Anticoagulation Management in COVID Extracorporeal Life Support (ECLS)

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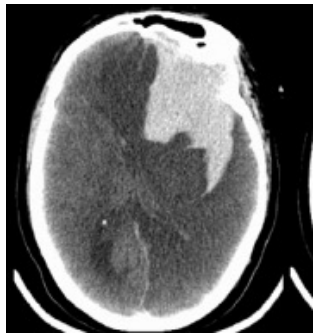
November 20-21, 2021
The Ritz-Carlton Hotel, St. Louis, Missouri

I have no relevant financial relationships to disclose.

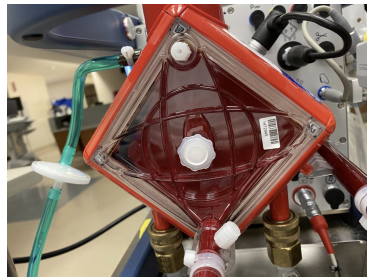
Hemostatic Balance

Bleeding

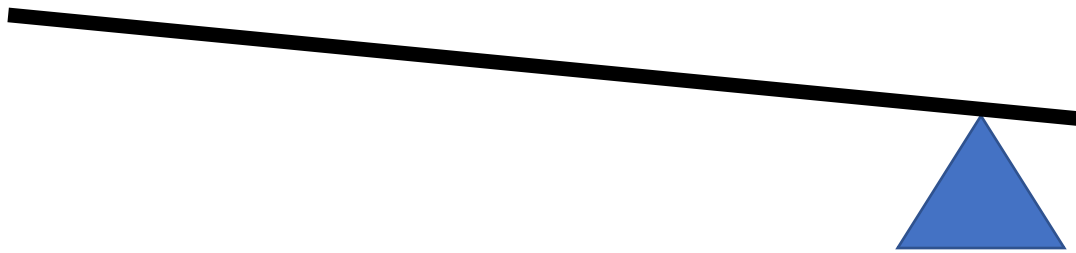


- Platelet dysfunction
- Von Willebrand factor dysfunction
- Fibrinolysis
- Consumption of coagulation factors

Clotting



- Protein accumulation
- Platelet activation
- Contact pathway (XII) activation



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Kato et al. *Eur J Haematol.* 2021;106:19–31.

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ELSO Guidance

UFH 50-100 unit/kg bolus at the time of cannulation followed by:

7.5-20 units/kg/h

***encompasses pediatrics & adults**

"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"

Paucity of data regarding:
Ideal monitoring parameter
Ideal goal/range of anticoagulation
Guidance for the use of alternative agents
Incorporation of clinical factors (patient and device) that may impact coagulation
Concurrent antiplatelets

2014 The Extracorporeal Life Support Organization (ELSO), Ann Arbor, MI, USA

Variable Practice Patterns

- Pediatric: 120 ECMO centers internationally
  - **UFH was used at all centers**; only 8% indicated use of alternative agents
  - Monitoring: **ACT (97%),** anti-xa (65%), TEG (43%), AT(82%)
- Adults: 54 ECMO centers internationally
  - 47/54 **(87%) used UFH** primarily
  - Monitoring: **ACT (42%), aPTT (42%),** anti-xa (10.4%), TEG (8.3%), AT (37%)
- Review of 20 additional adult centers:
  - Continuous heparin, anticoagulant-free approaches, heparin alternatives
  - aPTT & ACT

Bembea MM, et al. Pediatr Crit Care Med. 2013;14(2):e77–84.
EsPer et al. Vox Sang. 2017;112(5):443-452.
Kato et al. Eur J Haematol. 2021;106:19–31.

Heparin Monitoring

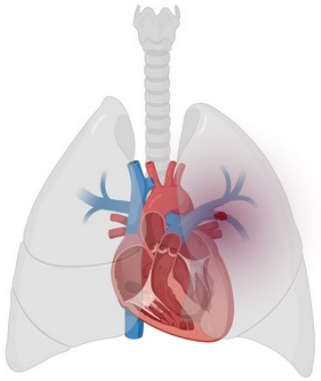
ACT	aPTT	Anti-Xa	TEG & ROTEM
Global Measures time to clot formation. Incorporates the effects of RBCs and platelets.	**Coagulopathy monitoring and anticoagulation management in COVID-19 patients on ECMO: Advantages of a heparin anti-Xa-based titration strategy** N= 31 aPTT & Anti-Xa discordance = 49.5% of cases 42% aPTT in range vs. 60% anti-xa in range Fewer UFH titrations, and a trend toward lower UFH doses		*Global* Measures the integrity of the coagulation cascade from the time of fibrin formation to clot lysis. Includes the contribution of platelets.
<u>May prolong ACT:</u> Hypothermia, Hemodilution Hypofibrinogenemia Thrombocytopenia Coagulation factor deficiencies	*<u>May prolong aPTT:</u>* Lupus anticoagulant Factor XII deficiencies Consumptive coagulopathy, Hemolysis, Warfarin *<u>May blunt aPTT response:</u>* AT deficiency, Increased Factor VIII Increased fibrinogen	*<u>May underestimate anti-Xa</u>*: Hyperlipidemia Hyperbilirubinemia High plasma-free hemoglobin Hemolysis	Doest not detect platelet dysfunction, effects of vWF, factor XIII is not adequately displayed

VAndiver JW, et al. Pharmacotherapy. 2012 Jun;32(6):546-58.
Lance, Marcus D. THROMB J. 2015; 13: 1.; Thrombosis Research 203 (2021) 1–4

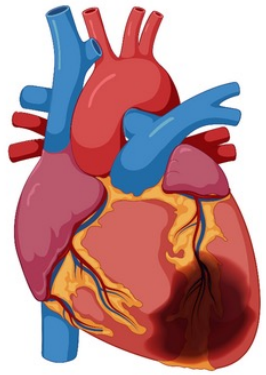
Alternative Agents

	Bivalirudin & Argatroban	Enoxaparin	Warfarin	Antithrombin	Tranexamic Acid
PROs	• More predictable PK • Greater reduction of thrombin generation, as compared to UFH • Does not cause HIT • Widely used in ECMO patients • Short half life	• Administration schedule • SQ injection	• Once daily administration • Potentially less bleeding	• Potentiates heparin effectiveness	• Focus on fibrinolysis pathway
CONs	• No reversal agent • Areas of stasis may lead to further thrombosis • INR elevations	• Renal dysfunction • Longer half life	• Longer Half life • Liver dysfunction • Drug & nutritional interactions	• Contradicting literature in ECMO • Ideal range unknown • Bleed risk	• Not as familiar • Not routinely utilized • Less information on optimal dose • TEG monitoring

COVID



Pulmonary embolism: ~ 24.0%



Myocardial injury: ~ 20.0%

Deep veein thrombosis: ~ 46.1%

Stroke: ~ 1.6%

Editorial > J Cardiothorac Vasc Anesth. 2020 Dec;34(12):3193-3196.
doi: 10.1053/j.jvca.2020.09.132. Epub 2020 Oct 2.

COVID-19 and ECMO: An Unhappy Marriage of Endothelial Dysfunction and Hemostatic Derangements

Troy G Seelhammer [1], Daniel Plack [2], Amos Lal [3], Christoph G S Nabzdyk [2]

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J Am Heart Assoc. 2021;10:e019650

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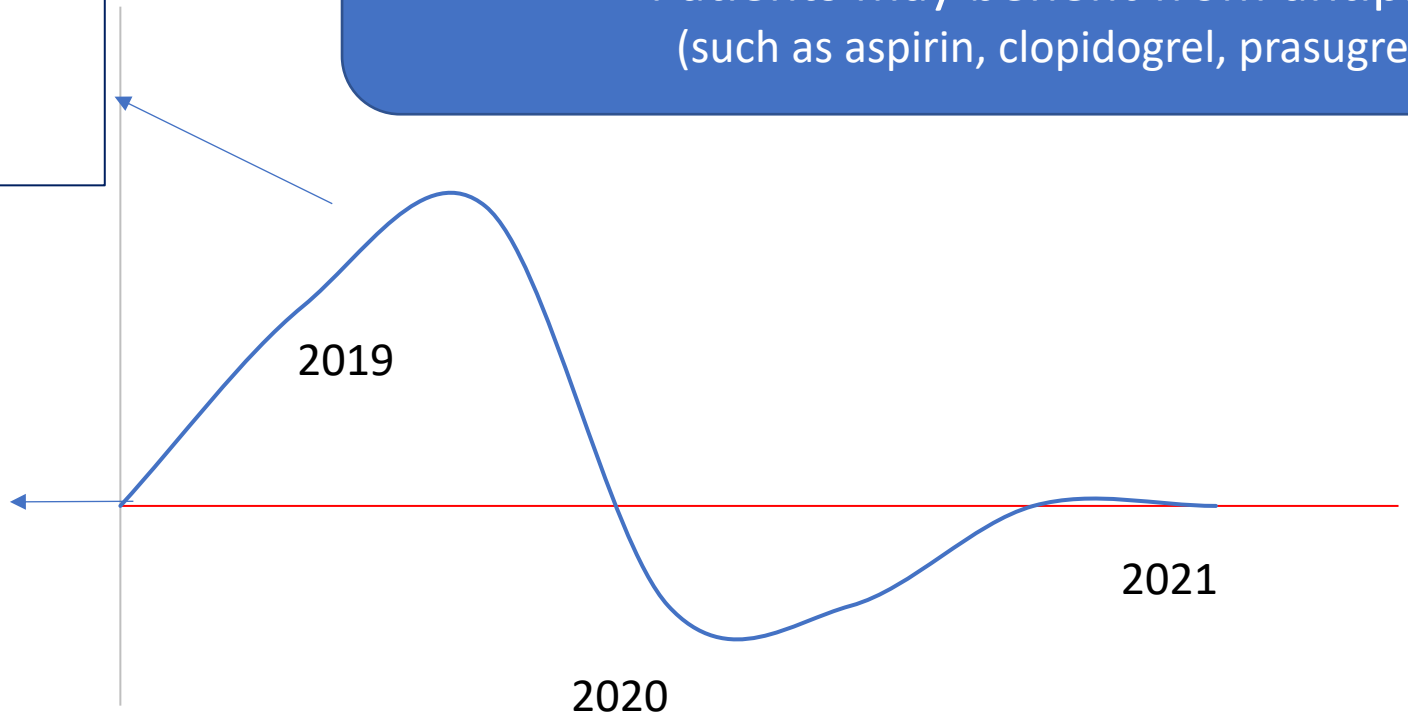
Anticoagulation Intensity During COVID

2020 ELSO

* Consider targeting anticoagulation at the higher end of normal
* Patients may benefit from antiplatelet agents
(such as aspirin, clopidogrel, prasugrel, ticagrelor)

Intermediate prophylactic intensity to full therapeutic Anticoagulation



Pre-COVID standard of care anticogulation for ECMO

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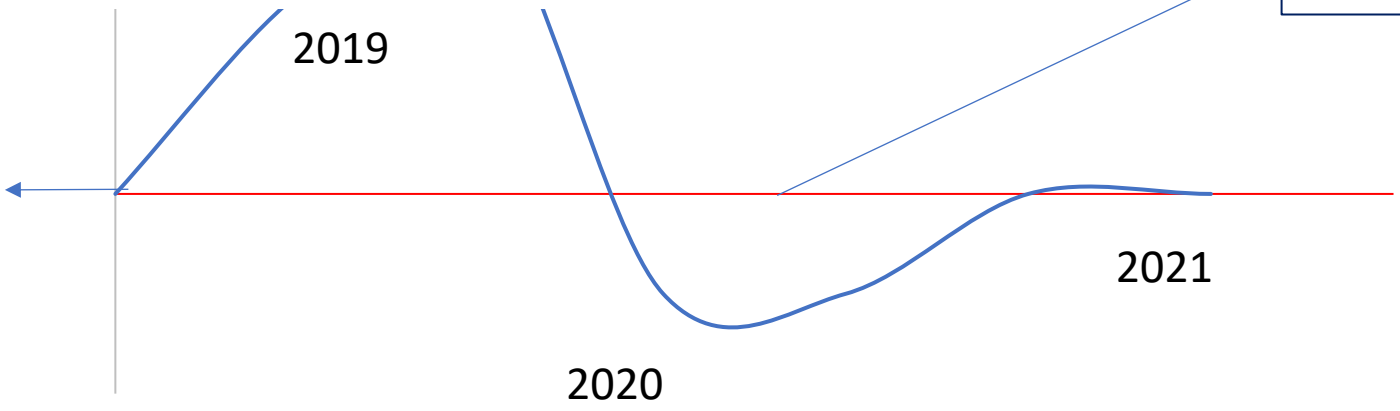
Anticoagulation Intensity During COVID

Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019

CHEST Guideline and Expert Panel Report

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19



Standard prophylaxis dosing to the complete omission of heparin

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Anticoagulation Intensity During COVID

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 26, 2021 VOL. 385 NO. 9

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

Organ support = requiring high-flow nasal oxygen, invasive or noninvasive MV, vasopressors or ECMO

Outcome	Therapeutic Anticoagulation (n=536)	Usual Care Prophylaxis (n=567)	AOR, 95% CI	Probability of Futility
Organ support free days up to day 21	1 (-1 to 16)	4 (-1 to 16)	0.83 (0.67 to 1.03)	99.9 %
Survival to hospital discharge	62.7%	64.5%	0.84 (0.64 to 1.11)	99.6%
Major bleeding	20/529 (3.8%)	13/562 (2.3%)	1.48 (0.75 to 3.04)	

OR adjusted for sex, trial site, enrollment time interval

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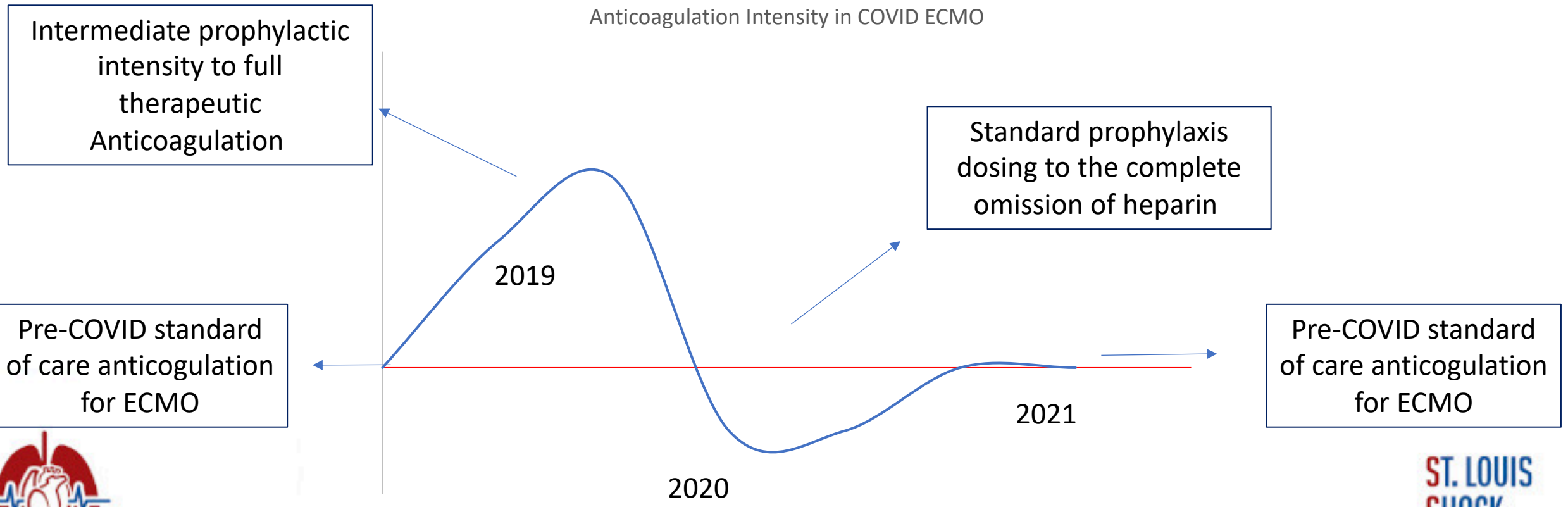
COVID ECMO

COVID-19 ECMO Working Group: A multicenter (17 centers), retrospective cohort study

- N= 292 adults, March 1, 2020 - September 30, 2020
- Heparin 71%, argatroban 32%, bivalirudin 10%
- **Bleeding requiring transfusions 74%**
- **Hemorrhagic stroke 6%**
- DVT 15%
- Ischemic stroke 1%

Saeed o, et al. J Thorac Cardiovasc Surg. 2021 May 18
Saeed o, et al. JTCVS Open. 2021 Sep 21.

Anticoagulation Intensity During COVID



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Questions Still Remain

Ideal agent?

Ideal monitoring parameter?

Ideal goal/range of anticoagulation?

Clinical patient and device factors?

Use of antiplatelets?

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Summary

- The ***optimal*** anticoagulation agent, monitoring parameter and anticoagulation goal for ECMO are undetermined
- Combined monitoring approach should be considered
- **Importance of center specific guidelines & education**
- Area of Research

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