ELSO Anticoagulation Guideline

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Significant advances in the materials and components used and the techniques employed for extracorporeal support have been made over the past 50 years. However, the inability to completely control the interaction between blood and the biomaterials of the extracorporeal circuit along with the subsequent inflammatory and coagulation response results in potential bleeding and thrombotic complications. During extracorporeal life support (ECLS), there is continuous contact between circulating blood and foreign surface of the extracorporeal circuit. As a result of this, the normal physiologic hemostatic balance is shifted to a hypercoaguable state, with patients, extracorporeal circuits and components at risk for thrombosis.

In order to suppress hemostatic activation and prevent thrombosis, administration of antithrombotic therapy is necessary. Ideally, when using antithrombotic therapy for ECLS, platelet and coagulation factor activation should be inhibited enough to minimize clot formation in the ECLS circuit while maintaining enough endogenous procoagulant activity to avoid bleeding in the patient. However, this can be a difficult balance to sustain. This guideline will briefly describe some of the issues that should be addressed when providing anticoagulation during ECLS applications.

The ELSO website contains general guidelines for ECLS providers including information on anticoagulation. This guideline provides a more detailed discussion of anticoagulation, including the use of classic and alternative anticoagulant agents, the role of antithrombin, the laboratory monitoring methods used to facilitate the delivery of safe, effective anticoagulation for ECLS applications as well the management of patient bleeding and circuit clotting. This guideline is not patient specific, as the anticoagulation needs and protocols that would be employed for a neonate with respiratory failure differ significantly from those for an adult respiratory failure patient on ECLS or that of a pediatric patient

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following cardiac surgery. Please see separate patient specific protocols for more detailed anticoagulation guidance.

A. Pre-ECLS Blood Tests

Once a patient is considered a candidate for ECLS, baseline laboratory values should be obtained, if time and arterial/venous access allows. These tests may include CBC, PT/ INR, APTT, Fibrinogen, D-dimer, activated clotting time (ACT), antithrombin activity (AT) and thromboelastography (TEG) or thromboelastometry (ROTEM). An attempt should be made, if possible, to correct significant coagulopathy by administering frozen plasma (FP), platelets, cryoprecipitate and vitamin K. Correcting pre-existing coagulopathy prior to initiation of ECLS may facilitate the anticoagulation management of the patient upon initiation of unfractionated heparin (UNFH).

B. ECLS Circuit Prime

There are many different combinations of blood products used for ECLS circuit priming. Packed red blood cells (PRBC's) and frozen plasma (FP) are used commonly for elective ECLS circuit priming. In addition, UNFH 50–100 units, may be added to each full unit of PRBCs used in the prime volume. In scenarios of more urgent ECLS circuit priming, such as that for ECPR initiation, ECLS can be initiated with a crystalloid primed circuit while waiting for crossmatched blood products to become available; however, emergency release of uncrossmatched PRBCs can also be used. In this situation, FP (10-20 ml/kg) and platelets (10-20 ml/kg) can be administered as soon as they are available and before laboratory values indicate a need for protocolized blood product transfusion.

C. The Optimal Delivery of Unfractionated Heparin

UNFH is an antithrombotic agent and is the most widely used systemic anticoagulant during the provision of ECLS. The anticoagulant effect of UNFH is mediated by its interaction with two endogenous anticoagulants: antithrombin (AT) and tissue factor pathway inhibitor (TFPI). UNFH is a complex glycosaminoglycan that binds to AT via a pentasaccharide sequence that is only present in approximately one third of UNFH molecules. Once bound, the UNFH-AT complex has an immediate, accelerated inhibitory effect on coagulation factors as compared to AT alone (1). UNFH inhibits thrombin after it is formed, but it does not prevent thrombin formation nor does it inhibit thrombin already bound to fibrin.

1. UNFH Bolus

Patients usually receive an initial UNFH bolus of 50-100 units per kg body weight at the time of cannulation for ECLS, and then UNFH is continued as a continuous infusion during the ECLS course. The bolus dose can be adjusted based on clinical factors such as evidence of pre-existing bleeding, and if the patient has had recent surgery or cardiopulmonary bypass (CPB), whether or not the UNFH given during CPB has been reversed to any degree with protamine. A thromboelastogram performed in the operating room or an anti-factor Xa assay activity soon after arrival to intensive care unit post-operatively, may be useful to establish the degree of residual UNFH effect under these circumstances.

2. Minimum and Maximum UNFH Dose Ranges

When the measured ACT drops to 300 seconds or below, the UNFH infusion is typically initiated at a dose of 7.5-20 units/kg/hr with lower dose range in adults, and higher for pediatric and neonatal patients, unless there is excessive bleeding. Patients who are experiencing significant bleeding or who have just had cardiac surgery may not be started on UNFH immediately. Therapeutic anticoagulation, classically defined by ACT range of 180-220 seconds, is typically achieved with UNFH infusion rates of 20-50 units/kg/hour. The administration of platelets, increased urine output or use of renal replacement therapy, may result in an increased UNFH requirement to maintain goal ACT's. Dependent upon other underlying coagulation changes, the ACT may both underestimate and overestimate the UNFH effect in children, which has the potential to lead to either supratherapeutic anticoagulation and bleeding as well as subtherapeutic anticoagulation and possible thrombosis. As a result, some neonatal/pediatric ECLS centers have adopted a minimum UNFH dose of 10-20 units/kg/hour and maximum UNFH dose of 40-50 units/kg/hour despite the ACT value.

3. Antithrombin Replacement

AT is produced by the liver and is a natural inhibitor of all serine proteases (except for factor VIIa and protein C) and the majority of its anticoagulant effect results from inhibition of thrombin and factor Xa (1). Since AT inhibits most of the coagulation enzymes to a varying degree, it is an important endogenous anticoagulant protein. Infants have developmentally low AT activity and antigen levels as compared to older children and adults. The optimal AT activity for any patient receiving UNFH anticoagulation for ECLS is unknown. However, in infants and children with escalating UNFH requirements, UNFH doses >35-40 units/kg/hour, and/or clinically subtherapeutic anticoagulation, acquired AT deficiency may be a contributing factor to the patient's heparin resistance. If low AT activity levels are confirmed, AT replacement may be considered. AT concentrates (plasma derived or recombinant) are now available and some centers routinely administer AT replacement for AT activities < 30 to 80%, while others will treat low AT activity only if there is evidence of reduced UNFH effect clinically or based on low ACT, low anti-Xa levels or minimal UNFH effect on kaolin and heparinase TEG samples (see later discussion).

Of the ECLS programs that routinely replace AT as part of their anticoagulation protocol, without consideration of other tests of UNFH effect, most target levels ranging from >50% to >100%. Some programs recommend >50% for all patients, while others prefer >80% for neonates and >100% for infants and children. The UNFH infusion can be decreased prior to administration of AT concentrates because of the potential for augmentation of UNFH's anticoagulant effect. Some centers empirically treat suspected or confirmed low AT levels by the administration of frozen plasma (FP), however, giving standard transfusions of FP alone may not easily achieve adequate AT activity levels in patients on ECLS due to the concentration of AT in FP (1u/mL) by volume.

A recent multicenter study demonstrated that off-label use of AT concentrate has increased significantly over the past decade, particularly in patients receiving ECLS (2). There are few parallel studies to substantiate its safety or efficacy and as a result the impact of AT replacement on clinical outcomes in critically-ill children is unclear. On the other hand, many ECLS centers neither test AT activity levels nor give AT concentrate.

D. Therapeutic Monitoring of UNFH

Assessing coagulation in critically ill patients is complex, and the addition of an extracorporeal circuit and anticoagulation increases this degree of complexity significantly. Ideally, one would prefer to measure the global function of the coagulation system *in vivo*, in order to best tailor anticoagulation therapy. Currently, there is a number of whole blood and plasma based tests to assess coagulation *in vitro*; however each have limitations when used to monitor anticoagulation in ECLS applications. A significant limitation of all of the assays discussed below is that they are not well standardized. Thus, an anti-Xa value (or ACT or PTT) performed in one machine or one laboratory, may vary greatly from results obtained from the same sample in another laboratory. Using one method of monitoring UNFH activity only, is likely no longer acceptable ECLS practice. However, using multiple tests of UNFH therapy, multiple times per day, is probably not necessary and will be very confusing for the ECLS team members. Ultimately, every ECLS program will have to come up with an approach to monitoring the anticoagulant effect of UNFH that works best for their patients in their individual center.

1. Activated Clotting Time (ACT)

The ACT has been used for decades to monitor UNFH therapy in extracorporeal applications and remains the most commonly utilized test in ECLS to dictate UNFH dosage (3). The ACT is a whole blood point of care test (POCT), in which

blood is mixed with an activator (celite, kaolin, glass beads, etc) to provide a global functional test of hemostasis, incorporating the important effects of red blood cells and platelets. ACT results can be affected by factors other than UNFH, including anemia, hypofibrinogenemia, thrombocytopenia and other coagulation factor deficiencies, which hopefully gives an accurate reflection of a patient's overall anticoagulation state. The ACT is a low cost, POCT available 24 hours per day in most centers. Hypothermia and hemodilution can also affect an ACT result and different ACT devices have been shown to yield divergent results (4). Because of some potential shortcomings of UNFH and the ACT alone, it may be useful to complement regular whole blood ACT measurements, intermittently, with more elaborate tests of UNFH anticoagulation discussed below.

2. Anti-Factor Xa Activity Levels (anti-Xa)

The optimal effect of UNFH concentration to provide adequate anticoagulation, whilst avoiding bleeding complications, has not been determined in proper studies. Measuring *ex-vivo* UNFH concentrations by protamine titration, is both reliable and reproducible, but is not as readily available or easy to automate. Outside of ECLS applications, many institutions use anti-factor Xa activity (anti-Xa) assay as the gold standard test to monitor and adjust the management of therapeutic UNFH and low molecular weight heparin (LMWH) therapy (5). The anti-Xa assay is not a measure of UNFH concentration, but rather a measure of UNFH effect, based on the ability of UNFH to catalyze AT's inhibition of factor Xa. In contrast to the ACT and aPTT, the anti-Xa assay is specific to the anticoagulant effect of UNFH and is not influenced by coagulopathy, thrombocytopenia or dilution. While some laboratories add exogenous AT to their anti-Xa assays, others do not and this can have a profound impact on the results. Anti-Xa assays without exogenously added AT, are preferable since the result is dependent on the patient's *in vivo* AT activity. Since Anti-Xa assays require AT to determine the result it is important to consider AT deficiency when anti-Xa concentrations are not increasing with increasing doses of UNFH. Furthermore, most calorimetric anti-Xa assay kits are affected by hyperlipidemia, hyperbilirubemia and high plasma free hemoglobin (hemolysis), which can occur in critically ill and ECLS patients and ultimately falsely lower the anti-Xa level (6).

A number of studies in ECLS patients have shown superior correlation of the anti-Xa assay to UNFH dose and poor correlation of anti-Xa assay to ACT (4, 7, 8). TThe anti-Xa assay approximates UNFH effect on hemostasis. Since there are other contributors to global hemostasis than fibrin formation the measure of anti-Xa may at times be misleading. Despite this concern, anti-Xa assay guided anticoagulation is increasing in frequency and may provide significant advantages over other methods. The majority of ELSO centers that use the anti-Xa assay as part of their anticoagulation protocol target levels of 0.3-0.7 IU/mL

(3). However, anti-Xa assays also vary in their responsiveness to UNFH and are subject to significant problems regarding assay standardization. Thus, adopting one anti-Xa range for all assays could lead to discrepant management results among centers. Some ECLS centers have recommended daily establishment of ACT therapeutic goal ranges based on the anti-Xa assays and AT activity levels for more than a decade (7,9). This practice has only recently become more common as more centers gain experience with the use of anti-Xa monitoring (3). Anti-Xa activity can be measured more frequently if there is clinical evidence of bleeding or thrombosis.

3. Activated Partial Thromboplastin Time (APTT)

The APTT is a plasma based test that uses an activator (silica, ellagic acid), calcium, and phospholipids, to measure the time to fibrin formation in the absence of cellular components. Each center's individual laboratory should establish a therapeutic range for APTT results to compensate for the variable response of APTT reagents to UNFH (10). The APTT may be a useful test in adults where moderate doses of UNFH are used and many adult ECLS programs use the APTT instead of the ACT to monitor and adjust UNFH therapy. Infants have baseline prolonged APTT values and as a result it has been thought that the APTT would be less reliable to guide UNFH therapy in pediatric populations. Point-of-care (POC) devices that provide bedside APTT results are now available; one such device was shown to correlate well with anti-Xa activity assays in pediatric cardiac catheterization patients (11). A recent study in pediatric ECLS patients showed that the APTT (clinical laboratory and POC) correlated to UNFH dose better than ACT and, as expected the APTT and UNFH dose correlation improved with increasing patient age (12).

4. Thromboelastography (TEG) and Thromboelastometry (ROTEM)

The thromboelastogram (TEG®) is a whole blood POCT of the viscoelastic properties of clot formation that measures the integrity of the coagulation cascade from the time of fibrin formation to clot lysis and importantly includes the contribution of platelets. TEG®/ROTEM provides information relating to multiple phases of coagulation in whole blood, which is extremely relevant to ECLS patients since there may be more than one reason for coagulation abnormalities (13). Paired TEG®/ROTEM samples with and without the addition of heparinase (kTEG/hTEG or APTEM/HEPTEM) allows for the underlying assessment of coagulation in the presence of UNFH. As a result, UNFH responsiveness can be evaluated by TEG®/ROTEM by examining the difference in R or CT-times between tests with and without heparinase, which may be beneficial when there is concern for heparin resistance (ACT levels are discrepant from anti-Xa assays). Some centers prefer replacement of AT to be based on evaluation of these parameters rather than AT activity levels alone. Using TEG®, it is also possible to evaluate the degree of platelet inhibition using arachidonic acid and adenosine diphosphiate.

Additional applications of TEG®/ROTEM include specific analysis of fibrinogen function that could indicate the need for a source of fibrinogen (cryoprecipitate or fibrinogen concentrate) for patients with active bleeding. TEG®/ROTEM can also evaluate hyperfibrinolysis and as a result differentiate between early DIC (short time to fibrin formation, increased clot strength with increased percent lysis) and primary hyperfibrinolysis (reduced clot strength with increased percent lysis). This is potentially a very important application of TEG®/ROTEM since the primary treatment for early DIC is increased UNFH and primary fibrinolysis is an antifibrinolytic such as tranexamic acid.

E. The Potential Role of Novel Anticoagulants

1. Direct thrombin inhibitors (DTIs)

Direct thrombin inhibitors (DTIs) are a relatively new class of short-acting anticoagulants that bind to active sites on thrombin directly, and demonstrate more predictable pharmacokinetics and greater reduction of thrombin generation, as compared to UNFH. These novel anticoagulants have several theoretical advantages over UNFH, especially in children (14). First, DTIs bind thrombin directly, independent of AT, making them more reliable in patients with low or fluctuating AT activity. Second, DTIs do not bind to other plasma proteins or cells and as a result are not prone to day to day changes in serum chemistry or cell counts. Therefore, DTIs may provide a more predictable dosing regimen that allows for consistent anticoagulant effect with less bleeding compared to UNFH making them useful in ECLS. Third, DTIs inhibit both clot–bound and circulating thrombin which can lead to improved efficacy. Finally, DTIs do not cause an immune mediated thrombocytopenia, such as heparin induced thrombocytopenia (HIT). For the reasons discussed above, emerging and expanding clinical experience with the use of DTIs in ECLS is expected in the coming years.

One potential problem, which potentially limits the use of DTIs, more so in CPB than ECLS, is the lack of a pharmacologic antidote or reversal agent such as protamine in the case of UNFH. However, unlike in CPB, the need to reverse anticoagulation during ECLS would rarely occur. If needed, in cases of severe bleeding, given their relatively short half lives, DTIs can be decreased or discontinued. Three synthetic DTIs, argatroban, bivalirudin and lepirudin, have been used in CPB, ECLS and VAD supports; however, the availability of lepirudin is currently limited. Argatroban has been most often cited in ECLS applications. Infusion of argatroban are started at 0.5-1 mcg/kg/min and adjusted to maintain APTT 1.5-2.5 times baseline values, but anti-IIa levels can also be used if available (15). Including argatroban in the ECLS circuit prime and administering an initial bolus before starting the continuous infusion has also been described (16). Published doses of Bivalirudin used in pediatric ECLS include an initial bolus dose of 0.05-0.5 mg/kg followed by an infusion rate of 0.03-0.1 mg/kg/hr which was subsequently adjusted to maintain APTT 1.5-2.5 times baseline

values or within the physician-defined range (17, 18). Dose escalations may be needed in accordance with longer time on ECMO and the use of continuous renal replacement therapy. The use of any anticoagulant should be considered with the potential of bleeding complications in mind.

2. New Oral Anticoagulants

Direct factor-Xa inhibitors ('xabans') are a new class of anticoagulant drugs which directly inhibit factor X without using AT as a mediator. Only one drug, rivaroxaban (Xeralto®), is marketed but several more are expected to be approved in the coming years. Preclinical data showed that rivaroxaban affects thrombin generation in umbilical cord blood at similar doses as those used in adults (19), suggesting that dosing may be both feasible and simpler in neonates than dosing of UNFH. A number of oral factor-IIa inhibitors including dabigatran and apixaban are also in preclinical stages. However, their enteral administration and the paucity of pediatric studies will likely limit their use in pediatric ECLS for the foreseeable future.

3. Factor-XIIa Inhibitor

An animal study using an antibody to Factor-XIIa as the anticoagulant for use in ECLS circuits was compared to UNFH anticoagulation. The Factor XIIa antibody prevented fibrin deposition and thrombus development as efficiently as UNFH. However, unlike UNFH, this antibody therapy did not impair the hemostatic capacity, nor did it increase clinical bleeding from wounds (20).

4. Nitric Oxide (NO) and Other Circuit Releasing Compounds

An ideal anticoagulation strategy for ECLS would be to modify the extracorporeal circuit to make it as non-thrombogenic as vascular endothelium.
Among other things, endothelial cells produce prostacyclin and nitric oxide (NO) which, inhibit thrombin induced platelet adhesion and activation as a way to maintain the fluidity of blood. Both prostacyclin and NO, exogenously added to extracorporeal circuits along with UNFH in an effort to inhibit the interaction between platelets and extracorporeal surfaces, have been shown to reduce platelet activation and consumption (21). NO and the creation of NO releasing polymers have been successfully demonstrated in a rabbit model of VV ECLS. 42 MAHAMA/NO was the first compound to be incorporated into a polymer matrix applied to an extracorporeal circuit that upon exposure to blood locally released NO at its surface and without systemic heparinization. The MAHAMA/NO-doped circuits showed significantly decreased platelet consumption when compared to both the heparinized and non-heparinized control groups (22).

F. Prevention and Management of Bleeding and Thrombotic Complications

1. Define Bleeding Thresholds in Various Patient Groups
Major bleeding would consist of clinically overt bleeding associated with a hemoglobin (Hgb) fall of at least 2 g/dl in a 24 hour period, greater than 20 ml/kg over a 24 hour period, or a transfusion requirement of one or more 10 ml/kg PRBC transfusions over that same time period. As well, bleeding that is retroperitoneal, pulmonary or involves the central nervous system, or bleeding that requires surgical intervention would also be considered major bleeding. Minor bleeding would be considered less than 20 ml/kg/day and require transfusion of one 10 ml/kg PRBC transfusion, or less. This is significant, because hemorrhagic complications and the requirement for greater red blood cell transfusion volumes are associated with increased mortality in both cardiac and non-cardiac ECLS (23, 24).

2. Optimal Blood Product Replacement
Blood product transfusion protocols are not currently evidence-based in most centers, but rather based on clinical experience, historical literature, and clinical guidelines. Thresholds for the transfusion of PRBCs vary from center to center and by type of patient, but are generally given as needed to replace any blood loss and maintain a near normal to normal hematocrit (> 35-40%), although many ECLS centers would accept lower hematocrit thresholds for transfusion. The PT/INR is not typically prolonged by UNFH and may be an adequate assessment of the extrinsic pathway. FFP may be administered in aliquots of 10 ml/kg as needed if the INR is > 1.5-2.0 and/or if there is significant bleeding. FP may also be used in an effort to increase the AT activity when heparin resistance occurs, but administration of AT concentrate is preferred. Cryoprecipitate can be given if the fibrinogen level is < 100-150 mg/dl. Frequent platelet transfusions of 10 ml/kg, are given to maintain a platelet count >100,000 cells/mm^3, particularly in neonates. The threshold for platelet transfusion may be reduced in older patients with an inherent lower risk of intracranial hemorrhage and who are stable on ECLS. In addition, there may also be significant platelet dysfunction despite regular platelet transfusions; platelet function tests can be performed to measure the platelet activity and aggregation. For patients with massive life-threatening bleeding, it is appropriate to use a massive transfusion protocol. For centers with whole blood availability, it can be considered for patients with massive bleeding within a massive transfusion protocol.

3. Antifibrinolytic Therapy
Antifibrinolytic agents, such as aminocaproic acid (Amicar), and tranexamic acid (TXA) are inhibitors of fibrinolysis and have been used successfully to manage significant surgical site bleeding. Amicar was shown to reduce the incidence of surgical bleeding in ECLS patients, particularly cardiac surgery patients while TXA reduced postoperative blood loss associated with congenital diaphragmatic hernia (CDH) repair while on ECLS. Subsequently, both aminocaproic acid and

TXA are used in many centers in an effort to reduce or prevent hemorrhagic complications in ECLS patients having surgical procedures (25, 26). TEG®/ ROTEM testing can be used to determine if there is increased fibrinolysis as an indication for antifibrinolytic therapy. TEG®/ROTEM can also be used to determine if antifibrinolytic therapy is contraindicated if the patient has an underlying hypercoaguable state such as DIC when there is increased fibrin formation and clot strength, despite active bleeding.

4. Recombinant Activated Factor VII (rVIIa) and Prothrombin Complex Concentrates

There are several reports, in both children and adults, of using recombinant activated factor VII (rFVIIa) for refractory bleeding during ECLS despite platelet transfusion and correction of all other coagulation factor deficiencies (27, 28). rFVIIa enhances thrombin generation and is given in doses ranging from 40–90 ug/kg. In multiple series, following treatment with rFVIIa, patients had significant reduction in chest tube drainage and reduced need for PRBC transfusions. However, there have been a few case reports of fatal thrombosis after administration of rFVIIa on ECLS, so it should be used with extreme caution. Thus, some centers will administer lower doses of rFVIIa (25–50 ug/kg) and if more than one dose is required, it is not administered more often than every 2-4 hours.

Some centers feel the risk of significant thrombosis too dangerous and do not use rFVIIa, particularly for ECLS patients. Instead, some prefer to administer prothrombin complex concentrate (PCC) which contains factors II, VII, IX and X, (not activated and therefore potentially less risk of thrombosis) and some additionally contain proteins C and S. In order to correct a prolonged PT and hepzymed APTT during ECLS in patients with active bleeding, PCC 25-50 international units/kg can be administered. It may be given together with FP to supplement factor VII when using a 3 factor PCC, avoided if DIC is present, and an attempt should be made to maintain a normal AT activity.

5. Define Thrombotic Complications in the Patient and Circuit

Thrombosis in the ECLS circuit is more likely to occur during periods of low flow or inadequate anticoagulation, for a variety of reasons. The ELSO registry reports significant circuit or component clots, necessitating a change of the ECLS circuit or circuit component, to occur in 20% of patients (29). Clots can be found anywhere in the circuit, especially at sites of stasis or turbulent flow and are more common on the venous (pre-oxygenator) side of the circuit rather than on the arterial (post-oxygenator) side. Extensive clot formation, particularly if it is associated with significant hemolysis, may require the entire circuit to be replaced. Most of these circuit thrombotic complications have occurred with classic ECLS circuitry.

Although some thromboses may be large and clinically apparent, many thrombotic events are likely not reported because they are subclinical or occult. In a single center adult series of postcardiotomy ECLS patients, 50% of patients who died underwent autopsy, and 75% had clinically unrecognized, postoperative, thromboembolic complications, which included venous thromboses, systemic thromboemboli, cerebral infarction, and bowel ischemia (30). In addition, the longer the duration of ECLS, the more likely there was to be a thromboembolic complication. A similar autopsy series of 29 ECLS children published recently demonstrated that 69% of autopsies revealed evidence for systemic thromboses, with thrombosis being significantly more common in children who had congenital cardiac disease (31). Novel ECLS circuitry, discussed below, has much less circuit thromboses.

6. Heparin-Induced Thrombocytopenia (HIT)

Heparin-induced thrombocytopenia (HIT) is a disorder characterized by thrombocytopenia and, paradoxically, an increased risk of thrombosis. It is frequently suspected due to the ubiquitous use of heparin and the high incidence of thrombocytopenia in critically-ill patients but the true incidence of HIT in ICU patients is estimated to be only 0.3-0.6% (32). Laboratory testing for HIT is insensitive and/or technically difficult so pretest probability should be high before ordering any blood test. Several scoring systems have been proposed to determine pretest probability but the “4Ts” is the most studied (32).

Most hospital labs offer an in-house ELISA-based immunoassay which tests for the presence of any antibody directed against the heparin-Platelet Factor 4 (PF4) conjugate. However, only a subset of activating heparin-PF4 antibodies cause of HIT, hence this test is highly sensitive, but not very specific and we risk withholding heparin from patients who could safely receive it. Each lab may improve specificity at the expense of sensitivity (or vice versa) so it is important to know the strengths and limitations for the assay used in your specific lab.

A functional assay, such as the serotonin-release or heparin-induced platelet assay, is both highly sensitive and specific. However, they are technically difficult to perform and therefore are conducted only at a handful of centers in the country. This confirmatory testing should be sent if the pretest probability is high, an immunoassay is positive, and if the patient is likely to need heparin in the future.

G. Circuit Components

ECLS systems expose a portion of the blood volume to a large surface area of artificial biomaterials. Contact with synthetic, non-endothelial lined surfaces, shear stress, turbulence, cavitation, and osmotic forces directly injure blood.

Newer ECLS circuitry and components that are heparin-bonded or surface-treated may allow minimal to no UNFH therapy for a number of hours to a number of days in an effort to reduce or control patient bleeding; particularly following CPB facilitated cardiac surgery or other surgical manipulations.

1. UNFH Bonded or Otherwise Coated Circuits

Many centers are using heparin bonded or surface treated circuits in an effort to make their circuits more biocompatible and limit or eliminate the need for anticoagulation during CPB and ECLS. However, the useful effects of the coated circuits may be measured in hours and be too short lived to be beneficial in longer ECLS runs that can last for days to weeks. Although, the benefit of a UNFH-bonded or otherwise surface-treated circuit is allowance of delayed initiation of anticoagulation at the start of ECLS, particularly when there are bleeding concerns such as immediately post-operatively or post ECPR.

2. ECLS Pumps and Oxygenators

Traditional roller and centrifugal pumps used for ECLS can cause significant hemolysis; however, with improved technology this becomes less of a problem with novel centrifugal pump systems. A number of studies have shown a reduction in circuit related complications and hemolysis when comparing the use of novel centrifugal pumps to either roller pumps or traditional centrifugal pumps (33, 34). The membrane oxygenator and bridge tubing are the most commonly reported sites for clot formation, although it is hoped that this would significantly decrease with newer ECLS equipment (oxygenator, pumps, circuits) that are now available. The early experience with the poly-methyl-pentene (PMP) devices established them to be robust and long-lasting, with limited incitement of inflammatory response and decreased transfusion requirements, making these oxygenators well suited for long-term ECLS use (35).

H. Summary

The provision and monitoring of antithrombotic therapy for ECLS can be challenging. Ideally, platelet function and hemostasis activation should be inhibited to minimize clot formation within the ECLS circuit and patient while maintaining endogenous procoagulant activity to prevent hemorrhagic complications. UNFH remains the most widely used antithrombotic agent used in ECLS; however, there are a number of whole blood and plasma based coagulation assays available to more accurately assess UNFH anticoagulant effect. Every ECLS program will have to come up with an approach to monitoring the anticoagulant effect of UNFH that works best for their patients in their individual center. As well, novel ECLS circuitry and components are associated with less circuit thromboses, hemolysis and other circuit related complications compared to traditional ECLS equipment. Ultimately, this will

simplify and improve the application of ECLS, result in fewer ECLS related complications, and improved patient outcomes.

For a more detailed review of anticoagulation and bleeding during ECLS, please see the recently published ELSO textbook chapter (36). Please also see separate patient specific anticoagulation protocols for more detailed patient related anticoagulation guidelines.

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