Anticoagulation and Pediatric Extracorporeal Life Support (ECLS). A review of current practice and recommendations

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ABSTRACT:
Pediatric ECLS and advances in ECMO management have truly evolved as a critical management strategy with improved outcomes and holistic survival over the last two decades. Excessive bleeding and thrombosis still constitute the principal cause of morbidity and mortality. The non-biological surface of an extracorporeal circuit provokes a massive inflammatory response initiating consumption and activation of procoagulant and anticoagulant components. Besides the vast difference in neonatal and adult coagulation and transfusion requirements, render anticoagulation on ECMO as a major determinant in reducing morbidity. Anticoagulation is a fluid science and it is imperative that caregivers are aware of the existing anticoagulants with their advantages and disadvantages and advances in monitoring tools to ensure that morbidity is minimized with better outcomes.

Keywords: anticoagulation, extracorporeal membrane oxygenation, bleeding, thrombosis

Extra corporeal life support (ECLS) is evolving as a treatment modality for multiple life threatening scenarios even in the neonatal and pediatric age group. The coagulation cascade of a neonate or infant is different from adult. Besides the immature coagulation mechanism, there is also a dysregulated balance of procoagulant and inherent anticoagulant systems such as altered fibrinogen sensitivity, elevated inhibitors (alpha 2 macroglobulin, Protein C and C3), further accentuated in cases with cyanotic congenital heart disease due to sticky platelets, thrombocytopenia, and deficiency in platelet adhesion and aggregation with increased fibrinolysis. It is hence advisable not extrapolate adult practice blindly on these substrates and titrate anticoagulation carefully, because an avoidable intracranial bleed can really damage the holistic prognosis.

During ECLS, there is a continuous contact between circulating blood and foreign surface of the extracorporeal circuit. Hence the physiological hemostatic balance is shifted to a hypercoagulable state with patients, extracorporeal circuits and components at risk for thrombosis. In order to suppress hemostatic activation and prevent thrombosis, anticoagulation is imperative. The goal of anticoagulation is to suppress platelet and coagulation factor activation, while sustaining adequate endogenous procoagulant activity to avoid spontaneous bleeding.1 The aim of the current document is to review the current guidelines with use of classic and alternative anticoagulants, role of antithrombin (AT), laboratory monitoring methods to facilitate delivery of safe, effective anticoagulation for ECLS and management of patient bleeding and circuit clotting.

Extracorporeal circuit (EC) and Hemostatic activation
Exposure of blood and cellular components to a non-biological surface of EC provokes a massive inflammatory and thrombotic response. The inflammatory response activates cellular and enzymatic components that interact with the activated coagulation system (Figure 1). A highly procoagulant state mediated primarily by thrombin is counterbalanced by an excessive fibrinolytic response mediated by plasmin. The result is a consumption and activation causing clotting factor deficiencies, impaired platelet function, thrombocytopenia and fibrinolysis. The ongoing nature of the procoagulant (thrombin) and anticoagulant (fibrinolysis) mechanisms in concert with the exaggerated inflammatory response, creates imbalance that
heightens the risk of thrombosis or excessive bleeding.² The inflammatory response is further accentuated in neonates and infants.³

Figure 1: Activation of coagulation and inflammatory cascade on extracorporeal circulation

For infant’s platelet activation in the first two hours of ECMO, initiates coagulation cascade, with activated platelets being far more attracted to the oxygenator surface and endothelium and this contact activation slows down during the next 48 hours and thrombin generation subsides. Ongoing surface activation not only forms clots due to thrombin and factor XII formation but also stimulates tissue plasminogen activator (tPA) to lyse the clots. The activated platelets and endothelial cells control the extent of tPA generation to maintain balance between procoagulant and anticoagulant factors.

Activation of the clotting system occurs not only on the surface of EC, but also within the patient’s vasculature, propagating overt thrombosis or Disseminated intravascular coagulation. EC activates the endothelium to express Tissue factor (TF), but also initiates a change in the endothelial membrane to support the TF: VII a complex (prothrombinase complex).

The coagulation system for neonates and infants is immature with clotting factors at 50% of adult levels except for factor VIII, XIII, V, fibrinogen and von Willebrand factor (vWF) occasionally exceeding adult values. Hence infant thrombin generation is weak compared to adults by approximately 20%.⁴ Newborn platelets are hyporeactive and achieve adult reactivity within 14 days. A majority of inhibitors of clotting Anti thrombin and proteins C and S are also at 50% of adult levels.⁴ Though clotting factors may be at a reduced level, Thromboelastography assays revealed a stronger coagulable state in individuals 1 to 3 months of age.⁵

**Anticoagulation**

The goal of anticoagulation for ECMO is to prevent life threatening thrombosis and excessive bleeding. Unidentified macroscopic clots cause a variety of thromboembolic events in patients apparently adequately anticoagulated. The effectiveness of anticoagulation worsens with the duration of ECMO. A recent autopsy series of ECMO patients reported unexpectedly high rates of systemic thromboembolic events approaching 50%, with a linear increase with duration of ECMO, with the study identifying a median time of 6 days with freedom from these events.⁶ Current management guidelines for ECMO are currently derived partially from the cardiopulmonary bypass experience with cardiovascular surgery.⁷

**Unfractionated Heparin (UFH)**

A continuous UFH infusion is the default gold standard anticoagulant currently used in ECLS. There are no large ECLS studies for any other anticoagulant other than UFH and till date an optimal measure to assess UFH efficacy.

Heparin is a heterogenous mixture of branched glycosaminoglycans in saccharide chains. It is a mixture of different molecular weights and corresponding saccharide chain lengths.⁸ Heparin is an indirect anticoagulant in that it requires AT for its primary anticoagulant action, inhibition of both thrombin and factor Xa. UFH does not inhibit the clot bound thrombin or thrombin bound to the ECLS circuit. The anticoagulant effect of UFH is variable for two reasons first, one third of the administered dose of UFH has the specific active pentasaccharide sequence that binds AT and second, the anticoagulant effect of UFH is influenced by the chain length of the molecules.⁸ The UFH/AT complex mediates the anticoagulant effect by UFH by inhibiting Factor IIa (thrombin), Factor Xa, factor IX a, factor Xla and XIIa. Once bound the UFH/AT complex has 1000 times the inhibitory effect compared with AT alone. The action of heparin is not solely limited to thrombin but also to TF inhibition as it stimulates tissue factor pathway inhibitor. Only heparin molecules with 18 or more saccharide units are able to catalyse the interaction of both AT and thrombin. Heparin with shorter saccharide chains may inhibit FXa but not thrombin and results in variable anticoagulation. The remaining two third of the UFH dose, without the active pentasaccharide
sequence, has minimal anticoagulant effect. It may actually inhibit anticoagulation by binding to plasma proteins and activating platelets.\(^8\)

Heparin currently dominates anticoagulation therapy for ECMO, due its rapid action, easy reversibility, easy availability and is well tolerated across age groups. Biological activity varies between 30 minutes to 6 hours depending on the systemic heparin concentration, and temperature. It is metabolized in the reticuloendothelial system as well as the liver and 50% will be excreted unchanged by the kidneys. Clearance of heparin is greater for children with congenital heart disease. Depending on the history of the patient prior to ECMO, profound coagulation abnormalities may exist and they need to be addressed and corrected, until bleeding is controlled. Preferably use of heparin coated circuits and good cardiac output through good ECMO flows are recommended.

The larger blood volume /weight ratios in neonates warrants higher dosage of heparin, besides a rapid metabolic rate with faster excretion by kidneys. The heparin clearance is less after ECMO in infants, compared to the initiation stage.\(^9\) Thrombin generation at a higher rate and increased circulating thrombin after cardiac surgery due to enhanced clot based thrombin secondary to intravascular devices also contributes to increased heparin resistance in infants and neonates.

Patients usually receive an initial UFH bolus of 100 units per kg of body weight at the time of cannulation. The bolus dose can be adjusted based on evidence of preexisting bleeding, or any recent surgery. Any preexisting bleeding diathesis attributed to deranged coagulation profile is ideally to be optimized with platelet transfusion for thrombocytopenia and Fresh frozen plasma or cryoprecipitate for deranged Prothrombin time (PT), Activated partial thromboplastin time(APTT). When the measured ACT drops below 300 seconds, UFH infusion is initiated at 10-20 units per kg per hour and titrated to 20-50 units per kg per hour with a target ACT of 180-220 seconds. The administration of platelets, increased urine output or use of renal replacement therapy, may result in increased UFH requirement. Depending upon underlying coagulation derangements the ACT may under estimate or overestimate the UFH effect in children. As a result, few neonatal pediatric ECLS centers have adopted a dose range of 20-50 units per kg per hour despite the variations in the ACT value.

**Antithrombin (AT) 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 primary anticoagulant effect results from inhibition of thrombin and factor Xa (10). Infants have developmentally low AT activity and antigen levels. The optimal AT activity for any patient receiving UFH anticoagulation is unknown. In infants and children with escalating UFH requirements, UFH doses >35-40 units per kg per hour and/or subtherapeutic anticoagulation, acquired AT deficiency may be a contributing factor to the patients heparin resistance. The major cause of heparin resistance is acquired deficiency of AT, secondary to severe hemodilution, liver abnormalities, consumption during ECLS, or preoperative heparin use especially in post congenital heart disease surgery scenarios. If low AT activity levels are confirmed, AT replacement may be considered. AT concentrates (plasma derived or recombinant ) are available and a few centres routinely administer AT, if activity levels <30-80%, while there are centers which will treat AT activity only if there is evidence of reduced UFH effect, based on low ACT, low anti Xa levels or minimal UFH effect on kaolin and heparinase TEG samples. A few centers use frozen plasma (FP) in similar scenario, but due to low concentration of AT in FP (1u/ml) the desired AT levels may not be achieved for ECLS patients at standard FP transfusion volumes. In the current scenario, ECLS programs that routinely replace AT target activity levels ranging from >50 to > 100% , with higher activity levels desired in neonates (>80%) and infants (>100%). It is clear that prolonged ECLS will result in AT depletion, and hence the monitoring of AT activity daily atleast once is a practice in quite a few centers, but replacement is still an individual preference.

**Monitoring of anticoagulation**

Monitoring of anticoagulation is an in vitro process and eliminates the effects of endothelium in vivo. Majority of coagulation tests are plasma based tests, partial functional measures of coagulation and not whole blood tests that incorporate platelet function and assessment of clot strength.

**Activated clotting time (ACT)**

ACT estimation is the most routinely performed point of care test (POCT) currently for titration of anticoagulation on ECLS. ACT measures the time in seconds of whole blood to form fibrin clot after the addition of various coagulation activators. ACT does
not estimate clot strength. ACT results will vary based on various factors like platelet number and function, fibrinogen level, coagulation factor deficiencies, patient temperature, hemodilution and technical factors. Baird and colleagues retrospectively reviewed over 600 pediatric ECMO patients and found only a modest correlation \((r=0.48)\) between ACT and UFH dosing. Due to the potential shortcomings of ACT alone to titrate UFH dosing. It may be useful to complement regular whole blood ACT measurements intermittently with more elaborate test to assess UFH activity. The correlation of ACT with anti-Xa derived heparin concentration was poor with crystalloid only hemodilution but improved with FFP substituting for crystalloid. This suggests that ACT management with ECMO may be improved if adequate clotting factor levels are maintained.  

**Activated partial thromboplastin time (APTT)**

The use of APTT for monitoring UFH dosing is based on the assumption that the patients baseline aPTT is comparable to normal controls. Unfortunately the baseline aPTT in sick pediatric patients is very different. Increased levels of non specific acute phase reactants, factor VIII and fibrinogen may falsely shorten the aPTT, masking true effect of UFH. In situations that do not require high heparin dosing, such as ECMO, the APTT is a valuable tool to assess anticoagulation. The APTT levels that will prevent thrombus extension with heparin has been reported as 1.5 times baseline and it corresponds to a heparin level of 0.2-0.3 u/ml and correlates well with laboratory derived anti Xa plasma heparin estimation. Codispoti et al compared heparin concentration management with HEPCON for pediatric and adult CPB and demonstrated adequate anticoagulation with increased heparin dosing, reduced bleeding and transfusion requirement compared with ACT management. Better platelet preservation due to lesser bleeding henceforth with higher heparin concentration is an advantage as thrombocytopenia and platelet dysfunction on ECLS in pediatric age group is a major problem.

Table 1: Anticoagulation Management and Monitoring during Pediatric extracorporeal life support. A review of current issues.

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>ACT</td>
<td>• Inexpensive • POC • Whole blood test</td>
<td>• Measures end point of the clotting cascade, but does not solely tell you about UFH effect</td>
</tr>
<tr>
<td>aPTT</td>
<td>• Accepted means of titrating anticoagulation therapy for both UFH and DTI • POC now available</td>
<td>• High degree of intra-and interpatient variability especially in infants • Less reliable in critical illness</td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>• Specific measures of UFH effect based on the ability of UFH to catalyze AT's inhibition of factor Xa</td>
<td>• Elevated plasma-free hemoglobin and hyperbilirubinemia will underestimate UFH activity by anti-Xa</td>
</tr>
<tr>
<td>TEG / ROTEM</td>
<td>• Better association with UFH dose • POC • Whole blood test • Provides information about both clot strength and fibrinolysis</td>
<td>• Limited availability</td>
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**Anti Xa assay**

The anti Xa (alternatively addressed the heparin level) is a measure of UFH effect based on the ability of UFH to catalyze AT inhibition of factor Xa. This does not incorporate platelet function nor measure inhibition of thrombin. The therapeutic aPTT range at 1.5-2.5 X baseline aPTT, demonstrated that this therapeutic range corresponded to an anti-Xa activity of 0.3-0.7 u/ml. The anti Xa is a chromogenic assay, and is falsely decreased when there is elevated plasma free hemoglobin or bilirubin and this limits its utility in ECLS.

The Hepcon (Medtronic Perfusion system Minneapolis, MN) is able to provide heparin concentration with good correlation to the laboratory derived anti Xa plasma heparin estimation. Codispoti et al 15 compared heparin concentration management with HEPCON for pediatric and adult CPB and demonstrated adequate anticoagulation with increased heparin dosing, reduced bleeding and transfusion requirement compared with ACT management. Better platelet preservation due to lesser bleeding henceforth with higher heparin concentration is an advantage as thrombocytopenia and platelet dysfunction on ECLS in pediatric age group is a major problem.
Viscoelastic testing

Viscoelastic tests (thromboelastography (TEG) and rotational thromboelastometry (ROTEM) examine whole blood clot formation (coagulation) and dissolution (fibrinolysis). Though limited by static condition (no flow) as well as the exclusion of the vascular endothelium, they are currently the best option to evaluate clot strength. Additional information from viscoelastic testing includes time until initial fibrin formation, kinetics of fibrin formation and clot development, the strength and stability of fibrin clot, clot lysis and platelet function. TEG monitoring with its holistic monitoring of the coagulation profile is a promising add on to the anticoagulation protocol bundle (Fig 2 a and b).

Figure 2a and 2b: TEG tracing depicting formation and degradation of clot and Interpretation of Thromboelastography

To manage anticoagulation with TEG, the reaction time R is the most important value as it represents the time for initial fibrin formation. It is affected by severe hypofibrinogenemia, hypercoagulability and heparin. The sensitivity of TEG to heparin renders it unsuitable for CPB due to flat trace at concentration approximating 1u/ml but for ECMO it holds promise as an important tool for anticoagulation monitoring. The addition of Kaolin to the TEG (kTEG) gives a rapid result, while the addition of heparinase (h TEG) permits a fully formed tracing to be generated even with a heparin infusion . If the kTEG and h TEG r times are similar, it indicates little systemic heparin, and if the kTEG r time exceeds 90 minute, the heparin activity may be too high. The recommended baseline for anticoagulation is a kTEG r more than 20 minutes. TEG also helps evaluate the degree of platelet inhibition using arachidonic acid and adenosine diphosphate.

Alternative anticoagulants

Direct thrombin inhibitors

Direct thrombin inhibitors (DTI) are independent of AT for their anticoagulant effect. They act directly to inhibit both circulating and clot bound thrombin and hence gain an edge over heparin. Bivalirudin is a potentially attractive DTI, as it is cleared mainly by the intravascular proteolytic degradation and less so by the kidneys. It can be used as an initial anticoagulant, but in the current role its primary role is as a replacement for heparin in heparin induced thrombocytopenia or heparin resistance. Bivalirudin has a short half-life of 25-35 minutes and even lesser in children. Bleeding following bivalirudin is potentially reversible with activated factor VII a. APTT with its limitations, of reproducibility and linearity, still is the most common monitoring tool for DTI. Most centers will initially target a APTT 1.5 to 2 times normal and extend it to 2.5 for optimal circuit mechanics. Argatroban and lepirudin are other DTI agents but are primarily metabolized in liver and kidney and hence do no fit well in a critical post ECMO scenario wherein both the systems may be actually compromised. There is minimal published experience with Bivalirudin usage in Pediatric ECLS. Nagle et al reported a series of 12 children transitioned to bivalirudin due to UFH resistance, UFH failure or HIT (Heparin induced
thrombocytopenia) on ECLS. The analysis revealed a wide variation in the dosing patterns with APTT monitoring. A few retrospective adult studies revealed no difference in thromboembolic complications. Published doses of bivalirudin used in pediatric ECLS include an initial bolus dose of 0.05-0.5 mg per kg followed by an infusion rate of 0.03-0.1 mg per kg per hour titrating APTT 1.5 -2.5 times baseline. Long ECMO duration and renal replacement therapy may warrant higher dose range. Stasis reduces the efficacy of bivalirudin.

**Novel anticoagulants**

Rivaroxaban, a highly specific inhibitor of Factor Xa, prevents the formation of thrombin burst and inhibits anticoagulation at the time of amplification. Oral factor IIa inhibitors such as dabigatran are in use for prevention of thromboembolism in adults but no pediatric data is currently available. A recombinant Factor XII, a neutralizing antibody prevented fibrin deposition and thrombosis in the extracorporeal circuit and is currently being evaluated in animal models.

**Factor XII a inhibitor**

An animal study using an antibody to Factor XIIa as the anticoagulant in ECLS circuits was compared to UFH anticoagulation. The factor XIIa antibody prevented fibrin deposition and thrombus development as efficiently as UFH. However unlike UFH this antibody therapy did not impair the hemostatic capacity nor did it increase clinical bleeding from wounds.\(^\text{19}\)

**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 indigenous vascular endothelium. Nitric oxide (NO) and other circuit releasing compounds

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Mechanism of action</th>
<th>Dosing range</th>
<th>Reversible</th>
<th>Monitoring tests</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| UFH          | Indirect- needs AT for maximal therapeutic effect | 10-70U/KG/h | Protamine sulfate | ACT, aPTT, anti, XA, and TEG/ROTEM | • Only one-third of UFH molecules has pentasaccharide sequence that binds AT, which leads to variable anticoagulation  
• Does not inhibit clot-bound thrombin  
• Thrombocytopenia |
| Bivalirudin   | Direct thrombin inhibitor | 0.3-1.2mg/kg/h | No specific antidote, but bleeding may be mitigated with factor VIIa | aPTT | • Expect INR will increase  
• Thrombosis with blood stasis (intra cardiac and circuit) |

Table 2. Anticoagulation Management and Monitoring during Pediatric extracorporeal life support. A review of current issues.\(^\text{16}\)

Endothelial cells release prostacyclin and nitric oxide (NO) which inhibit thrombin induced platelet adhesion and activation as a way to maintain the unhindered fluid circulation in animal models.\(^\text{42}\) MAHAMA / NO was the first compound to be incorporated into a polymer matrix applied to an extra corporeal circuit, which on exposure to blood released NO at its surface without systemic heparinization. These coated circuits demonstrated significantly decreased platelet consumption when compared to both heparinized and non heparinized controls.\(^\text{20}\)

**Transfusion and ECMO**

Stronger anticoagulation to lessen thrombotic complications induces more bleeding and use of blood products. Transfusion related morbidity is attributed to increased inflammatory response and deranged immunomodulation and also enhances the risk of sepsis. Hence it is imperative that efficient and appropriate anticoagulation to minimize bleeding and transfusion requirements may contribute greatly to the reduction of morbidity and mortality associated with ECMO.
Bleeding and transfusion with ECMO manifests in two different forms. Serious Hemorrhage in neonate with respiratory distress syndrome with ECMO is related to injury of the central nervous system. Intracranial hemorrhage may occur in 15% neonates, resulting in premature disruption of ECMO. Preexisting coagulation abnormalities in a neonate enhances the risk further. The other group is the post cardiac surgery infants requiring ECMO, with persistent massive blood loss and transfusion.

It is imperative to ensure a protocol based assessment and maintenance of coagulation mechanisms to prevent or reduce catastrophic bleeding and its complications and thereby prevent excessive transfusions. Optimal transfusion management during ECMO requires an array of routine coagulation tests (RCT) to assess hemostatic capability such as platelet count (PC), prothrombin time (PT), APTT and TEG besides AT and hemoglobin levels.

The PT assesses the extrinsic and common pathway integrity by measuring clotting of recalci
brinogen and helps reduce bleeding. Cryoprecipitates contain mature fibrinogen and helps reduce bleeding significantly in infants after CPB. hTEG with a prolonged r is suggestive of fibrinogen deficiency. Thresholds for transfusion of PRBCs may vary for individual centers but the aim is to target a near normal hematocrit (>35-40%). For centers with availability of whole blood, it can be considered for patients with massive bleeding within a massive transfusion protocol.

**Antifibrinolytic therapy**

Antifibrinolytic agents such as epsilon amino caproic acid (EACA) and tranexamic acid(TA) are inhibitors of fibrinolysis and currently do help in controlling surgical site bleeding especially in post cardiac surgery scenarios. TEG/ROTEM testing can be used to determine if antifibrinolytic therapy is required or contraindicated in DIC like situations, with increased fibrin formation and clot strength, despite active bleeding.

**Recombinant factor VII (VIIa ) and prothrombin complex concentrate**

Recombinant factor VII(rVIIa) usage has been reported in both pediatric and adult groups for refractory
bleeding on ECMO despite platelet transfusion and correction of all other coagulation factor deficiencies. rVIIa enhances thrombin generation and is given in doses ranging from 40-90 mcg per kg. However, with few case reports of fatal thrombosis, a few centers advocate lower doses of rVIIa (25-50 mcg per kg) and if required more than one dose repeated every 2-4 hours. Prothrombin complex concentrate (PCC) rich in factors II, VII, IX and X in their inactive forms with potentially less risk of thrombosis and additionally also rich in protein C and S, can be used when available. In bleeding patients on ECMO with deranged PT, and hepzymed APTT, PCC 25-50 international units /kg can be administered.

**Thrombotic Complications**

Thrombosis in the ECLS circuit is more likely to occur during periods of low flow or inadequate anticoagulation. The ELSO registry reports significant circuit or component clots, necessitating a change of the ECLS circuit or circuit components in approximately 20% patients\(^{(26)}\). Clots are more common on the venous (pre-oxygenator) side of the circuit rather than on the arterial (post –oxygenator) side and the incidence is directly proportional to the duration of ECMO. An autopsy series of 29 ECLS children demonstrated that 69% cases revealed evidence of systemic thromboses, with thrombosis being significantly more common in children with congenital heart disease\(^{(6)}\). Significant thrombosis warrants a circuit change in most situations. UFH bonded or coated circuits, besides the advantage of delayed anticoagulation initiation in patients immediate post surgery or post ECPR, can help in longer usage of circuits without thrombosis and improved ECLS equipment (poly methyl pentene based devices) have been reported to be robust, with lesser inflammatory response, decreased transfusion requirements and suitable for long term ECLS use\(^{(27)}\).

**Conclusion**

Pediatric ECLS as a treatment modality is evolving in India significantly over the last decade, with the practicing physicians realizing that protocol based approach definitely results in better survival. Anticoagulation is a need and also a risk and a balanced approach with cognizance of the monitoring aids and their drawbacks with alternative approaches, will only result in preventing mishaps. UFH continues to be a mainstay and ACT as a POCT but with the caveat that the immature coagulation systems of neonate differ from adults and sick infant or neonate with a preexisting deranged coagulation profile will challenge the bedside clinician to go beyond this occasionally, especially in cases with prolonged extracorporeal support and heparin resistance.

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