

52. Kim GG, El Rouby S, Thompson J, Gupta A, Williams J, Jobes DR. Monitoring unfractionated heparin in pediatric patients with congenital heart disease having cardiac catheterization or cardiac surgery. J Thromb Thrombolysis 2010;29:429-36.

53. Maul TM, Wolff EL, Kuch BA, Rosendorff A, Morell VO, Wearden PD. Activated partial thromboplastin time is a better trending tool in pediatric extracorporeal membrane oxygenation. Pediatr Crit Care Med 2012;13:e363-71.

54. Liveris A, Bello RA, Friedmann P, Duffy MA, Manwani D,

Killinger JS, et al. Anti-factor Xa assay is a superior correlate of heparin dose than activated partial thromboplastin time or activated clotting time in pediatric extracorporeal membrane oxygenation. Pediatr Crit Care Med 2014;15:e72-9.

55. Northrop MS, Sidonio RF, Phillips SE, Smith AH, Daphne HC, Pietsch JB, et al. The use of an extracorporeal membrane oxygenation anticoagulation laboratory protocol is associated with decreased blood product use, decreased hemorrhagic complications, and increased circuit life. Pediatr Crit Care Med 2015;16:66-74.

56. O'Meara LC, Alten JA, Goldberg KG, Timpa JG, Phillips J, Laney D, et al. Anti-xa directed protocol for anticoagulation management in children supported with extracorporeal membrane oxygenation. ASAIO J 2015;61:339-44.

57. Kostousov V, Nguyen K, Hundalani SG, Teruya J. The influence of free hemoglobin and bilirubin on heparin monitoring by activated partial thromboplastin time and anti-Xa assay. Arch Pathol Lab Med 2014;138:1503-6.

58. Newall F, Ignjatovic V, Johnston L, Summerhayes R, Lane G, Cranswick N, et al. Clinical use of unfractionated heparin therapy in children: time for change? Br J Haematol 2010;150:674-8.

59. Urlesberger B, Zobel G, Zenz W, Kuttnig-Haim M, Maurer U, Reiterer F, et al. Activation of the clotting system during extracorporeal membrane oxygenation in term newborn infants. J Pediatr 1996;129:264-8.

60. Muntean W. Coagulation and anticoagulation in extracorporeal membrane oxygenation. Artif Organs 1999;23:979-83.

61. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg 2008;106:1366-75.

62. Saini A, Hartman ME, Gage BF, Said A, Gazit AZ, Eghtesady P, et al. Incidence of platelet dysfunction by thromboelastography-platelet mapping in children supported with ECMO: a pilot retrospective study. Front Pediatr 2016;3:116.