


PLEX Out:
**COVID-19-associated coagulopathy, hyperviscosity,
 and the use of therapeutic plasma exchange**

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Disclosure

I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

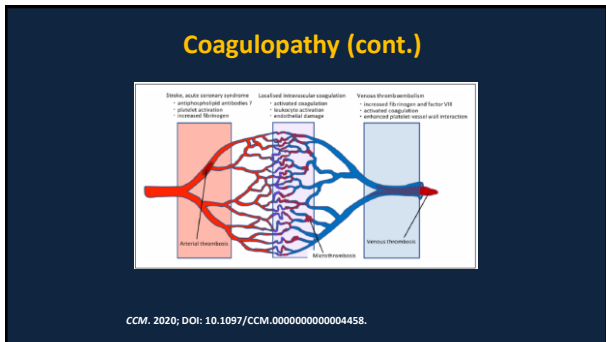
- Describe COVID-19 associated hyperviscosity
- Recognize factors that influence drug removal during plasma exchange
- Identify drugs which are likely to be removed by plasma exchange

COVID-19-associated Coagulopathy



JAMA Network Open
CARDIOVASCULAR FLASHLIGHT
Acute pulmonary embolism and COVID-19 pneumonia: a random association?
 With Coronavirus Disease 2019 (COVID-19)

N Engl J Med. 2020; 382: e38. *JAMA Network Open.* 2020; DOI:10.1001/jamanetworkopen.2020.10478.
N Engl J Med. 2020; 382: e60. *Eur Heart J.* 2020; 41:1858.
N Engl J Med. 2020; DOI: 10.1056/NEJMc2009020.



Coagulopathy (cont.)



THE A-TEAM

Coagulopathy (cont.)

Early Emory Data
D-dimer and CRP trends

128 patients
March 12 – April 16

VTE and/or death

J Thromb Haemost. 2020; DOI: 10.1111/jth.14768.
J Thromb Haemost. 2020; DOI: 10.1111/jth.14817.

Coagulopathy (cont.)

	Variable	OR	95% CI	Sig.
Univariate	Age	1.03	1.01-1.057	0.022
	Ho_CAD	2.57	0.87-7.37	0.074
	Known active cancer (1=yes, 0=no)	7.04	1.2-40.1	0.012
	ICU admission	2.85	1.1-7.3	0.03
	Median_CRP	1.007	1.002-1.013	0.014
	D-dimer>3000 (any)	5.62	1.8-17.6	0.02
Multivariable	D-dimer>3000 (Any)	4.46	1.27-15.66	0.019

Coagulopathy (cont.)

EMORY UNIVERSITY HEALTHCARE SYSTEMS
COVID-19: VTE Guidelines

	LEVEL 1	LEVEL 2	LEVEL 3
DEFINITION	NO VTE D-DIMER < 1000*	NO VTE D-DIMER 1000-1500*, ICU admit	KNOWN OR SUSPECTED VTE
MINIMUM DOSE	1.4 mg/kg qd *or 100mg, once daily	1 mg/kg qd	1 mg/kg qd
ALL PATIENTS		<p>1.1. DO NOT START ENOXAPARIN + PCC/3C4 IF AVAILABLE, START ENOXAPARIN + PCC/3C4 IF NOT AVAILABLE, START ENOXAPARIN + PCC/3C4 IF NOT AVAILABLE, START ENOXAPARIN</p>	<p>HEAVY BLOODING IN PATIENTS WITH VTE OR SUSPECTED VTE DO NOT START ENOXAPARIN + PCC/3C4 IF AVAILABLE, START ENOXAPARIN + PCC/3C4 IF NOT AVAILABLE, START ENOXAPARIN</p>
INITIAL DOSE	When COX-2iB	YES	YES
COX-2 INHIBITORS	ES-90 oral tablet	ES-90 oral tablet	ES-90 (XRAY) 1 mg/kg qd *or 100mg, once daily
ADJUSTING DOSE	ES-90 100mg qd	ES-90 100mg qd	ES-90 100mg qd
RECHARGE HC	ES-90 100mg qd	ES-90 100mg qd	ES-90 100mg qd

*1000 is the upper limit of the normal range for D-dimer in patients with COVID-19.
*1000 is the upper limit of the normal range for D-dimer in patients with COVID-19.

Coagulopathy (cont.)

Still clotting?
Citrate CRRT +/- Level 2 or Level 3 anticoag
Level 2 anticoagulation
Level 3 anticoagulation

Why?

Coagulopathy (cont.)

Other mechanisms/targets:
platelet activation
fibrinolysis shutdown
enhanced cytokine signaling (storm)
antiphospholipid antibodies
endothelial injury

hyperviscosity?

CCM. 2020; DOI: 10.1097/CCM.00000000000004458

COVID-19-associated Hyperviscosity

Viscosity
fibrinogen
globulins
albumin
RBCs
WBCs

Blood. 2018; 132(13): 1379-85.

Hyperviscosity (cont.)

Hyperviscosity Syndrome
 Endothelial damage -> thrombus
 Altered blood flow -> hypoperfusion

Table 2. Syndromes seen with hyperviscosity

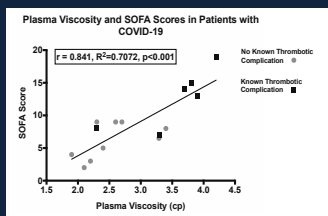
Mucosal hemorrhage	Visual disturbance	Neurologic	Cardiac
Epistaxis bilateral	Bilateral retinal hemorrhage or thrombosis	Somnolence or coma	Heart failure-high output
Gingival	Papilledema	Cerebral hemorrhage	
Gastrointestinal	Blurring	Seizure	
Retinal		Ataxia	

Blood. 2018; 132(13): 1379-85.
 Lancet. 2020; DOI: 10.1016/S0140-6736(20)31209-5

Hyperviscosity (cont.)



Hyperviscosity (cont.)



Lancet. 2020; DOI: 10.1016/S0140-6736(20)31209-5

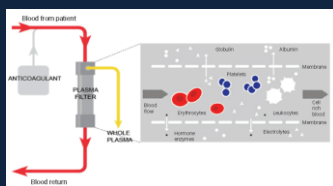
Hyperviscosity (cont.)



Lancet. 2020; DOI: 10.1016/S0140-6736(20)31209-5

Enter PLEX

Therapeutic Plasma Exchange (TPE)



Eur Oncol Haematol. 2018; 14(2): 105-9

PLEX (cont.)

	Patient 1	Patient 2	Patient 3	Patient 4
Age	56	44	75	49
Sex	M	M	M	M
Comorbidities	HTN	Seizure disorder	COVID, HTN	HTN, DM
ICU day	23	14	13	43
SOFA score	17	15	15	14
CRP	246	286	329	312
D-dimer	6,302	4,345	6,271	2,40,000
Fibrinogen	1,188	717	601	*
Plasma viscosity before TPE	4.2	3.9	3.7	3.8
Mechanical ventilation	Yes	Yes	Yes	Yes
Ventilator day when TPE was	19	14	13	39
SOFA	65	232	128	210
PLT	14	12	14	6
TCO2	80%	60%	90%	40%
Vasopressors	Yes	Yes	Yes	Yes
Renal replacement therapy	Yes	Yes	Yes	Yes
Thrombosis	CRRT circuit clots	Vascular access and CRRT circuit clots	Radial artery line thrombosis	CRRT circuit clots, presumed PE
Venous ultrasound	negative	Not done	Formal ultrasound negative	Not done
Anticoagulation	Heparin infusion	Argatroban	Bivalirudin	Bivalirudin

PLEX (cont.)

Patient 1	
Age	56
Sex	M
Comorbidities	HTN
ICU day	23
SOFA score	17
Crp	246
D-dimer	6,972
Fibrinogen	1,108
Plasma viscosity before TPE	4.2
Mechanical ventilation	Yes
Ventilator day when TPE was given	19
P/F ratio	65
PEEP	14
FiO2	90%
Vasopressors	Yes
Renal replacement therapy	Yes
Thrombosis	CRRT circuit clots
Venous ultrasound	POCUS examination negative
Anticoagulation	heparin infusion

Passed away 24 hours after TPE

PLEX (cont.)

Patient 2	
Age	44
Sex	M
Comorbidities	Scleroderma
ICU day	14
SOFA score	15
Crp	286
D-dimer	4,346
Fibrinogen	717
Plasma viscosity before TPE	3.9
Mechanical ventilation	Yes
Ventilator day when TPE was given	14
P/F ratio	232
PEEP	12
FiO2	40%
Vasopressors	Yes
Renal replacement therapy	Yes
Thrombosis	Vascular access and CRRT circuit clots
Venous ultrasound	Not done
Anticoagulation	Argatroban

Gradual improvement Tracheostomy LTAC hospital day 34

PLEX (cont.)

Patient 3	
Age	76
Sex	M
Comorbidities	COVID, HTN
ICU day	13
SOFA score	15
Crp	329
D-dimer	6,771
Fibrinogen	604
Plasma viscosity before TPE	3.7
Mechanical ventilation	Yes
Ventilator day when TPE was given	13
P/F ratio	128
PEEP	14
FiO2	90%
Vasopressors	Yes
Renal replacement therapy	Yes
Thrombosis	Radial artery line thrombosis
Venous ultrasound	Femoral ultrasound negative
Anticoagulation	Bivalirudin

Passed away 48 hrs after TPE

PLEX (cont.)

Patient 4	
Age	69
Sex	M
Comorbidities	HTN, DM
ICU day	41
SOFA score	21.2
Crp	> 60,000
D-dimer	3.8
Fibrinogen	Yes
Plasma viscosity before TPE	39
Mechanical ventilation	210
Ventilator day when TPE was given	6
P/F ratio	40%
PEEP	Yes
FiO2	Yes
Vasopressors	Yes
Renal replacement therapy	CRRT circuit clots, presumed PE
Thrombosis	Not done
Venous ultrasound	Not done
Anticoagulation	Bivalirudin

Gradual improvement Liberated from vent Wards for 2 weeks ICU for 3 days Passed away

PLEX (cont.)

Conclusions

- Impact
- Efficacy threshold?
- Plasma vs albumin
- Convalescent plasma

PLEX (cont.)

Next steps

- RCT
- Lower viscosities
- TPE vs standard care
- Albumin/Plasma/Convalescent Plasma

Trouble with the Pharm

What about drug removal with PLEX?

What attributes increase drug removal by PLEX?

What strategies should be employed to mitigate the effects/extent of drug removal by PLEX?

Drug Removal with PLEX

Factors impacting drug removal in PLEX

Drug properties

PLEX properties

Am J Clin Pathol. 2017; 148: 190-8.
Int Immunoharmacol. 2021; 97: 107707.

Drug Removal with PLEX

Factors impacting drug removal in PLEX

Drug properties

$V_d < 0.2 \text{ L/kg}$

protein binding $> 80\%$

half life $> 2 \text{ hours}$

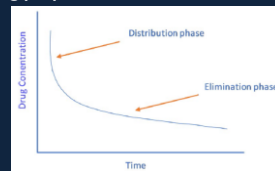
distribution phase

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Int Immunoharmacol. 2021; 97: 107707.

Drug Removal with PLEX

Factors impacting drug removal in PLEX

Drug properties



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Int Immunoharmacol. 2021; 97: 107707.

Drug Removal with PLEX

Factors impacting drug removal in PLEX

PLEX properties

Timing (distribution phase)

Duration

Frequency

Protein replacement

Am J Clin Pathol. 2017; 148: 190-8.
Int Immunoharmacol. 2021; 97: 107707.

Drug Removal with PLEX Strategy

	Yes	No	Unsure
Is the volume of distribution (Vd) $< 0.2 \text{ L/kg}$?			
Is protein binding (fb) $> 80\%$?			
Is the half-life (t1/2) $> 2\text{h}$?			
Will TPE start during the distribution phase of the drug OR will the drug be dosed immediately prior to or during TPE?			
Does the patient have dysfunction of a drug elimination organ?			
Are transient changes in concentration of clinical relevance?			
Is there any new evidence that suggests removal of the drug by TPE?			
Mostly "Yes"	It is likely that some of this drug will be removed with TPE; administer dose after TPE when available; dose supplementation after TPE may be required; use TDM when possible.		
Mostly "No"	It is unlikely that this drug will be removed using TPE; no drug adjustment is required.		
Unsure	Use TDM when possible; closely monitor patient for changes in clinical status that could suggest sub-therapeutic drug levels.		

Am J Clin Pathol. 2017; 148: 190-8.
Int Immunoharmacol. 2021; 97: 107707.

Drug Removal with PLEX

Important drugs known/likely to be removed by PLEX

Anticoagulants

apixaban, rivaroxaban
enoxaparin, dalteparin
heparin

Antiepileptics

phenytoin, valproic acid, phenobarbital

COVID

tocilizumab

Am J Clin Pathol. 2017; 148: 199-8.
Int Immunohistochemol. 2021; 97: 107707

Summary

COVID-19 Severe coagulopathy
Refractory → Hyperviscosity → PLEX?

PLEX and drugs

Vd < 0.2 L/kg
Protein binding > 80%
half life > 2 hours

When in doubt, dose after PLEX and use TDM

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