Clinical Considerations: Pharmacotherapy in Extracorporeal Therapies

David P. Reardon, Pharm.D., BCPS
Amy L. Dzierba, Pharm.D., BCCCP, BCPS, FCCM
Rami Ibrahim, Pharm.D., M.Sc.
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.
Clinical Considerations: Anticoagulation in Extracorporeal Membrane Oxygenation

David P. Reardon, Pharm.D., BCPS
Pharmacy Executive
Vizient, Inc.
Irving, TX
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

Lindstrom et al. MJA. 2009; 191:178-82
1971: First adult ECMO for respiratory failure

1979: Randomized trial demonstrated no benefit (9.5% survival)

1990-2000: Observational studies demonstrated improved survival of 47-66%

2009: H1N1-associated respiratory failure (72% survival)

2011: ELSO registry for H1N1-associated respiratory failure (67% survival)
ECMO Indication by Modality

- Respiratory Support
  - VV ECMO
  - VA ECMO*

- Hemodynamic Support
  - VA ECMO

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

- 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

ECMO is not a way of life!!!
Circuit
Risk of thromboembolic complications – Coagulation cascade activation due to:
• Contact with ECMO oxygenator
• Contact with ECMO circuit
• Turbulence through ECMO pump
• High risk of bleeding secondary to anticoagulant use, fibrinolytic state, and large-bore cannula

5-13% of patients experience a CVA

ECMO Associated Coagulopathy

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

- Contact activation
  - XIIa, Kallikrein
- Tissue Factor activation
  - Tissue injury
  - Monocyte-related
  - Pericardial blood
- Activation of fibrinolysis
  - Increased tPA
  - Intrinsic activation

Consumption

- 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
# Anticoagulation in ECMO

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unfractionated Heparin</th>
<th>Bivalirudin</th>
<th>Argatroban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Typical Dosing</td>
<td>Initial dose range: 50-200 units/kg with maintenance infusion of 10 to 30 units/kg</td>
<td>Initiation at 0.08 to 0.2 mg/kg/h. Maintenance change of rate between 0 and 0.03 mg/kg/h</td>
<td>Initiation at 0.25 mcg/kg/h to 2 mcg/kg/min. Maintenance change of rate between 0 and 0.6 mcg/kg/h</td>
</tr>
<tr>
<td>Monitoring</td>
<td>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</td>
<td>Goal Activated Clotting Time (ACT) range: 180 – 220 seconds Goal aPTT range: 60-90 seconds</td>
<td></td>
</tr>
<tr>
<td>Half life</td>
<td>1 to 2 h</td>
<td>25 min to 3.5 h</td>
<td>39 to 51 min</td>
</tr>
</tbody>
</table>
# Bivalirudin as Alternative to UFH

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


$r^2 = 0.76$
ACT versus Anti-Xa Correlation


Anti-Xa Level (0-1 Units/mL)

ACT (Seconds)

$r^2 = 0.32$
aPTT versus Anti-Xa Correlation

\[ r^2 = 0.32 \]

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

Hemorrhage group

Infarct group

Anti-factor Xa (IU/mL)

Activated Clotting Time (seconds)

Cases Controls

0.0 0.2 0.4 0.6 0.8

24-hr period 72-hr period 24-hr period 72-hr period

p 0.89 p 0.60 p 0.35 p 0.18

p 0.10 p 0.24 p 0.87 p 0.46

Cases Controls

0.0 0.2 0.4 0.6 0.8

24-hr period 72-hr period 24-hr period 72-hr period

p 0.10 p 0.24 p 0.87 p 0.46

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

Coagulation

- R value: 4 - 8 min
- α Angle: 47-74°
- K: 0 - 4 min
- MA: 54-72 MM

Fibrinolysis

- LY30: (0-8%)
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
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 thrombosis 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

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

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

<table>
<thead>
<tr>
<th>Fibrinogen (mg/dL)</th>
<th>Pre-EACA</th>
<th>Post-EACA</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemoglobin (g/dL)</th>
<th>Pre-EACA</th>
<th>Post-EACA</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
Optimizing Drug Dosing During Extracorporeal Membrane Oxygenation

Amy L. Dzierba, Pharm.D., BCCCP, BCPS, FCCM
Department of Pharmacy
NewYork-Presbyterian Hospital
Columbia University Irving Medical Center
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.
Increased α₁-acid glycoprotein and decreased albumin concentrations; Mostly affecting hydrophilic drugs

Pharmacokinetic Alterations

Extracorporeal Membrane Oxygenation

- Augmented cardiac output
  - Increased clearance
  - Decreased plasma concentrations
- Hemodilution
  - Increased volume of distribution
- Drug sequestration
- End-organ dysfunction (renal or hepatic)
  - Decreased clearance
  - Increased plasma concentrations

1 Mostly affecting hydrophilic drugs
Extracorporeal Factors

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

Other factors:
- Administration of the drug
- Recirculation
- Age of the circuit
## Drug Factors

### Lipophilicity

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

### Ionization

- Protein binding: 95-99%
- 79-87%
- 85-91%
- 97%
- 94%
- 8-19%
- 20-35%

### Molecular weight

- 4.0
- 3.9
- 3.5
- 3.3
- 3.3
- 0.9
- 0.8

### Protein binding

- Propofol: 95-99%
- Fentanyl: 79-87%
- Lorazepam: 85-91%
- Midazolam: 97%
- Dexmedetomidine: 94%
- Hydromorphone: 8-19%
- Morphine: 20-35%

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

- Safe environment
- Minimizing agitation
- Preventing toxicity

- Unpredictable medication effects
- ECMO indication
- Patient temperament
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
Stable Sedation Requirements

Prospective analysis of 32 adult patients receiving VV/VA ECMO
Local protocol = light sedation at ECMO initiation

## Influence of ECMO on Sedation

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

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>138</th>
<th>97</th>
<th>98</th>
<th>242</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.5</td>
<td>21</td>
<td>2.8</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>336</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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

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

<table>
<thead>
<tr>
<th></th>
<th>Incidence (episodes/1000 ECMO days)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood stream infections</td>
<td>3.0-20.6</td>
<td>3-18%</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>1.6-55.4</td>
<td>4-55%</td>
</tr>
</tbody>
</table>

- 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

One Dose Does Not Fit All

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

<table>
<thead>
<tr>
<th>PK/PD data</th>
<th>Ampicillin (n=18)</th>
<th>Cefepime (n=14)</th>
<th>Piperacillin (n=109)</th>
<th>Meropenem (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% fT\textsubscript{&gt;MIC} achieved</td>
<td>56%</td>
<td>79%</td>
<td>81%</td>
<td>95%</td>
</tr>
<tr>
<td>50% fT\textsubscript{&gt;4xMIC} achieved</td>
<td>28%</td>
<td>50%</td>
<td>49%</td>
<td>69%</td>
</tr>
<tr>
<td>100% fT\textsubscript{&gt;MIC} achieved</td>
<td>33%</td>
<td>79%</td>
<td>67%</td>
<td>70%</td>
</tr>
<tr>
<td>100% fT\textsubscript{&gt;4xMIC} achieved</td>
<td>22%</td>
<td>71%</td>
<td>30%</td>
<td>42%</td>
</tr>
</tbody>
</table>

\( fT_{>\text{MIC}} = \) free drug concentration above minimum inhibitory concentration of dosing interval

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

## Beta-Lactam Antimicrobials

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

<table>
<thead>
<tr>
<th></th>
<th>Meropenem (n=27)</th>
<th>Piperacillin/tazobactam (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECMO</td>
<td>Control</td>
</tr>
<tr>
<td>Volume of distribution, L/kg</td>
<td>0.5 (0.3-0.9)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>Half-life, hr</td>
<td>3.0 (2.1-4.8)</td>
<td>2.9 (2.4-3.7)</td>
</tr>
<tr>
<td>Clearance, mL/min</td>
<td>125 (53-198)</td>
<td>144 (97-218)</td>
</tr>
</tbody>
</table>

Data represented as median (interquartile range)
<table>
<thead>
<tr>
<th>Patients</th>
<th>Regimen</th>
<th>Changes in clearance and volume of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 ECMO 11 Controls</td>
<td>Vancomycin 35 mg/kg over 4 hrs followed by continuous infusion to provide serum concentrations of 20-30 mcg/mL within 24 hrs</td>
<td>No change in clearance or volume of distribution</td>
</tr>
<tr>
<td>20 ECMO 60 Controls</td>
<td>Vancomycin dosed to achieve trough concentrations of 15-30 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>11 ECMO 11 Controls</td>
<td>Vancomycin 15-25 mg/kg to achieve trough concentrations of 10-20 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>10 ECMO</td>
<td>Teicoplanin 400 mg every 4 hrs x 3 doses followed by 400 mg every 24 hrs</td>
<td>No change in clearance; decreased volume of distribution</td>
</tr>
</tbody>
</table>

# Amikacin

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

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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein binding</th>
<th>Log $p$</th>
<th>Expected effect from ECMO circuit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>&lt;30%</td>
<td>-5.0</td>
<td>Minimal sequestration</td>
</tr>
<tr>
<td>Cefepime</td>
<td>20%</td>
<td>-2.8</td>
<td>Minimal sequestration</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>85-95%</td>
<td>-1.7</td>
<td>Moderate sequestration</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>24-38%</td>
<td>2.1</td>
<td>Moderate sequestration</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2%</td>
<td>-0.7</td>
<td>Minimal sequestration</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>30%</td>
<td>0.3</td>
<td>Minimal sequestration</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>55%</td>
<td>-3.1</td>
<td>Minimal sequestration</td>
</tr>
</tbody>
</table>

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

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
Pharmacotherapy in Extracorporeal Therapies: Therapeutic Plasma Exchange

Rami Ibrahim, Pharm.D., M.Sc.
Assistant Professor, Department of Pharmacology and Toxicology, College of Osteopathic Medicine, Michigan State University and Clinical Associate Professor, the School of Medicine, Wayne State University
Detroit, Michigan
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
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: $\frac{1.4}{1.8} \times 100 = \sim 75\%$

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).

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Type of Publication (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Amphotericin</td>
<td>case report (n=1)</td>
<td>overdose</td>
</tr>
<tr>
<td>2013</td>
<td>Dabigatran</td>
<td>?; n=1</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Rituximab</td>
<td>pharmacokinetic study (n=20)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Valproic acid</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Voriconazole</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Ganciclovir</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Warfarin</td>
<td>prospective observational study (n=8)</td>
<td>pharmacodynamic study per se</td>
</tr>
<tr>
<td>2015</td>
<td>Interferon</td>
<td>an open-label, single-center proof of concept study (n=6)</td>
<td>neutralizing antibodies assessed</td>
</tr>
<tr>
<td>2015</td>
<td>Bivalirudin</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>cisplatin</td>
<td>case report (n=1)</td>
<td>pediatric</td>
</tr>
<tr>
<td>2017</td>
<td>enoxaparin</td>
<td>Case report (n=1)</td>
<td>pediatric</td>
</tr>
</tbody>
</table>
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. *Semin Dial* 2012; 25(2):176-89.
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**

<table>
<thead>
<tr>
<th>Drug dependent</th>
<th>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., $t_{1/2_a}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein binding:</td>
<td>the lower the drug’s protein binding, the less likely it will be removed</td>
</tr>
<tr>
<td>Volume of distribution:</td>
<td>the higher the drug’s volume of distribution, the less likely it will be removed</td>
</tr>
</tbody>
</table>

**TPE dependent**
- Duration of TPE
- Successive TPE sessions
- Volume of plasma removed
- TPE replacement fluid (equivocal; please see text)

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

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

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

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

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

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

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

- Similar findings were reported with the antibiotic ceftazidime

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

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

<table>
<thead>
<tr>
<th></th>
<th>Total Concentration Valproic Acid (mg/L)</th>
<th>Unbound Concentration Valproic Acid (mg/L) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough level before dosing</td>
<td>43.6</td>
<td>4.7 (10.7%)</td>
</tr>
<tr>
<td>At start of plasmapheresis (3.5 h after dose)</td>
<td>80.1</td>
<td>8.5 (10.6%)</td>
</tr>
<tr>
<td>At end of plasmapheresis</td>
<td>44.2</td>
<td>4.0 (9.0%)</td>
</tr>
<tr>
<td>Plasmapherete (2.85 L)</td>
<td>45.5</td>
<td>4.1 (9.0%)</td>
</tr>
</tbody>
</table>

Immediate release formulation used

- **Amphotericin overdose**

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.

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

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

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

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

---

Ibrahim RB, Balogun RA. *Semin Dial* 2012;25(2):176-89  
Drug Removal by TPE principles:
Time to distribution might be key

Not all $V_d$s 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,
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**

<table>
<thead>
<tr>
<th>Monoclonal antibody</th>
<th>Plasma protein binding; $V_d$</th>
<th>Time from TPE</th>
<th>Extracted by TPE; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basiliximab</td>
<td>N/A; 4.8-8 L</td>
<td>&gt; 4 hours</td>
<td>Yes; ~65%</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>N/A; ~6 L</td>
<td>10-14 days</td>
<td>Yes; ~75%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>N/A; 2-5 L</td>
<td>see discussion</td>
<td>Yes – see discussion</td>
</tr>
</tbody>
</table>

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

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

- No pharmacokinetic analysis

**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

<table>
<thead>
<tr>
<th>Publications</th>
<th>Time of rituximab dose from TPE</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald V, et al. <em>J Thromb Haemost</em> 2010;8(6):1201-8</td>
<td>24 hours (?)</td>
<td>Yes; ~70%</td>
</tr>
<tr>
<td>Scully M, et al. <em>Blood</em> 2011;118(7):1746-53</td>
<td>At a minimum 4 hours</td>
<td>CD19+ B-cells depressed; ADAMTS13 activity increased and Anti-ADAMTS13 IgG decreased; appropriate hematologic response to TTP seen</td>
</tr>
<tr>
<td>Puisset F, et al. <em>Br J Clin Pharmacol</em> 2013;76(5):734-40</td>
<td>24-72 hours</td>
<td>Yes; 47% - 54% (mostly with after the first session)</td>
</tr>
</tbody>
</table>
Drug Removal by TPE principles: Relation between the amount removed and biologic effect: *Monoclonal Antibodies* - Rituximab

\[ X \text{ dose 1} \quad X \text{ dose 2} \quad X \text{ dose 3} \quad X \text{ dose 4} \]

** Weekly intervals  
** PK simulation

Drug Removal by TPE principles:

TPE = troubled waters

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

**Warfarin**

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

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

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

Drug Removal by TPE principles:

Check List

✓ Time between dose administration and TPE
  ✓ distribution half-life ($t_{1/2a}$)

✓ 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

• 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
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

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

PK=Pharmacokinetic

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

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE (y)</th>
<th>GENDER</th>
<th>SCr (mg/dL)</th>
<th>k_e (h⁻¹)</th>
<th>V_d (L)</th>
<th>Cl_pr (L/h)</th>
<th>Cl_peg (L/h)</th>
<th>Cl_t (L/h)</th>
<th>% INCREASE IN Cl_t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>49.3 ± 19.2</td>
<td></td>
<td>3.2 ± 2.5</td>
<td>0.04 ± 0.03</td>
<td>49.2 ± 16.3</td>
<td>1.9 ± 1.2</td>
<td>1.6 ± 0.4</td>
<td>3.6 ± 1.1</td>
<td>285 ± 191</td>
</tr>
</tbody>
</table>

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

An example from the NCAA...sort of

% increase in PPG from 2014-2016:

\[
PFP (2016)/PPG (2014) = \frac{0.6}{0.2} \times 100 = 300%
\]
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

  ![Graph showing drug serum concentration over time with TPE intervention.]

  - 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?

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*)

* red cell exchange

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.
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