Continuous Renal Replacement Therapy: Antimicrobial Dosing Considerations

A presentation for HealthTrust Members
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HaYoung Ryu, PharmD
PGY-1 Pharmacy Resident
Robert Wood Johnson University Hospital

***Deepali Dixit**, PharmD, BCPS, BCCCP, FCCM, Preceptor*
Clinical Associate Professor, Ernest Mario School of Pharmacy
Rutgers University

Conflict of Interest Disclosure

- There are no relevant financial interest to disclose for myself or my spouse/partner within the last 12 months.
- Preceptor conflict of interest disclosure: There are no relevant financial interest to disclose.
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Learning Objectives

- *At the end of this session, participants should be able to…*
  - Compare and contrast various modalities of continuous renal replacement therapy (CRRT)
  - Identify CRRT-specific considerations impacting pharmacokinetic and pharmacodynamic properties of antimicrobial drugs
  - Recommend optimal antimicrobial dosing in patients receiving CRRT

Review of Physiologic Changes in the Critically-ill

Physiologic Changes

Fluid shift "Third spacing"	Fluid overload	Impaired tissue perfusion	Hypo-albuminemia
Endothelial damage & capillary leakage → increased interstitial volume	Resuscitation fluid boluses, decreased urine output, drugs → increased volume of distribution	Hemodynamic instability, vascular dysfunction → impaired drug delivery to tissues	Decreased protein in serum → increased free drug concentration

Source: Roberts et al. *Lancet Infect Dis.* 2014;14(6):498-509.

Acute Kidney Injury (AKI)

- Kidney Disease: Improving Global Outcomes (KDIGO) criteria
  - Increase in SCr $\geq$ 0.3 mg/dl within 48 hours
  - $\geq$ 50% increase in SCr from baseline, occurring within 7 days
  - Urine output of < 0.5 ml/kg/hour for 6 hours

Source: KDIGO 2012 Clinical practice guideline for acute kidney injury.

AKI in the Critically-ill

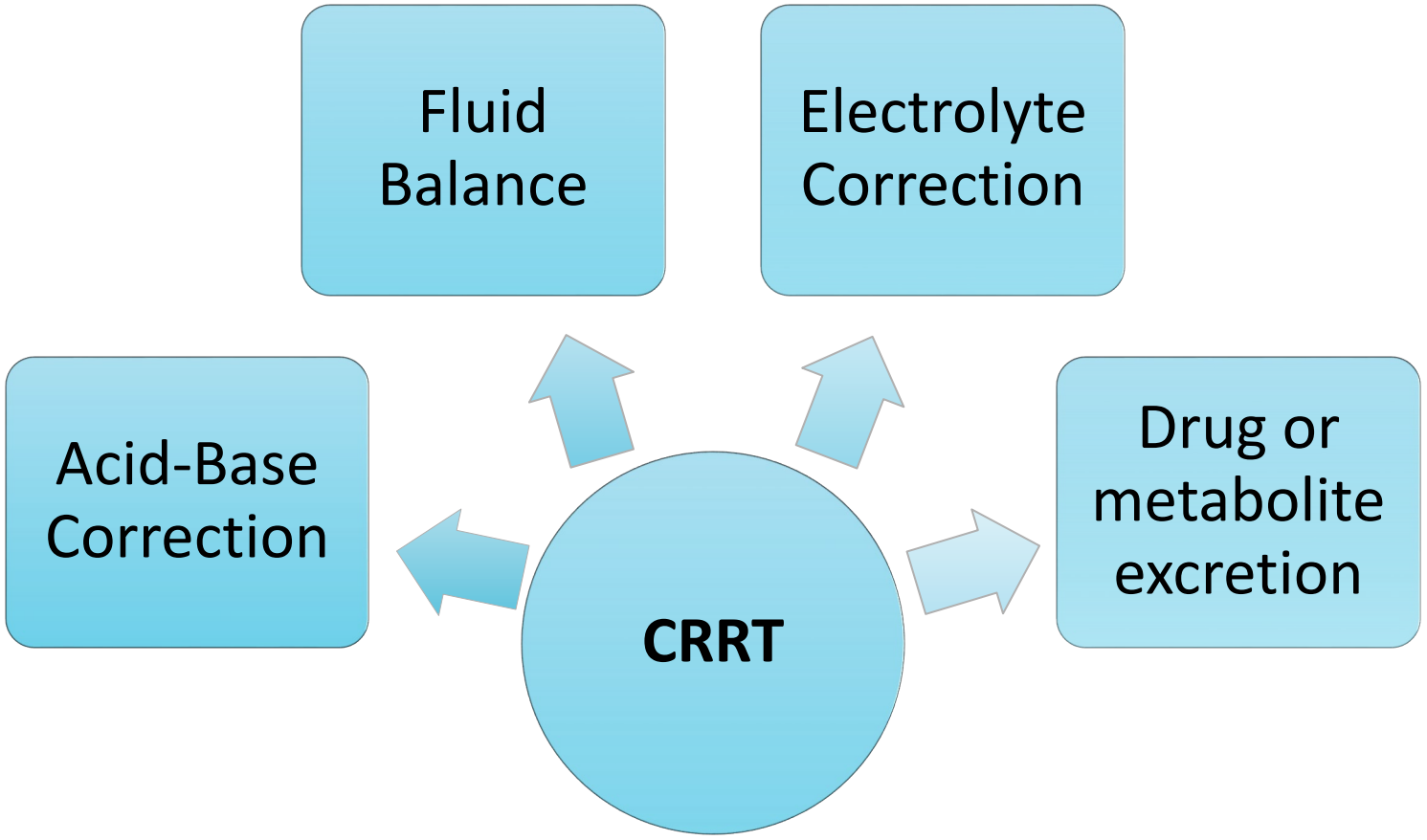
- Reported incidence rates vary (~25%)
- Impacts drug clearance
- Initiation of renal replacement therapy (RRT)

Source: Susla GM. *AACN Adv Crit Care.* 2015;26(3):244-251.

Continuous Renal Replacement Therapy (CRRT)

What is CRRT?

- 24-hour continuous therapy indicated for solute and/or fluid removal in the critically-ill

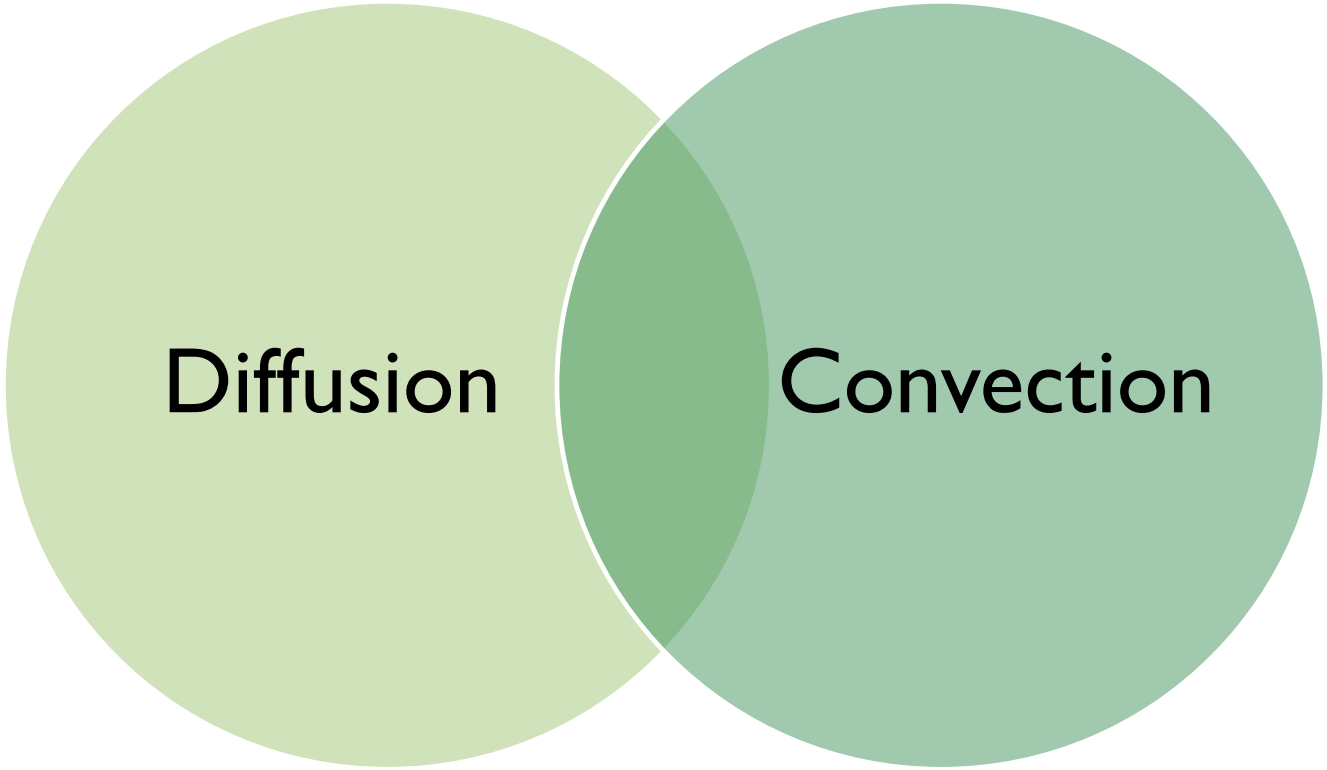


Source: Coritsidis et al. *Critical Care.* McGraw-Hill; Accessed February 9, 2021.

CRRT Modalities

- Continuous veno-venous hemo**dialysis** (CVVHD)
- Continuous veno-venous hemo**filtration** (CVVH)
- Continuous veno-venous hemo**diafiltration** (CVVHDF)

Solute Removal in CRRT



Diffusion

- Movement of solutes from an area of higher to lower concentration until equilibrium is established
- Efficient method for removing small molecules
- Occurs as blood flows on one side of a membrane while dialysate solution flows counter-current on the other side
  - Membrane pore size, surface area, molecular size, and solute concentration affect clearance

Source: Coritsidis et al. *Critical Care.* McGraw-Hill; Accessed February 9, 2021.

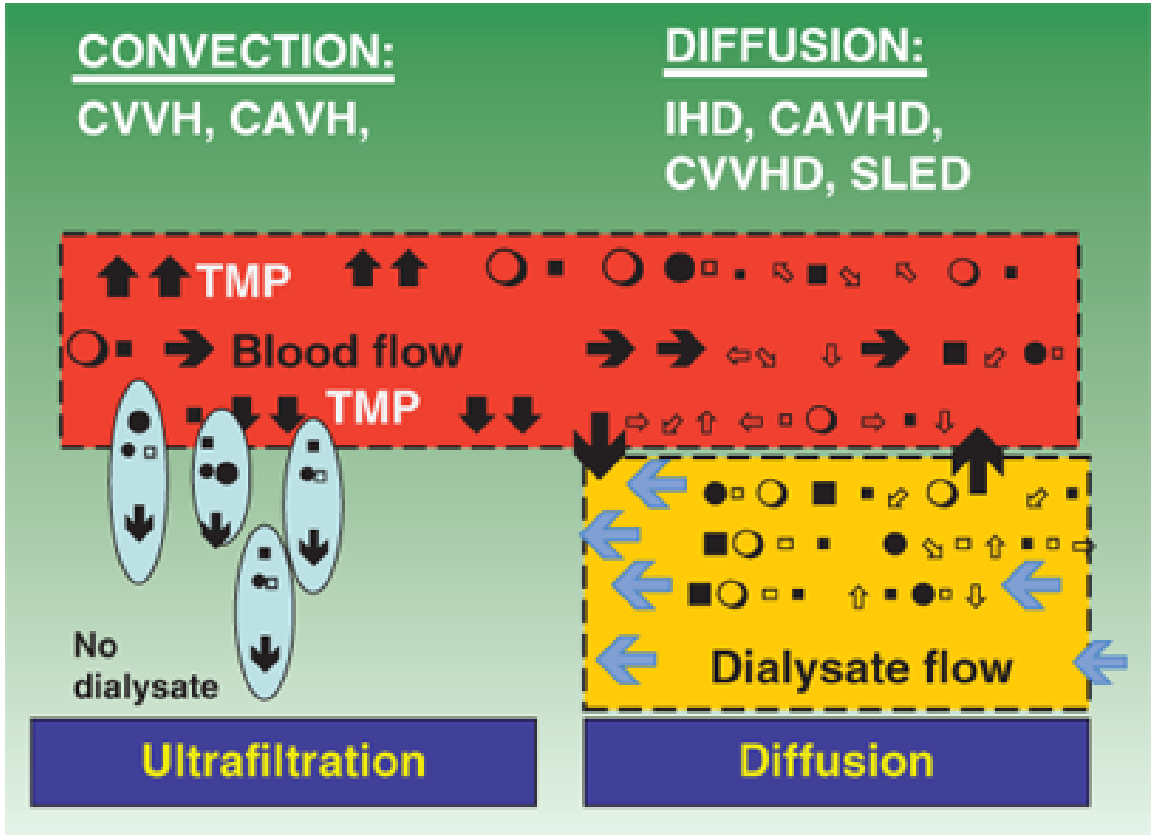
Convection

- A one-way movement of solutes through a semipermeable membrane with a water (replacement fluid) flow
- Movement driven by a transmembrane pressure gradient in response to an osmotic force
  - Dissolved solutes are dragged along with ultrafiltrated plasma water
  - Allows clearance of both small and large molecules

Source: Coritsidis et al. *Critical Care.* McGraw-Hill; Accessed February 9, 2021.

Mechanisms of solute clearance in various modalities of Renal Replacement.

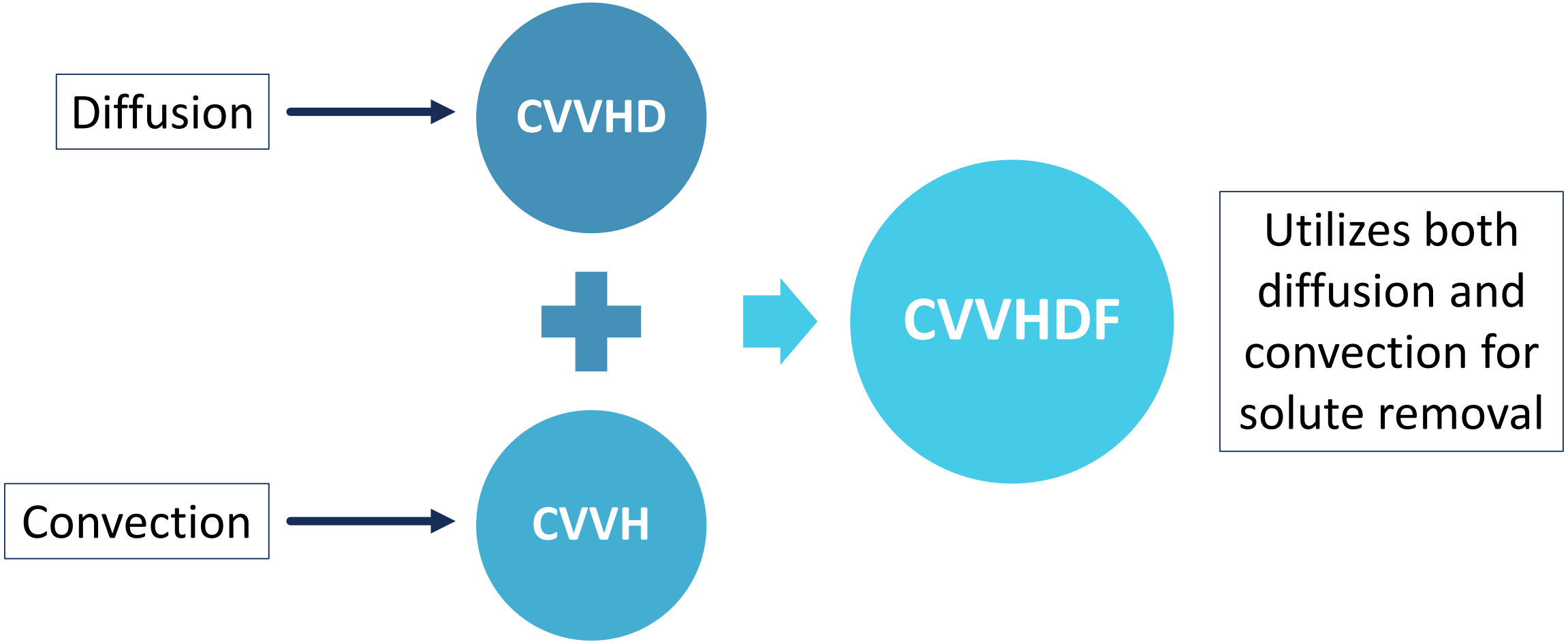
TMP, transmembrane pressure, or hydrostatic pressure; UF, ultrafiltration; •☐*■ = solutes.



Source: John M. Oropello, Stephen M. Pastores, Vladimir Kvetan: Critical Care
www.accessmedicine.com

Source: Chapter 31 Renal Replacement Therapy, Oropello JM, Pastores SM, Kvetan V. *Critical Care;* 1. Available at: https://accessmedicine.mhmedical.com/content.aspx?sectionid=143517688&bookid=1944 Accessed: February 09, 2021

Principles of CRRT



Source: Coritsidis et al. *Critical Care.* McGraw-Hill; Accessed February 9, 2021.

Question #1

Through what mechanism are drugs removed from the blood in a patient receiving CVVHD?

A. Convection
B. Diffusion
C. Both convection and diffusion

Question #1 - Response

Through what mechanism are drugs removed from the blood in a patient receiving CVVHD?

A. Convection

B. **Diffusion**

C. Both convection and diffusion

Factors Affecting Drug Removal in CRRT

CRRT System-specific Factors

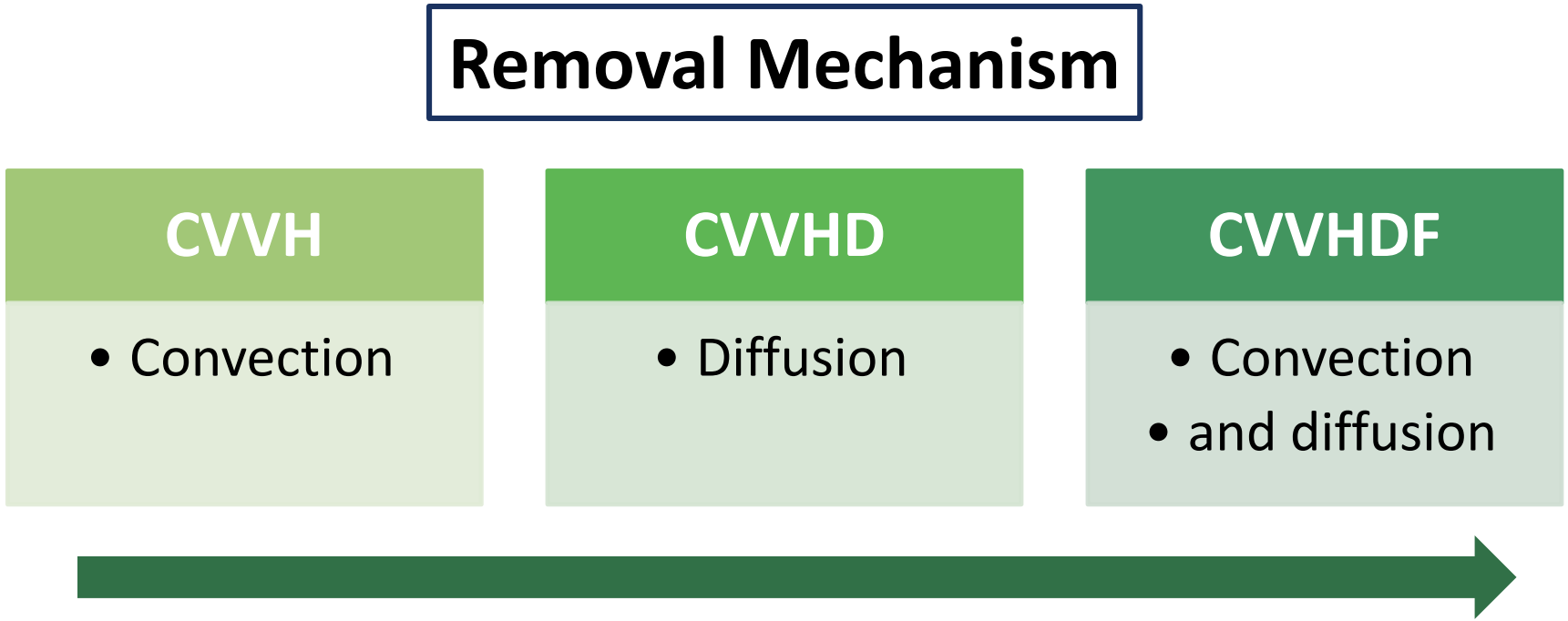
Flow Rates

- Dialysate volume
- Replacement fluid volume
- Blood flow rate

- Increasing dialysate and replacement fluid flow rate increases drug removal
- Blood flow rate generally has little effect on drug removal

Source: Choi et al. *Crit Care Med*. 2009;37(7): 2268-2279.

CRRT System-specific Factors



Source: Choi et al. *Crit Care Med*. 2009;37(7): 2268-2279.

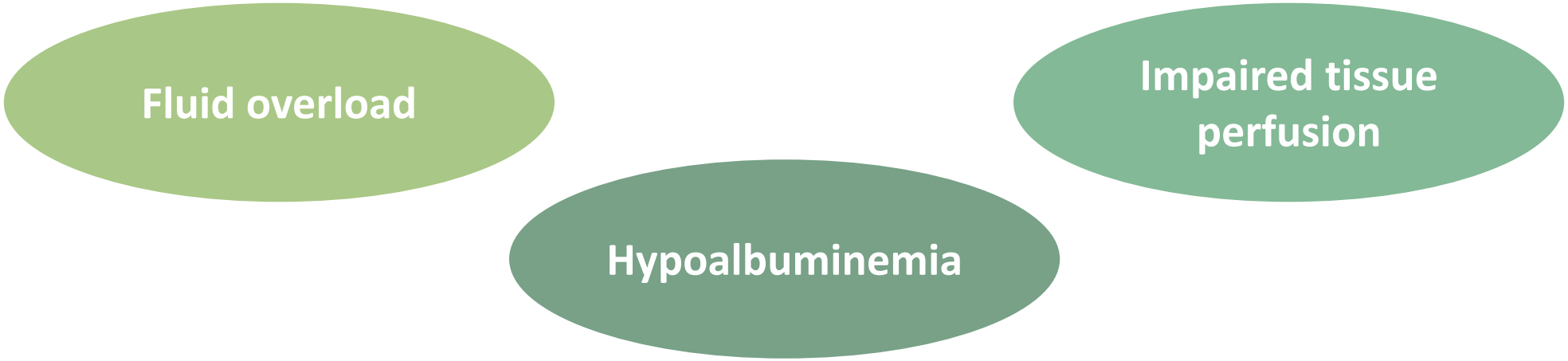
CRRT System-specific Factors

- Placement of replacement fluid pre-dilution vs. post-dilution
  - Predilution method will dilute the contents prior to the contact with the filter → ↓ drug concentration in blood → reduced elimination
- Membrane/filter type
- Flow interruptions

Sources: Choi et al. *Crit Care Med*. 2009;37(7): 2268-2279. Jang et al. *Pharmacy*. 2020;8(1).

Patient-specific Factors

- Pharmacokinetic/pharmacodynamic (PK/PD) changes in the critically-ill
  - Altered drug distribution and protein binding due to hemodynamic instability, changes in fluid distribution, and hypoalbuminemia



Source: Roberts et al. *Lancet Infect Dis.* 2014;14(6):498-509.

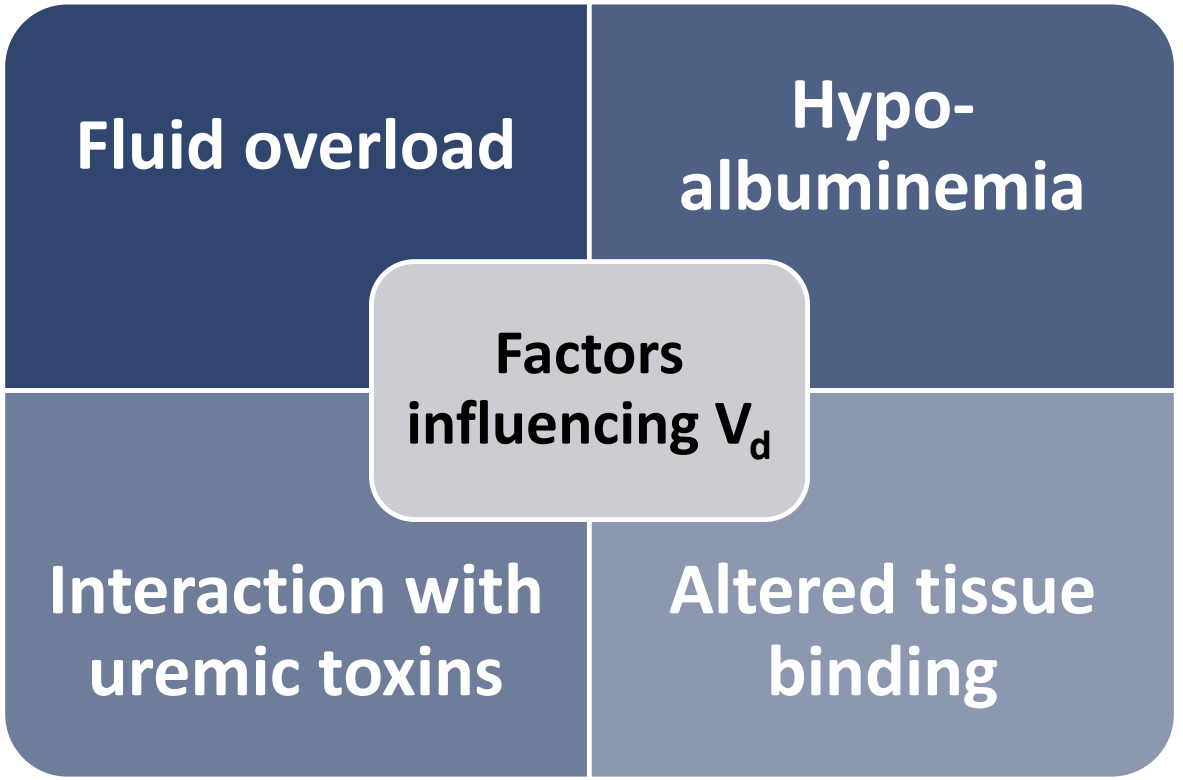
Patient-specific Factors

- Residual renal function
  - Underlying kidney functionality
  - Drug elimination as a result of the residual renal function in addition to the elimination via CRRT
  - May fluctuate → important to assess changing residual renal function!

Sources: Susla GM. *AACN Adv Crit Care.* 2015;26(3):244-251. Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19.

Drug-specific Factors

- Volume of distribution (V_d)
  - Ratio of the amount of drug in the body over the plasma concentration
  - Small V_d associated with clinically significant drug removal via CRRT



Source: Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19.

Drug-specific Factors

- Molecular weight
  - Small molecules are more easily removed
  - Most CRRT utilize “high-flux” membranes
    - Large surface areas, high porosity (~20,000 Da), and high ultrafiltration rate
    - Contribute to significant removal of larger drugs such as vancomycin and daptomycin

Sources: Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19. Hoff et al. *Ann Pharmacother.* 2020;54(1):43-55.

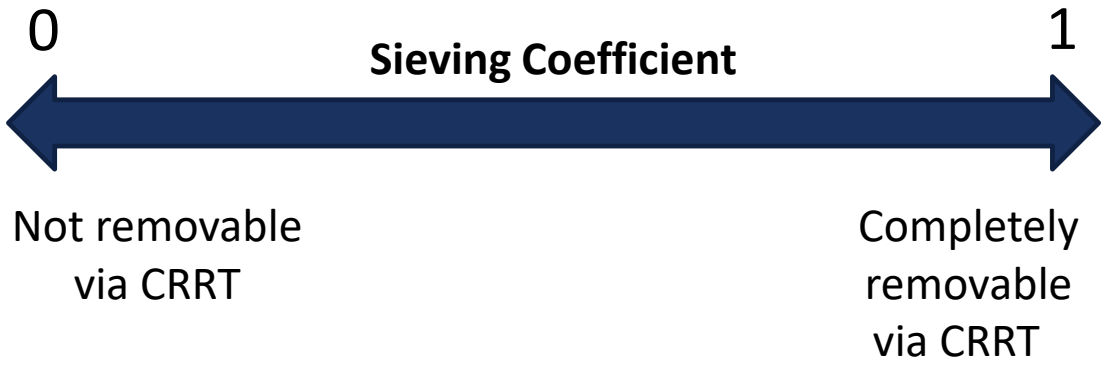
Drug-specific Factors

- Protein binding
  - Drugs with high affinity (≥ 70%) to proteins → less free drug available for elimination
  - Protein binding may be altered due to multiple factors
- Drug adsorption
  - Binding of drug to the dialyzer membrane
  - Elimination via adsorption is negligible

Sources: Susla GM. *AACN Adv Crit Care.* 2015;26(3):244-251. Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19. Choi et al. *Crit Care Med*. 2009;37(7): 2268-2279.

Drug-specific Factors

- Sieving coefficient (SC)
  - $SC = \frac{Ultrafiltrate\ concentration}{Blood\ concentration}$
  - Different for each drug
  - Dependent on multiple factors
    - Molecular size
    - Protein binding
    - Charge of the solute and the filter membrane
    - Size and number of pores in the filter membrane



Sources: Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19. Jang et al. *Pharmacy*. 2020;8(1).

Question #2

Which of the following factors affect drug clearance in patients receiving CRRT? *Select all that apply.*

A. Volume of distribution
B. Protein binding
C. Dialysate flow rate
D. Blood flow rate
E. Non-renal elimination

Question #2 - Response

Which of the following factors affect drug clearance in patients receiving CRRT? *Select all that apply.*

A. **Volume of distribution**
B. **Protein binding**
C. **Dialysate flow rate**
D. Blood flow rate
E. **Non-renal elimination**

Optimizing Antimicrobial Dosing

Infections in the Critically-ill

- International study observing intensive care unit (ICU) patients across 1150 centers showed **54%** had either suspected or proven infection
  - In-hospital mortality = **30%** (2404/8135)
  - **70%** with suspected/proven infection received at least 1 antibiotic

Source: Vincent et al. *JAMA*. 2020;323(15):1478-1487.

Considerations for Dose Adjustment

Lower Dose

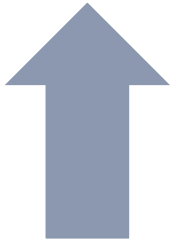
Reduced renal elimination

Minimize drug toxicity

Increased V_d

Achieve PK/PD targets

Possible antimicrobial resistance



Higher Dose

Sources: Hoff et al. *Ann Pharmacother.* 2020;54(1):43-55. Susla GM. *AACN Adv Crit Care.* 2015;26(3):244-251.

Antimicrobials Not Requiring Dose Adjustment

- Highly protein-bound ($\geq$ 70%)
- Large V_d ($\geq$ 2 L/kg)
- Mainly cleared by a non-renal route (e.g., hepatic elimination, feces)

Sources: Hoff et al. *Ann Pharmacother.* 2020;54(1):43-55. Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19.

Antimicrobials Not Requiring Dose Adjustment

Antibiotics		Antifungals
• Ciprofloxacin • Moxifloxacin • Ceftriaxone • Polymyxin B	• Linezolid • Tedizolid • Tigecycline • Clindamycin • Azithromycin	• Voriconazole • Posaconazole • Echinocandins • Amphotericin B

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19.

Antimicrobials Requiring Dose Adjustment

Antibiotics		Antifungal
• β-lactam and β-lactamase inhibitors • Cephalosporins • Carbapenems	• Levofloxacin • Vancomycin • Daptomycin • Aminoglycosides	• Fluconazole
		Antiviral
		• Acyclovir

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19. Hoff et al. *Ann Pharmacother.* 2020;54(1):43-55.

Acyclovir

- Small molecular size, low protein-binding capacity, water-soluble
  - Readily cleared *via* CRRT, 24-hour clearance ≅ clearance during a single session of intermittent hemodialysis
  - A narrow therapeutic index in patients with renal dysfunction
- Suggested dose adjustment: 5 to 7.5 mg/kg IV Q24H
  - Same for all types of CRRT
  - Utilize therapeutic drug monitoring (TDM) if available

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Trotman et al. *CID*. 2005;41(8):1159-1166.

β-lactam/β-lactamase Inhibitors

- Piperacillin-tazobactam
  - Clearance reliably predictable based on effluent flow rate
  - Continuous infusion (total 9 grams/day) or extended infusion is ideal (i.e., 3.375 g IV Q8H, 4-hour infusion)
  - If extended or continuous infusion is not possible
    - CVVH: 2.25 or 3.375 grams IV Q6H
    - CVVHD or CVVHDF: 3.375 grams IV Q6H or 4.5 grams IV Q8H

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Trotman et al. *CID*. 2005;41(8):1159-1166.

β-lactam/β-lactamase Inhibitors

- Ceftazidime-avibactam: limited data available for dosing during CRRT
  - 2.5 gram IV every 8 hours recommended

- Ceftolozane-tazobactam: dosing largely based on effluent flow rate
  - For high-flux dialyzers with flow rates of 1.5-3 L/hour: 1.5 g IV every 8 hours
    - Shown to achieve concentration above the minimum inhibitory concentration (MIC) for entire dosing interval

Source: Li et al. *Front Pharmacol.* 2020;11:786.

Cefepime & Ceftazidime

- Clearance dependent on CRRT modality & effluent rate
  - Goal %*f*T≥MIC: 70% and higher
    - MIC breakpoint for *P. aeruginosa* 8 μg/mL
    - Prior studies have demonstrated suboptimal rate of goal attainment

Cefepime	Ceftazidime
High flow rate (> 1.5 L/h): 2 g IV Q8H Low flow rate (≤ 1 L/h): 1 g IV Q8H	Loading dose: 2 grams Maintenance dose: 1-2 g IV Q12H

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Jang et al. *Pharmacy*. 2020;8(1).

Ceftaroline

- Low molecular weight, highly water-soluble, low protein binding
  - Goal %*f*T≥MIC: 45-50%
- Renal clearance ~65%; non-renal clearance ~35%
- Limited data available for dosing adjustment in CRRT
  - Adjust based on patient's adjusted body weight and effluent flow rate

Source: Kalaria et al. *Pharmacotherapy.* 2021.

Suggested Dosing Regimen for Ceftaroline[a,b,c]

Effluent Flow Rate (L/h)[d]	Adjusted Body Weight (kg)[e]				
	50	60	70	80	90
1	200	200	300	300	300
1.5	200	300	300	300	400
2	300	300	300	300	400
2.5	300	300	300	400	400
3	300	300	400	400	400
3.5	300	400	400	400	400
4	300	400	400	400	500
4.5	400	400	400	500	500
5	400	400	400	500	500

[a]Recommended dosages (mg) are to be given as an IV infusion over 60 min every 12 h.

[b]CRRT clearance was calculated using the following variables and range of values: hematocrit (25%–60%), effluent flow rate (1–5 L/h), blood flow rate (100–300 ml/min), pre-filter replacement therapy dilution percent (50%–100%), and adjusted body weight (50–90 kg).

[c]Justification for proposed dosages are based on matching exposures (AUC) in patients with normal renal function receiving a dose of 600 mg every 12 h and achieving a %fT ≥ 1 mg/L of 50% and 45% for S. pneumoniae and S. aureus, respectively.

[d]Effluent flow rate is calculated by the summation of replacement fluid rate, pre-blood pump rate, net ultrafiltrate rate, and dialysate flow rate.

[e]Adjusted body was calculated using the following formula: Ideal Body Weight + 0.4 × (Actual Body Weight − Ideal Body Weight), where Ideal body weight was calculated using the Devine formula.

Source: Table adapted from Kalaria et al. *Pharmacotherapy.* 2021.

Meropenem & Imipenem

- Significant variability in data
  - Dosing regimen should be adjusted based on effluent flow rate and MIC of the target pathogen
  - Residual renal function also contributes to overall clearance
- Utilizing a continuous infusion may improve clinical efficacy (%T>MIC)

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Trotman et al. *CID*. 2005;41(8):1159-1166.

Suggested Dosing Regimen for Meropenem and Imipenem

TABLE 3 | Recommendation of drug adjustment in CRRT.

Drug	CRRT mode		
	CVVH	**CVVHD**	**CVVHDF**
Meropenem	Ultrafiltration rate: 22 ± 12 ml/kg/h 1 g q12h (MIC ≤ 1 mg/L) (Seyler et al., 2011) Ultrafiltration rate: ≥4 L/h 1 g q8h (Bilgrami et al., 2010) Ultrafiltration rate: 35 ml/kg/h 1 g q8h 1h infusion (Onichimowski et al., 2020b)	Dialysate rate: 20–35 ml/kg/h 2 g q12 h; or Loading dose:1 g, Maintenance dose:500 mg q8 h; or Loading dose:1 g LD, Maintenance dose:1 g q12 h (Shaw and Mueller, 2017) Dialysate rate:35 ml/kg/h 1 g q8h 1h infusion (Onichimowski et al., 2020b) Dialysate rate: 0.7–1 L/h 0.25 q24h for MIC ≤2 mg/L >0.5 g q8h for MIC = 16 mg/L (Kawano et al., 2015) Dialysate rate: 30 ml/kg/h 1 g q8h or 2 g q8h or 3 g continuous infusion q24h (Grensemann et al., 2020)	Ultrafiltration rate: 22 ± 12 ml/kg/h Dialysate rate: 23 ± 9 ml/kg/h 1 g q12h (MIC ≤1 mg/L) (Seyler et al., 2011) Ultrafiltration rate: 2 L/h Dialysate rate: 1 L/h 500 mg q8h (MIC ≤4mg/L) (Varghese et al., 2015) Ultrafiltration rate: 1.5–2 L/h Dialysate rate: 1–1.5 L/h 1 g q8h
Imipenem	Ultrafiltration rate: 52 ± 14 ml/kg/h 1.0 g q6h Ultrafiltration rate: 20 or 37 ml/kg/h 0.5 g q6h for MIC ≤2 mg/L, 1.0 g q6h for MIC 4–16 mg/L (Li and Xie, 2019)	Dialysate rate: 20 or 37 ml/kg/h 0.5 g q6h for MIC ≤2 mg/L, 1.0 g q6h for MIC 4–16 mg/L (Li and Xie, 2019)	Combined flow rate: 20 or 37 ml/kg/h 0.5 g q6h for MIC ≤2 mg/L, 1.0 g q6h for MIC 4–16 mg/L (Li and Xie, 2019)

Source: Li et al. *Front Pharmacol.* 2020;11:786.

Levofloxacin

- Low V_d compared to moxifloxacin and ciprofloxacin
  - Clearance dependent on effluent rate (“CRRT intensity”)
- Dosing recommendations vary
  - Loading dose of 500-750 mg followed by daily doses of 250 to 750 mg
  - PK/PD studies have shown that these recommended dose may not be sufficient to achieve target $AUC_{24}/MIC \geq 125$ in the first 72 hours
- May not be suitable as a monotherapy for *P. aeruginosa*

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Trotman et al. *CID*. 2005;41(8):1159-1166.

Fluconazole

- Low molecular size, low V_d, and low protein binding
  - 80% eliminated unchanged *via* the kidneys
  - ~70% cleared by CRRT – significant clearance
- General dosing recommendation
  - 400 mg daily (CVVH), 800 mg daily (CVVHD/CVVHDF)
  - May consider lower dose of 200-400 mg daily if known MIC $\leq$ 8 mg/L and no concern for *C. glabrata*

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19. Trotman et al. *CID*. 2005;41(8):1159-1166.

Aminoglycosides

- Pharmacokinetic considerations
  - V_d to determine dose; elimination rate to determine dosing interval
- Loading patients with larger than usual initial dose associated with possible increased risk of toxicity
- Individualize dosing regimen to each patient and use of TDM strongly recommended
  - In general, dose every 24 to 48 hours

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Pistolesi et al. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19. Trotman et al. *CID*. 2005;41(8):1159-1166.

Vancomycin

- TDM recommended to ensure adequate dosing and safety
  - Monitoring of trough levels or AUC_{24}/MIC if available
- Consider loading dose of 20-35 mg/kg (max: 3 grams)
- Clearance is dependent on effluent flow rate

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Trotman et al. *CID*. 2005;41(8):1159-1166. Rybak et al. *Am J Health-Syst Pharm.* 2020;77(11):835-864.

Daptomycin

- High protein binding and low V_d
- Daily doses of 6 to 12 mg/kg have been studied
  - Dosing based on target pathogen and infection type
  - Population-based PK studies have shown doses > 8 mg/kg in patients receiving CVVHDF may increase the risk of toxicity (e.g., increased creatinine phosphokinase)
  - Comparison of PK/PD parameters between Q24H and Q48H dosing showed Q48H dosing may result in suboptimal exposure

Sources: Li et al. *Front Pharmacol.* 2020;11:786. Trotman et al. *CID*. 2005;41(8):1159-1166. Xu et al. *Br J Clin Pharmacol*. 2017;83(3):498-509.

Question #3

Which of the following antimicrobial agents do not require dosing adjustment in a patient receiving CRRT? *Select all that apply.*

A. Vancomycin
B. Amphotericin B
C. Meropenem
D. Ciprofloxacin
E. Tigecycline

Question #3 - Response

Which of the following antimicrobial agents do not require dosing adjustment in a patient receiving CRRT? *Select all that apply.*

A. Vancomycin

B. **Amphotericin B**

C. Meropenem

D. **Ciprofloxacin**

E. **Tigecycline**

Pharmacist's Role

- Selection of an appropriate antimicrobial agent based on indication
- Identify when and how to adjust antimicrobial dose
  - Requires understanding of the CRRT modality as well as drug- and patient-specific factors affecting drug clearance
- CRRT order also may change frequently, be interrupted, or switched to intermittent hemodialysis
  - Stay vigilant of patient's "renal" function (residual renal function + CRRT)

Sources: Hoff et al. *Ann Pharmacother.* 2020;54(1):43-55. Li et al. *Front Pharmacol.* 2020;11:786.

Nurse's Role

- Recognition of antimicrobials in which clearance may be affected by CRRT
- Bedside assessment and communication of changes in patient's status to caring team members
  - Changes in patient's residual renal function
  - Changes and/or interruptions of CRRT

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Continuous Renal Replacement Therapy: Antimicrobial Dosing Considerations

Thank you for attending!

HaYoung Ryu, PharmD.
PGY-1 Pharmacy Resident
E-mail: hayoung.ryu@rwjbh.org