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.

**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 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].

**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.
Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06723-z.

Author details
1 Departments of Anesthesiology, Critical Care, and Surgery, Duke University School of Medicine, Duke University Medical Center, 2301 Erwin Rd., 5691H HAFS, Box 3094, Durham, NC 27710, USA. 2 Department of Medicine I, Medical University of Vienna, Vienna, Austria. 3 Divisions of Critical Care and Hematology/Oncology, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA.

Author contributions
JHL wrote the first draft, TS and MES reviewed and made critical edits and revisions.

Funding
No source of funding was used in the preparation of this manuscript.

Declarations
Conflicts of interest
JHL is member of research steering committees, data safety monitoring boards, or advisory boards for, Instrumentation Laboratories, Octapharma, Leading Biosciences, and Merck. TS reports Speaker fees from Getinge, Xenios, Mitsubishi Pharma. MES is member of data safety monitoring board for Infant Jarvik Heart trial, advisory committee for Octapharma.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 31 March 2022 Accepted: 29 April 2022
Published: 11 June 2022

References
1. Nunez JI, Gosling AF, D’Gara B, Kennedy KF, Rycus P, Abrams D, Brodie D, Shaefi S, Garan AR, Grandin EW (2022) Bleeding and thrombotic events in adults supported with venovenous extracorporeal membrane oxygenation: an ELSO registry analysis. Intensive Care Med 48:213–224
2. Chung M, Cabezas FR, Nunez JI, Kennedy KF, Rick K, Rycus P, Mehra MR, Garan AR, Kociol RD, Grandin EW (2020) Hemocompatibility-related adverse events and survival on venoarterial extracorporeal life support: an ELSO registry analysis. JACC Heart Fail 8:892–902
3. Koster A, Ljajikj E, Faraoni D (2019) Traditional and non-traditional anticoagulation management during extracorporeal membrane oxygenation. Ann Cardiothorac Surg 8:129–136
4. McMichael ABV, Ryerson LW, Ratano D, Fan E, Faraoni D, Annich GM (2022) 2021 ELSO adult and pediatric anticoagulation guidelines. ASAIO J 68:303–310
5. Price EA, Jin J, Nguyen HM, Krishnan G, Bowen R, Zehnder JL (2013) Discordant aPTT and anti-Xa values and outcomes in hospitalized patients treated with intravenous unfractionated heparin. Ann Pharmacother 47:151–158
6. Sklar MC, Sy F, Lequier L, Fan E, Kanji HD (2016) Anticoagulation practices during venovenous extracorporeal membrane oxygenation for respiratory failure. A systematic review. Ann Am Thorac Soc 13:2242–2250
7. Buchtele N, Schwameis M, Schellongowski P, Quehenberger P, Knobl P, Traby L, Schmid M, Schoengenhofer C, Herkner H, Jilma B, Staudinger T (2021) Prevalence and clinical impact of reduced coagulation factor XI activity in patients receiving extracorporeal membrane oxygenation. Crit Care Med 49:e1206–e1211
8. Levy JH, Connors JM (2021) Heparin resistance—clinical perspectives and management strategies. N Engl J Med 385:826–832
9. Koster A, Faraoni D, Levy JH (2018) Argatroban and bivalirudin for perioperative anticoagulation in cardiac surgery. Anesthesiology 128:390–400
10. Delmas C, Jacquemin A, Vardon-Bounes F, Georges B, Guerrero F, Hernandez N, Marcheix B, Seguin T, Mirville V, Conil JM, Silva S (2020) Anticoagulation monitoring under ECMO support: a comparative study between the activated coagulation time and the anti-xa activity assay. J Intensive Care Med 35:679–686
11. Erdoes G, Koster A, Levy JH (2021) Viscoelastic coagulation testing: use and current limitations in perioperative decision-making. Anesthesiology 135:342–349
12. Levy JH, Sniecinski RM, Welsby IJ, Levi M (2016) Antithrombin: anti-inflammatory properties and clinical applications. Thromb Haemost 115:712–728
13. Chlebowski MM, Baltagi S, Carlson M, Levy JH, Spinella PC (2020) Clinical controversies in anticoagulation monitoring and antithrombin supplementation for ECMO. Crit Care 24:19
14. Taylor T, Campbell CT, Kelly B (2021) A review of bivalirudin for pediatric and adult mechanical circulatory support. Am J Cardiovasc Drugs 21:395–409
15. Bembea MM, Schwartz JM, Shah N, Colantuoni E, Lehmann CU, Kickler T, Pronovost P, Strouse JJ (2013) Anticoagulation monitoring during pediatric extracorporeal membrane oxygenation. ASAIO J 59:63–68
16. Levy JH, Faraoni D, Almond CS, Baumann-Kreuziger L, Bembea MM, Connors JM, Dalton HJ, Davies R, Dumont LJ, Griselli M, Karkouti K, Massicotte MP, Teruya J, Thiagarajan RR, Spinella PC, Steiner ME (2022) Consensus statement: hemostasis trial outcomes in cardiac surgery and mechanical support. Ann Thorac Surg 113:1026–1035