PLEX Out:

COVID-19-associated coagulopathy, hyperviscosity, and the use of therapeutic plasma exchange

Derek M. Polly, PharmD, BCCCP
Clinical Pharmacy Specialist
Medical ICU - EUHM

EMORY HEALTHCARE

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.

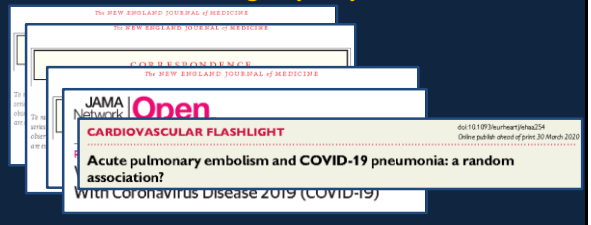
Objectives

Describe COVID-19 associated hyperviscosity

Recognize factors that influence drug removal during plasma exchange

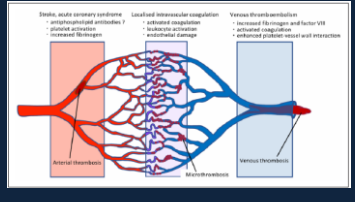
Identify drugs which are likely to be removed by plasma exchange

COVID-19-associated Coagulopathy



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.)



CCM. 2020; DOI: 10.1097/CCM.0000000000004458.

Coagulopathy (cont.)

THE A-TEAM

Coagulopathy (cont.)

Early Emory Data
- D-dimer and CRP trends

- 128 patients
- March 12 – April 16

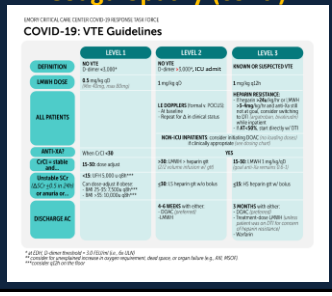
- VTE and/or death

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.)



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.0000000000004458

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

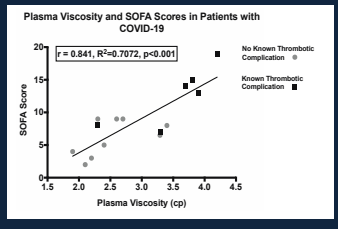
Table 2. Syndromes seen with hyperviscosity

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

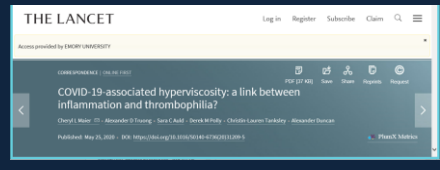
Hyperviscosity (cont.)

Hyperviscosity (cont.)



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

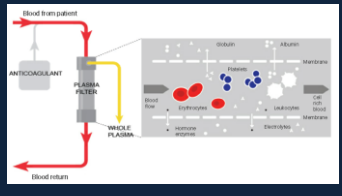
Hyperviscosity (cont.)



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	COPD, HTN	HTN, DM
ICU day	23	14	13	43
SOFA score	17	15	15	14
CRP	246	286	329	312
D-dimer	6,972	4,346	6,771	> 60,000
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 given	19	14	13	39
P/F ratio	65	232	128	210
PEEP	14	12	14	6
FiO2	80%	40%	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	POCUS examination negative	Not done	Formal ultrasound negative	Not done
Anticoagulation	Heparin infusion	Argatroban	Bivalirudin	Bivalirudin

PLEX (cont.)

	Patient1
Age	56
Sex	M
Comorbidities	HTN
ICU day	23
SOFA score	17
CRP	246
D-dimer	6,972
Fibrinogen	1,188
Plasma viscosity before TPE	4.2
Mechanical ventilation	Yes
Ventilator day when TPE was given	19
P/F ratio	65
PEEP	14
FIO2	80%
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.)

	Patient2
Age	44
Sex	M
Comorbidities	Seizure disorder
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	75
Sex	M
Comorbidities	COPD, HTN
ICU day	13
SOFA score	15
CRP	329
D-dimer	6,771
Fibrinogen	601
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	Formal ultrasound negative
Anticoagulation	Bivalirudin

Passed away 48 hrs after TPE

PLEX (cont.)

	Patient 4
Age	49
Sex	M
Comorbidities	HTN, DM
ICU day	43
SOFA score	14
CRP	312
D-dimer	> 60,000
Fibrinogen	*
Plasma viscosity before TPE	3.8
Mechanical ventilation	Yes
Ventilator day when TPE was given	39
P/F ratio	210
PEEP	6
FIO2	40%
Vasopressors	Yes
Renal replacement therapy	Yes
Thrombosis	CRRT circuit clots, presumed PE
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 Immunopharmacol. 2021; 97: 107707.

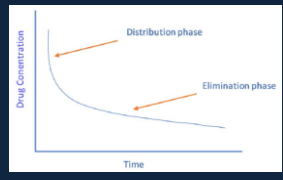
Drug Removal with PLEX

Factors impacting drug removal in PLEX
- Drug properties
  - Vd < 0.2 L/kg
  - protein binding > 80%
  - half life > 2 hours
  - distribution phase

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

Drug Removal with PLEX

Factors impacting drug removal in PLEX
- Drug properties



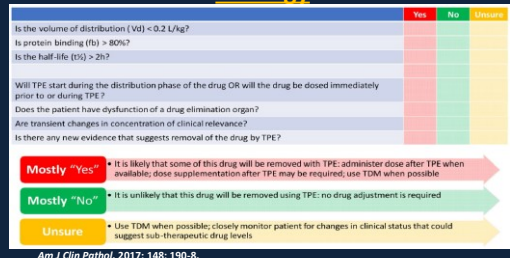
Am J Clin Pathol. 2017; 148: 190-8.
Int Immunopharmacol. 2021; 97: 107707.

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 Immunopharmacol. 2021; 97: 107707.

Drug Removal with PLEX Strategy



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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

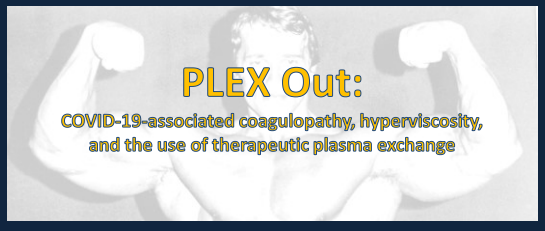
Am J Clin Pathol. 2017; 148: 190-8.
Int Immunopharmacol. 2021; 97: 107707.

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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