ECMO in the Era of COVID-19: Optimizing Medication Management

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Disclosures

- No conflicts of interest

- Off-label drug use will be discussed

Pharmacist Objectives

1. Describe the indications and outcomes of extracorporeal membrane oxygenation (ECMO) for adult patients with and without severe coronavirus disease 2019 (COVID-19)

2. Explain altered pharmacokinetics and pharmacodynamics of medications in critically ill patients receiving ECMO

3. Devise an approach to optimize medication management in critically ill patients receiving ECMO

Pharmacy Technician Objectives

1. List the indications for ECMO for adult patients

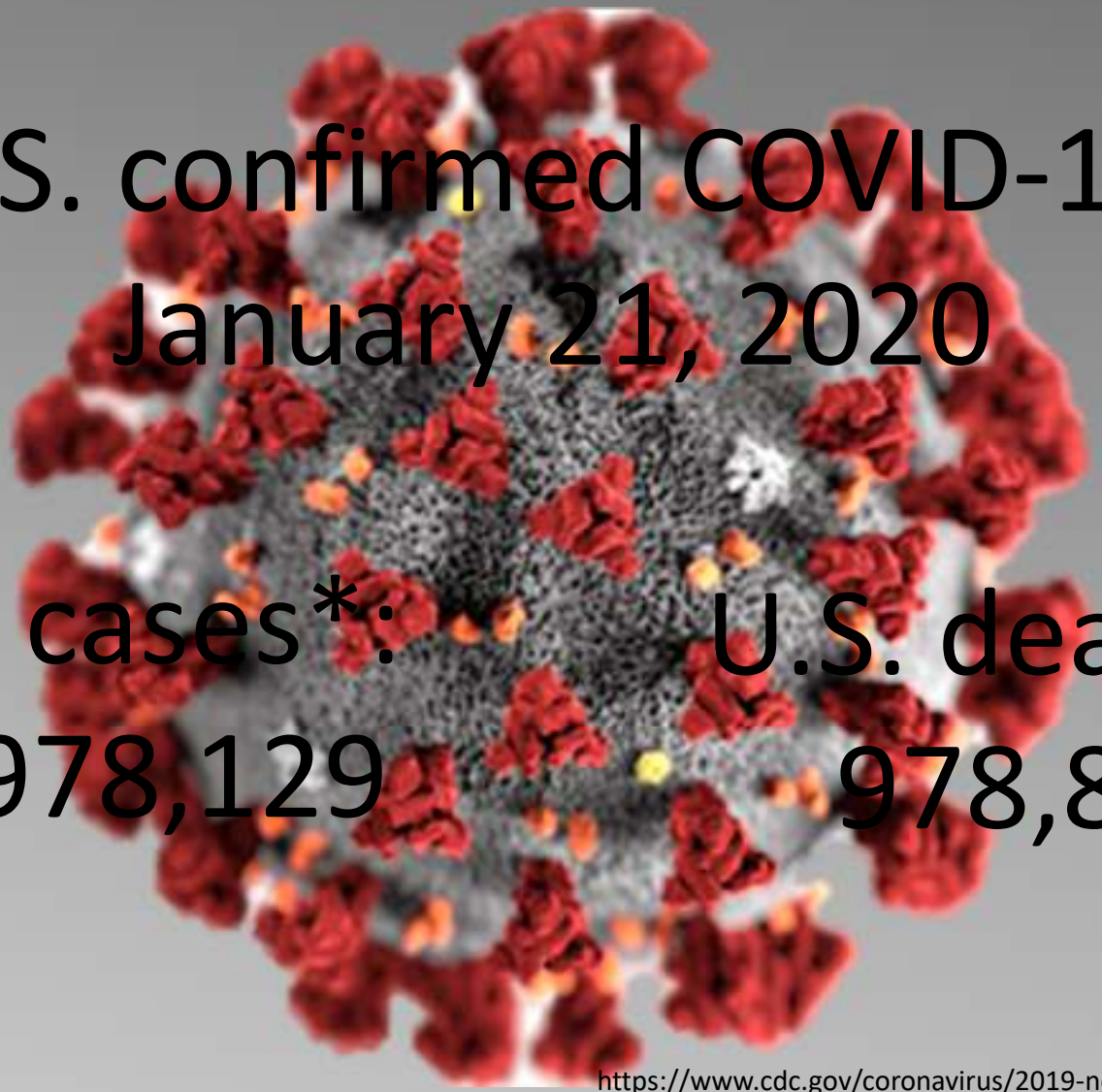
2. Recognize common medications used in adult patients receiving ECMO with and without severe COVID-19

3. Recognize the potential for increased medication requirements for adult patients receiving ECMO

First U.S. confirmed COVID-19 case:
January 21, 2020

U.S. cases*:
79,978,129

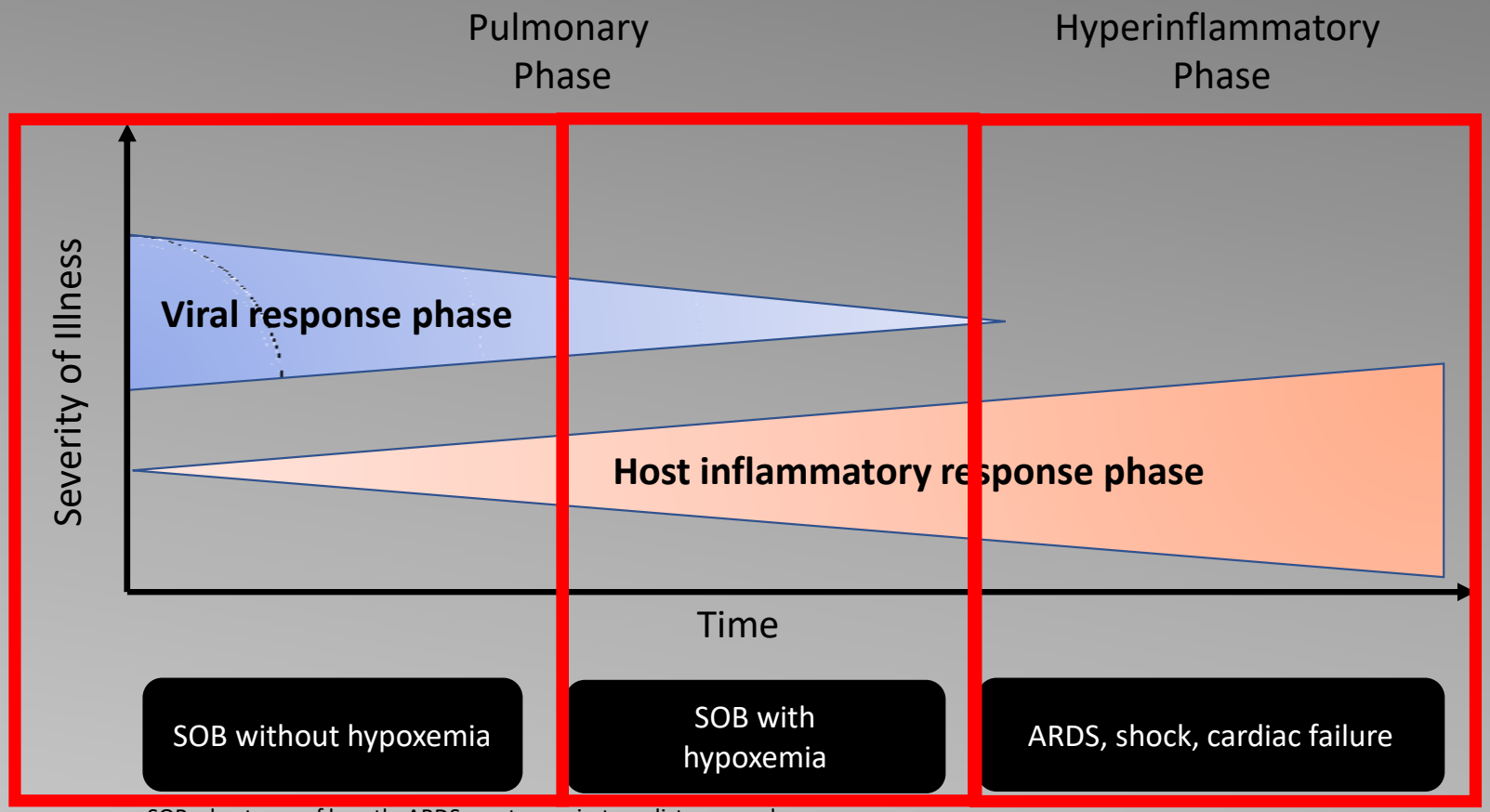
U.S. deaths*:
978,852



*As of April 3, 2022

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.

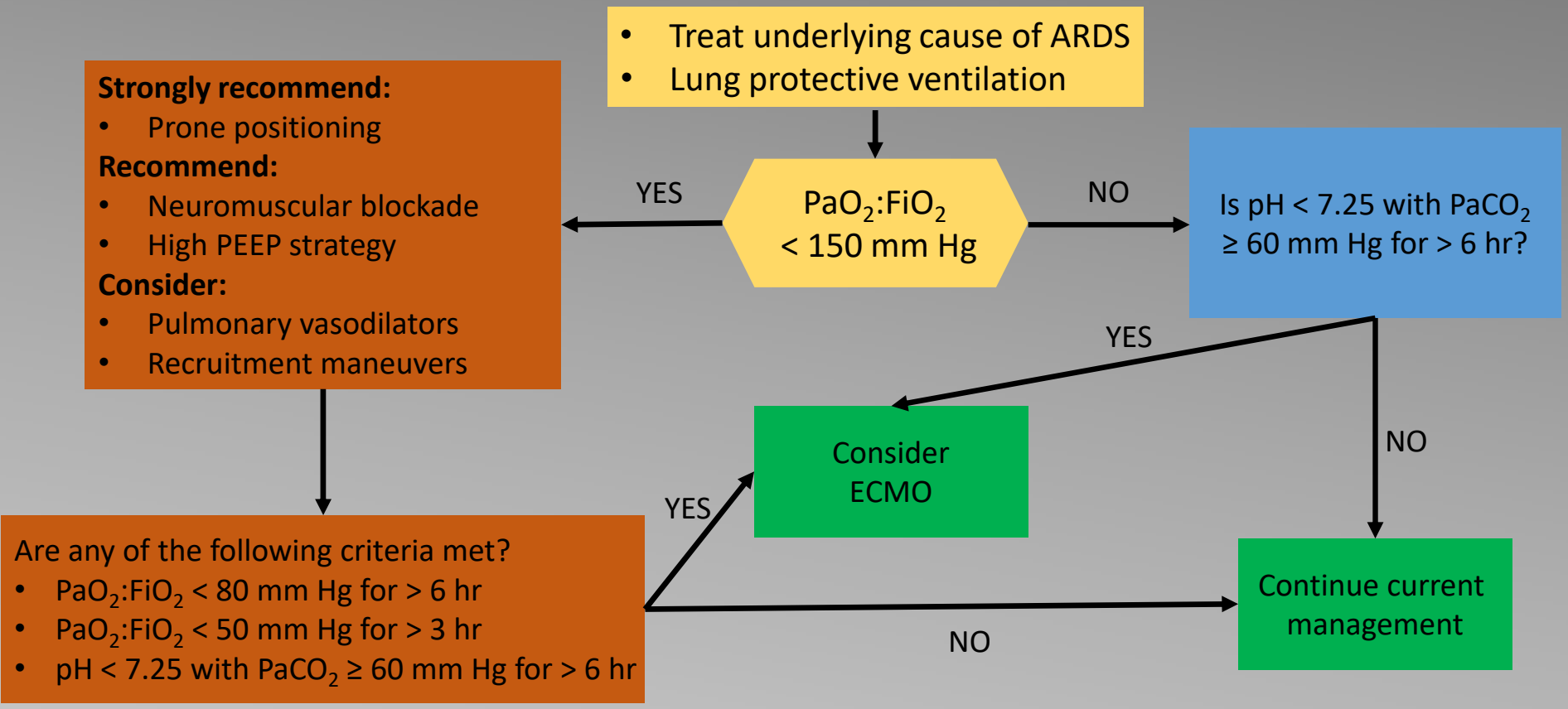
Stages of COVID-19



SOB=shortness of breath; ARDS=acute respiratory distress syndrome

Wiersinga WJ, et al. JAMA. 2020;324:782-93.
Siddiqi HK and Mehra MR. J Heart and Lung Transplant. 2020;39:405-7.

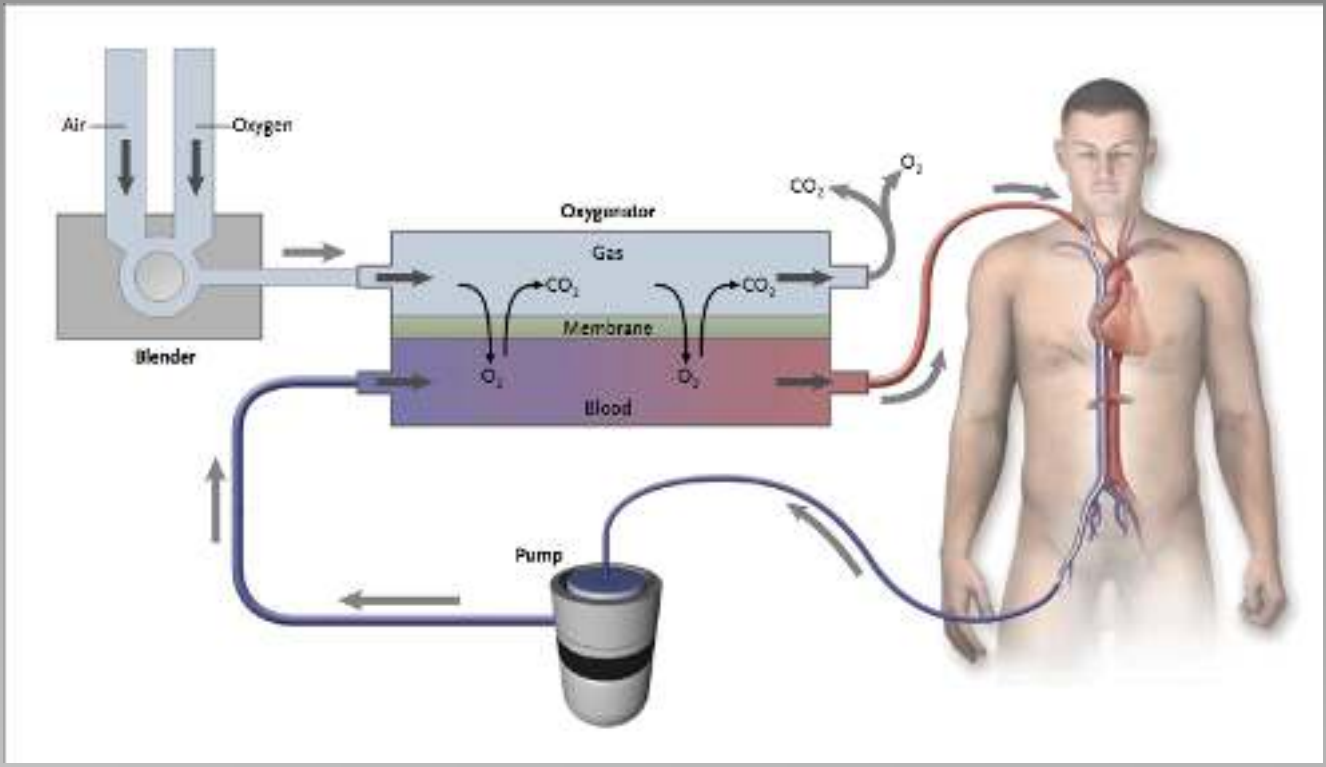
COVID-19-associated ARDS



PaO_2:FiO_2=ratio of partial pressure of oxygen in arterial blood to the fractional concentration of oxygen in inspired air; PEEP=positive end-expiratory pressure; $PaCO_2$=partial pressure of carbon dioxide in arterial blood

Abrams D, et al. Lancet Respir Med. 2019;7:108-10.

What is ECMO?

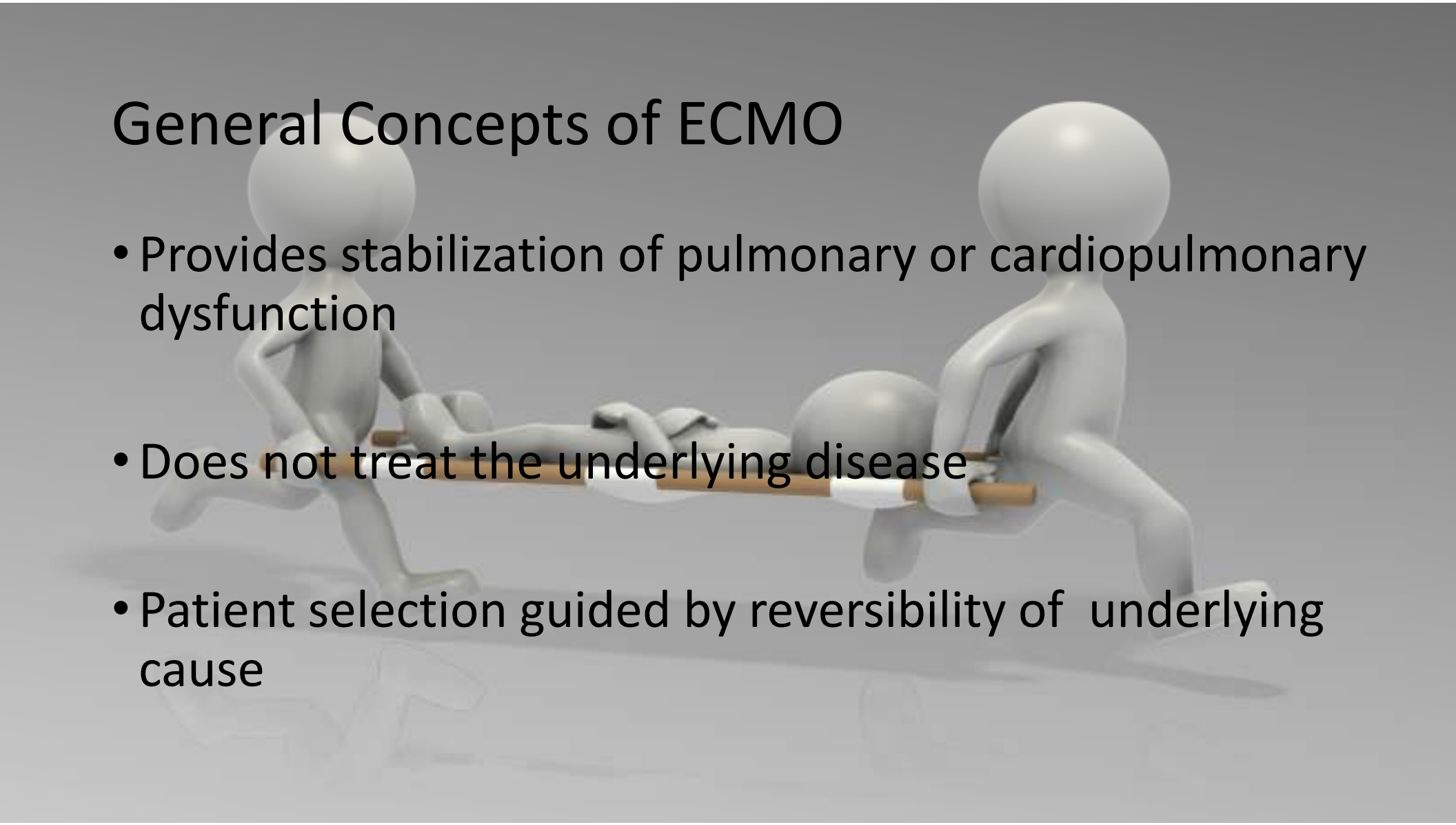


Brodie D, et al. N Engl J Med. 2011;365:1905-14.

Photo courtesy of Robert Bartlett, MD

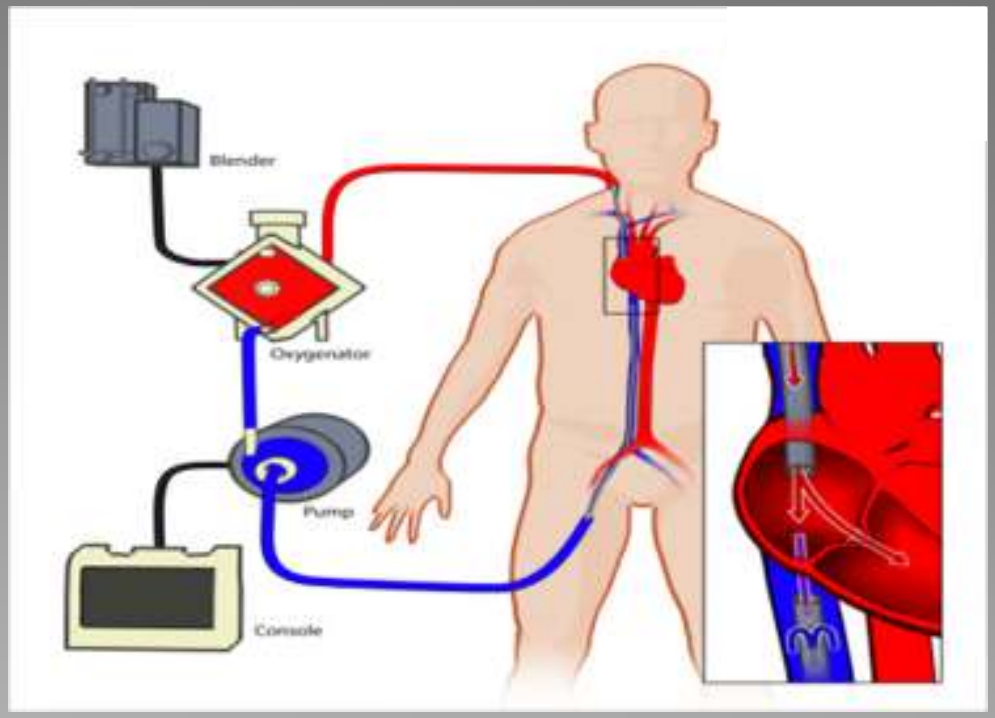
Photo courtesy of Dana Mullin, MS, CCP, LP

General Concepts of ECMO



- Provides stabilization of pulmonary or cardiopulmonary dysfunction
- Does not treat the underlying disease
- Patient selection guided by reversibility of underlying cause

Veno-venous (VV) ECMO



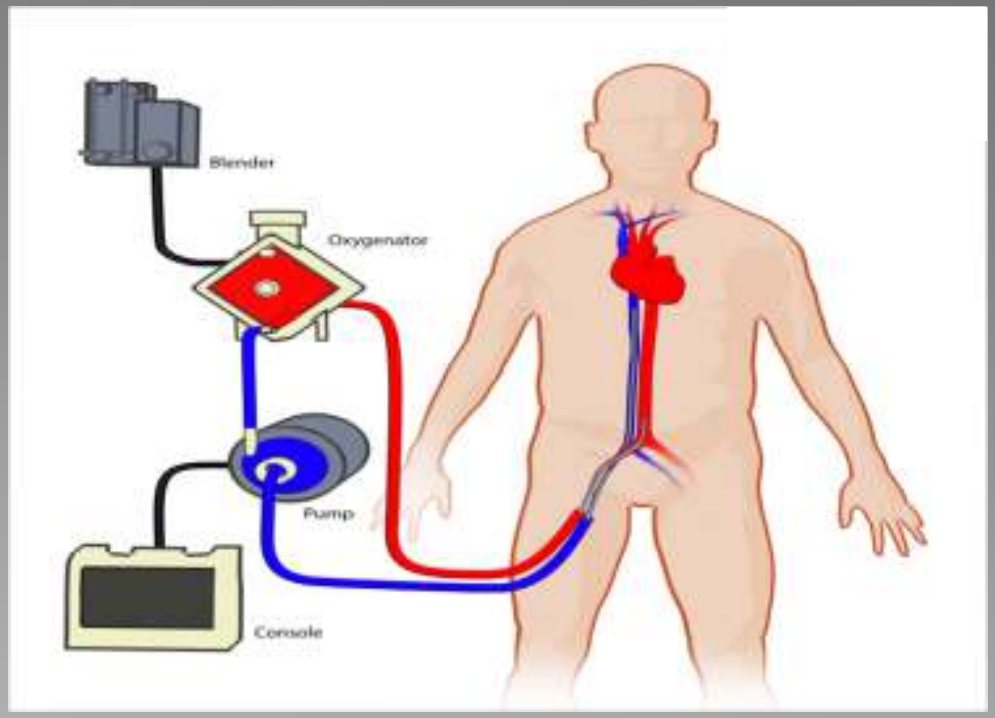
Blood Drainage: Vein

Blood Reinfusion: Vein

Conditions Treated: ARDS; hypercapnic respiratory failure; bridge to lung transplantation; primary graft dysfunction after lung transplantation

Abrams D, et al. Clin Chest Med. 2014;35:765-79.
Abrams D, et al. J Am Coll Cardiol. 2014;63:2769-78.

Veno-arterial (VA) ECMO



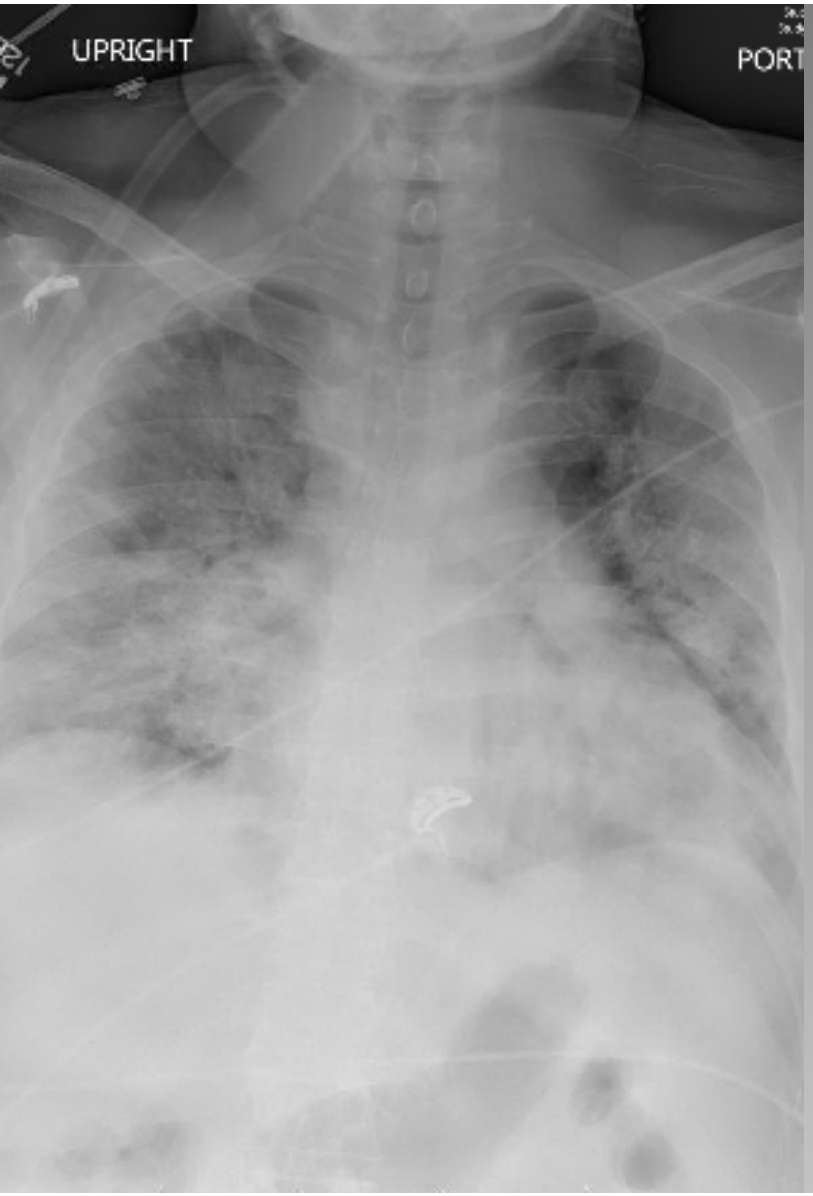
Blood Drainage: Vein

Blood Reinfusion: Artery

Conditions Treated: Cardiogenic shock (myocardial infarction, sepsis, post-cardiotomy); fulminant myocarditis; pulmonary hypertension; cardiopulmonary resuscitation; primary graft failure after heart transplantation; bridge to VAD implantation or heart transplantation; prevention of acute RV failure after LVAD implantation

Abrams D, et al. Clin Chest Med. 2014;35:765-79.
Abrams D, et al. J Am Coll Cardiol. 2014;63:2769-78.

RV=right ventricle; LVAD=left ventricular assist device



Patient Case

- A 45-year-old woman with an unremarkable medical history presents to the emergency room with severe shortness of breath, tachypnea, and altered mental status
- Chest radiography reveals diffuse, bilateral opacities
- In the ICU, she is intubated with lung protective ventilation, initiated on continuous fentanyl and propofol infusions to allow for a deep level of sedation, and is in the prone position
- It is decided to initiate extracorporeal support

Patient Case

Which one of the following forms of extracorporeal support is best to recommend for this patient?

1. VV-ECMO
2. VA-ECMO

Patient Case

Which one of the following forms of extracorporeal support is best to recommend for this patient?

VV-ECMO

(Bridge to recovery)

Patient Cases

A 65-year-old man with interstitial lung disease and pulmonary hypertension (PH), presenting with decompensated PH and RV failure → desaturates despite high flow nasal cannula and non-rebreather mask → VA-ECMO

Bridge to transplant

A 44-year-old woman presents with sudden cardiac arrest (ventricular fibrillation) → conventional CPR performed for 12 minutes without return of spontaneous circulation → VA-ECMO

Bridge to decision

CPR=cardiopulmonary resuscitation

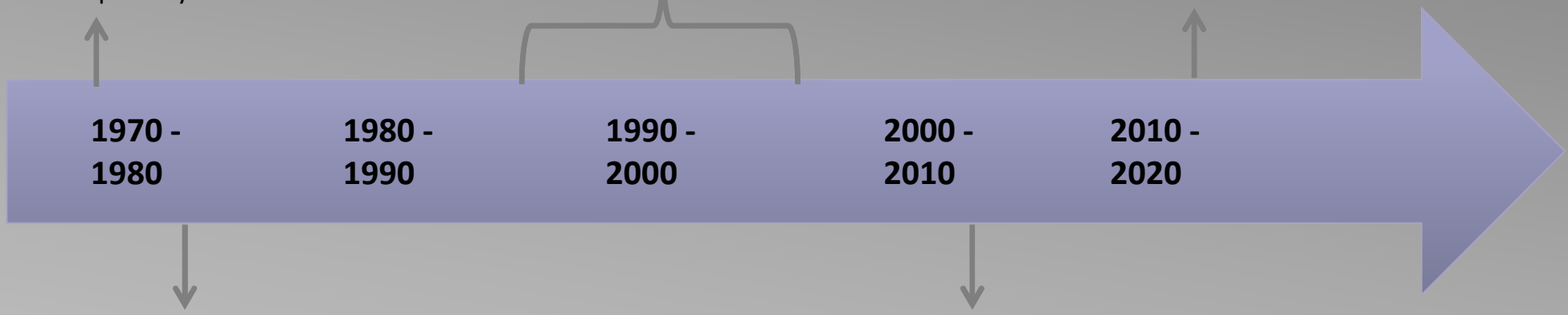
Improved Survival Over Time

1971: First adult ECMO for respiratory failure

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

2018: (EOLIA trial)

- 60-day mortality: 35% in ECMO group vs. 46% in controls; p=0.09
- Treatment failure at day 60: relative risk of 0.62 (95% CI 0.47-0.92, p<0.001) in favor of the ECMO group



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

2009: (CESAR trial)
Survival without severe disability at 6 months:
63% in ECMO-referred patients vs. 47% in controls; p=0.03

Zapol WM, et al. JAMA. 1979;242:2193-6.
Peek GJ, et al. Lancet. 2009;374:1351-63.
Combes A MA, et al. N Engl J Med. 2018;378:1965-75.

Changes in Survival with COVID-19

1182 patients received ECMO at 236 early-adopting centers

2824 patients received ECMO at one of the early-adopting centers

May 1, 2020

In-hospital mortality 90 days after starting ECMO

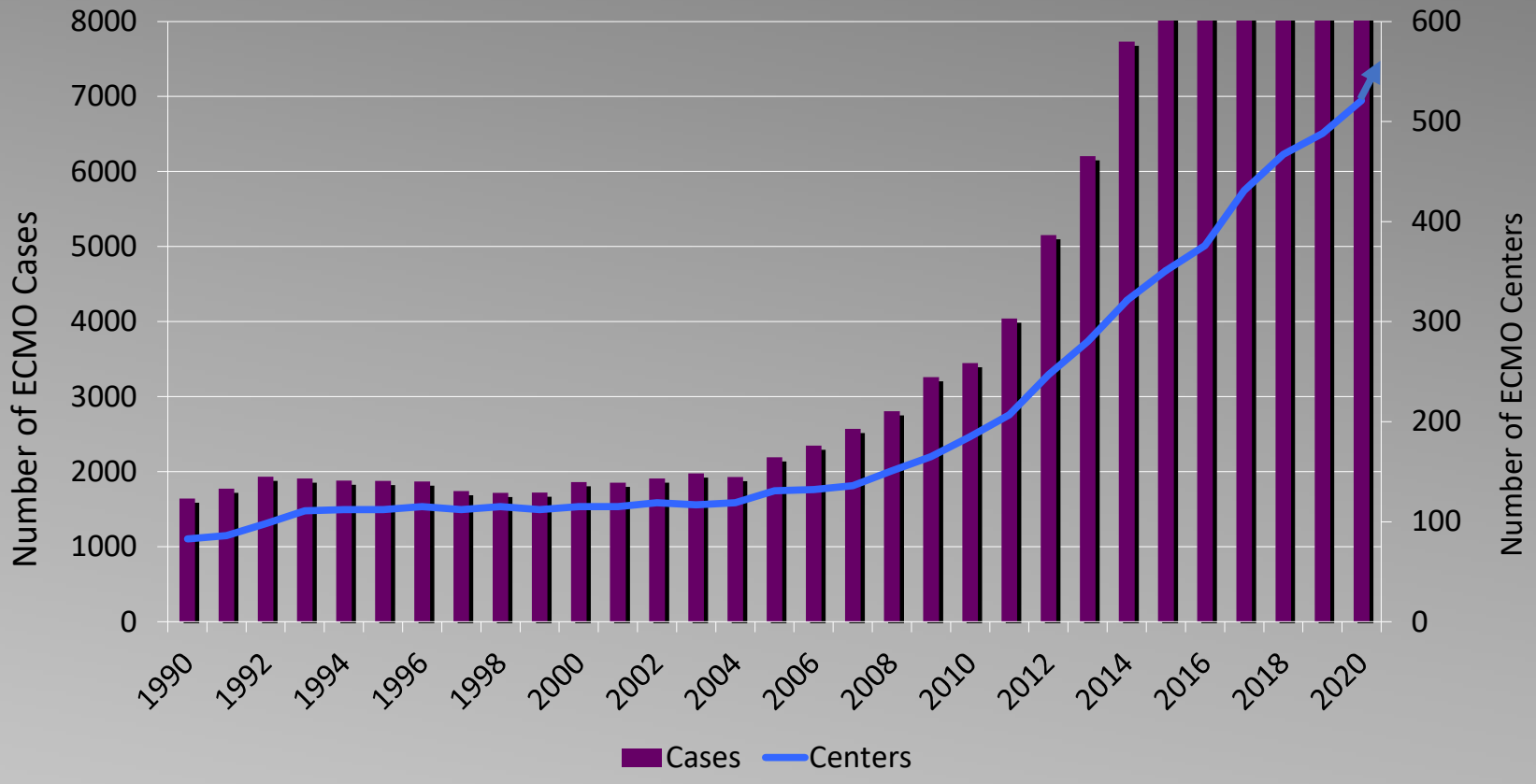
36.9% (95% CI 34.1–39.7)

51.9% (95% CI 50.0–53.8)

15%

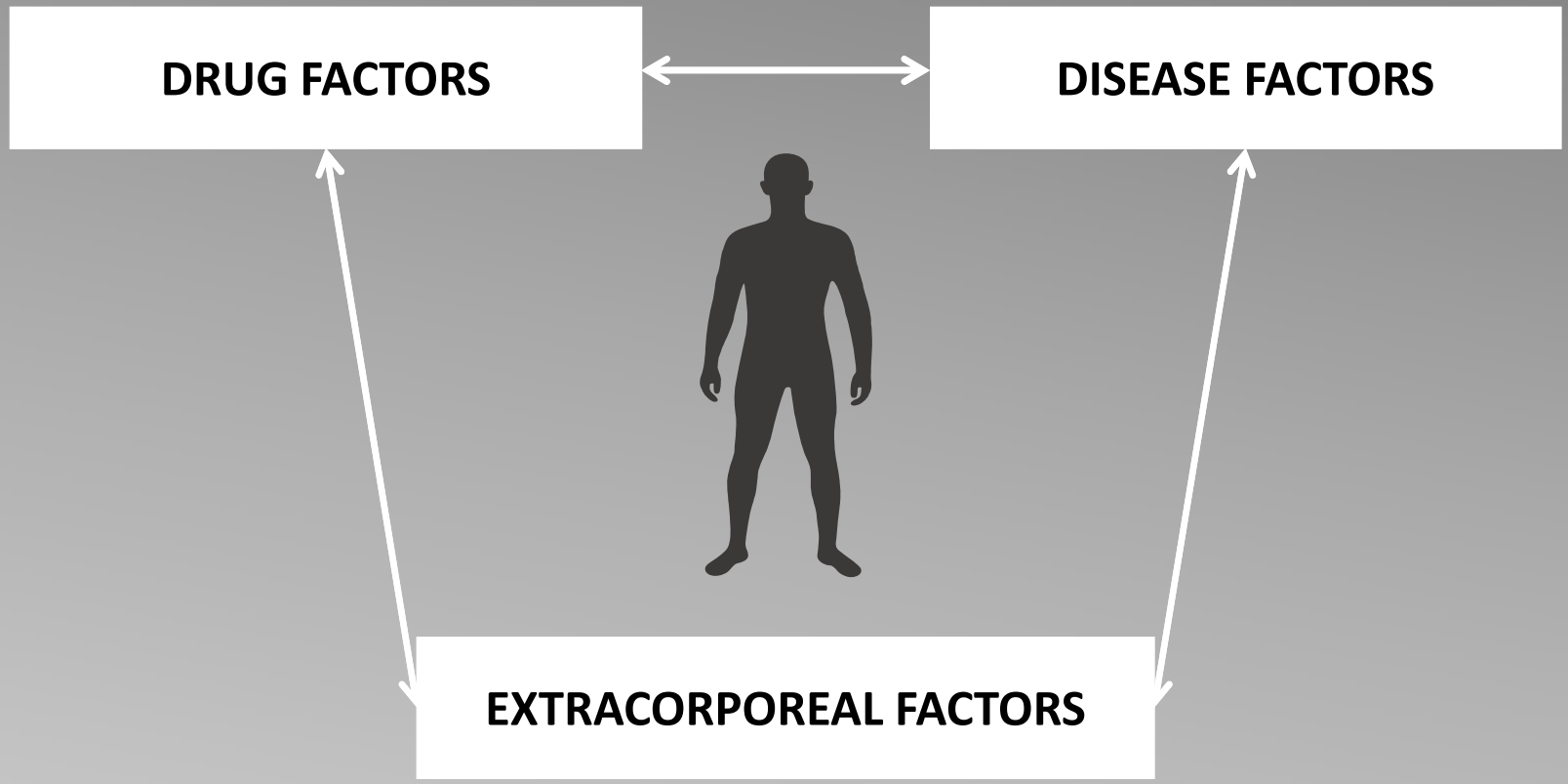
Barbaro RP, et al. Lancet. 2021;398:1230-38.

International ECMO Growth

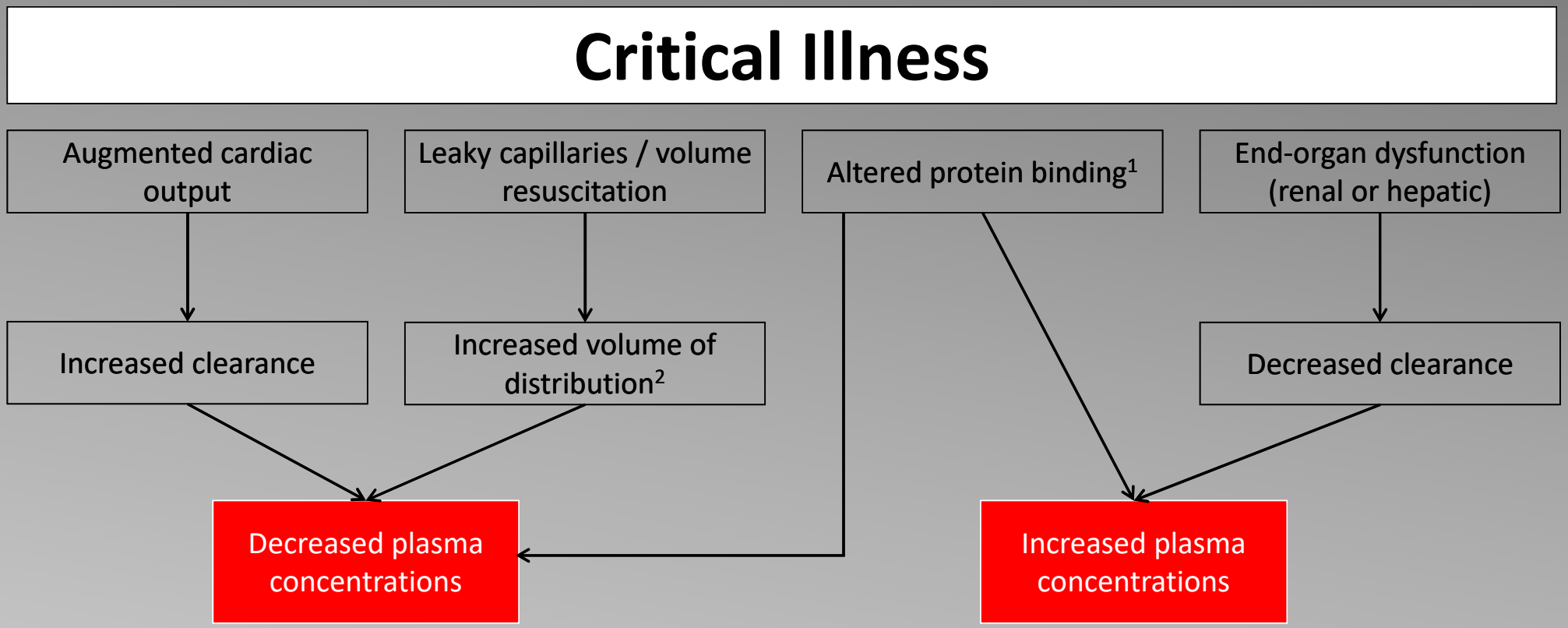


http://www.elsonet.org

Pharmacotherapy in Critically Ill



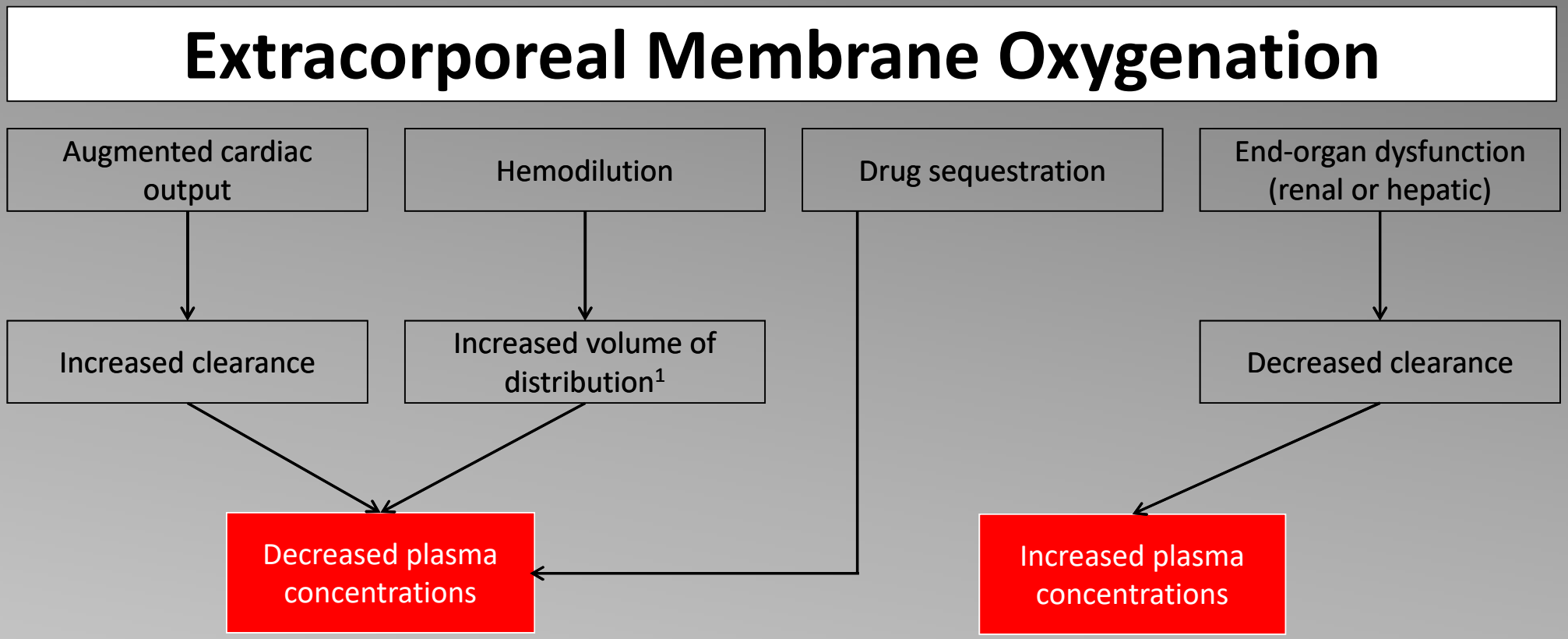
Pharmacokinetic Alterations



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

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

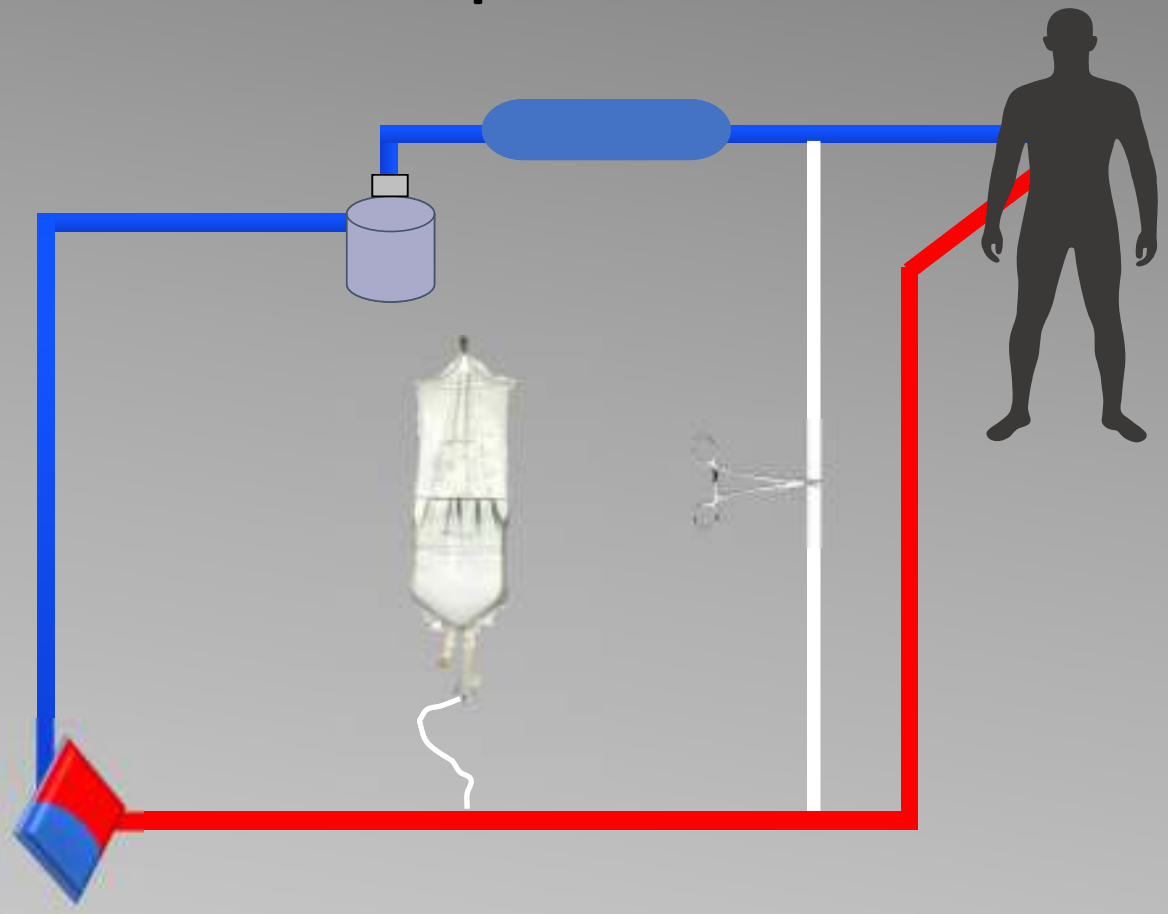
Pharmacokinetic Alterations



[1]Mostly affects hydrophilic drugs

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

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

Ionization

Molecular weight

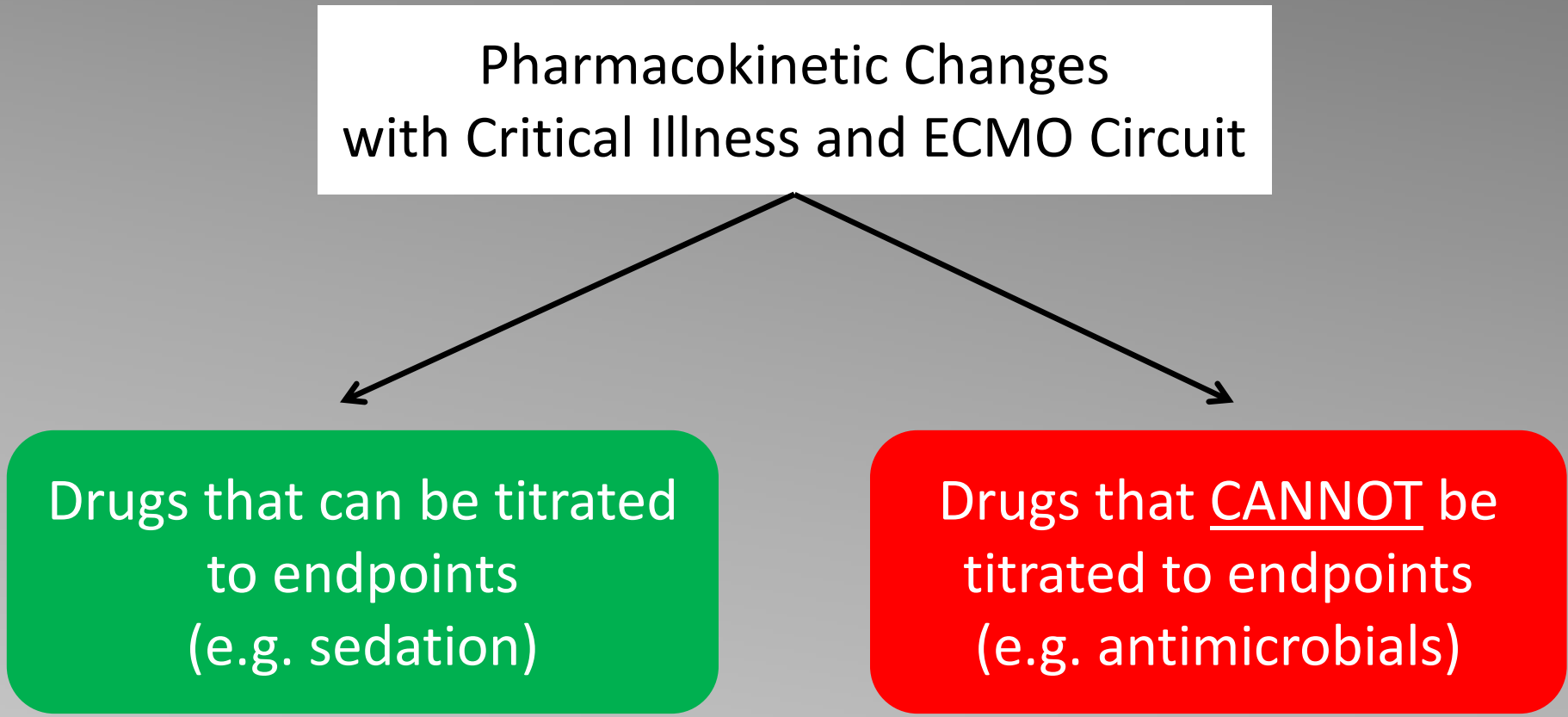
Protein binding

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

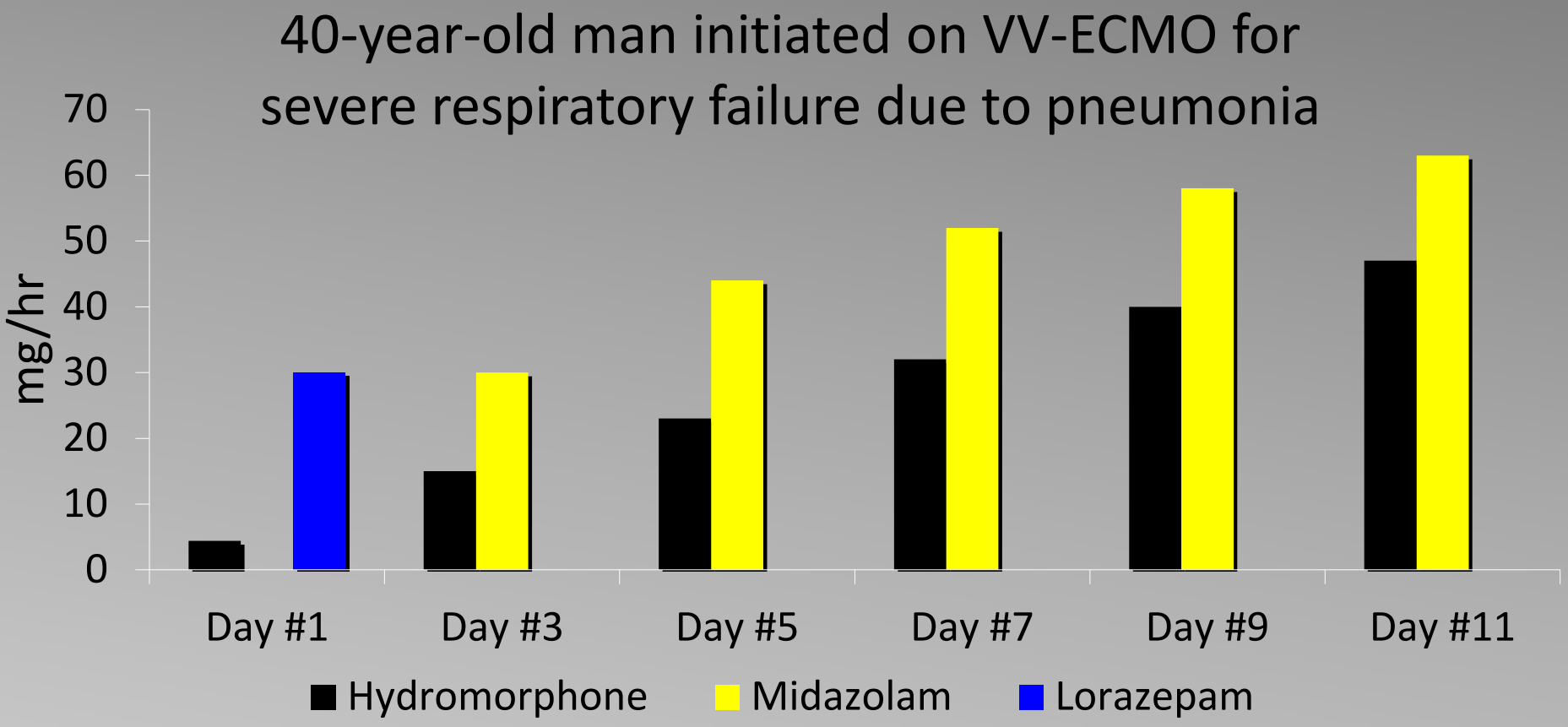
Lipophilicity

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

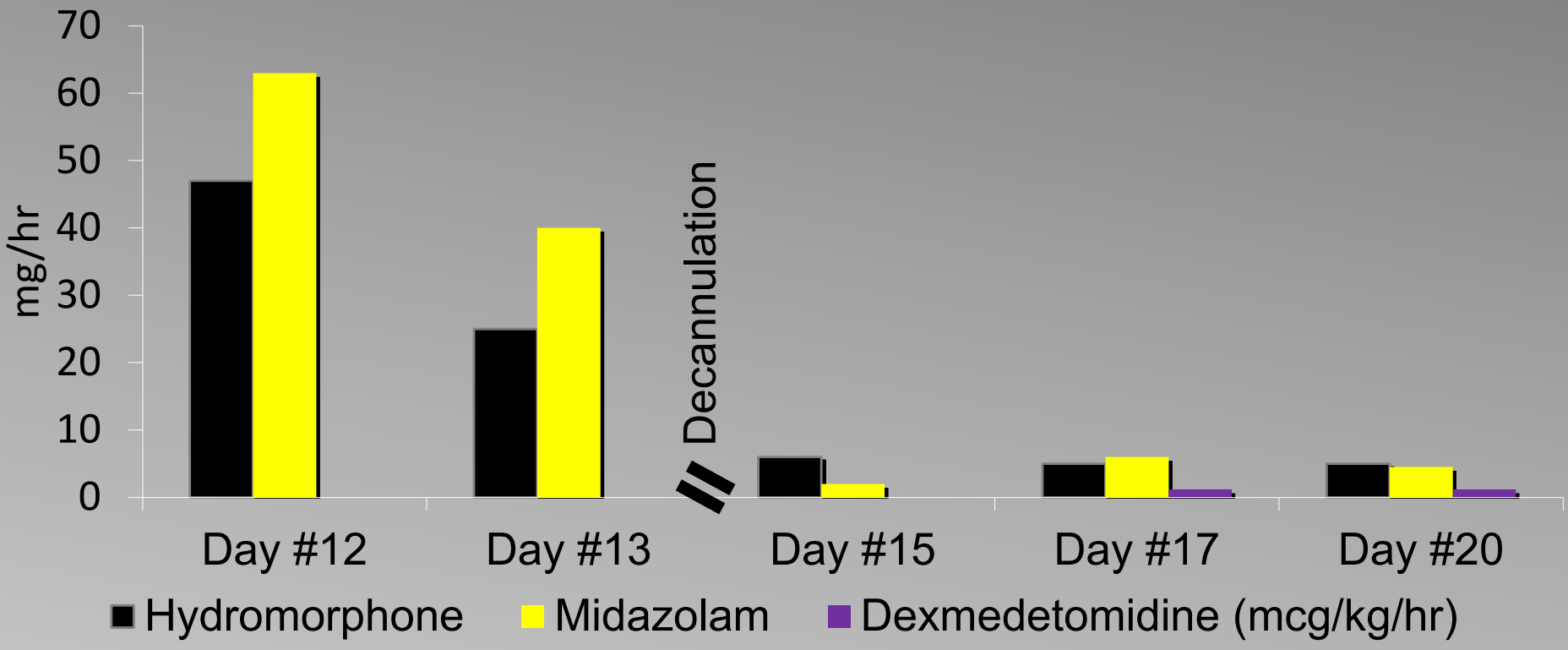
Challenges in Drug Dosing



Patient Experience

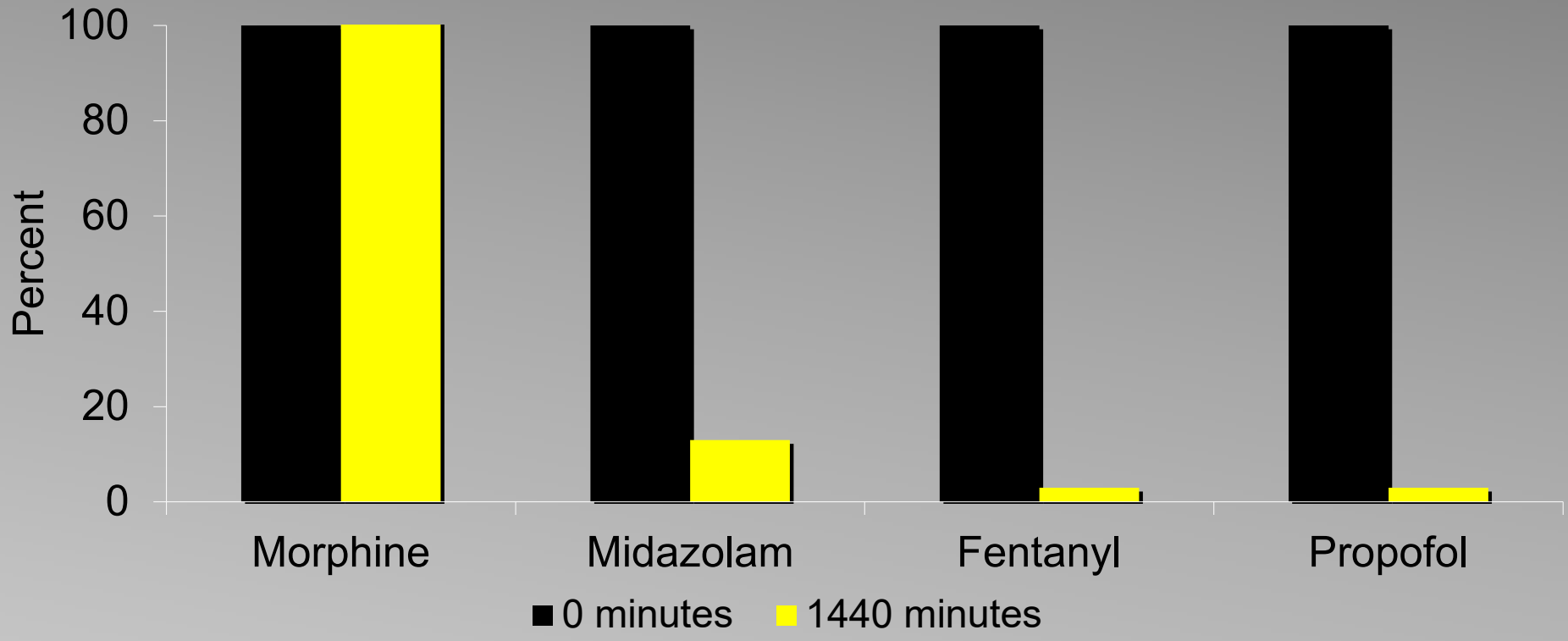


Patient Experience



Analgesics and Sedatives

Simulated adult ECMO circuits



Shekar K, et al. Crit Care. 2012;16:194.
Lemaitre F, et al. Crit Care. 2015;19:40.

Analgesics and Sedatives

Drug	Protein binding (%)	Log p
Fentanyl	79-87	3.9
Remifentanil	60-70	1.7
Hydromorphone	8-19	0.9
Morphine	20-35	0.8

Sequestration by ECMO circuit:
Fentanyl > Remifentanil>>>
Morphine > Hydromorphone

Drug	Protein binding (%)	Log p
Propofol	95-99	4.0
Lorazepam	85-91	3.5
Midazolam	97	3.5
Dexmedetomidine	94	3.3

Sequestration by ECMO circuit:
Propofol >>> Midazolam >
Lorazepam > Dexmedetomidine

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

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

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

Sedation Requirements

Retrospective analysis of 45 patients receiving VV-ECMO for ARDS

	48-hrs post VV-ECMO initiation (n=45)
Deeply sedated, n (%)	43 (96)
Continuous infusion sedative, n (%)	43 (96)
Continuous infusion opioid, n (%)	44 (98)
Daily propofol dose in mg, median (IQR)	3,380 (1,105-4,110)
Daily midazolam equivalents dose in mg, median (IQR)	202 (103-247)
Daily fentanyl equivalents dose in mcg, median (IQR)	4,800 (3,000-5,820)

DeBacker J, et al. ASAIO J. 2018;64:544-51.

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 (IQR)
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

DerNigoghossian C, et al. Pharmacotherapy. 2016;35:2527-16.

Sedation Requirements with COVID-19

Opioid and sedative requirements in patients with COVID-19-associated ARDS compared to non-COVID-19 ARDS

Younger age

High respiratory drive

Intense inflammatory response

Ego A, et al. Microorganisms. 2021;9:2393.
Tapaskar N, et al. Ann Pharmacother. 2022;56:117-23.

Sedation Requirements with COVID-19 and ECMO

Retrospective, observational matched cohort of patients with ARDS receiving VV-ECMO

	COVID-19 Positive (n=22)	COVID-19 Negative (n=22)	p-value
Proportion of ECMO days with RASS $\geq$ -2	0.48 (0.32-0.87)	0.28 (0-0.69)	0.07
Number of sedative infusions while on ECMO	2.5 (1.0-3.0)	2.0 (1.0-3.0)	0.71
Total propofol dose (mg/kg/ECMO hr)	0.77 (0.46-0.98)	0.48 (0.34-0.84)	0.37

Median (IQR)
Only the first 20 days after ECMO cannulation included

RASS=Richmond Agitation Sedation Scale

Bohman JK, et al. J Cardiothorac Vasc Anesth. 2022;36:524-8.

Guideline Key Concepts

- Routinely assessment for pain, agitation, and delirium
- Consider pain as a source of agitation
- Target light sedation (vs. deep sedation)
- Use propofol or dexmedetomidine as preferred sedative over benzodiazepines
- Preform rehabilitation or mobilization

Barr J, et al. Crit Care Med. 2013;41:263-306.
Devlin JW, et al. Crit Care Med. 2018;46:e825-73.

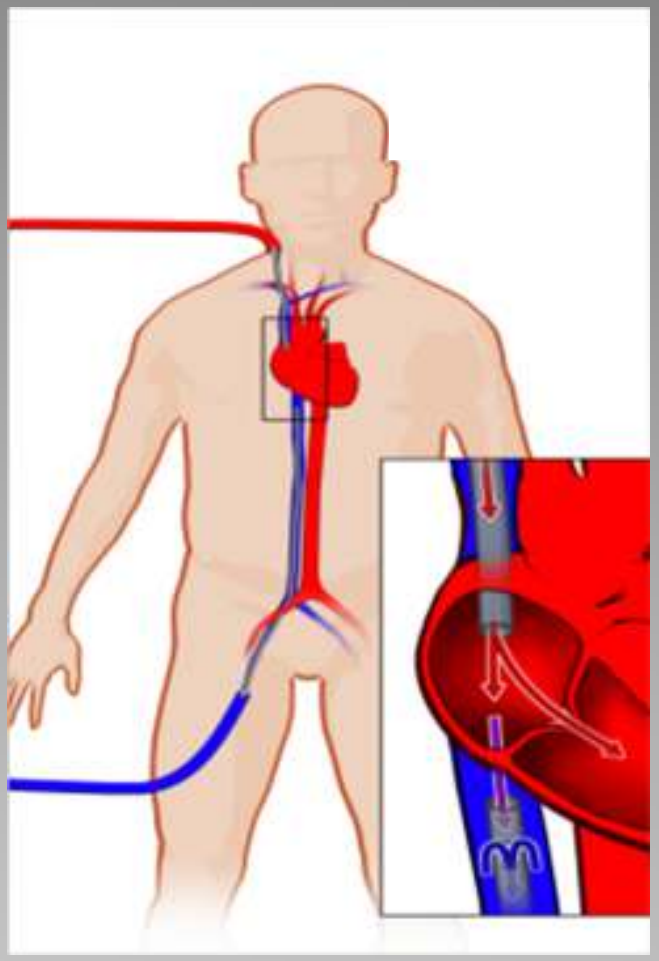
- Severe respiratory failure:
  - Requirements usually exceed standard doses
  - Establish daily sedative goals with potential sedative reduction / interruption when clinically indicated
  - Anticipate significant dose reduction at ECMO discontinuation
  - Monitor for signs of delirium / withdrawal

Minimal sedative exposure

Bridge to Transplantation

Photo courtesy of Daniel Brodie, MD

Bridge to Decision



Patient Case

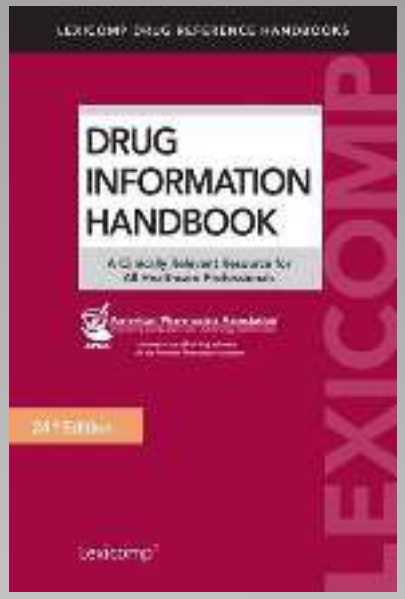
- VV-ECMO is initiated
- Current analgesia and sedation:
  - Fentanyl 100 mcg/hr and propofol 40 mcg/kg/min
  - Current RASS -2; goal RASS -5, no pain documented

How can analgesia and sedation be optimized in this patient?

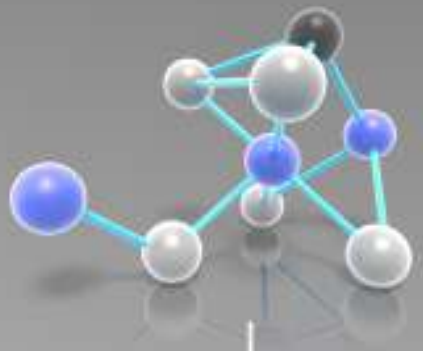
1. Double the dose of fentanyl, no change to propofol
2. Change propofol to a midazolam infusion, no change to fentanyl
3. Change fentanyl to a morphine infusion, no change to propofol
4. Change propofol to a midazolam infusion and fentanyl to a morphine infusion

Antimicrobials

Can population pharmacokinetics of antimicrobials be applied to all patients receiving ECMO?



Drug Development



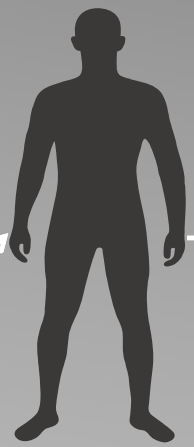


Photo courtesy of Robert Bartlett, MD

Implications of Inappropriate Antimicrobial Dosing

- Therapeutic failures
- Toxicity
- Development of resistance

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

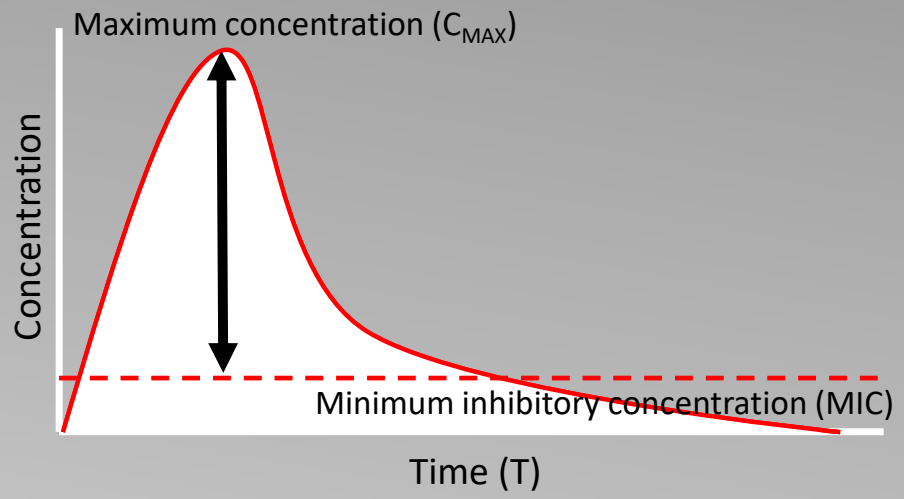
16% of patients treated for infections did not achieve 50% $fT_{>MIC}$ and were 32% less likely to have a favorable outcome [OR 0.68 (95% CI 0.52-0.91); p=0.009]

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

Aminoglycosides

Hydrophilic, low protein binding

Concentration-dependent (C_{MAX}/MIC)



ECMO:

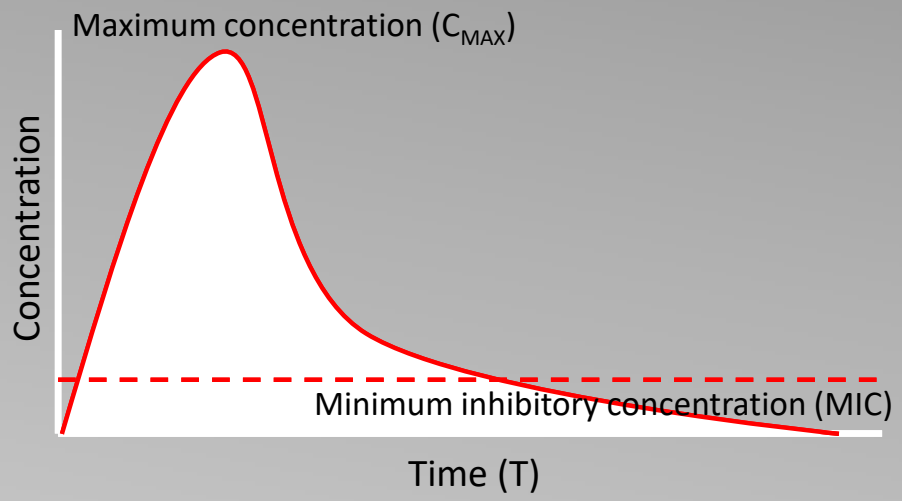
- ~40% of patients do not achieve adequate PK/PD targets
- Larger volume of distribution compared to patients not receiving ECMO
- Risk factors:
  - Lower body mass index
  - Positive 24 hour fluid balance
- Recommendations:
  - Use higher than recommended loading dose
  - Employ therapeutic drug monitoring to guide dosing

Touchard C, et al. Crit Care. 2018;22:199.
Ruiz-Ramos J, et al. ASAIO J. 2018;64:686-8.
Gelisse E, et al. Intensive Care Med. 2016;42:946-8.

Vancomycin

Hydrophilic, moderate protein binding

Concentration-dependent with time (Area under the curve (AUC)/MIC)



ECMO:

- No difference in volume of distribution of clearance compared to patients not receiving ECMO
- Recommendations:
  - Use weight-based loading and maintenance dose for critically ill patients
  - Employ therapeutic drug monitoring to guide dosing

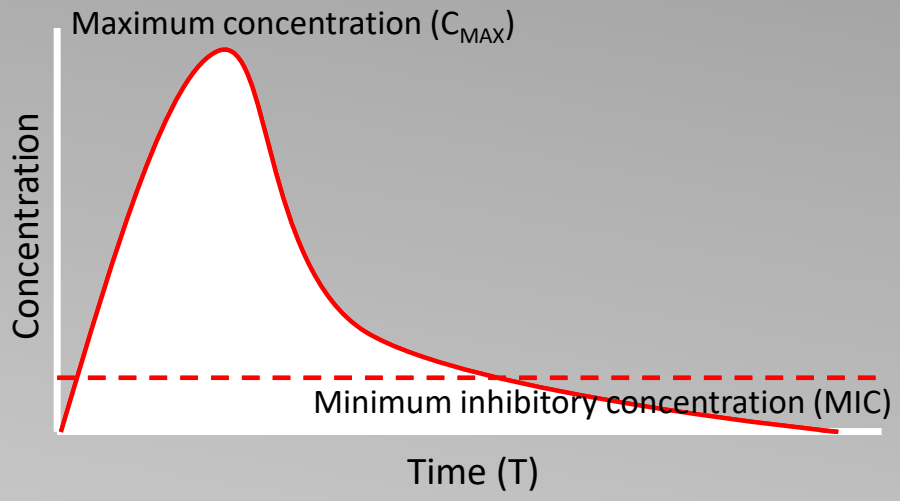
Donadello K, et al. Crit Care. 2014;22:632.
Park SJ, et al. PLoS One. 2015;10:e0141016.
Wu CC, et al. J Formos Med Assoc. 2016;115:560-70.

Beta-Lactam Antimicrobials

Hydrophilic, low-moderate protein binding

Time-dependent

%T>MIC



ECMO:

- Prospective case-controlled study[1]
  - 86% of patients did not obtain a trough concentration of piperacillin above the target after the first dose
- Prospective observational study[2]
  - Significantly lower median serum concentrations of piperacillin and standard-dose meropenem in patients receiving ECMO

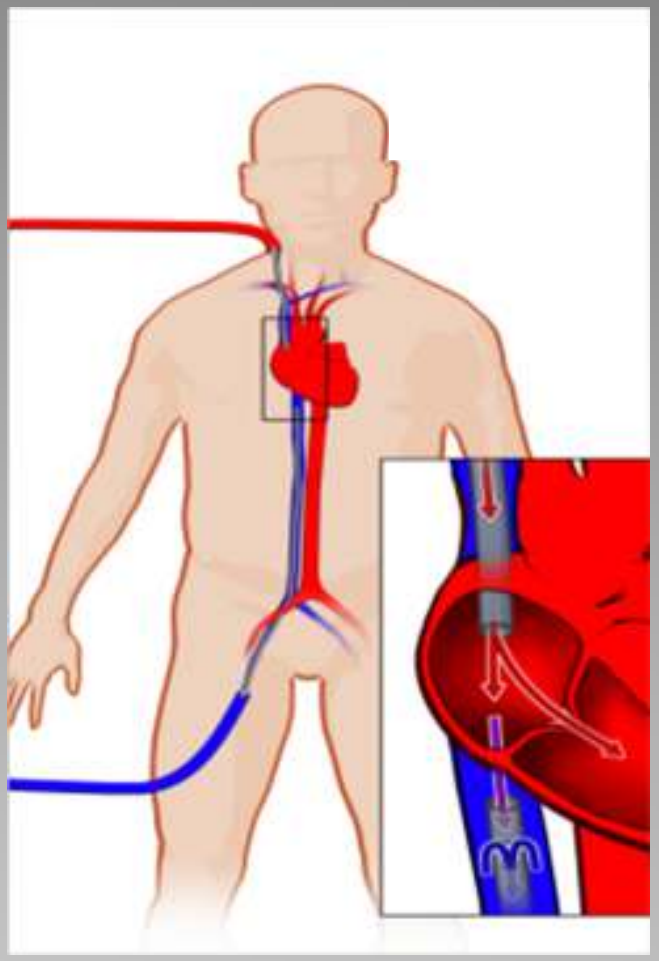
[1]Fillâtre P, et al. J Antimicrob Chemother. 2021;76:1242-9.
[2]Kühn D, et al. Crit Care. 2020;24:664.

Beta-Lactam Antimicrobial Recommendations

- Use continuous infusions to optimize pharmacokinetic and pharmacodynamic parameters
- Employ therapeutic drug monitoring
  - Early detection of subtherapeutic concentrations
  - Decrease the risk of adverse events

Antimicrobial Management

- Couple source control with timely and appropriate antimicrobial administration
- Use published pharmacokinetic data in the critically ill to make dosage adjustments
- Employ therapeutic drug monitoring for dose adjustments



Patient Case

- 10 days after the initiation of VV-ECMO the patient develops septic shock from a ventilator-associated pneumonia
- Meropenem, vancomycin, and tobramycin are initiated

Which would be the most appropriate to consider?

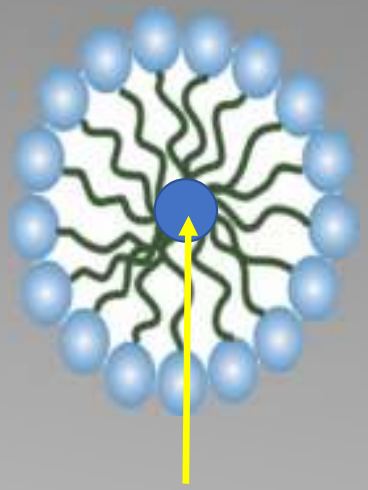
1. Double the vancomycin loading dose
2. Decrease tobramycin loading dose
3. Increase meropenem dose
4. Use doses from the package insert

What Changes Can Be Made?

Change the Tubing?

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

Change the Drug?



Drug solubilized in the hydrophobic core

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

Summary

- ECMO is an important device that can be used in appropriate patients for the management of cardiorespiratory failure
- The ECMO circuit influences pharmacokinetics of commonly used drugs
- Drug dosing recommendations for adult patients receiving ECMO are unlikely to be evidenced-based

ECMO in the Era of COVID-19: Optimizing Medication Management

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