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Clinical Meeting & Exhibition

Clinical Considerations: Pharmacotherapy in Extracorporeal Therapies

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Objectives

- Evaluate recent literature on the management of pain, agitation, delirium, antimicrobial, and anticoagulation therapy in patients receiving extracorporeal therapies (ECMO).
- Apply ways to provide optimal pain, agitation, delirium, antimicrobial, and anticoagulation therapy to patients receiving ECMO therapy.
- Develop an optimal pharmacotherapy plan for patients receiving plasmapheresis in the ICU.

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Clinical Considerations: Anticoagulation in Extracorporeal Membrane Oxygenation

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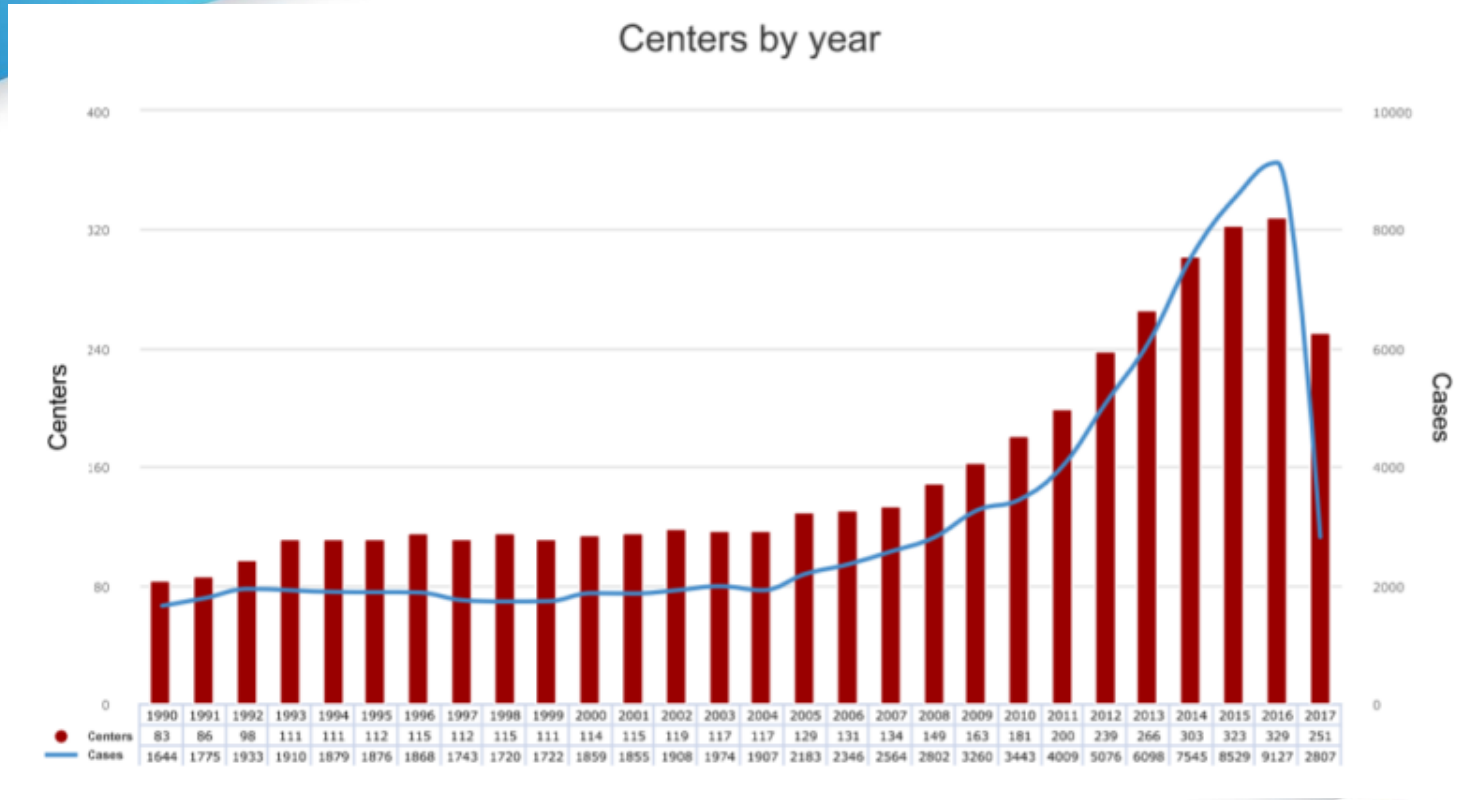
Objectives

- Review general principles and indications for extracorporeal membrane oxygenation (ECMO) therapy.
- Evaluate recent literature on the management of anticoagulation therapy in patients receiving ECMO.
- Apply ways to provide optimal anticoagulation therapy to patients receiving ECMO.

Extracorporeal Membrane Oxygenation

- Extracorporeal Membrane Oxygenation: a high-flow technique with a drainage and return cannula allowing for gas exchange outside the body with a large surface area oxygenator allowing the lungs and/or heart to rest

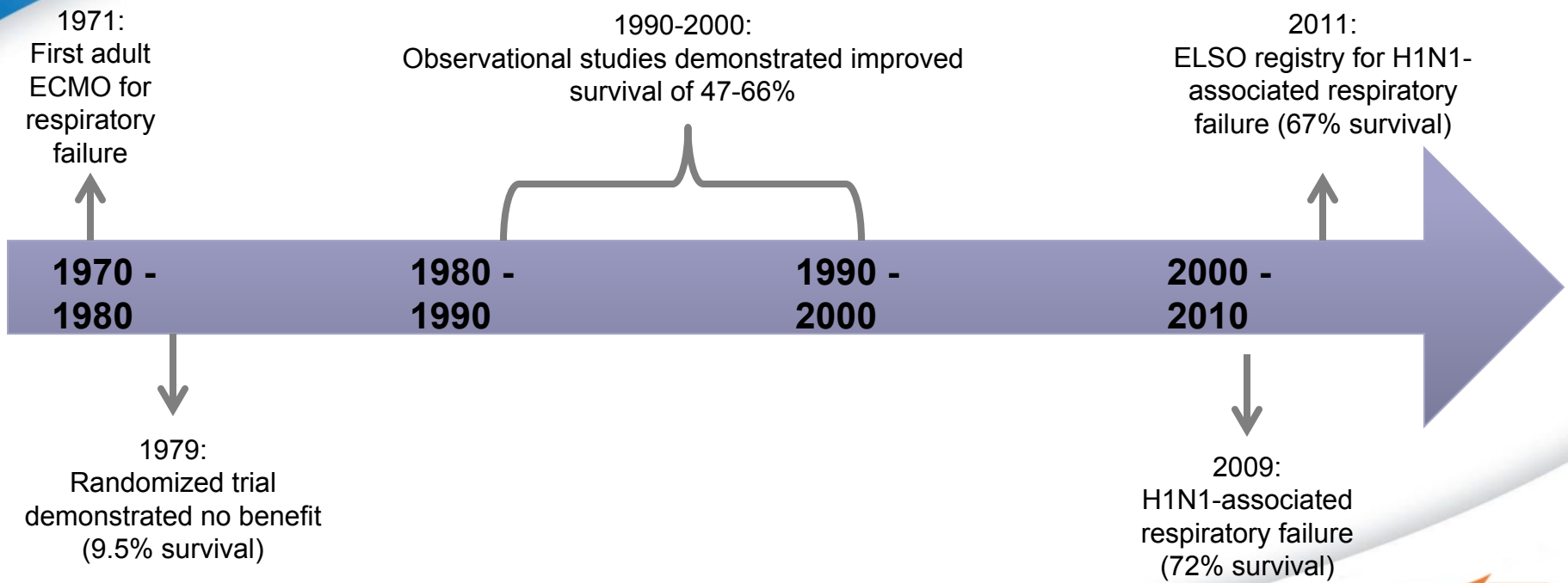
Ichibo et al. *Ann Thorac Surg*. 2000; 69: 298-99
Lindstrom et al. *MJA*. 2009; 191:178-82



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Centers	83	86	98	111	111	112	115	112	115	111	114	115	119	117	117	129	131	134	149	163	181	200	239	266	303	323	329	251
Cases	1644	1775	1933	1910	1879	1876	1868	1743	1720	1722	1859	1855	1908	1974	1907	2183	2346	2564	2802	3260	3443	4009	5076	6098	7545	8529	9127	2807

https://www.elso.org/Registry/Statistics.aspx © 2017

Improved Survival Over Time



ECMO Indication by Modality

- Respiratory Support
  - VV ECMO
  - VA ECMO*

- Hypoxic Respiratory Failure
- Hypercapnic Respiratory Failure
- Bridge to Transplant

- Hemodynamic Support
  - VA ECMO

- Cardiac Arrest
- Cardiogenic Shock
- Acute RV Failure
- Failure to wean CPB after surgery
- Bridge to transplant

Proper Patient Selection

Indications

- Is the underlying cause reversible/correctable?
- Do logistics allow ECMO to be provided?
- Does the patient have a “reasonable” chance for survival?
- Does the patient have any contraindications for ECMO?

Contraindications

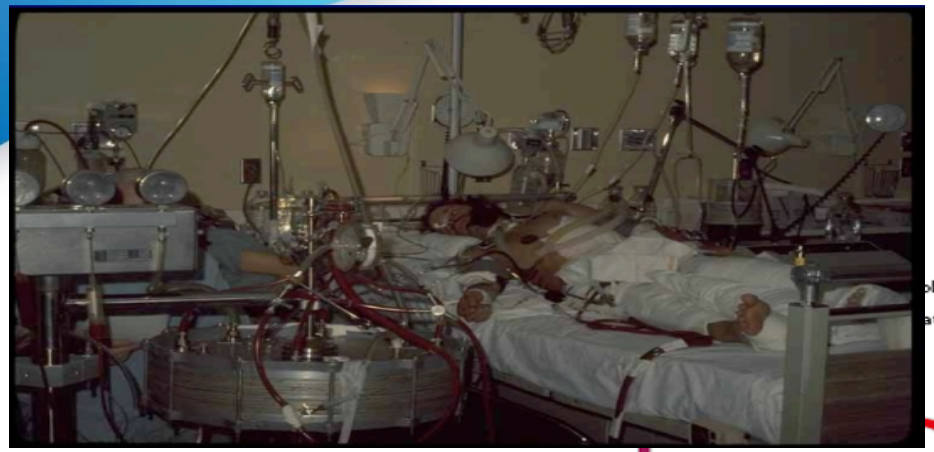
- Cannot be anticoagulated
- Metastatic malignancy
- Non-curable chronic extrapulmonary infection*
  - Hepatitis B, Hepatitis C, HIV
- Untreatable advanced dysfunction of another organ
- Poor nutritional status/rehabilitation potential
- Significant psychosocial problems

ECMO therapy indications and treatment strategies vary by center

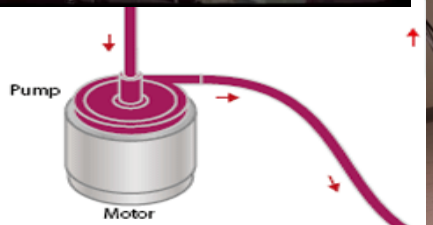
Bartlett et al. *Miverva Anestesiol.* 2010;76:534-40

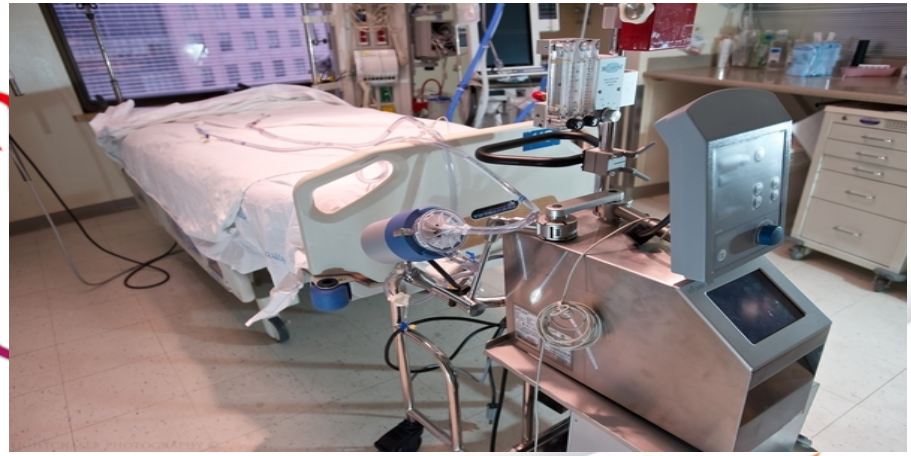
ECMO is not a way of life!!!

http://neuroskeptic.blogspot.com/2012/06/bipolar-disorder-bridge-to-nowhere.html (C) 2012



Circuit





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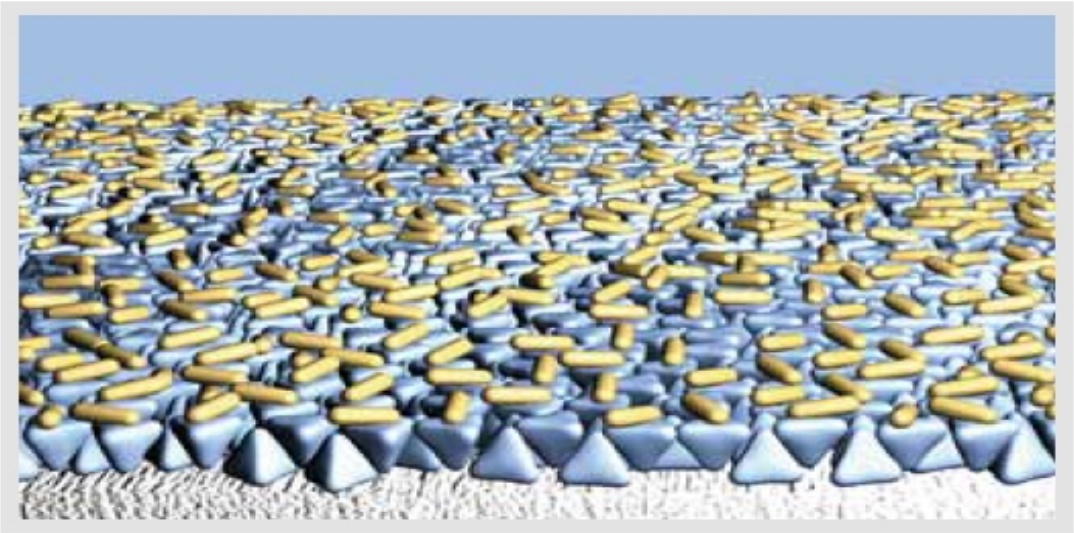
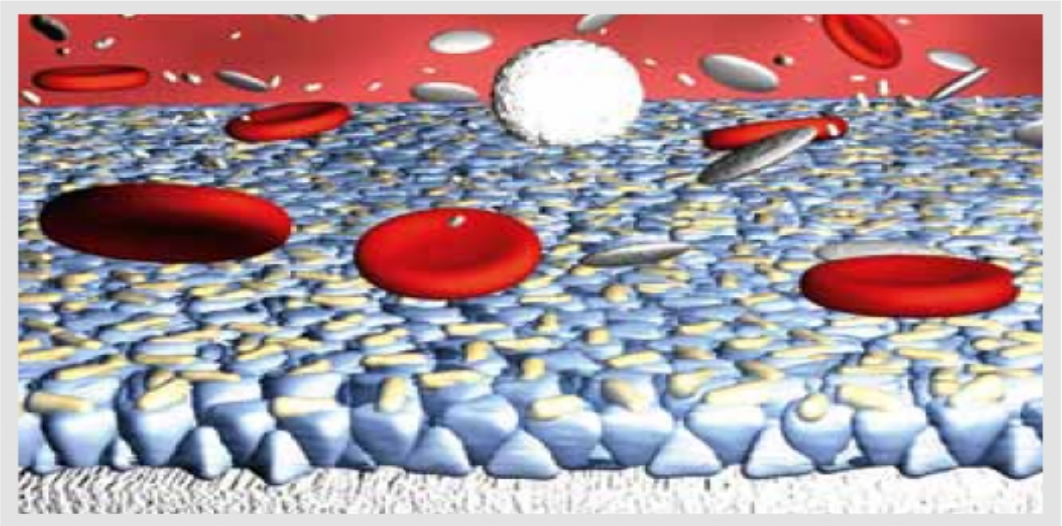
Bartlett et al. *Miverva Anestesiol.* 2010;76:534-40
Rubino et al. *Int J Artif Organs.* 2014; 37(10): 741 - 747

Technological Advancements



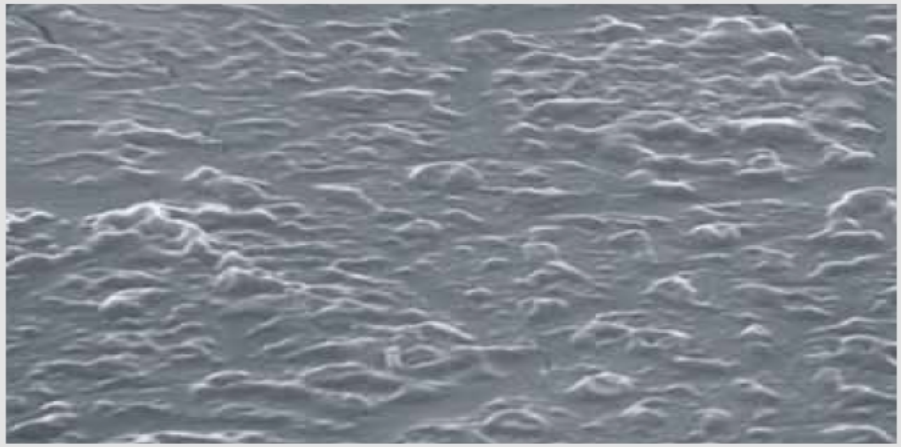
- PVC tubing coated with covalently bonded heparin and albumin
- Creates a hydrophilic environment to prevent cell and protein absorption

Technological Advancements

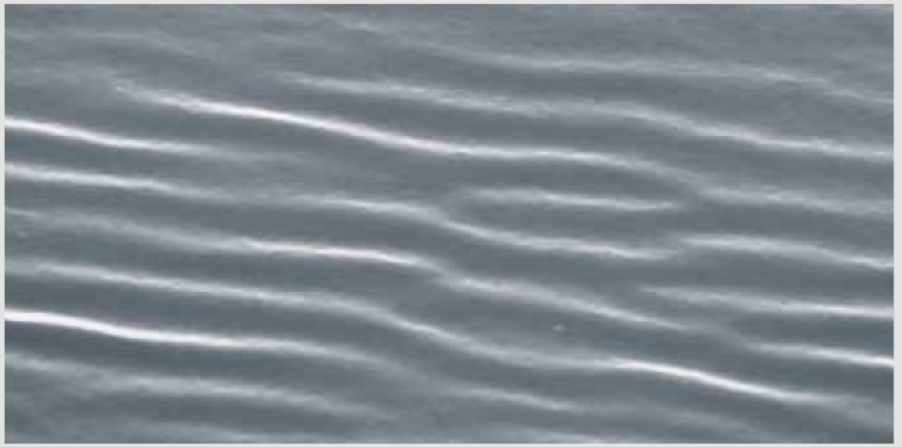


Absorption of hydrophilic fluids causes swelling of the albumin/heparin coating creating a homogenous surface

Technological Advancements

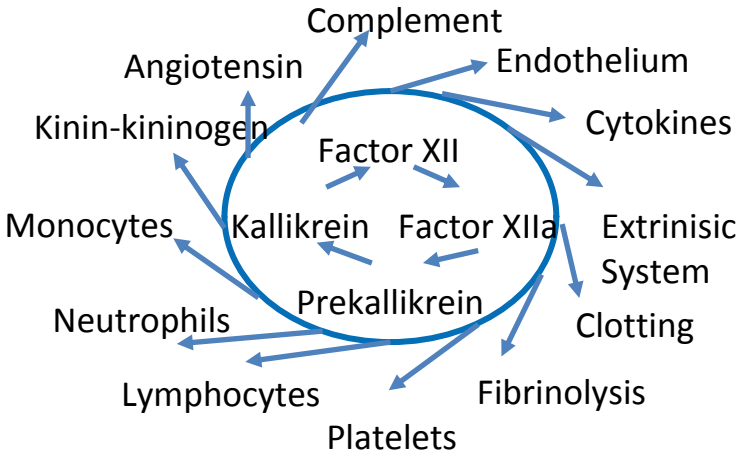


Uncoated inner surface of PVC tubing
(5000 x magnified)



Coated inner surface of PVC tubing
(5000 x magnified)

ECMO Associated Coagulopathy



Pathophysiology of ECMO Related Hemostatic Abnormalities

Activation	Consumption

• Contact activation
  • XIIa, Kallekrein
• Tissue Factor activation
  • Tissue injury
  • Monocyte-related
  • Pericardial blood
• Activation of fibrinolysis
  • Increased tPA
  • Intrinsic activation
	• Thrombin-mediated
	• Plasmin-mediated
	• Inflammation-mediated
	  • Elastase
	  • Complement
	• Mechanical

Oliver WC. *Semin Cardiothorac Vasc Anesth.* 2009;13:154-75

ECMO Associated Coagulopathy

- If left unchecked, this state of procoagulation and fibrinolysis
  - Increases risk for thromboembolic event
  - Will eventually lead to excessive bleeding

- Need for anticoagulation, close monitoring, and replacement of clotting factors if needed

Oliver WC. *Semin Cardiothorac Vasc Anesth.* 2009;13:154-75

Anticoagulation in ECMO

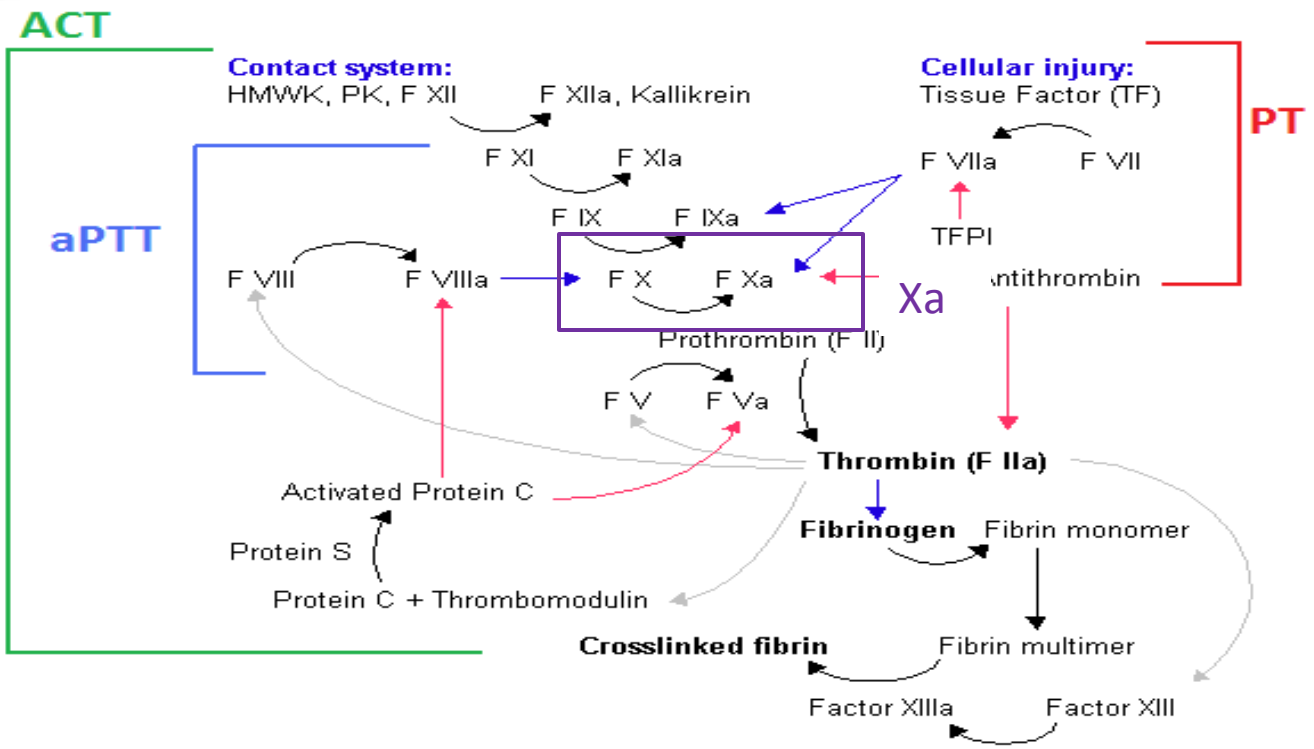
Variable	Unfractionated Heparin	Bivalirudin	Argatroban
Administration	Parenteral	Parenteral	Parenteral
Typical Dosing	Initial dose range: 50-200 units/kg with maintenance infusion of 10 to 30 units/kg	Initiation at 0.08 to 0.2 mg/kg/h. Maintenance change of rate between 0 and 0.03 mg/kg/h	Initiation at 0.25 mcg/kg/h to 2 mcg/kg/min. Maintenance change of rate betwenn 0 and 0.6 mcg/kg/h
Monitoring	Goal Activated Clotting Time (ACT) range: 180 – 220 seconds Goal aPTT range: 60-90 seconds Goal Anti-Xa range: 0.3 – 0.8 u/ml	Goal Activated Clotting Time (ACT) range: 180 – 220 seconds Goal aPTT range: 60-90 seconds	
Half life	1 to 2 h	25 min to 3.5 h	39 to 51 min

Esper SA. *Anesth Analg.* 2014;118:731-43

Bivalirudin as Alternative to UFH

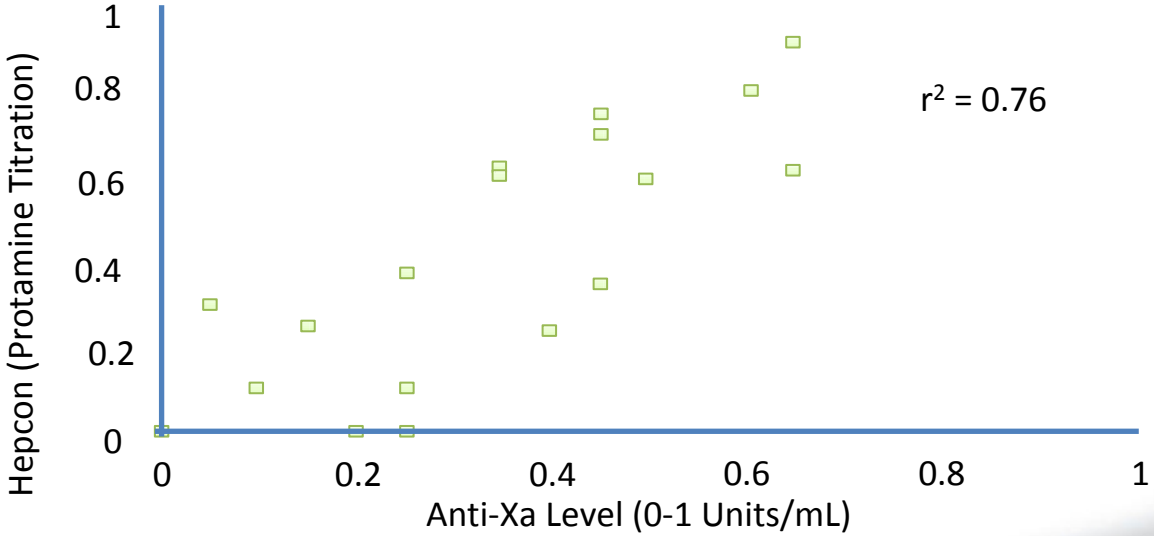
First Author, Year	Study Design	ECMO Patients Included	Outcomes
Koster, 2007	Case report	40 yo postcardiotomy on VA-ECMO w/ HIT	Successful transition to RVAD
Pappalardo, 2009	Case report	71 yo postcardiotomy on VA-ECMO w/ HIT	HIT persisted duration of ECMO (heparin-coated tubing), ECMO weaned and pt DC'd home
Pollak, 2011	Case report	5 day old w/ left diaphragmatic hernia on VA-ECMO w/ HIT	Hernia repaired on ECMO. Pt died after 21 days on ECMO (multi-organ dysfunction)
Rannucci, 2011	Case-control retrospective study	21 patients (11 adult, 10 pedi) postcardiotomy VA-ECMO. 8 patients on UFH, 13 on bivalirudin	Bivalirudin: longer ACTs, PTTs, R time Heparin: higher blood loss, more platelet, FFP, antithrombin infusions
Pieri, 2013	Case-control retrospective study	20 adult patients (10 VV-ECMO). 10 patients on Bival:UFH split between VA:VV	Heparin group significantly more episodes of aPTT variation (>20%)
Nagle, 2013	Case series	12 pediatrics, 3 on VV and 9 on VA-ECMO all transitioned to bival	No ICH, 3 pts required recombinant FVII activated. Cost of bival $13.7/kg/d compared to $0.5/kg/d with heparin
Jyoti, 2014	Case report	54 yr old w/ H1N1 on VV-ECMO w/ antithrombin deficiency, heparin resistance, thrombosis	Platelet count stable, no bleeding or thrombotic complications. ECMO weaned after 23 days
Preston, 2015	Case report	8 yr old on VV-ECMO as bridge to lung transplant w/ HIT	Less fluctuation of aPTT

Sanfilippo F. *J Int Care Med.* 2017;32:312-19



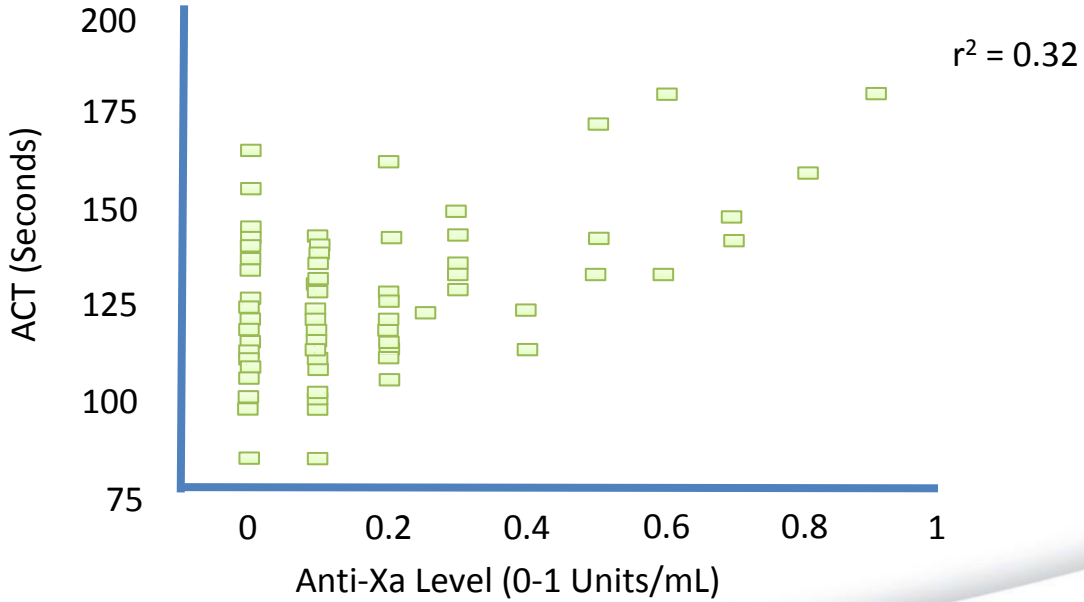
http://usmlewiki.org/index.php?title=Image:Coagulation_cascade.png © 2004

Whole Blood Heparin versus Anti-Xa Correlation



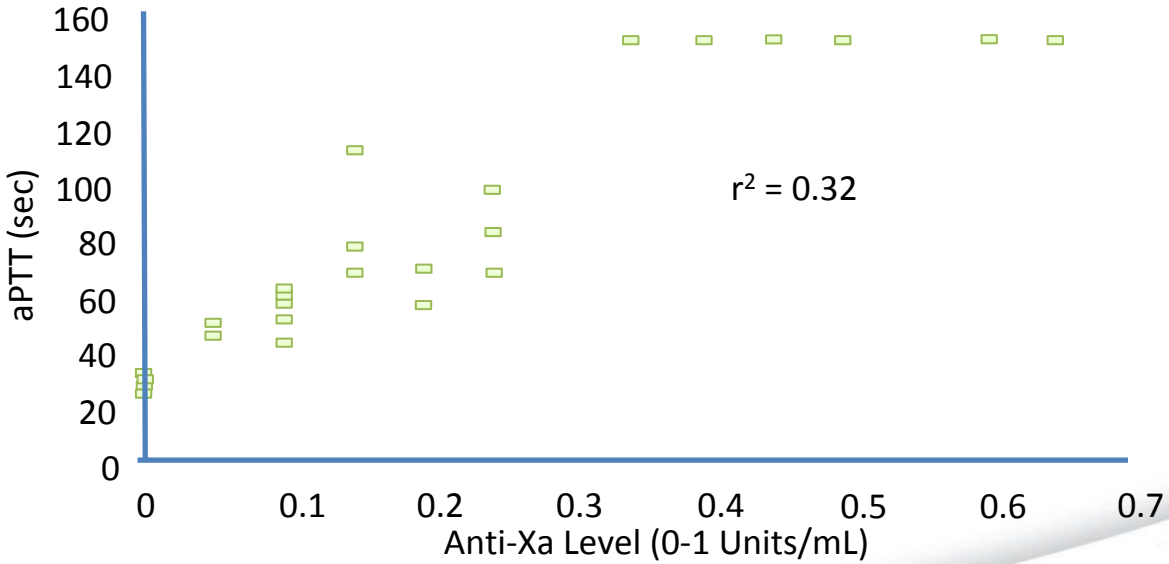
Murray DJ. *J Cardiothor Vasc Anesth*. 1997;11(1):24-28

ACT versus Anti-Xa Correlation



Murray DJ. *J Cardiothor Vasc Anesth*. 1997;11(1):24-28

aPTT versus Anti-Xa Correlation



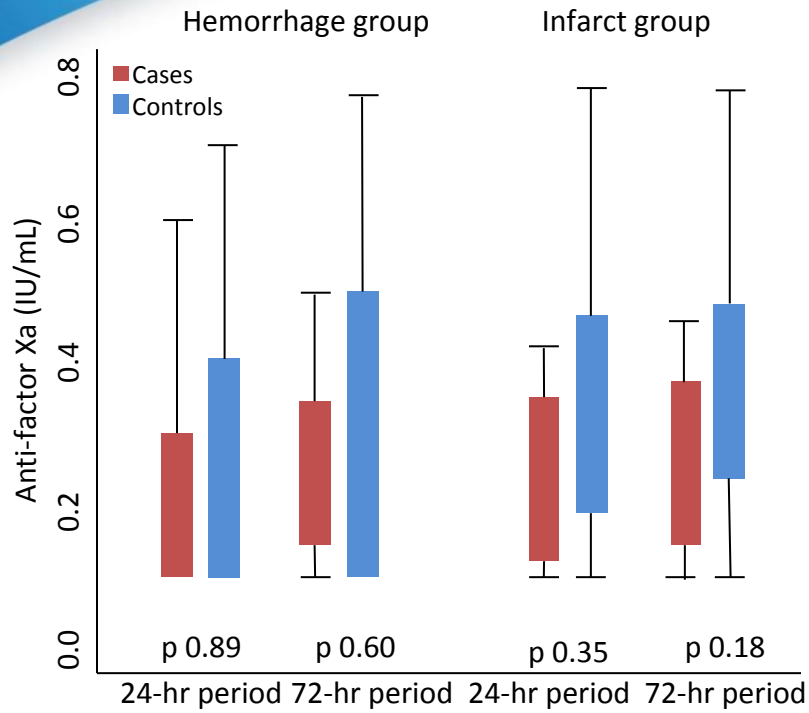
Murray DJ. *J Cardiothor Vasc Anesth*. 1997;11(1):24-28

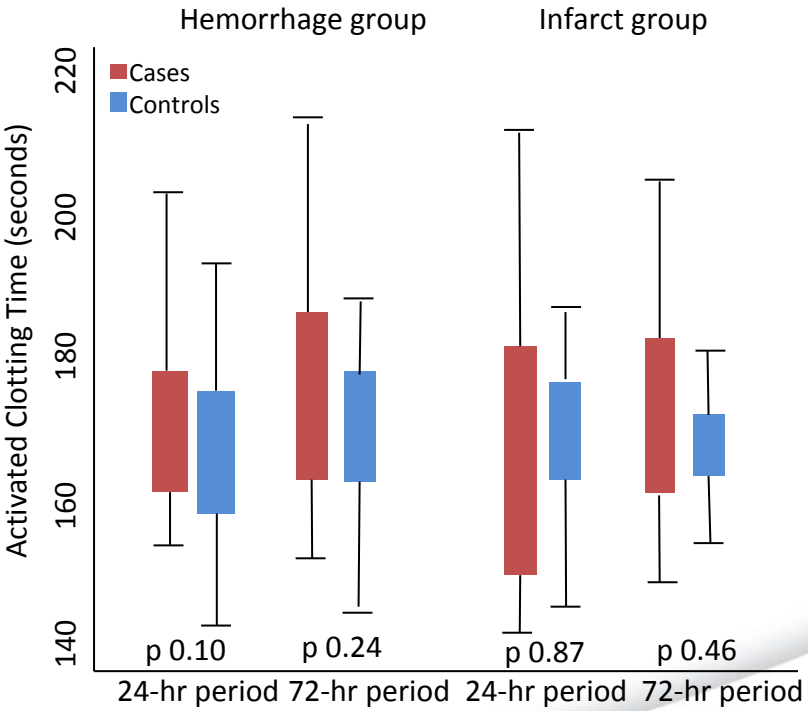
Coagulation Profile Not Predictor of Acute Cerebrovascular Events

- Retrospective matched case-control study
  - 241 consecutive pediatric patients screened for inclusion
    - 22 patients (9.2%) had intracranial hemorrhage
    - 19 patients (7.9%) had an infarct
  - 36 cases included (19 ICH, 17 infarct) and matched 1:1
    - No significant difference expect mortality higher in cases (75 vs. 22%, $p<0.01$)
  - Laboratory data compared during 24 and 72 hours prior to event
    - Heparin anticoagulation monitoring
    - Blood product administration

Anton-Martin P. *ASAIO Journal*. 2017;[Epub ahead of print]

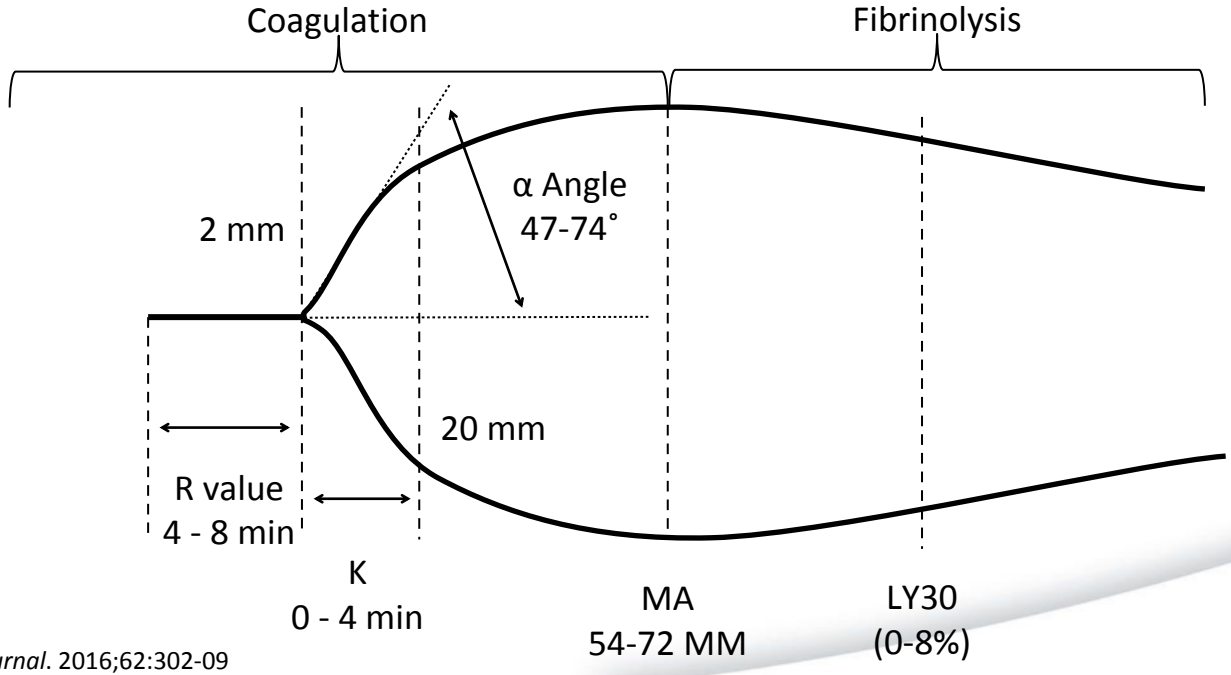
Median Values for Coagulation Markers





Anton-Martin P. *ASAIO Journal*. 2017;[Epub ahead of print]

Thromboelastography Monitoring



Panigada M. *ASAIO Journal*. 2016;62:302-09

TEG “Flat-Line” in ECMO

- 32 Adult patients on ECMO for respiratory failure
  - Heparin with aPTT goal 1.5 – 2x normal
  - 46% paired TEG and coagulation assays were “flat-line”
    - Non “Flat-line” patients: mean heparin dose 15 units/kg/hr
    - “Flat-line” patients: mean heparin dose 17 units/kg/hr

R value	K	MA	LY30
4 - 8 min	0 - 4 min	54-72 MM	(0-8%)

Panigada M. *ASAIO Journal*. 2016;62:302-09

Which of the following represents the most effective coagulation monitoring assay for patients receiving heparin on ECMO?

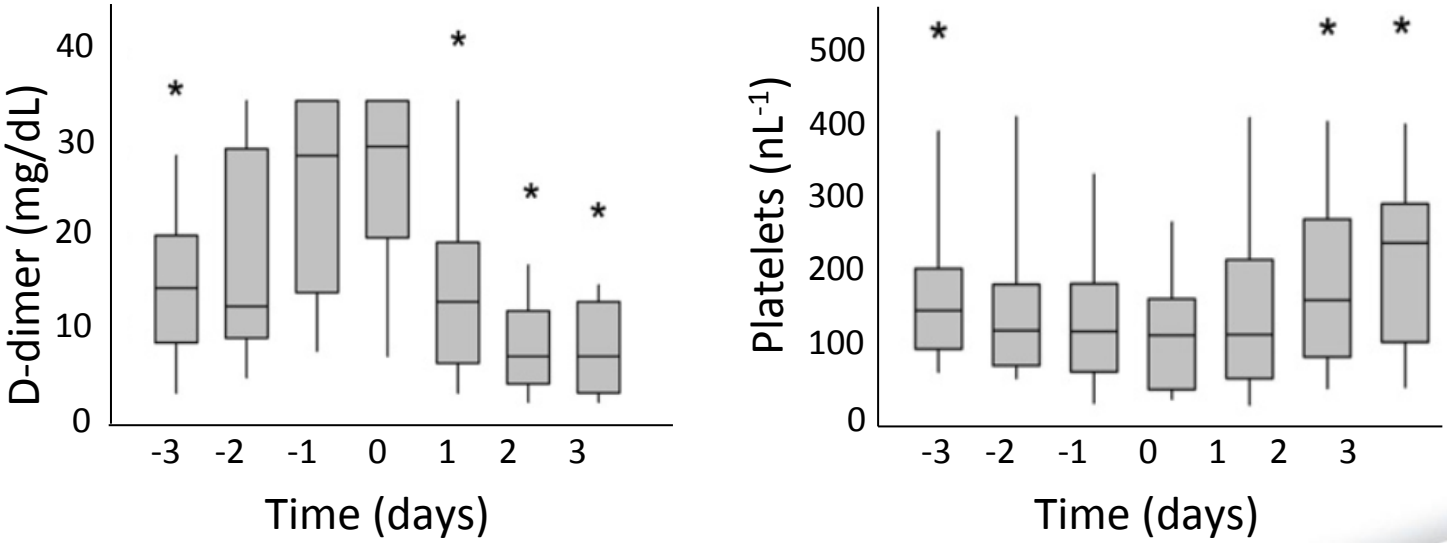
A. aPTT
B. ACT
C. Thromboelastography
D. A combination of available assays should be evaluated

D-Dimer Early Marker for Oxygenator Exchange

- Retrospective study of 24 adult patients with ARDS requiring long-term VV ECMO and ≥ 1 membrane oxygenator exchange
  - Median ECMO support duration 20 (15-29) days
  - 34 membrane oxygenator exchanged
    - 16 for throbmus formation
    - 11 for worsening gas exchange
    - 6 for activation of coagulation with diffuse bleeding
    - 1 for increased blood flow resistance
  - D-dimers evaluated daily and recorded 3 days prior to and after exchange

Lubnow. *J Crit Care*. 2014;473:e1-5

D-dimer and Platelet Trend prior to and after Membrane Oxygenator Exchange



*P < 0.05

Lubnow. *J Crit Care*. 2014;473:e1-5

Treatment of Ongoing Bleeding

- Reduction in anticoagulation
  - Continue intravenous infusion vs. subcutaneous injection vs. hold
- Laboratory Monitoring
  - D-Dimer, Fibrinogen, Coagulation Assays
- Administration of Product
  - Blood products
  - Clotting factors (recombinant FVII activated, FEIBA)
  - Antifibrinolytic agents

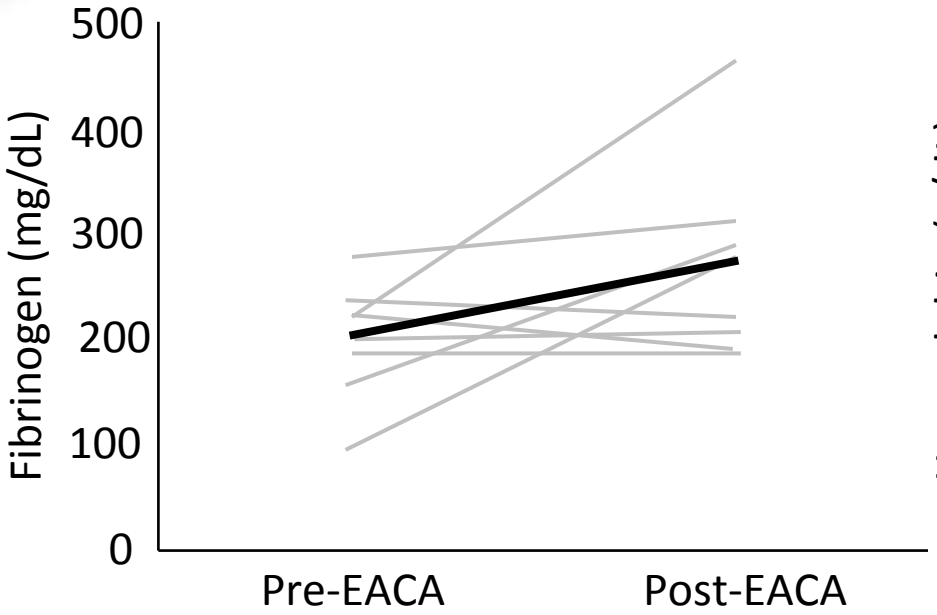
Buckley LF. *Heart Lung*. 2016;45:232-36

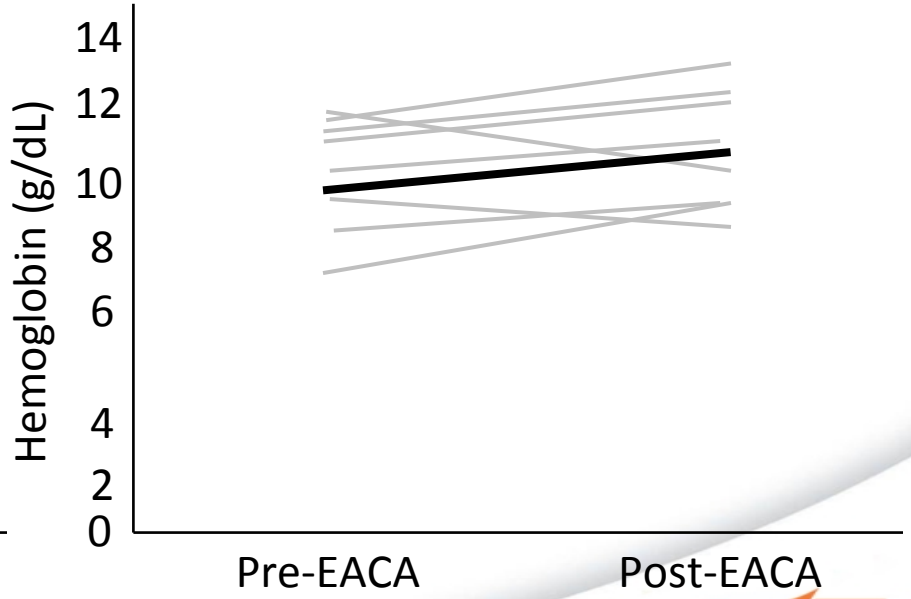
Antifibrinolytic Therapy for the Management of ECMO-related bleeding

- Case series of four adult patients with ECMO-associated bleeding
  - 3 patients on VV-ECMO
  - All patients received standard transfusion therapy prior to aminocaproic acid
    - Doses of 4-5g followed by a 1-1.25 g/h infusion were used

Buckley LF. *Heart Lung*. 2016;45:232-36

Effects of Anti-Fibrinolytics on Bleeding





EACA = ε-aminocaproic acid

Buckley LF. *Heart Lung*. 2016;45:232-36

LF, a 44 yom, is currently on day 6 of VV-ECMO therapy for H1N1 influenza pneumonia. He is anticoagulated with IV heparin and aPTTs, ACTs and Anti-Xa assays have been within therapeutic range. His platelet count and fibrinogen are stable but D-dimer was elevated with morning labs. Based on these labs, what is LF potentially at risk for?

A. Life-threatening bleeding
B. Acute thrombosis
C. Heparin-induced thrombocytopenia
D. Worsening of his underlying condition

Key Takeaways

- Key Takeaway #1
  - Extracorporeal membrane oxygenation (ECMO) therapy is a last-line therapy for patients with pulmonary or cardiopulmonary failure and requires closely monitored anticoagulation therapy for the prevention of bleeding and thrombosis

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Optimizing Drug Dosing During Extracorporeal Membrane Oxygenation

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Department of Pharmacy
NewYork-Presbyterian Hospital
Columbia University Irving Medical Center

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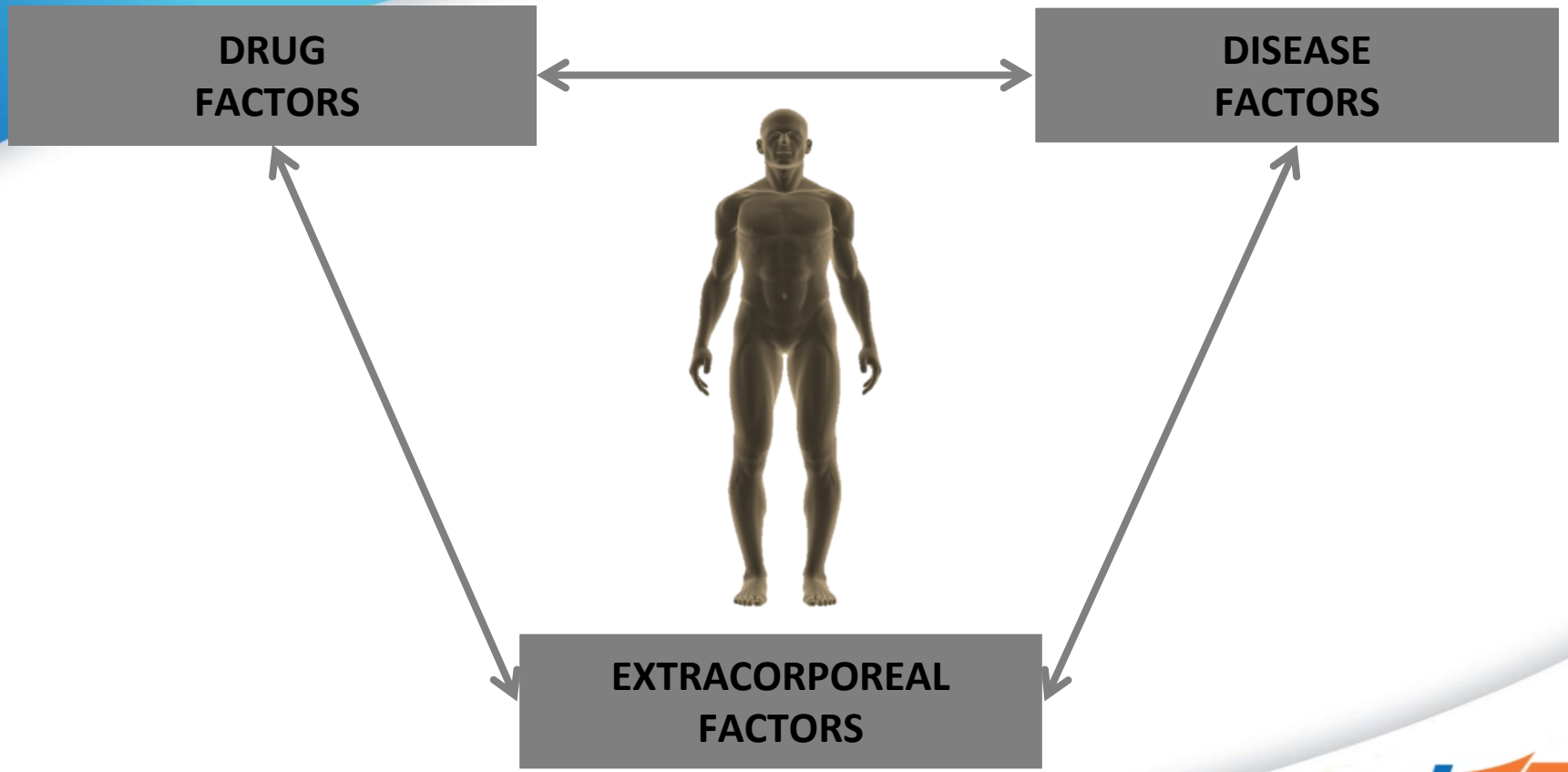
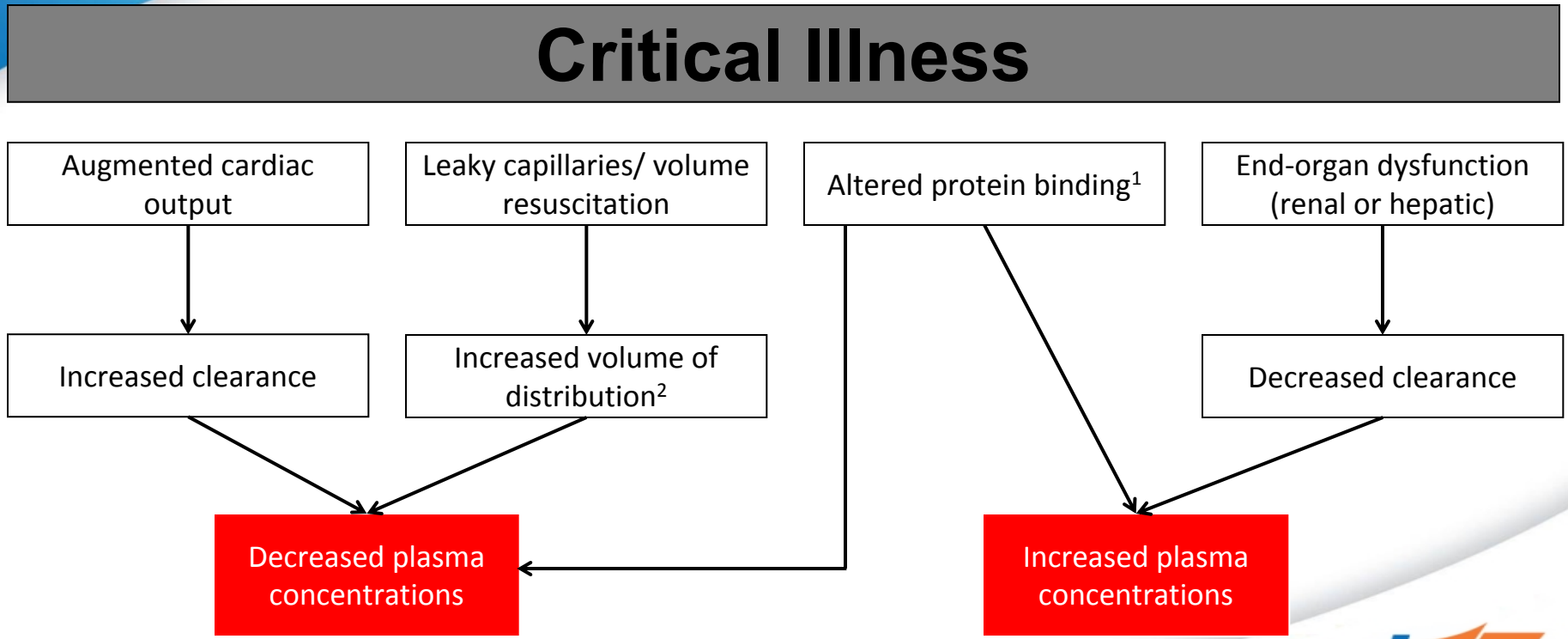
Objectives

- Discuss the role of extracorporeal membrane oxygenation (ECMO) in adult critically ill patients and the role of supportive pharmacotherapy.
- Evaluate recent literature on the management of pain, agitation, and delirium, antimicrobial, and anticoagulation therapy in patients receiving ECMO.
- Discuss ways to provide optimal pain, agitation, and delirium, antimicrobial, and anticoagulation therapy to patients receiving ECMO.


DRUG FACTORS
DISEASE FACTORS
EXTRACORPOREAL FACTORS

Pharmacokinetic Alterations

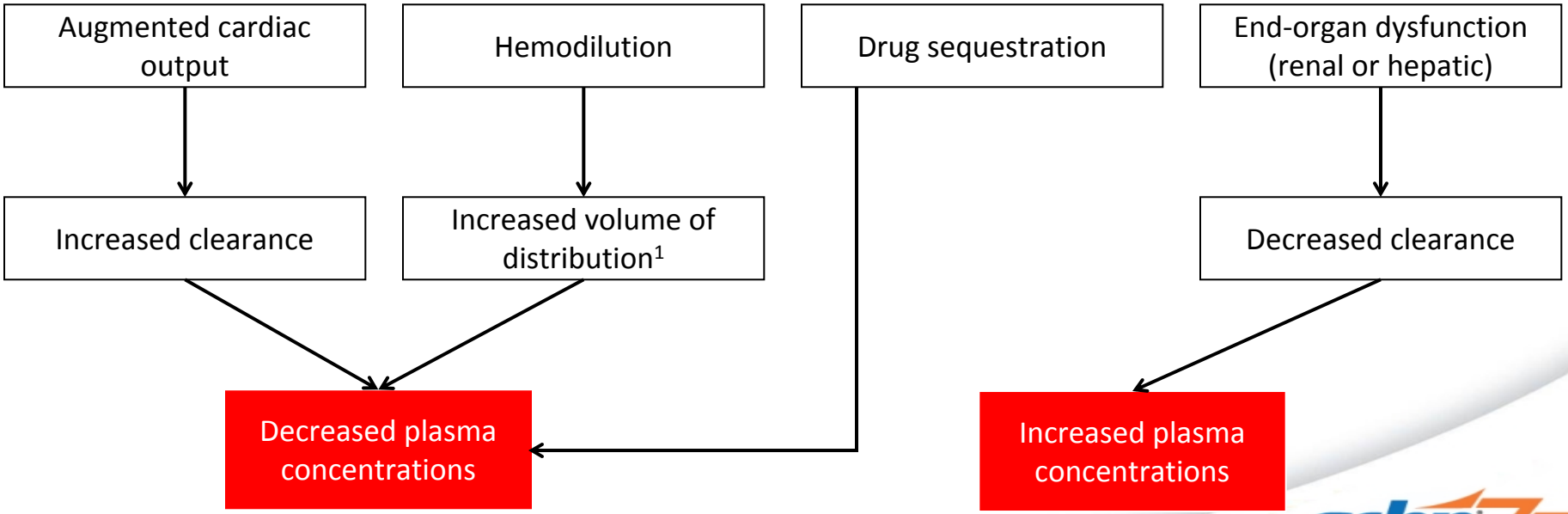


[1]Increased α_1-acid glycoprotein and decreased albumin concentrations;[2]Mostly affecting hydrophilic drugs

Dzierba AL, et al. *Crit Care* 2017;21:66

Pharmacokinetic Alterations

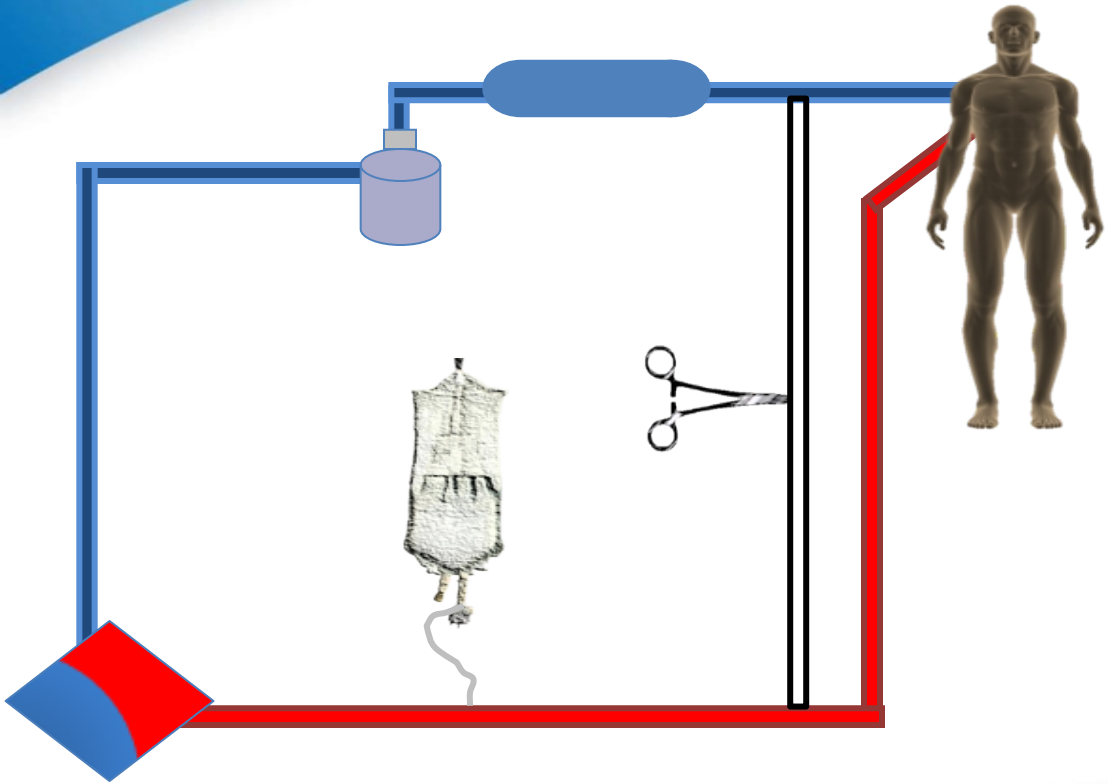
Extracorporeal Membrane Oxygenation



[1]Mostly affecting hydrophilic drugs

Dzierba AL, et al. *Crit Care* 2017;21:66

Extracorporeal Factors



- Polyvinyl chloride tubing
- Membrane oxygenator
- Better Bladder®
- Bridge line
- Priming solution

<u>Other factors:</u>

- Administration of the drug
- Recirculation
- Age of the circuit

Drug Factors

Lipophilicity

Ionization

Molecular weight

Protein binding

Drug	Protein binding	Octanol/ water partition (log p)
Propofol	95-99%	4.0
Fentanyl	79-87%	3.9
Lorazepam	85-91%	3.5
Midazolam	97%	3.3
Dexmedetomidine	94%	3.3
Hydromorphone	8-19%	0.9
Morphine	20-35%	0.8

Lipophilicity

Wishart DS, et al. *Nucleic Acids Res* 2008;36:D901-6

Challenges in Drug Dosing

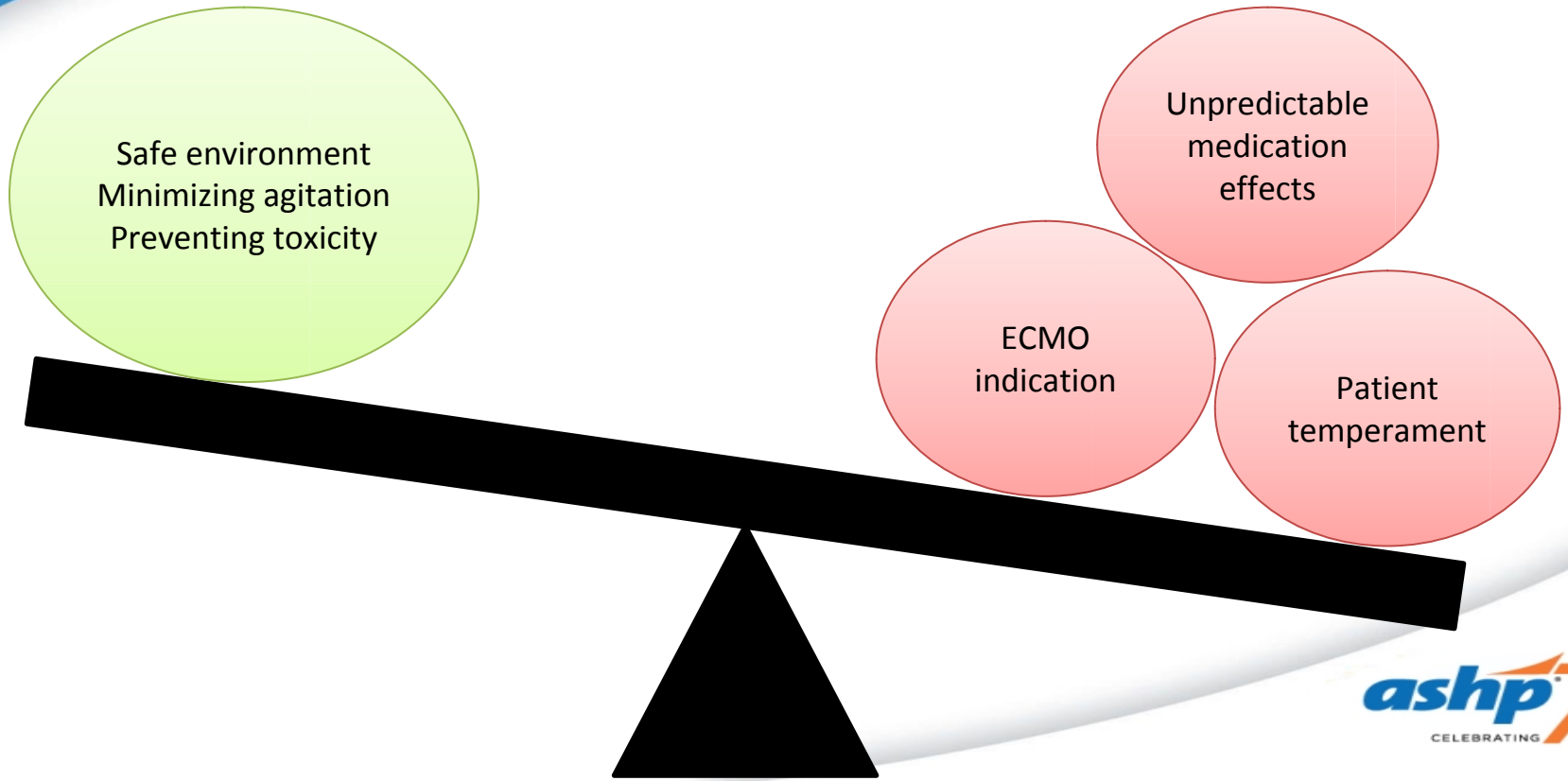
Pharmacokinetic changes with ECMO

Drugs that can be titrated to endpoints (e.g., sedation)

Drugs that CANNOT be titrated to endpoints (e.g., antimicrobials)

PAIN, AGITATION, and DELIRIUM

Analgesia and Sedation During ECMO



Increased Sedation Requirements

Retrospective analysis of 29 patients receiving VV/VA ECMO

Local protocol = deep sedation at ECMO initiation → lightened when possible

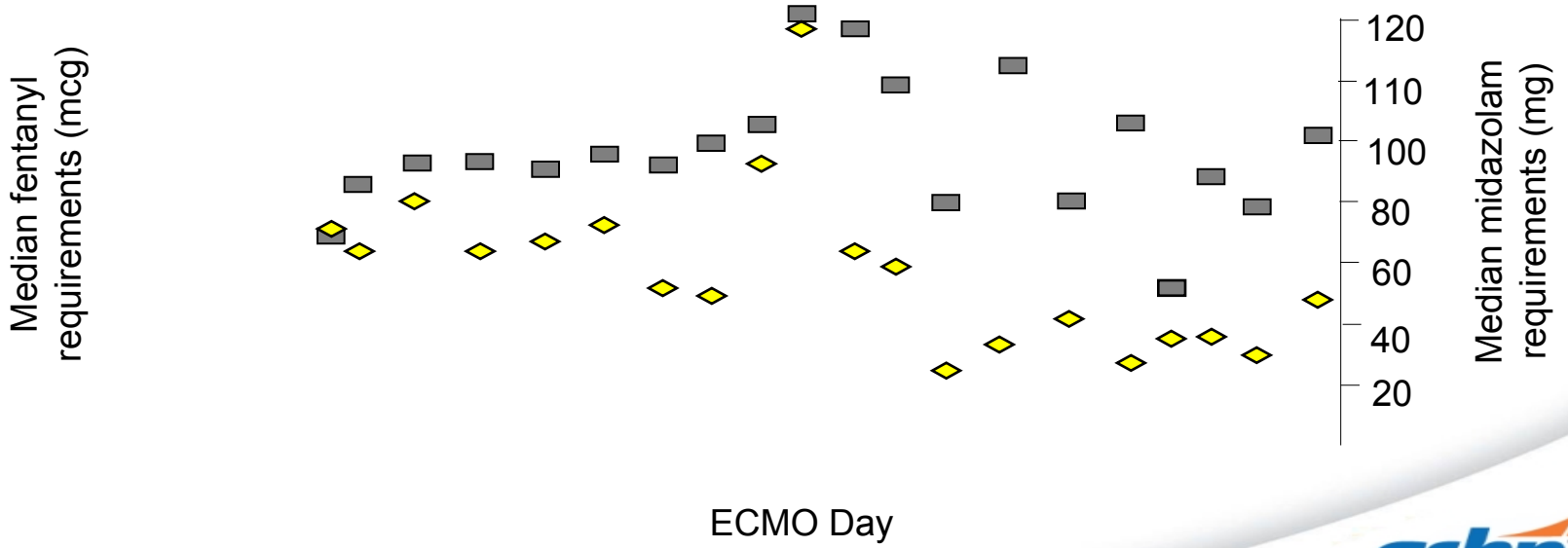
- Daily dose of midazolam increased on average by 18 mg (95%CI 8-29); p=0.001
- Daily dose of morphine increased on average by 29 mg (95%CI 4-53); p=0.02
- No difference in daily dose of fentanyl; p=0.94

Shekar K, et al. *Anaesth Intensive Care* 2012;40:648-55

Stable Sedation Requirements

Prospective analysis of 32 adult patients receiving VV/VA ECMO

Local protocol = light sedation at ECMO initiation



DeGrado JR, et al. *J Crit Care* 2016;37:1-6

Influence of ECMO on Sedation

	ECMO Group (n=34)	Non-ECMO Group (n=60)	p-value
Sedative infusion exposure during the 6 hr maximum period, mg	118 (48-225)	60 (37-99)	0.004
Days of sedative infusion use prior to the 6 hr maximum	4 (1-8)	1 (0.5-6)	0.004
Sedative infusion rate at the time 6 hr maximum was reached, mg/hr	10 (5-22)	6 (4-12)	0.04

Median (interquartile range)
Includes all benzodiazepines, propofol, and dexmedetomidine infusions (expressed in midazolam equivalents)

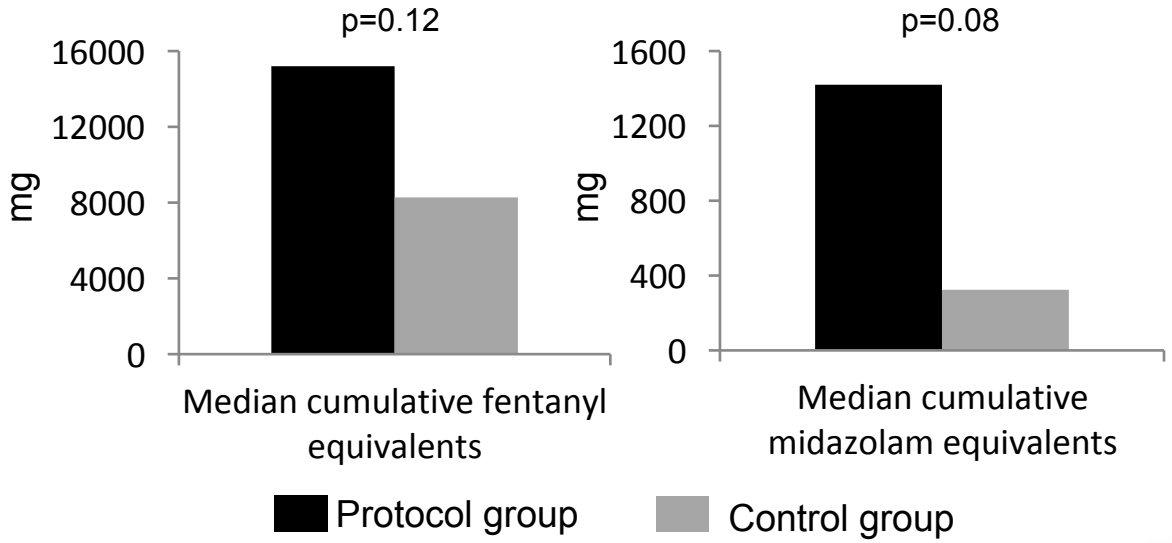
Adjusted model to estimate the impact of ECMO on the 6 hr maximum sedative exposure failed to show significance

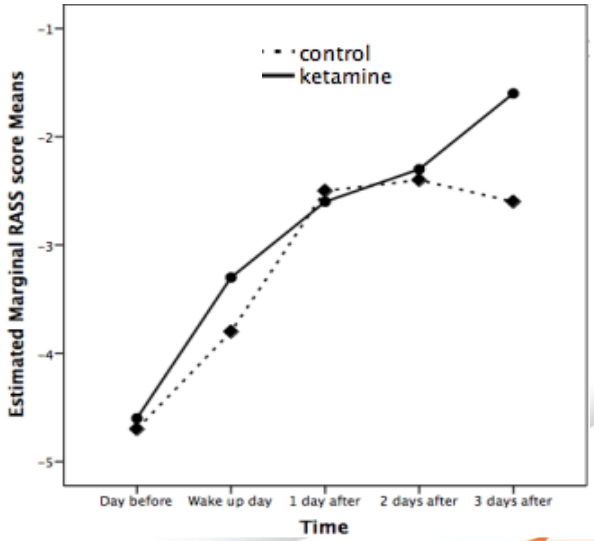
Der-Nigoghossian C, et al. *Pharmacother* 2016;35:2527-16

Ketamine Use in ECMO

Prospective, randomized trial including 20 patients requiring VV ECMO

- Protocol group = low-dose ketamine infusion + standard sedation practices
- Control group = standard sedation practices

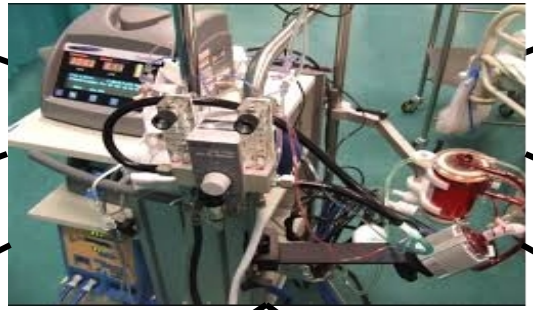




Dzierba AL, et al. *Intensive Care Med* 2016;42:1822-3

Study Limitations

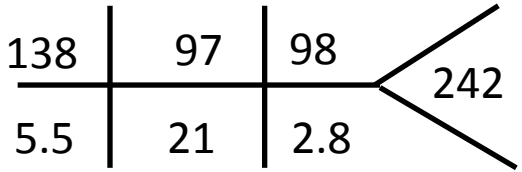
- Simulated circuits
- Tolerance
- Organ function (RRT)
- Mechanical ventilation practices
- ECMO configuration
- Liberation from ECMO
- Lack of clinical outcomes
- Absence of control subjects

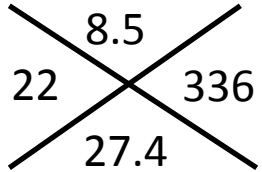


Patient Case

22-year-old woman with no past medical history presents to the ED with severe, hypoxemic respiratory failure secondary to influenza A

- Hypoxemia persists despite optimized ventilator management, deep sedation, prone position, and neuromuscular blockade
- Decision to initiate VV-ECMO





- ECMO initiated and neuromuscular blockade discontinued
- Current medications:
  - Norepinephrine 30 mcg/min and vasopressin 0.04 units/min
  - Fentanyl 100 mcg/hr and propofol 40 mcg/kg/min (current RASS -2; goal RASS -5 and CPOT 4)
  - Appropriate antimicrobials, stress ulcer / VTE prophylaxis, and bowel regimen

Patient Case

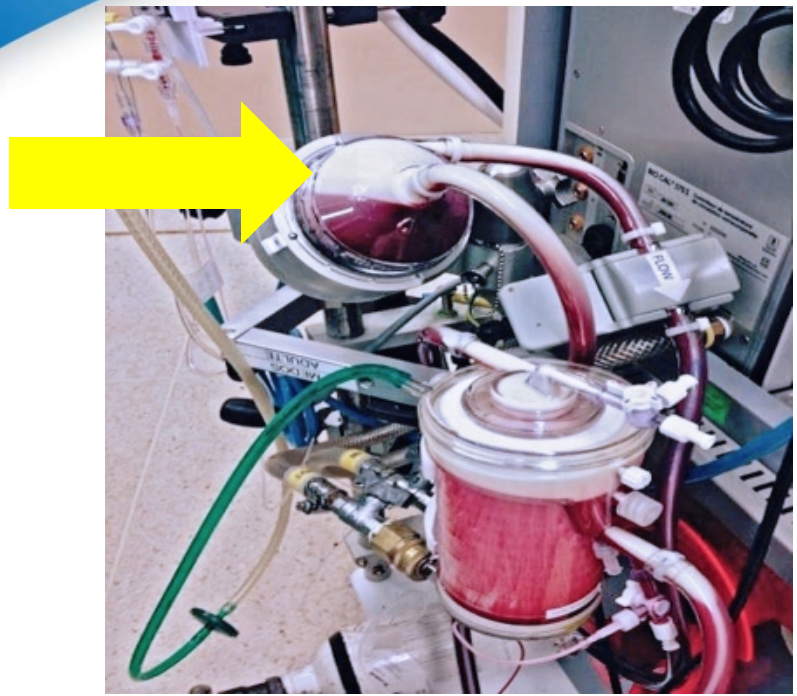
How can analgesia and sedation be optimized in this patient?

1. Double the rates of both fentanyl and propofol infusions
2. Change propofol to a midazolam infusion and keep fentanyl
3. Keep propofol and change fentanyl to a hydromorphone infusion
4. Change propofol to a midazolam infusion and fentanyl to a hydromorphone infusion

Patient Case

- Severe respiratory failure (Bridge to Recovery):
  - Use continuous infusions of analgesics and sedatives at ECMO initiation (requirements usually exceed standard doses)
  - Establish daily sedative goals with potential sedative reduction / interruption
  - Anticipate significant dose reduction at ECMO discontinuation
  - Monitor for signs of delirium / withdrawal

Propofol



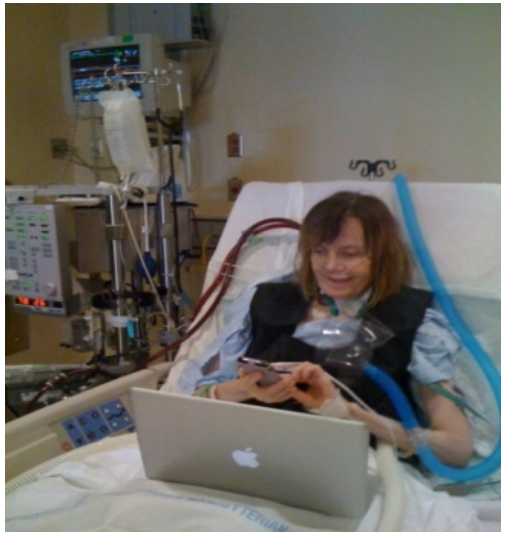
- Retrospective analysis concluded the use of propofol did not decrease oxygenator lifespan

Albrecht E, et al. *Intensive Care Med* 2016;42:1806-7
Hohlfelder B, et al. *ASAIO* 2017;63:179-84

Other Patient Cases

Bridge to Transplantation

Bridge to Decision



Consider minimal sedative exposure

Delirium Management

- Minimize exposure to sedatives
- Non-pharmacologic bundle
- Use of adjunct therapies

ANTIMICROBIALS

Infectious Complications

- Prevalence of adult nosocomial infections = 21% per ELSO registry
- VA-ECMO > VV-ECMO

	Incidence (episodes/1000 ECMO days)	Prevalence
Blood stream infections	3.0-20.6	3-18%
Lower respiratory tract infections	1.6-55.4	4-55%

- Do patients receiving ECMO have a higher risk of infection?
  - Increased number of catheters
  - Temperature modulation
  - Fibrin debris in the membrane oxygenator
  - Loss of bowel mucosal integrity

Biffi S, et al. *Int J Antimicrob Agents* 2017;50:9-16

One Dose Does Not Fit All

- Prospective, multicenter, pharmacokinetic point-prevalence study of beta-lactams
- 68 ICUs and 361 critically ill patients

PK/PD data	Ampicillin (n=18)	Cefepime (n=14)	Piperacillin (n=109)	Meropenem (n=89)
50% $fT_{>MIC}$ achieved	56%	79%	81%	95%
50% $fT_{>4xMIC}$ achieved	28%	50%	49%	69%
100% $fT_{>MIC}$ achieved	33%	79%	67%	70%
100% $fT_{>4xMIC}$ achieved	22%	71%	30%	42%

$fT_{>MIC}$= free drug concentration above minimum inhibitory concentration of dosing interval

16% of patients treated for infections did not achieve 50% $fT_{>MIC}$ and were 32% less likely to have a favorable outcome [OR 0.68 (95% CI 0.52-0.91); p=0.009]

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Roberts JA, et al. *Clin Infect Dis* 2014;58:1072-83

Beta-Lactam Antimicrobials

Retrospective, case-control cohort including patients receiving ECMO and meropenem or piperacillin/tazobactam

	Meropenem (n=27)		Piperacillin/tazobactam (n=14)	
	ECMO	Control	ECMO	Control
Volume of distribution, L/kg	0.5 (0.3-0.9)	0.6 (0.4-0.9)	0.3 (0.3-0.5)	0.3 (0.2-0.4)
Half-life, hr	3.0 (2.1-4.8)	2.9 (2.4-3.7)	2.0 (1.1-4.2)	1.6 (1.0-4.7)
Clearance, mL/min	125 (53-198)	144 (97-218)	156 (91-213)	134 (47-179)

Data represented as median (interquartile range)

Donadello K, et al. *Int J Antimicrob Agents* 2015;45:278-82

Glycopeptides

Patients	Regimen	Changes in clearance and volume of distribution
11 ECMO 11 Controls	Vancomycin 35 mg/kg over 4 hrs followed by continuous infusion to provide serum concentrations of 20-30 mcg/mL within 24 hrs	No change in clearance or volume of distribution
20 ECMO 60 Controls	Vancomycin dosed to achieve trough concentrations of 15-30 mcg/mL	
11 ECMO 11 Controls	Vancomycin 15-25 mg/kg to achieve trough concentrations of 10-20 mcg/mL	
10 ECMO	Teicoplanin 400 mg every 4 hrs x 3 doses followed by 400 mg every 24 hrs	No change in clearance; decreased volume of distribution

Donadello K, et al. *Crit Care* 2014;22:632; Park SJ, et al. *PLoS ONE* 2015;10:e0141016
Wu CC, et al. *J Formos Med Assoc* 2016;115:560-7; Wi J, et al. *Antimicrob Agents Chemother* 2017; [Epub ahead of print]

Amikacin

	ECMO (n=50)	Control (n=50)	p-value
Age, years	61 (43-68)	64 (54-72)	0.03
SOFA score	12 (10-14)	9 (6-11)	<0.001
Continuous renal replacement therapy	22 (44)	25 (50)	0.69
Amikacin dose, mg/kg	25 (25-26)	25 (25-26)	0.10
Maximum concentration, mg/L	72 (59-80)	68 (53-81)	0.36
Minimum concentration, mg/L	9 (2-5)	10 (3-17)	0.45

Data represented as median (interquartile range) or n (%)

Gelisse E, et al. *Intensive Care Med* 2016;42:946-8

Antimicrobial Management

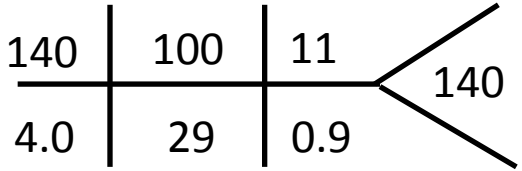
Drug	Protein binding	Log *p*	Expected effect from ECMO circuit
Aminoglycosides	<30%	-5.0	Minimal sequestration
Cefepime	20%	-2.8	Minimal sequestration
Ceftriaxone	85-95%	-1.7	Moderate sequestration
Levofloxacin	24-38%	2.1	Moderate sequestration
Meropenem	2%	-0.7	Minimal sequestration
Piperacillin/tazobactam	30%	0.3	Minimal sequestration
Vancomycin	55%	-3.1	Minimal sequestration

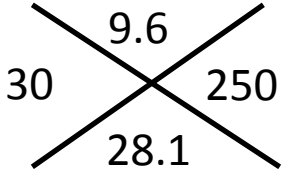
Wishart DS, et al. *Nucleic Acids Res* 2008;36:D901-6

Patient Case

45-year-old man with interstitial lung disease and pulmonary hypertension (PH); on day 12 of ICU stay, patient has worsening desaturation despite high flow nasal cannula and non-rebreather mask secondary to decompensated PH and right ventricular failure and hospital-acquired pneumonia

- VA-ECMO initiated
- Initiated on piperacillin/tazobactam, IV tobramycin, and IV vancomycin





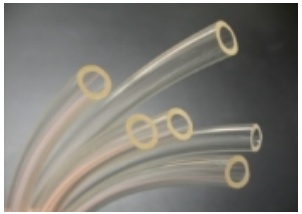
Which antimicrobial might you consider empirically increasing the dose?

1. Vancomycin
2. Piperacillin/tazobactam
3. Tobramycin
4. No adjustments necessary

Antimicrobial Management

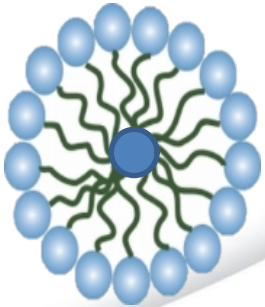
- Use published pharmacokinetic data in the critically ill to make dosage adjustments
- Therapeutic drug monitoring is critical for dose adjustments
- Monitor the clinical status of the patient

What Changes Can Be Made?



- Change the composition of the tubing?
  - Polyvinyl-chloride tubing may drive drug sequestration
  - Change to silicone-caoutchouc mixture with less absorption?

- Alter the drug?
  - Solubilize appropriate portions of drugs into the hydrophobic core of the micellar phase of surfactants



Unger JK, et al. *Biomaterials* 2001;22:2031-7

Key Takeaways

- Key Takeaway #1
  - The ECMO circuit influences pharmacokinetics of commonly used drugs
- Key Takeaway #2
  - Drug dosing recommendations for an adult patient receiving ECMO are unlikely to be evidenced-based
- Key Takeaway #3
  - Lipophilicity and protein binding appear to be important factors affecting pharmacokinetics

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Clinical Meeting & Exhibition

Pharmacotherapy in Extracorporeal Therapies: Therapeutic Plasma Exchange

Rami Ibrahim, Pharm.D., M.Sc.

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Detroit, Michigan

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Conflict of Interest Statement

- No receipt of salary, royalties, honorarium, intellectual property rights/patent holder and consulting fees (e.g., advisory boards)
- No receipt of fees for non-CE services received directly from a commercial interest *or their agents* (e.g., speakers' bureaus)
- No contracted research
- No ownership interest (stocks, stock options or other ownership interest *excluding diversified mutual funds*)

Objectives

Upon completion of this presentation, the participant will be able to:

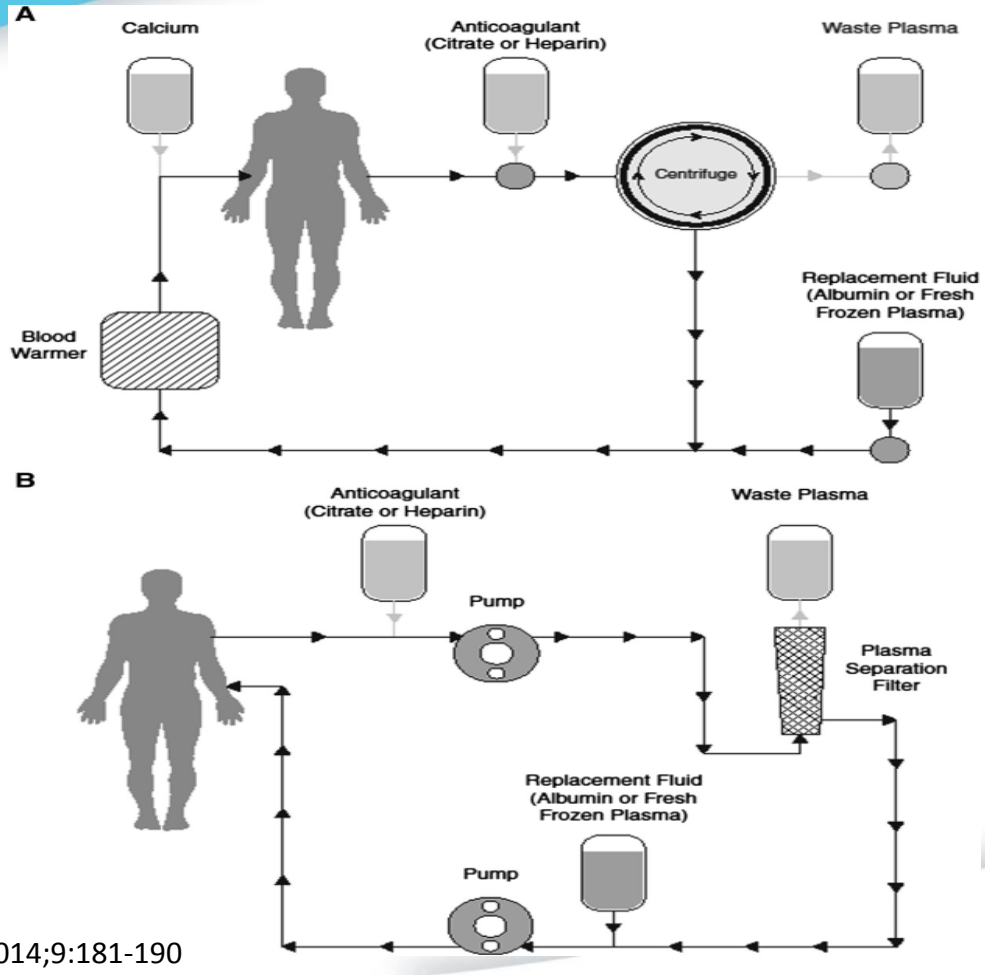
1. Discuss drug-related pharmacokinetics characteristics which lead to more efficient removal by therapeutic plasma exchange (TPE).
2. Apply knowledge in clinical scenarios as to how to handle medications in patients actively receiving TPE.

Outline

- Introduction

- Drug removal by TPE principles
  - Time between dose administration and TPE
  - Relation between the amount removed and biologic effect
  - How to assess the amount removed?

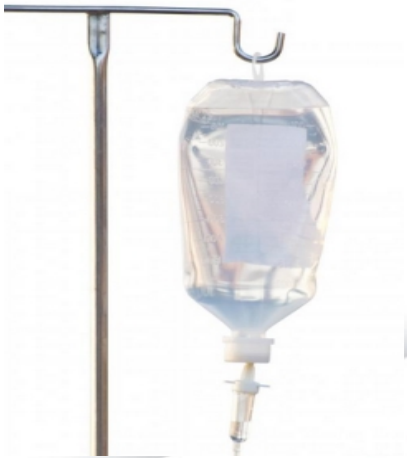
Introduction



Williams ME, Balogun RA. *CJASN* 2014;9:181-190

Patient Case 1

A 55-year-old female patient status post allogeneic hematopoietic stem cell transplant for acute leukemia is on intravenous mycophenolate mofetil (MMF) 1g Q8H for the treatment of refractory gastrointestinal graft-versus-host-disease. She is initiated on TPE for the treatment of TTP:



- IV mycophenolate dose given at 8:00 a.m. over 2 h
- TPE initiated at ~ 8:30 a.m. for about 2 hours

Introduction

- Pharmacokinetics:
  - Trough (serum) total MMA* level prior to TPE = 1.8 mg/L
  - MMA concentration in waste plasma = 1.4 mg/L

Ratio waste plasma/patient's serum concentration: 1.4/1.8 x 100= ~ 75%

TPE eliminated a substantial amount of IV MMA when it overlapped with the latter's infusion for about 1.5 hours

*** mycophenolic acid, the active ingredient of mycophenolate mofetil (MMF)**

Patient Case 2

- Pediatric patient with pulmonary arterial hypertension awaiting lung transplant

- On Treprostinil (Remodulin®) IV infusion

- TPE scheduled pre-transplant and post-transplant

Introduction

- TPE is used in a host of renal, hematological and neurological indications (to name a few)
- The likelihood of patients actively receiving TPE to be on multiple oral (or IV) medications is high
- TPE can remove these medications and, as such, can affect their disposition and, by extension, their therapeutic action

Audience Question #1

Which of the following most accurately describes the bulk of the literature evaluating drug removal by TPE?

1) Case reports of overdose situations
2) Case reports of therapeutic dose situations
3) Phase II pharmacokinetics studies of overdose exposure
4) Phase II pharmacokinetics studies of therapeutic dose exposure

Literature evaluating drug removal by TPE

- Of all published reports, approximately 25% are formal pharmacokinetic trials evaluating TPE's impact on drug disposition

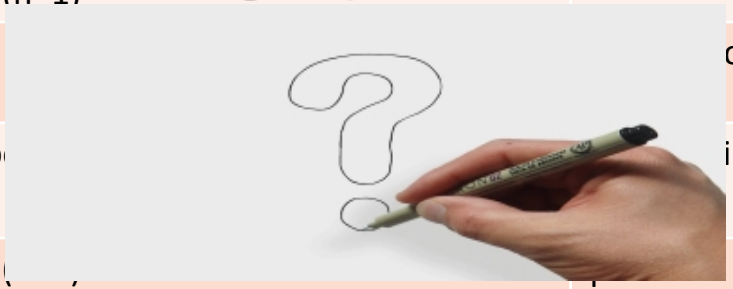
- The majority are case reports (predominately dealing with overdose exposure to medicines)

Ibrahim RB, et al. *Pharmacotherapy* 2007;27(11):1529-49

Drug removal by TPE: state of the literature

Year	Drug	Type of Publication (n)	Comments
2013	Amphotericin	case report (n=1)	overdose
2013	Dabigatran	?; n=1	
2013	Rituximab	pharmacokinetic study (n=20)	
2013	Valproic acid	case report (n=1)	
2013	Voriconazole	case report (n=1)	
2014	Ganciclovir	case report (n=1)	
2014	Warfarin	prospective	odynamic study per se
2015	Interferon	an open-lab study (n=6)	ing antibodies assessed
2015	Bivalirudin	case report	
2016	cisplatin	case report (n=1)	pediatric
2017	enoxaparin	Case report (n=1)	pediatric

2017 =



Outline

- Introduction

- Drug removal by TPE principles
  - **Time between dose administration and TPE**
  - Relation between the amount removed and biologic effect
  - How to assess the amount removed?

Drug Removal by TPE principles

- In general, drugs are likely to be removed if:
  - Low **volume of distribution** (V_d)

    and/or
  - **high rate of plasma protein binding**

Some have proposed that TPE ability to remove drugs occurs when plasma protein binding of a substance is > 80% and when the V_d is <0.2 L/kg

Ibrahim RB. Balogun RA. *J Clin Apheresis* 2013; 28: 73-77.

Ibrahim RB, Balogun RA. *Semin Dial* 2012 ;25(2):176-89.

Ibrahim RB, et al. *Pharmacotherapy* 2007;27(11):1529-49.

Drug Removal by TPE principles:
Not just V_d and protein binding!

TABLE 1. Important determinants of the effectiveness of TPE in removal of a given drug

Drug dependent
Time between dose administration and TPE initiation: the higher the drug plasma concentration at the time of TPE, the more likely it will be removed (a function of the drug's distribution half-life, i.e., $t_{1/2\alpha}$)
Protein binding: the lower the drug's protein binding, the less likely it will be removed
Volume of distribution: the higher the drug's volume of distribution, the less likely it will be removed
TPE dependent
Duration of TPE
Successive TPE sessions
Volume of plasma removed
TPE replacement fluid (equivocal; please see text)

$t_{1/2\alpha}$ = distribution half-life is the amount of time it takes for half of the drug to be distributed throughout the body

):176-89.

Drug Removal by TPE principles: Time between dose administration and TPE

Strong correlation between drug concentration before initiating TPE and the amount removed by the procedure

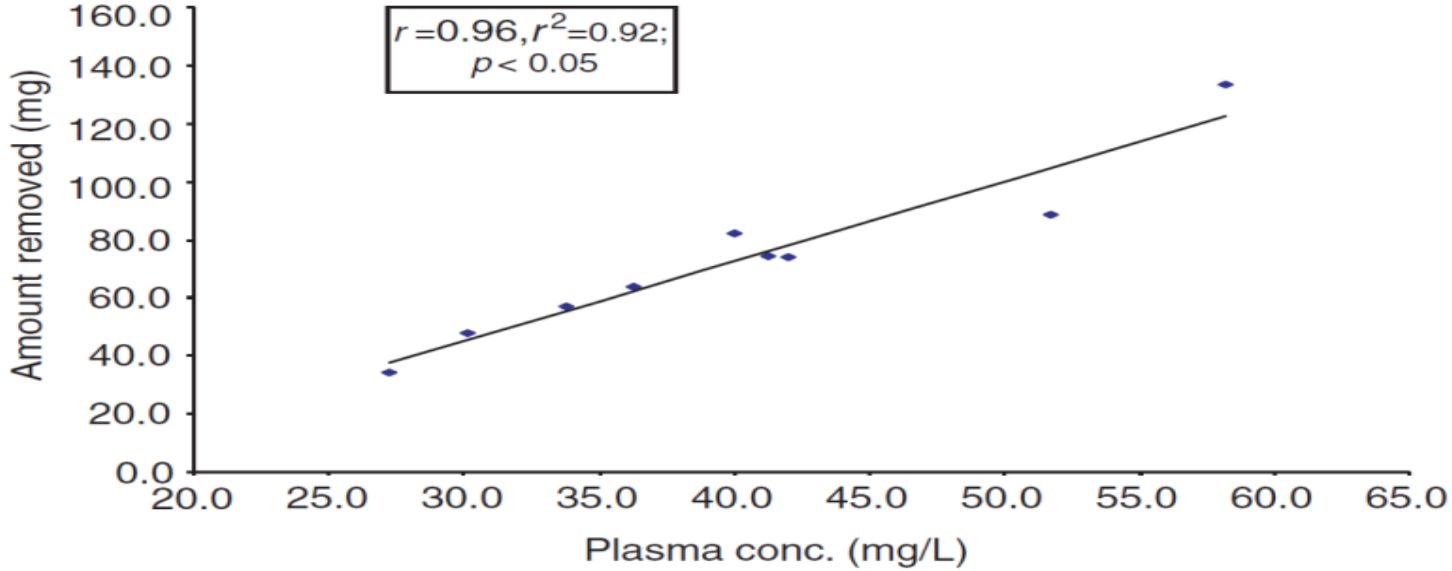


Figure 1. Correlation between amount of cefepime removed (mg) by PE and cefepime plasma concentration (mg/dL) before PE.

Ibrahim RB, et al. *J Oncol Pharm Pract* 2009;15(4):217-22

Drug Removal by TPE principles: Time between dose administration and TPE

- This correlation was also observed with:
  - aspirin
  - gentamycin
  - rituximab
  - thyroxine
  - vancomycin
  - valproic acid
- It is unclear if this parameter **"trumps"** the V_d and protein binding effects but a drug with a small V_d (~0.2L/kg) may be negligibly removed by TPE if given time to fully distribute

McClellan SD, et al. *Ann Pharmacother* 1997; 31:1132–1136. Kliegman RM, et al. *J Pediatr* 1980; 96:927–930. Bertino Jr JS, et al. *Dev Pharmacol Ther* 1982; 4:205–215. Binimelis J, et al. *Intensive Care Med* 1987; 13:33–38. White RL, et al. *Clin Pharm* 1984 ;3:396–402. Puisset F, et al. *Br J Clin Pharmacol* 2013;76(5):734-40

Drug Removal by TPE principles: Time between Dose administration and TPE

TPE started **1.5 hours** from the end of a single-dose infusion

* Cefepime's protein binding is 20% and Vd ~0.2 L/kg

Table 2. Summary of cefepime pharmacokinetics parameters in patients receiving PE ($n = 9$)[a,b]

Patient #	Volume removed (L)	Duration of PE (min)	Plasma concentration before PE (mg/dL)	Amount removed by PE (mg)	% removed by PE (relative to 2 g dose)
1	3.5	120	41.3	74.5	3.7
2	3	104	33.8	56.9	2.8
3	3.5	124	30.1	47.9	2.4
5	2.5	130	27.3	34.3	4.4
6	3.5	209[c]	51.7	88.5	2.1
7	3.5	147	40	82.1	4.1
8	3	94	36.3	63.7	3.2
9	3.5	100	42	74	3.7
10	3.5	107	58.2	133.4	6.7
Mean ± SD (range)	3.3 (2.5–3.5)	126 (94–209)	40.1 ± 9.9 (27.3–58.2)	72.8 ± 28.4 (34.3–133.4)	3.7 ± 1.36 (2.1–6.7)

SD: standard deviation. [a]Patient # 4 was not included in the analysis due to an aborted PE session secondary to loss of venous access. [b]All patients received 5% albumin except patients 7 and 9 who received fresh frozen plasma. [c]Slower PE run time owing to use of a non-PE catheter (Hickman).

- Similar findings were reported with the antibiotic ceftazidime

Ibrahim RB, et al. *J Oncol Pharm Pract* 2009;15(4):217-22
Bozkurt F , et al. *Eur J Clin Pharmacol* 1987: 33(2):197-201

Drug Removal by TPE principles: Time between dose administration and TPE

TABLE 1. Drug Concentration Levels of Valproic Acid in Plasma and Plasmapherate

	Total Concentration Valproic Acid (mg/L)	Unbound Concentration Valproic Acid (mg/L) (%)
Trough level before dosing	43.6	4.7 (10.7%)
At start of plasmapheresis (3.5 h after dose)	80.1	8.5 (10.6%)
At end of plasmapheresis	44.2	4.0 (9.0%)
Plasmapherate (2.85 L)	45.5	4.1 (9.0%)

Immediate release formulation used

- Amphotericin overdose

Bastiaans DET, et al. *Ther Drug Monit* 2013;35:1-3

Wang GS, et al. *Ann Pharmacother* 2013;47:e9

Drug Removal by TPE principles: Time between dose administration and TPE

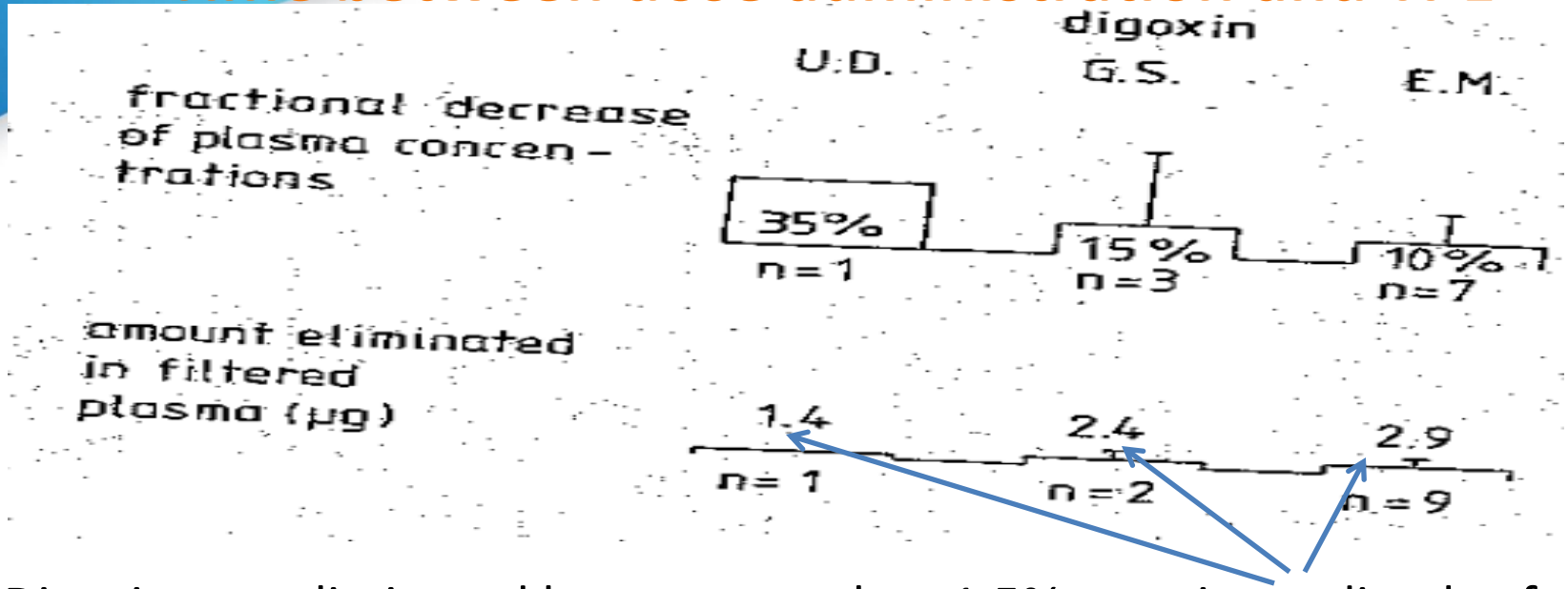
- Drugs with a low V_d (and low protein binding) are likely to be unaffected by TPE if given the time to distribute

- Scarce published pharmacokinetic analysis with drugs who have a low V_d (and high protein binding)

- While not giving drugs after TPE is customarily adopted, a drug like digoxin can be given immediately before TPE without any meaningful impact on its disposition

Keller F, et al. *Arzneimittelforschung* 1984;34:83-86
Keller F, et al. *Clin Pharmacokinet* 1985;10:514–523

Drug Removal by TPE principles: Time between dose administration and TPE



Digoxin was eliminated by not more than 1.5% even immediately after dosing

Keller F, et al. *Arzneimittelforschung* 1984;34:83-86

Drug Removal by TPE principles: Audience Question #2

Which drug is likely to be removed the most by TPE? *assume they're all given 2 hours after TPE*

1) Ceftriaxone (protein binding 96%; 0.1 L/Kg)
2) Cyclosporin (protein binding 90-98% and V_d 13 L/kg)
3) Digoxin (protein binding 25% and V_d 8 L/kg)
4) Vancomycin (protein binding 70% and V_d 0.4 L/kg)

Drug Removal by TPE principles:

Answer to Question # 2

Drug class, drug	PK characteristics: plasma protein binding; V_d[a]	TPE exchange: Drug removal	TPE exchange: Time from last dose (hours)
Ceftriaxone	1 g dose (10): 96%; 0.1 l/kg	No; 5.7–16.6% of 2-g dose	3–15
	2–3 g dose: 83%; 0.2 l/kg	Yes; 23–25% of dose (group 1; $n = 6$)[b]	0 (group 1)
		No; 11.5–16.6% of dose (group 2; $n = 6$)	6 (group 2)

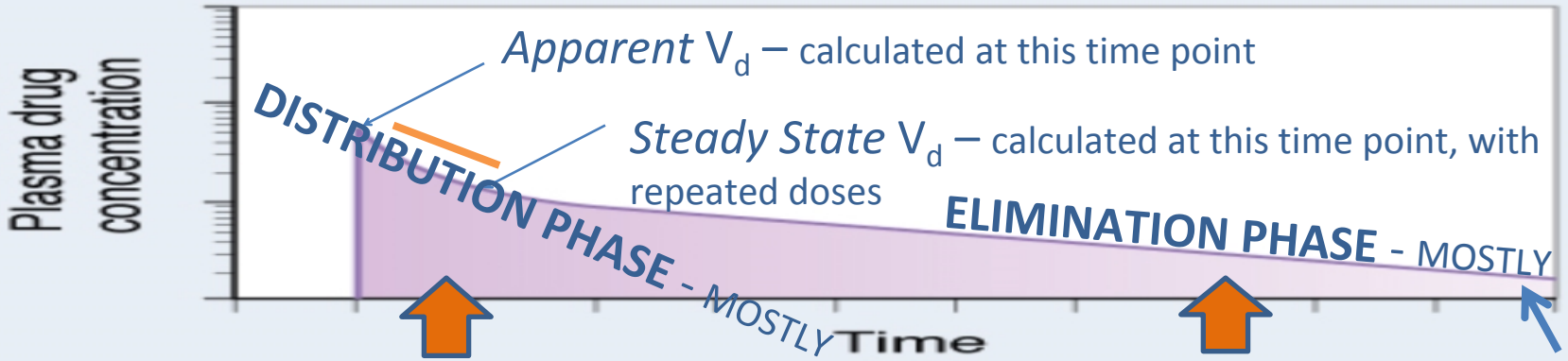
Ibrahim RB, Balogun RA. *Semin Dial* 2012;25(2):176-89

Fauvelle F, et al. *Antimicrob Agents Chemother* 1994;38:1519–1522

Bakken JS, et al. *Antimicrob Agents Chemother* 1993;37(5):1171–3.

Drug Removal by TPE principles:
Time to distribution might be key

Not all V_ds are equal



TPE = troubled waters TPE = home free

Adapted with permission from Katzung BG, ed. Basic & clinical pharmacology. 7th ed. New York: Lange Medical Books/McGraw-Hill; 1998:38,

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Outline

- Introduction
- Drug removal by TPE principles
  - Time between dose administration and TPE
  - **Relation between the amount removed and biologic effect**
  - How to assess the amount removed?
- Future directions

Drug Removal by TPE principles: Relation between the amount removed and biologic effect

- In a significant number of compounds (e.g., B-blockers), blood levels do not correlate with clinical effects
- By extension, TPE may reduce blood levels of some drugs without altering their biologic effect
- e.g., monoclonal antibodies

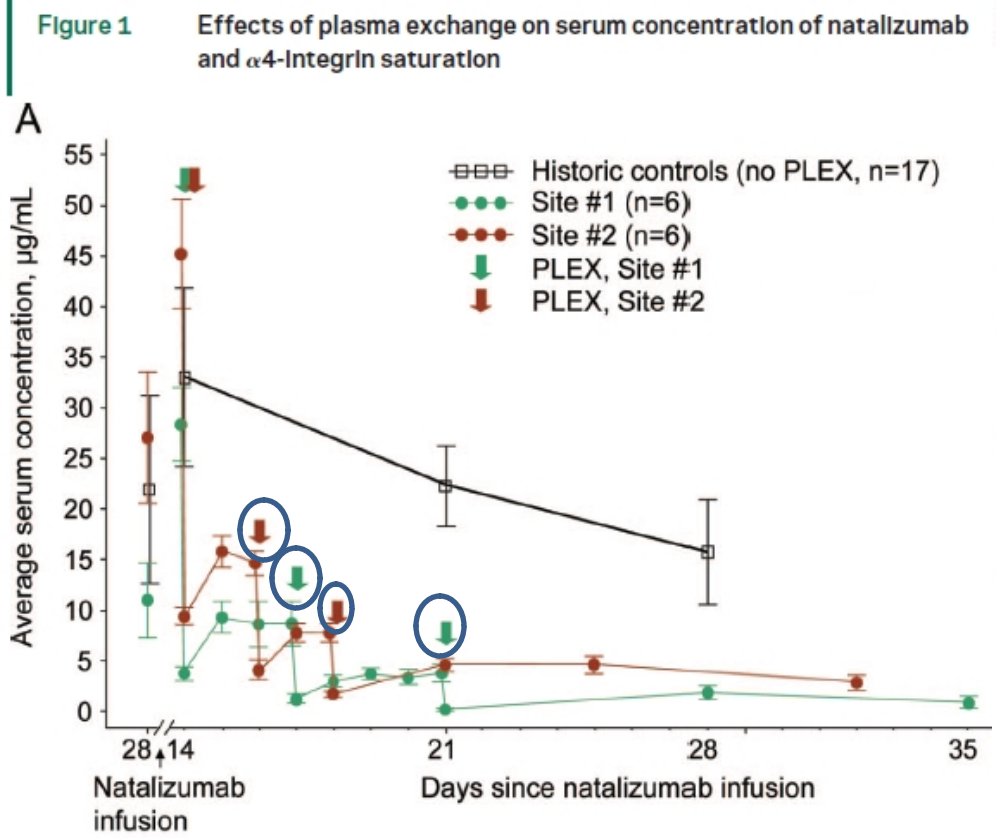
Drug Removal by TPE principles:
Relation between the amount removed and biologic effect:
Monoclonal Antibodies

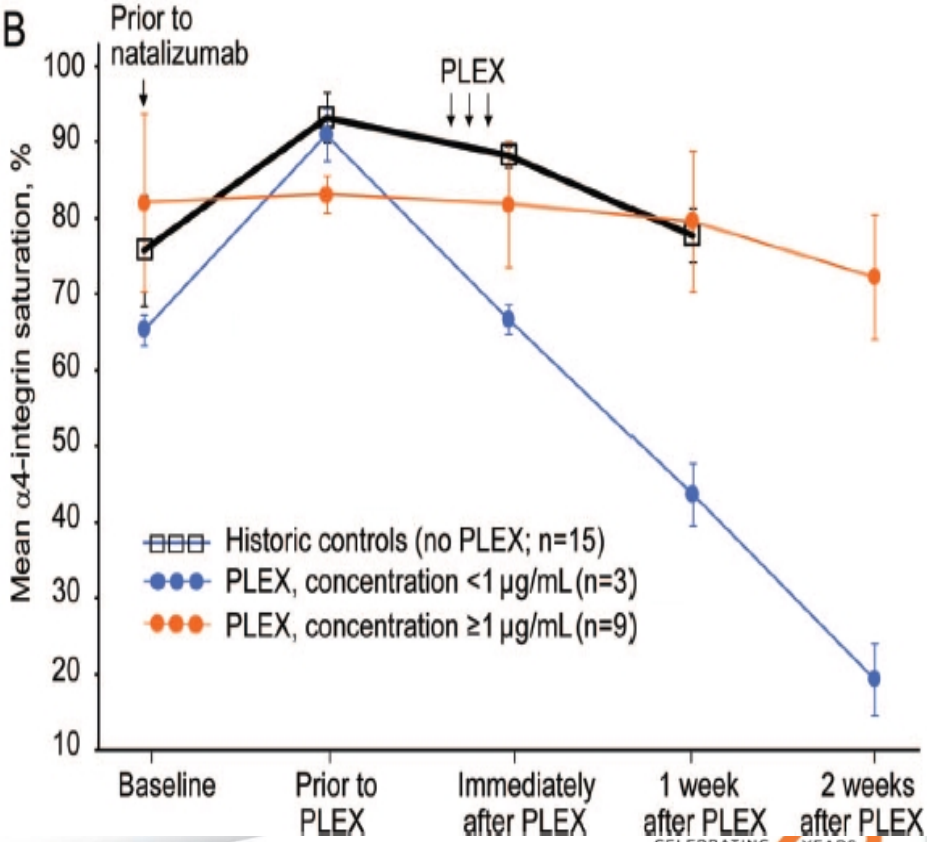
Monoclonal antibody	Plasma protein binding; V_d	Time from TPE	Extracted by TPE; %
Basiliximab	N/A; 4.8-8 L	> 4 hours	Yes; ~65%
Natalizumab	N/A; ~6 L	10-14 days	Yes; ~75%
Rituximab	N/A; 2-5 L	see discussion	Yes – see discussion

Okechukwu CN, et al. *Am J Kidney Dis* 2001;37:E11
Khatri BO, et al. *Neurology* 2009;72: 402-409

Drug Removal by TPE principles: Relation between the amount removed and biologic effect: *Monoclonal Antibodies* - Natalizumab

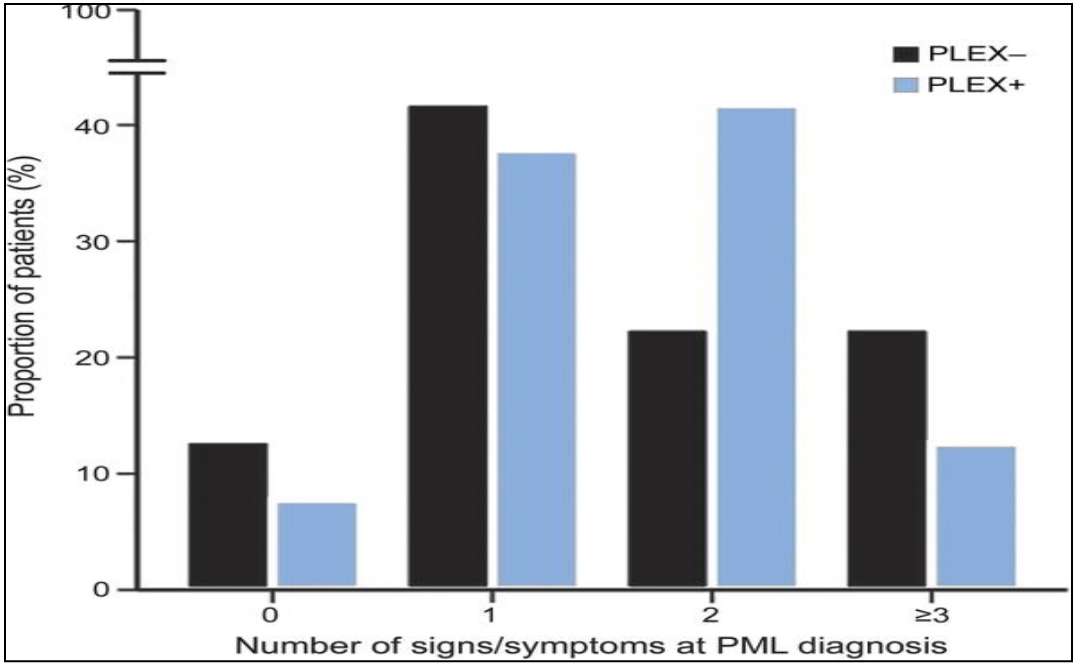
Figure 1 Effects of plasma exchange on serum concentration of natalizumab and α4-Integrin saturation





Khatri BO, et al. *Neurology* 2009;72: 402-409

Relation between the amount removed and biologic effect: *Monoclonal Antibodies* - Natalizumab



- No pharmacokinetic analysis

Landi D, et al. *Neurology* 2007; 88(12):1144-1152

Drug Removal by TPE principles:
Relation between the amount removed and biologic effect:
Monoclonal Antibodies - **Rituximab**

Distribution half-life ($t_{1/2\alpha}$)~1.5-3 days and elimination $t_{1/2}$ of ~ 20 days

Publications	Time of rituximab dose from TPE	Results
Darabi K, et al. *Am J Clin Pathol* 2006;125:592–597	24-36 hours	CD19+ and CD20+ B-cells depressed; activity against TTP maintained
McDonald V, et al. *J Thromb Haemost* 2010;8(6):1201-8	24 hours (?)	**Yes**; ~70%
Scully M, et al. *Blood* 2011;118(7):1746-53	At a minimum 4 hours	CD19+ B-cells depressed; ADAMTS13 activity increased and Anti-ADAMTS13 IgG decreased; appropriate hematologic response to TTP seen
Puisset F, et al. *Br J Clin Pharmacol* 2013;76(5):734-40	24-72 hours	**Yes**; 47% - 54% (mostly with after the first session)

Drug Removal by TPE principles: Relation between the amount removed and biologic effect: *Monoclonal Antibodies* - Rituximab

X dose 1 **X** dose 2 **X** dose 3 **X** dose 4

TPE

exposure = or slightly higher than

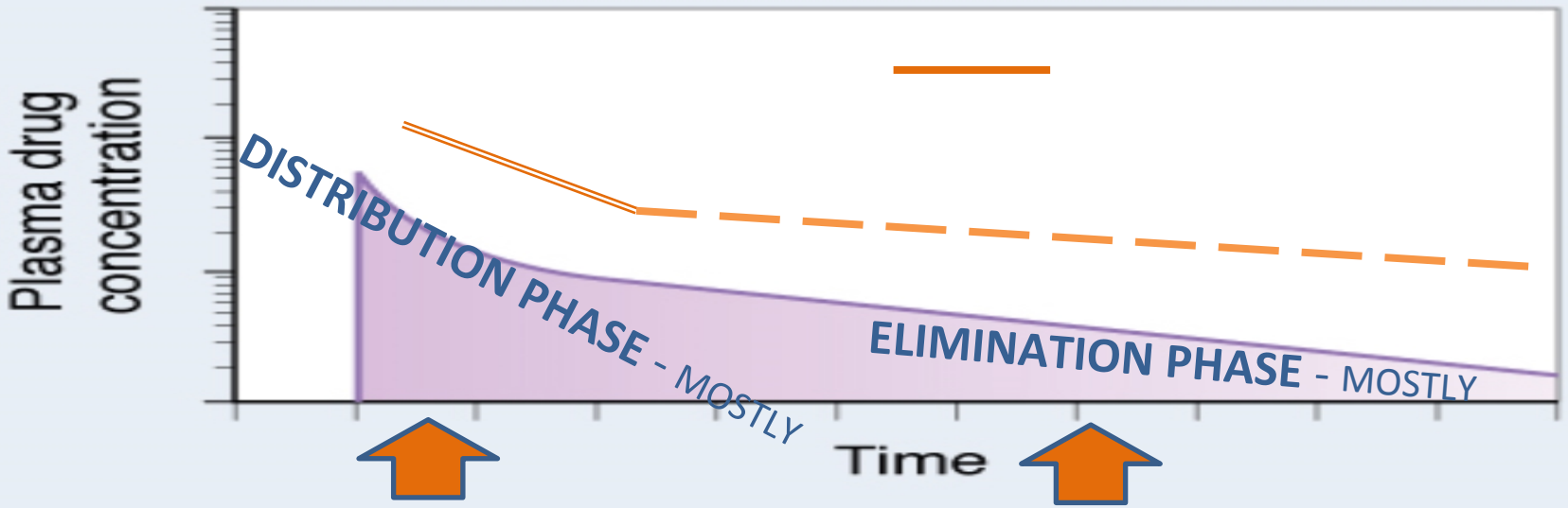
X dose 1 **X** dose 2

*Weekly intervals

** PK simulation

Puisset F, et al. *Br J Clin Pharmacol* 2013;76(5):734-40

Drug Removal by TPE principles:

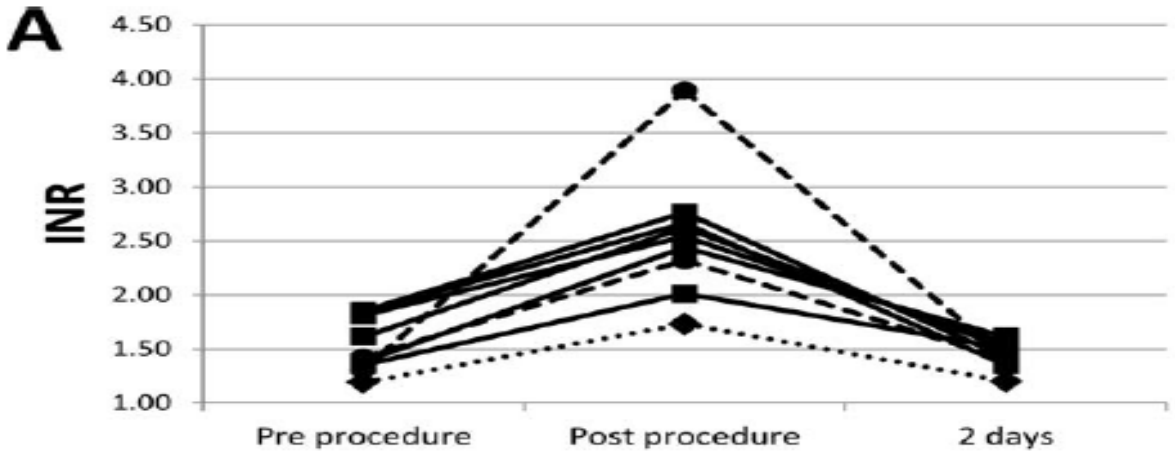


TPE = troubled waters

Adapted with permission from Katzung BG, ed. Basic & clinical pharmacology. 7th ed. New York: Lange Medical Books/McGraw-Hill; 1998:38.

Drug Removal by TPE principles: Relation between the amount removed and biologic effect - Warfarin

- Patients on warfarin (n=8; 121 TPEs)



5% albumin replacement

- Pre-procedure INR influences the post-INR increase
- Similar effect on Factor II and fibrinogen

Zantek N, et al. *J Clin Apher* 2014; 29:75–82

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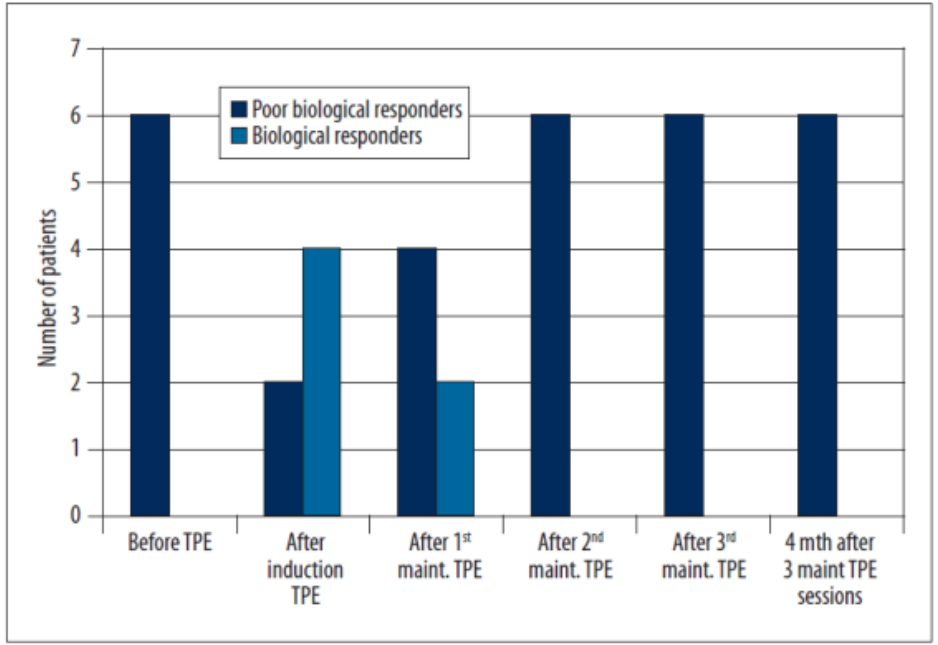
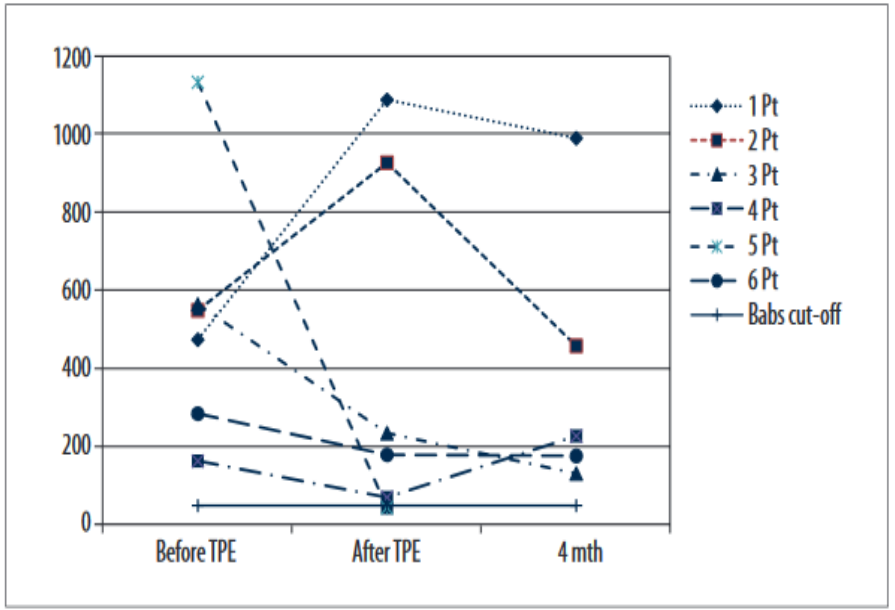
Drug Removal by TPE principles: Relation between the amount removed and biologic effect – IFN-β





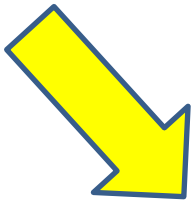
Giedraitiene N, et al. Med Sci Monit 2015;21:1512-9

Drug Removal by TPE principles: Check List

- ✓ Time between dose administration and TPE
  - ✓ distribution half-life ($t_{1/2\alpha}$)
- ✓ Plasma protein binding and V_d
- ✓ Relationship between plasma levels (and removed drug) and biologic effect (or pharmacodynamic $t_{1/2}$ is important)
  - Despite being removed, the biologic effect of some monoclonal antibodies was unaffected.
  - That said, the optimal time cut-off between dose and TPE initiation for each monoclonal antibodies is ill-defined

Drug Removal by TPE principles: Check List

- ✓ **Be wary:** pharmacokinetics tenets ($t_{1/2\alpha}$, plasma protein binding and V_d) can all change in:



Overdose Situations

e.g., ceftriaxone, levothyroxine

Outline

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Drug Removal by TPE principles: Audience Question # 3

A patient presents with acute TTP and is slated for TPE. Which pharmacologic treatment can be given with TPE without its pharmacokinetics being affected by the procedure ?

1) Drug A (started 4 hours before; $t_{1/2\alpha}$= 0.5 hours)
2) Drug B (started 2 hours before; $t_{1/2\alpha}$= 0.5 hours)
3) Drug C (started 4 hours before; $t_{1/2\alpha}$= 24 hours)
4) Drug D (started 2 hours before; $t_{1/2\alpha}$= 24 hours)

Drug Removal by TPE principles: Audience Question # 4

- In your view, what is the most objective way to assess TPE influence on drug disposition?

1) calculate drug serum concentration before and after TPE
2) calculate TPE's drug clearance
3) determine the amount of drug in waste plasma
4) determine TPE's flow rate

Drug Removal by TPE principles: how to assess the amount removed?

- The "Vancomycin" example

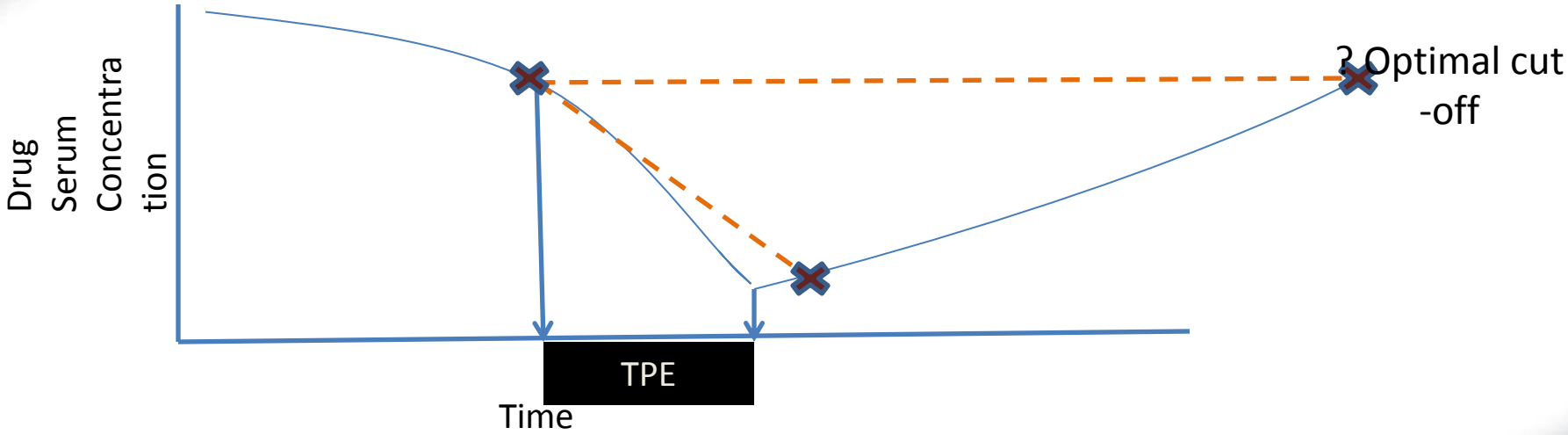
Publications type/# of patients	Endpoint	Findings
Case report (n=1)[1]	Reduction in serum concentration	Yes; ~ 49% reduction
Case report (n=1)[2]	Reduction in serum concentration	Yes
Case report (n=1)[3]	Reduction in serum concentration	Yes; ~ 27% reduction
Case report (n=1)[4]	Reduction in serum concentration	No
PK trial (n=12)[5]	Total body stores (derived from amount in waste plasma)	No; 6.3% of total body stores

PK=Pharmacokinetic

[1]*Ann Pharmacother* 2006;40:2279–2280. [2]*Ann Pharmacother* 2001;35:1400–1402.
[3]*Pharmacol Toxicol* 1997; 81:245–246 . [4]*Ann Pharmacother* 1996;30:1038. [5] *Ann Pharmacother* 1997; 31:1132–1136

Drug Removal by TPE principles: how to assess the amount removed?

- The Vancomycin example: explanation



The pitfalls of before/after TPE serum concentration evaluation:

– It does not take into account post-redistribution from tissues

→ Overestimation of removal

Drug Removal by TPE principles: how to assess the amount removed?

- Even if drug clearance is increased on TPE, it does not mean that significant amount of the drug is removed by TPE

PATIENT	AGE (y)	GENDER	SCr (mg/dL)	k_e (h^{-1})	V_d (L)	Cl_{Pt} (L/h)	Cl_{PE} (L/h)	Cl_T (L/h)	% INCREASE IN Cl_T
Mean ± SD	49.3 ± 19.2		3.2 ± 2.5	0.04 ± 0.03	49.2 ± 16.3	1.9 ± 1.2	1.6 ± 0.4	3.6 ± 1.1	285 ± 191

	PE TIME (h)	PE VOLUME (L)	Cp_{prePE} (mg/L)	TBS_{prePE} (mg)	PE PROD AMT (mg)	% REMOVED by PE	% REMOVED PER HOUR
Mean ± SD	2.0 ± 0.4	3.67 ± 0.85		727.6 ± 475.9	42.3 ± 20.6	6.3 ± 1.8	3.2 ± 0.9

- Clearance relies on serum concentrations, which decline faster than tissue levels

McClellan SD, et al. *Ann Pharmacother* 1997; 31:1132–1136

An example from the NCAA…*sort of*

% increase in PPG from 2014-2016:

PPG (2016)/PPG (2014) = 0.6/0.2 x 100 = 300%

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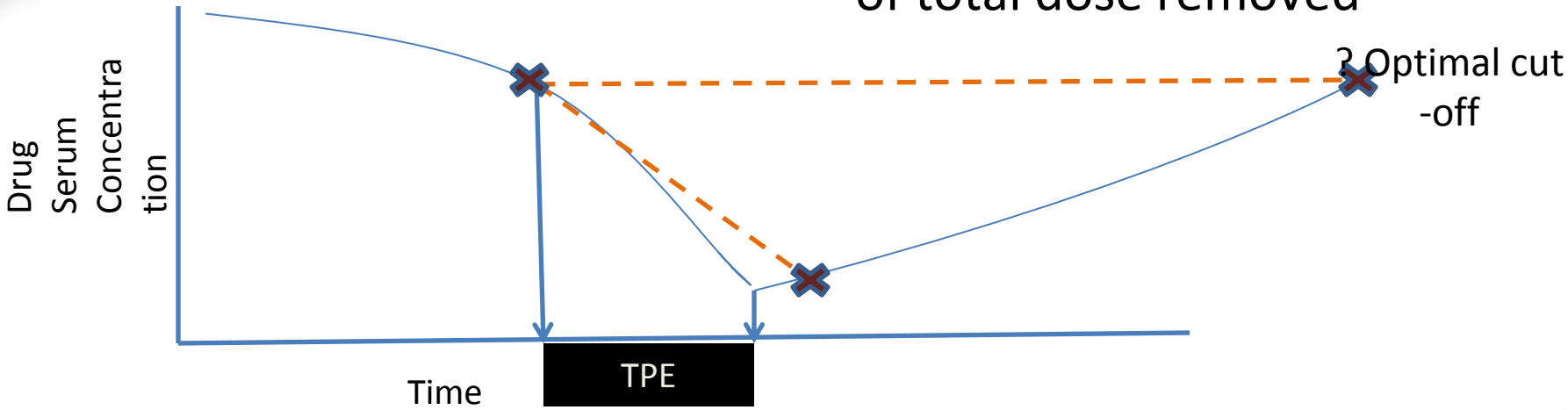
Drug Removal by TPE principles: how to assess the amount removed?

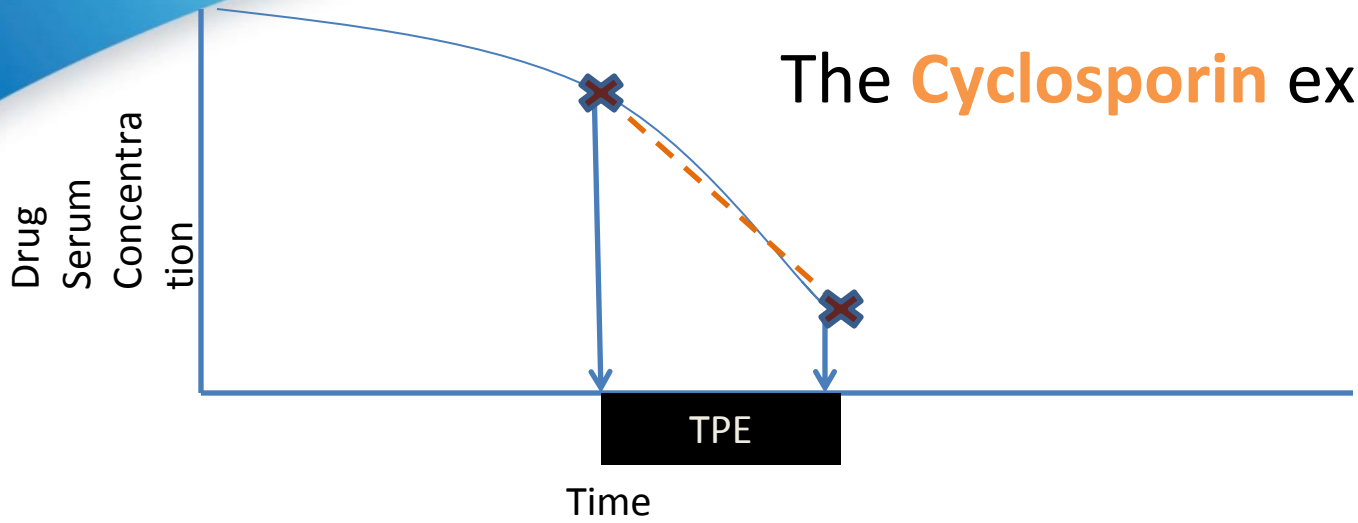
- The Valproic acid example: 32% cleared by TPE but only 8.6% of total dose removed



- The pitfalls of before/after TPE serum concentration evaluation:
  - It does not take into account post-redistribution from tissues
    → Overestimation of removal

Bastiaans DET, et al. *Ther Drug Monit* 2013;35:1-3

Drug Removal by TPE principles: how to assess the amount removed?



The Cyclosporin example

The pitfalls of before/after TPE serum concentration evaluation:

The observed drop in serum concentration may not be due to TPE but normal endogenous elimination of the drug (e.g., cyclosporin removal*)

→ Overestimation of removal

* red cell exchange

Moorman MT, et al. *J Clin Apher* 2011;26:156–158.

Drug Removal by TPE principles: *Other factors*

- Concurrent renal failure
  - Observation suggesting a trend to remove more drug when patients with TPE have underlying renal dysfunction

- Replacement fluid
  - Equivocal (FFP and anticoagulants?)

Ibrahim RB, Balogun RA. *Semin Dial* 2012 ;25(2):176-89.
Ibrahim RB, et al. *Pharmacotherapy* 2007;27(11):1529-49
Zantek N, et al. *J Clin Apher* 2014;29:75–82
Preston TJ, et al. *World J Pediatr Congenit Heart Surg* 2015;6(1):119-22

Patient Case 2 Cont

- Pediatric patients with pulmonary arterial hypertension awaiting lung transplant
- On Treprostinil (Remodulin®) IV infusion
- TPE scheduled pre-transplant and post-transplant

Conclusion

- TPE has the ability to remove drugs

- The extent of the removal is a function of many factors, not the least of which are the drug's own pharmacokinetics (at normal and *overdose* conditions)

- By removing the pharmacodynamic target, TPE can influence drug action – independent of the impact on the drug pharmacokinetics