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THE CRITICAL CARE PODCAST

Medication Dosing in CRRT

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What percentage of patients develop acute kidney injury (AKI) within their time in the ICU and does this drastically affect their short- or long-term outcomes?

- Our understanding of chronic kidney disease (CKD) compared to AKI has changed over the years
  - We are finding out they are different and patient outcomes are different
- When AKI occurs, and it occurs commonly, it causes very high mortality
  - An observational study looked at > 23,000 ICU admissions and found 5.5% of patients developed AKI needing some sort of renal replacement therapy (RRT)
    - ~60% of these patients died in the hospital
  - Only 50% of patients who develop AKI recover their renal function
- If you develop AKI in the hospital, 72% 3-year mortality rate
- Often is AKI can be caused by the healthcare team
  - 22% of all adult ICU medication orders are potentially nephrotoxic
  - 40% of pediatric ICU medication orders are potentially nephrotoxic

What different RRT modalities exist and are in use for patients in AKI?

- Classic modality is intermittent hemodialysis (iHD) is the first line RRT
  - In the ICU, iHD may not be three times per week, it may be daily or five times per week because these patients are so highly catabolic or fluid overloaded
- Some patients can't tolerate the hemodynamic shifts that may occur during iHD
- Can we remove fluid, electrolytes, waste products, and drugs more slowly over 24 hours so patients can tolerate this? The answer to this question is CRRT.
  - CRRT is slower, but not less effective than iHD
    - The clearance is happening over 24 hours rather than 3-4 hours

How does CRRT differ from iHD?

- iHD is short, rapid clearance whereas CRRT is slower

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- CRRT is great for removing fluid (the hourly negative fluid balance can lead to big volume changes)
  - With CRRT, you can account for all the fluid the ICU patient may receive

How long has CRRT been around? Is this a relatively newer therapy?

- First described in Germany in the 1980's and tried CAVH
  - Inserted cannula into an artery and had the heart pump the blood through the tubing/filter and back into the vein
    - No dialysate, just hemofiltration
- CRRT didn't get popular until machines were available to be used
  - Which was during/around the early 1990's

Will all ICU patients use CRRT as their RRT modality of choice? Or should this be reserved for a more selective group of critically ill patients?

- CRRT is more expensive than iHD
  - iHD should be used if the patient can tolerate it
- When a patient is not receiving 24 hours of RRT per day they can ambulate, go to procedures easier, etc.
- CRRT is preferred for those patients with hemodynamic instability or massive fluid overloaded
- Patients with increased intracranial pressure (ICP) can't handle the massive osmotic shifts that happen with iHD

Are there patients or disease states where we should avoid using CRRT?

- If you need to fix a problem quickly, then CRRT is inappropriate
  - Examples include drug overdose or hyperkalemia with EKG changes
- CRRT will remove electrolytes or medications/toxins but will simply do it slower

What are definitions to some of the more common terms used in CRRT?

- Three common modalities: CVVH, CVVHD, CVVHDF

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- CVVH
- C = continuous
- VV = veno-venous (venous blood returned to the venous system via dual lumen venous catheter)
- H = hemofiltration (blood is pulled from the body, pumped through a filter, and given back to the patient)
  - Suction is being applied to the blood as it goes through the thin membranes and pull the plasma water from the blood and discard it
  - Need to replace some of that plasma water that is removed, or patients would get dehydrated very quickly
    - A typical CVVH order may say remove 1-2 L of plasma water every hour, then we must give ultrafiltration replacement fluid
      - Can give this replacement fluid post-filter
      - Can give this replacement fluid pre-filter (to lower hematocrit and help prevent the filter from clotting off)
  - No dialysate used in CVVH
    - Suction pulls plasma water (which contains medications, waste, and electrolytes) and replaces it with "clean" water with a perfect electrolyte profile

- CVVHD
  - Same CVV
  - HD – hemodialysis
    - Blood is pumped through the filter
    - On the other side of the filter, the dialysate is running in a counter-current fashion and diffusion is occurring
      - Diffusion means molecules (e.g. electrolytes) in a high concentration travel to a low concentration
    - An ultimate goal is to have the dialysate mirror what you'd like the patient's blood chemistry to be

- CVVHDF
  - HDF (hemodiafiltration)
    - Have dialysis and hemofiltration occurring at the same time
    - Dialysate is running and suction pulls the plasma water out
  - This is the most complicated but has some advantages

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    - Less clotting and may remove higher solutes

- What is actually removed by the filter depends on drug specific and CRRT system characteristics
  - Drugs: Volume of distribution, protein binding
    - If Vd is high then it won't be filtered readily since it's so widely distributed in the body
    - Drugs that are highly protein bound to albumin can't be removed by the membrane due to the large molecular weight
  - CRRT system: effluent rate
    - Effluent rate (combination of ultrafiltrate + dialysate) – the volume coming out determines how much drug (or other waste products/electrolytes) is removed
      - This is the most important thing from a drug dosing perspective
      - Studies have shown that high-volume CRRT (higher effluent rates) outcomes are no different compared to more moderate CRRT
        - KDIGO guidelines recommend a 20-25 mL/kg/hr CRRT effluent rate in AKI (1A recommendation)
  - From a drug removal perspective, there is minimal difference between CVVH, CVVHD, and CVVHDF
    - The biggest determination of dosing requirements is the effluent rate because the filters that are used today have such big pores that everything diffuses through the membrane similar to convection

- We do know that CRRT systems go down and the patient doesn't always get the 20-25 mL/kg/hr effluent rate
  - May try to err on the side of prescribing a higher effluent rate, so as a net effluent rate they get the recommended amount
- The longer we use the hemofilter, the clearance slowly gets worse
  - There is a protein membrane that forms on the membrane filter
    - A higher effluent rate may make up for some of this clogging

Why is underdosing of medications so prevalent in patients receiving CRRT?
- The biggest mistake started with assuming that all AKI patients are the same as all ESRD patients
  - The septic shock patient with an 8-10 L positive fluid balance and AKI likely are different than the stable patient (with a PMH of DM and HTN) receiving iHD three times a week as an outpatient
    - But we were using the same CrCl interpretation to guide dosing in both patient populations
  - Researchers started wondering why the mortality rate was so high and then found that our antibiotics aren't achieving therapeutic concentrations in patients with AKI
    - The patients were dying not because of drug-resistant infections, but because antibiotics weren't achieving therapeutic concentrations
- CKD patients have different drug metabolism rates (primarily due to the liver) that are slower than other patient populations
  - ICU patients may not have the same co-morbidities, thus having higher drug metabolism rates from other organs such as the liver
- Instead of thinking about achieving pharmacodynamic goals, we historically focused on preventing adverse effects in these patients instead
  - "Want to give enough, but not too much"

Why do older studies or review articles recommend sometimes drastically different dosing regimens than newer research does?
- CRRT flow rates are much higher now
  - Also have guidelines with effluent rate recommendations
    - Doses needed to be lower d/t lower effluent rates
- The new CRRT membrane filters are extremely porous that allow much more substances/medications to be filtered compared to the past
- Better understanding of antibiotic pharmacodynamic targets and how that affects the recommended medication dosing
- Bacteria have more resistance now, especially in the ICU
  - May need to give higher doses to overcome this resistance
- The pharmacokinetics of AKI patients are much different than CKD patients
- The bottom line: much more aggressive antibiotic dosing is warranted in these patients

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What specific drug properties will increase clearance via CRRT?
- Water soluble drugs are cleared more readily than lipid soluble drugs
- Smaller volume of distribution in the bloodstream
  - Higher Vd drugs won't have as high of a bloodstream concentration
- Highly protein bound drugs will have lower clearance because it is unable to cross the porous membrane due to the size of the protein
  - Only the free fraction is cleared
- Some exceptions to this rule include:
  - Daptomycin – It is highly protein bound but also has a very low volume of distribution (0.1 L/kg) and as a result it is in the blood and is cleared by the filter
- What we do know is that our drug dosing is much more aggressive today compared to past recommendations to achieve pharmacodynamic targets
- Look at the therapeutic index and if it's wide, may err on the side of dosing more aggressive
- Think about what the patient's biggest problem is, if it's an infection may want to dose more aggressive and manage side effects as they arise
- Also keep in mind from a safety perspective, what happens if the CRRT is stopped and the same dosing regimen is continued

In the absence of dosing recommendations, would you apply evidence from dosing in CVVH to a patient receiving CVVHD or CVVHDF? Does the modality have a large effect on medication clearance?
- Historically, would have said it has an effect
- But the CRRT membrane filters have such big pores, there isn't an appreciable difference of clearance based on the modality
  - The most important factor is the overall effluent rate

After how many hours with CRRT off/paused, would you re-time or re-dose your antibiotics?
- We know many of these patients aren't achieving their pharmacodynamic targets, so some may delay re-timing antibiotics more than others
- Once the CRRT machine is down for > 4 hours, will likely make changes and re-time or modify antibiotic dosing recommendations.

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How can we apply CRRT dosing recommendations from drug references that don't focus or specify dosing based on the patient's effluent rate?
- Many drug dosing recommendations are old, and if they specify different doses based on the type of CRRT modality they are outdated
- Bruce is working with UpToDate and Lexi-Comp to update their dosing recommendations and this shouldn't be a problem much longer for these information sources
  - Working to standardize the language used in these references

What should we do regarding medication dosing for the patient on CRRT but not necessarily in AKI?
- There are two types of clearance happening (the patient's kidneys and the CRRT machine)
- Treat these patients similar to patients with augmented renal clearance
  - Shouldn't be applying Cockcroft-Gault or eGFR equations to these patients or any patient on CRRT

Why do we need anticoagulation for CRRT when we typically don't need it for other RRT modalities?
- The blood flows that are used in the CRRT systems are much lower than iHD
  - iHD blood flow is 300-400 mL/min, CRRT blood flow is 150-200 mL/min
- The venous access is also not specifically designed for RRT, which differs from iHD venous access
- In CRRT, can decide if we want to anticoagulate the entire patient or just the CRRT filter
  - Some don't use anticoagulation and use higher blood flow rates
- Many will do "regional" anticoagulation
  - Only anticoagulate the filter using either citrate or heparin
  - Want to avoid full therapeutic anticoagulation, but also want to keep the filter patent
- The anticoagulation is administered as the blood is flowing from the patient to the CRRT membrane filter
  - The blood going in is anticoagulated and then is typically reversed once it leaves the filter

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- The classic method is with citrate
  - Citrate binds to the calcium in the patient's blood going to the CRRT filter
    - Calcium is required for activation of the clotting cascade
      - If citrate binds to calcium, the blood can't clot
  - Before the blood goes back into the patient, a calcium infusion is administered to ensure the patient's calcium is WDL
    - Calcium levels are closely monitored to prevent ADE
    - The patient is not anticoagulated, but the CRRT filter is

Is there evidence to support one anticoagulation option compared to others?
- Would recommend picking one option and using it as your primary anticoagulation modality within CRRT
  - If certain people use citrate and other use heparin it is a medication error waiting to happen
- KDIGO guidelines suggest citrate is better
  - Filters can last longer and avoid bleeding complications
- If your hospital uses CRRT infrequently, would recommend using UFH rather than citrate

What are some other important considerations we need to think about when choosing the patient-specific anticoagulation?
- The classic example is liver disease
  - Patients with liver disease can't convert citrate to bicarbonate and that creates problems
  - Would prefer using UFH in these patients
- For patients with COVID-19 infections, these patients seem to be hypercoagulable and UFH might be preferred because of their higher VTE risk
  - An idea for researchers to start studying

Is there any hybrid CRRT modality that is gaining momentum in terms of use within the US?
- SLED (slow low efficiency dialysis) but this doesn't really exist because we don't have low efficiency dialyzers anymore
- EDD (extended daily dialysis)
- PIRRT (prolonged intermittent renal replacement therapy)

- The hybrid modalities are slower than iHD but faster than traditional CRRT
  - Can allow patients to not be hooked up to the CRRT machine for 24 hours per day
- When there is a big increase in critically ill patients with AKI, a hybrid RRT modality would allow 1 machine to help treat multiple patients
  - Whereas with CRRT, 1 machine can only treat 1 patient
- A big problem is these hybrid CRRT modalities aren't standardized
- Drug dosing becomes extremely difficult because of these differences
- The question isn't: "What is the right dose of drug X in PIRRT?"
  - The question should be: "When is the dose"
    - If you give a dose during a fast RRT is running, much of the dose will be cleared
    - If the drug is given after the session, the drug will hang around for awhile
      - May also need supplemental doses during the RRT session

There's not great evidence on appropriate dosing for the majority of medications when using a newer RRT modality. For drugs that don't have these specific dosing recommendations, what should Pharmacists do?

- Speak to the nephrology/critical care team and figure out the plan
  - If it's given every other day, may follow iHD dosing
  - If they're receiving this RRT every day, likely will use CRRT dosing
- Be sure to give a loading dose in these scenarios
- Try to determine when the RRT will start and end to ensure appropriate dosing and timing

What are general dosing considerations to keep in mind when dosing medications in CRRT?

- Give a loading dose
- Know the pharmacodynamic goal of the medication
  - Maybe consider continuous infusion for time-dependent pharmacodynamic goals
- Working in conjunction with the CRRT therapy
- If there's no recommendation, "calculate" their CRRT creatinine clearance and use that as a starting point to help guide your dosing
  - Effluent rate (in mL/hr) / 60 minutes

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What are currently the best resources to look for evidence-based dosing recommendations for critically ill patients on CRRT?

- Lexi-Comp/UpToDate
- University of Louisville has adult and pediatric dosing recommendations
  - https://kdpnet.kdp.louisville.edu/