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UNDERSTANDING THE DISEASE

How to manage anticoagulation during extracorporeal membrane oxygenation

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Extracorporeal membrane oxygenation (ECMO) use is increasing worldwide, driven by device simplification and increasing need during the coronavirus disease 2019 (COVID-19) pandemic, while bleeding and thrombotic events remain a major challenge. An analysis of 7579 veno-venous ECMO (VV-ECMO) patients from 2010 to 2017 in the Extracorporeal Life Support Organization (ELSO) database reported that 40.2% experienced one or more bleeding or thrombotic event, with circuit thrombosis the most common in 54.9% of events [1]. Comparatively, an analysis of 11,984 veno-arterial (VA-ECMO) patients from the same database reported 8,457 events, of which 62.1% were bleeding events [2]. Balancing anticoagulation to prevent thrombotic complications against bleeding in these complex critically ill patients during ECMO is an ongoing challenge for clinicians. In this pragmatic state-of-the-art summary, we review managing anticoagulation in ECMO.

Anticoagulation monitoring: laboratory testing

Laboratory testing is used to balance thrombosis versus bleeding in ECMO and optimize patient management beyond treating the primary critical illness that necessitated extracorporeal life support (ECLS), including acute lung injury and/or shock. Beyond the standardized tests, including hemoglobin, platelet counts, antithrombin (AT) levels, and others, specific anticoagulation management strategies are listed in Fig. 1 and supplemental Table 1 and include activated clotting time (ACT), activated partial thromboplastin time (aPTT), and, anti-factor Xa (anti-Xa) [3, 4]. Individual monitoring tests will be reviewed. The required anticoagulation levels may differ between VV and VA-ECMO, depending on underlying diseases, thrombosis risk, and factors determining the patient's critical illness.

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Activated clotting time

The ACT, a whole blood test, evaluates contact activation/intrinsic coagulation inhibition by heparin or direct thrombin inhibitors (DTIs). Factors that prolong ACT include hypothermia, platelet function/number, and coagulation factor levels. The suggested ACT range for ECMO is 180–200 seconds. However, the correlation of ACT with other coagulation tests, including anti-Xa/heparin levels and aPTT, is frequently discordant [4, 5].

Activated partial thromboplastin time

The aPTT evaluates contact activation/intrinsic coagulation, as is used to monitor heparin and DTIs, a test that evaluates clot formation. Suggested therapeutic targets are 40–50 seconds initially, then titrated to 60–80 seconds depending on bleeding and/or thrombosis risk [3, 4, 6]. The activator used is a phospholipid (ellagic acid), and clot formation is determined based on mechanical or optical clot detection. The aPTT test is affected by antithrombin, factor VIII, factor XII, and fibrinogen levels [7, 8]. For heparin monitoring, there is often discordance of aPTT with anti-Xa monitoring. The aPTT is also used for evaluating DTIs (argatroban and bivalirudin) [4, 9]. Variability and therapeutic ranges differ between clinical sites and should be individualized.

Anti-factor Xa levels

For unfractionated heparin (UFH) management, anti-Xa levels are increasingly used and correlate better with UFH

levels than aPTT [5, 10]. Suggested ECMO target levels range from 0.3 to 0.7 IU/mL; however, anti-Xa levels do not evaluate clot formation. Testing can be influenced by patient AT deficiency, hyperlipidemia, coagulation factor levels, and hemolysis with increased plasma hemoglobin and/or hyperbilirubinemia.

Viscoelastic testing

Viscoelastic testing assesses clot-based assays using specific activators (e.g., tissue factor, ellagic acid, kaolin) to evaluate whole blood clot formation, and is often used for bleeding management evaluation rather than anticoagulation monitoring [11].

Antithrombin

AT is critical for heparin effectiveness. However, levels during ECMO decrease due to consumptive coagulopathy and other causes [12]. Despite its use, there are no data supporting improved outcomes with supplementation in ECMO patients [13].

Anticoagulation therapy

Unfractionated heparin (heparin)

Unfractionated heparin (heparin) is the mainstay of therapy due to its titratability, reversibility, and short duration of effect (~1 hour). Although increasingly used, anti-Xa monitoring does not provide information about clot formation or other factors influencing hemostatic balance. In an era of goal-directed therapy, there are no data to suggest that maintaining a specific anti-Xa concentration is associated with improved outcomes, as the diseases necessitating ECMO inherently impact morbidity and mortality.

Heparin resistance

Heparin resistance is poorly defined as current definitions suggest >35,000 units/day, without specific weight-based dosing, and based on clot-based coagulation tests that are highly influenced by hypercoagulability and thrombocytosis [8]. Checking an anti-Xa level if not routinely used can be diagnostically helpful when high doses of heparin do not achieve desired aPTT or ACT values. The benefit versus risk considerations of DTIs for heparin resistance should be carefully evaluated.

Argatroban

Argatroban, a synthetic ~ 500 Daltons L-arginine derivative, reversibly inhibits thrombin by univalent binding to thrombin. Argatroban may be the preferred DTI in renal failure due to hepatic elimination (half-life = 40–50 minutes), and has been studied in intensive care unit (ICU) and ECMO populations [9].

Bivalirudin

Bivalirudin is a small peptide (~2400 Daltons) DTI that inhibits reversibly binds thrombin. The half-life is 20–30 minutes but is prolonged in renal failure up to 240 minutes. Bivalirudin is widely used as a heparin alternative in the catheterization laboratory and reported for ECMO [9, 14].

Heparin-induced thrombocytopenia

The DTIs argatroban and bivalirudin are administered used in patients with diagnosed or suspected HIT requiring ECMO, and other indications [9]. In ICU and ECMO patients, multiple causes of thrombocytopenia occur, often making the diagnosis challenging.

In conclusion, with different anticoagulation tests, variable anticoagulation protocols, and ECMO outcomes dependent on the patient's underlying disease process, optimizing anticoagulation practices continues to be refined. In addition, newer simplified ECMO circuits have greatly facilitated its application in worldwide use.

Heparin, the mainstay agent for ECMO anticoagulation, can be managed using multiple laboratory tests. When using clot-based assays (aPTT or ACT) for routine monitoring, anti-Xa levels can be helpful to determine whether targeted heparin levels are achieved [3]. Viscoelastic testing can be used to help define the coagulopathy defect with bleeding. In heparin resistant patients, weight-based dosing should be considered, anti-Xa levels evaluated, and titrated accordingly. Alternatively, switching to a DTI or AT supplementation are potential considerations.

There is no uniform ECMO anticoagulation practice as there is no evidence-based consensus guiding anticoagulation agents, monitoring, therapeutic targets, optimal levels, and management of complications and outcomes [15]. Considerable research remains to be done for a modality in use since the 1980s, and further studies are required to determine proper targets [16]. A potential algorithm for clinical management is shown in Fig. 1.

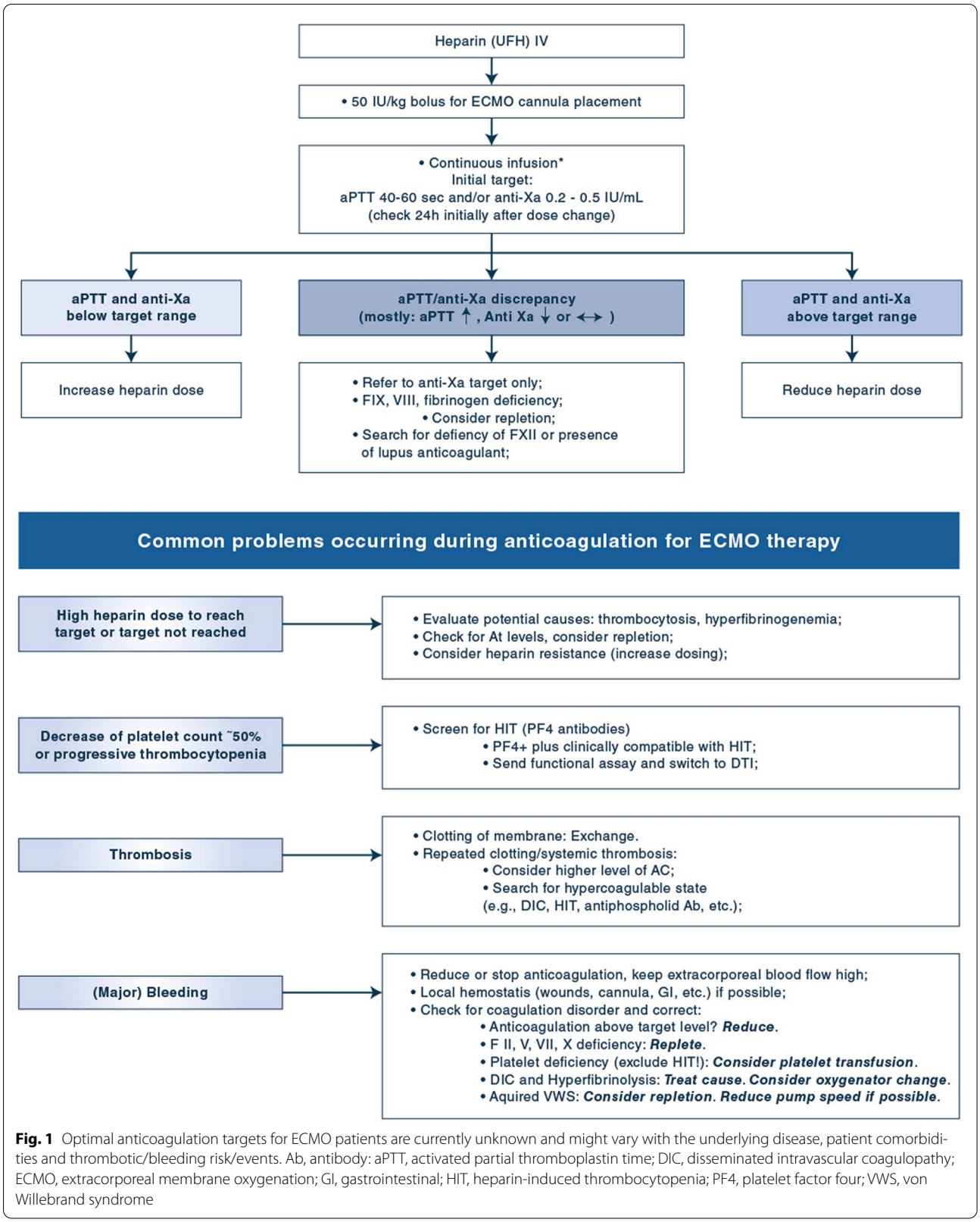

Fig. 1 Optimal anticoagulation targets for ECMO patients are currently unknown and might vary with the underlying disease, patient comorbidities and thrombotic/bleeding risk/events. Ab, antibody: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulopathy; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; HIT, heparin-induced thrombocytopenia; PF4, platelet factor four; VWS, von Willebrand syndrome

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Conflicts of interest
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