Background: Acute Kidney Injury (AKI) in the ICU

- AKI occurs in approximately 7% of all hospitalized patients
- AKI occurs in up to 67% of critically ill patients
  - RIFLE stage F (failure) occurs in 10-20% of ICU patients
- In patients with AKI requiring RRT, mortality ranges 50-70%
- Sepsis is the most common cause of AKI in the ICU (up to 50%)
- Reported incidence varies due to different definitions
Definitions/AKA: “Alphabet Soup”

- SCUF -> Slow Continuous Ultrafiltration
- CVVH -> Continuous Venovenous Hemofiltration
- CVVHD -> Continuous Venovenous Hemodialysis
- CVVHDF (CVVH + CVVHD) -> Continuous Venovenous Hemodiafiltration

CRRT: Molecular Transport Mechanisms

- **Ultrafiltration**
  - Fluid Transport
  - SCUF CVVH CVVHD CVVHDF
- **Diffusion**
  - CVVHD CVVHDF
- **Convection**
  - CVVH CVVHDF
- **Adsorption**
  - CVVH CVVHD CVVHDF

Case #1

47 year old male with vasopressor dependent septic shock secondary to CAP complicated by respiratory failure and oliguric AKI

Which of the following are appropriate indications to initiate CRRT? (choose all that apply)

a) Hyperkalemia
b) Refractory hypoxemia
c) Serum creatinine of 7 mg/dL, BUN 80 mg/dL
d) Fluid overload
e) Pericardial rub
Indications for Renal Replacement Therapy (RRT)

Indications for RRT: Classic
- A - acidosis
- E - electrolyte disturbances (e.g. hyperkalemia)
- I - intoxication (e.g. ethylene glycol, salicylate, lithium)
- O - overload (e.g. hypoxemia)
- U - uremia (e.g. encephalopathy, pericardial rub, bleeding)

Indications for RRT
- Renal
  - Oliguria -> Volume Overload
  - Azotemia WITH uremic symptoms
  - Hyperkalemia
  - Metabolic acidosis

How Much?
- > 10%
- > 20%

How High?
- BUN > 70 mg/dL
- BUN > 100 mg/dL

How Low?
- pH < 7.2
- pH < 7
Why **Continuous** Therapies?
- Closely mimic the native kidney in treating AKI and fluid overload
- Slow, gentle and better tolerated in hemodynamically unstable patients
- Remove large amounts of fluid and waste products over time
- Preserve homeostasis over time
- Provide renal support during critical illness
- Allow other important supportive measures; nutritional support, blood products…

Volume Overload in AKI

Increased mortality?
How much is too much?

Fluid Overload is Bad

OR for death 2.07 associated with fluid overload at dialysis initiation

Fluids in AKI: Avoid Volume Overload?

- Conservative fluid strategy decreases time on ventilator in ARDS
  - (FAACT Trial, ARDSnet)
- Association between positive fluid balance and increased mortality in patients with AKI, HR 1.21
  - Mean fluid balance significantly different between survivors and nonsurvivors
  - Among patients requiring RRT mortality higher in those with greater increase in fluid balance 64.6% vs 44.8% 
  - (SOAP study, 3120 AKI patients)

Fluid Overload

- Critical illness is a dynamic process, requires frequent reassessment of volume status
- Associated with increased mortality
- Consider obligatory fluid intake
  - Nutrition
  - Medications
  - Blood products
- Consider fluid overload in decisions re timing and modality
- Need prospective randomized trial

Timing:
When to Start?
Timing: When to Start?

- For now... consider typical criteria -> elevated BUN, hyperkalemia, acidosis, fluid overload, CNS manifestations, pericardial rub, etc...
- “Before Complications Arise”/THINK AHEAD!
- There may be a point when it is too late but we don’t yet know when that is...
- Unfortunately... NO consensus in the nephrology or critical care literature
- Need a RCT (randomized controlled trial) and need to define early/late

Is it time to transition from CRRT to IHD?

- Little data... but a few things to consider
  - Hemodynamically stable?
  - No vasopressor support?
  - Wish to mobilize patient?
  - Need CRRT machine for more unstable patient?

Case #1

47 year old male with vasopressor dependent septic shock secondary to CAP complicated by respiratory failure and oliguric AKI

Which of the following are appropriate indications to initiate CRRT? (choose all that apply)

a) Hyperkalemia ✅
b) Refractory hypoxemia ✅
c) Serum creatinine of 7 mg/dL, BUN 80 mg/dL
  ❌
d) Fluid overload ✅
  ❌
e) Pericardial rub ✅
Case #2
57 year old hemodynamically stable female with oligoanuric AKI and a GI bleed needs RRT.
What additional piece of clinical history would necessitate a continuous modality of RRT instead of intermittent? (choose all that apply)

a) Encephalopathy due to ESLD
b) Acute CVA
c) Acute myocardial infarction
d) BUN of 150 mg/dL
e) Subarachnoid hemorrhage

Modality:
Intermittent vs Continuous?

Why Continuous RRT (CRRT)?
- Continuous more closely approximates “normal physiology”
  - Slow correction of metabolic derangements
  - Slow volume removal better tolerated
- Hemodynamic Instability
- Cerebral edema
  - Acute hepatic failure
  - Acute CNS event or injury
- High obligatory fluid intake (anticipate)
- Local expertise and resource availability
Outcomes:
Intermittent vs. Continuous

- Conflicting outcome data
- Recent meta-analysis (9 trials) demonstrated no difference in mortality
  - (Bagshaw et al. CCM, 2008)
- What about renal recovery?
  - 2 studies – CRRT improved renal recovery
  - 4 studies – no difference in renal recovery
  - No definitive data

Intermittent vs Continuous

- NOTE...Patient populations excluded from these studies
  - Hemodynamically unstable
  - Brain injured patients
  - Fulminant hepatic failure
- Current practice based on...
  - Availability
  - Local Expertise
  - Resources
  - Cost
  - Clinician bias

Risks with Intermittent RRT

- More rapid fluid and electrolyte shifts
- Increased risk of increased intracranial pressure
- Higher incidence of hemodynamic instability
  - Decreased cerebral and/or cardiac perfusion with hypotension
Intensive vs Continuous

<table>
<thead>
<tr>
<th>Therapeutic Goal</th>
<th>Hemodynamics</th>
<th>Preferred Therapy</th>
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<tbody>
<tr>
<td>Fluid Removal</td>
<td>Stable</td>
<td>Intermittent UF</td>
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<tr>
<td></td>
<td>Unstable</td>
<td>SCUF</td>
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<tr>
<td>Urea Clearance</td>
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<td>HD, intermittent</td>
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<td></td>
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<td>HyperK, Severe</td>
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</tbody>
</table>

Adapted from Kellum et al CRRT handbook, 2010.

Dose:

Is More Better?

It depends...

Sometimes...More is Better
Dose: CRRT Trials

6 RCT of dosing strategies for CRRT

4 WITHOUT mortality benefit
2 WITH mortality benefit

Dose: Bottom Line

- Prescribed dose does not always = delivered dose
- Time off machine
  - What can you do? Try to coordinate “road trips”
  - Filter clotting
- Delivered dose should be at least 25ml/kg/hr
- Take Home Point re Dose: Dose Matters even if “more is not better”

Role of Hemofiltration in Sepsis

In the absence of renal failure?
Indications for RRT: Alternative
- Sepsis - #1 Cause of AKI in the ICU
- Rhabdomyolysis
- Thermoregulation
- Refractory congestive heart failure
- Hepatic failure
- ARDS
- IV Contrast (CIN)
- ...

Sepsis: Treatment
- Hemodynamic stabilization
  - Restoration of blood flow
- Optimization of oxygen delivery
- Eradication of infection
  - Antibiotics
  - Source control
- ? Role of Hemofiltration...

Cytokines: What We Know...
- Cytokines play a role in multi system organ failure (MSOF)
- Cytokine levels predict mortality
- Cytokines are relatively low molecular weight proteins (e.g. IL-6 28 kd, TNF-α 52 kd)
- BUT... Plasma levels of cytokines unchanged with standard CVVH in sepsis
Hemofiltration for Severe Sepsis and Septic Shock (Without AKI)

- Prospective multi-center RCT
- Hemofiltration group (HF) - 96 hours isovolemic CVVH (25 mL/kg/hr)
- Control group (C) - 96 hours standard sepsis management
- Designed to enroll 400 patients within 24 hours of 1st organ failure related to sepsis (severe sepsis)
- Stopped at interim analysis
- 80 patients enrolled

Primary Endpoint: Time to Worsening SOFA

- p < 0.01

Renal Failure

- No difference between groups at baseline
- Increased frequency in HF group
- Use of CVVH higher in HF group (after 96 hours)
  - 19 of 37 in HF vs 8 of 39 in C, p < 0.05
Conclusions

- Early use of classic CVVH (2L/hr) in severe sepsis without AKI
- Does not limit or improve organ failure
- Prolonged requirement for organ support
- Trend toward higher mortality at 14 days
- Weaning from ventilator and catecholamines significantly longer in HF group
- No modification in cytokine plasma levels could be detected

Case #2

57 year old hemodynamically stable female with oligoanuric AKI and a GI bleed needs RRT. What additional piece of clinical history would necessitate a continuous modality of RRT instead of intermittent? (choose all that apply)

a) Encephalopathy due to ESLD ✓
b) Acute CVA ✓
c) Acute myocardial infarction ✓
d) BUN of 150 mg/dL ✓
e) Subarachnoid hemorrhage ✓

Case #3

70 year old male with known history of significant cardiovascular disease admitted with gram negative septic shock 2/2 indwelling foley associated UTI. After 3 days on CRRT which of the following might explain a new leukocytosis in the absence of a fever?

a) Line infection
b) Hospital Acquired Pneumonia
c) Bowel Ischemia
d) All of the above
e) None of the above
Managing Your Patient on CRRT: Special Considerations

Taking Care of the Patient on CRRT
- Requires 1:1 nursing
- Dynamic, needs frequent reassessment of volume status & volume removal goals
- Needs dedicated access
  - Avoid subclavian if at all possible in patients with CKD, those likely to require longterm HD
- Net ZERO means everything goes in must come off (therefore helps to limit what goes in if not tolerating volume removal)
- OK to give fluid while on CRRT, must specify to nursing NOT to remove (net ZERO for days will be net negative with insensible losses)

Fluid Removal in CRRT
- Fluid is removed primarily from intravascular compartment
- Plasma refill rate from interstitial compartment determines rate of change of intravascular blood volume
- If ultrafiltration rate exceeds plasma refill rate, decreased blood volume ensues and contributes to hemodynamic instability
- Goal is to find maximally tolerated ultrafiltration rate
Fever

- Patients on CRRT are much less likely to “spike” a temperature
- Patients on CRRT are frequently hypothermic due to exposure to large volumes of room temperature ("cool") fluids
- Pay attention to low grade temperatures

Hypotension: Considerations on CRRT

- Bleeding
  - Line associated (? retroperitoneal bleed)
  - Blood loss due to frequent filter clotting
  - Coagulopathy
- Hypovolemia
  - ~ 250 cc blood volume extracorporeal
  - Too much volume removal (ultrafiltration)
  - Fluid shifts (exceeding refill rate)
- Ischemia
  - Cardiac (hemodynamic stress)
  - Bowel (hypotension)
- Infection (sepsis)
  - May not spike a temperature

Laboratory Data: Special Considerations

- REMEMBER!...CRRT “buffs” your labs...don’t let that fool you
  - Lactate cleared...if it’s rising or NOT falling, be concerned about ongoing source of ischemia
  - Anion Gap...corrected with CRRT, use your clinical skills
  - Potassium and/or phosphorous remains high? Think about cell lysis...ongoing endogenous source
Medications on CRRT

- Maximally concentrate all drips, medications whenever possible (easier to remove volume)
- Dose medications appropriately for CRRT
  - Check with your pharmacist
  - Avoid under dosing antibiotics due to high clearance
  - Moving target, adjust appropriately if CRRT held or discontinued

Management of Electrolytes

- Hypophosphatemia and hypomagnesemia occur in almost all patients on CRRT for ≥ 48 hours (ongoing losses)
- Watch for hypokalemia (ongoing losses)
- Hypoglycemia seen in patients without diabetes if no nutrition and no glucose in replacement fluid

Acid/Base Considerations

- Follow ABG on CRRT
- Example: ventilated patient started on CRRT with severe acidemia (pH 7.09)
  - High minute ventilation set to compensate
  - CRRT corrects acidemia
  - Next pH 7.6 due to respiratory alkalosis (previously appropriate) in setting of corrected metabolic acidosis
Nutritional Considerations

- Malnutrition associated with increased mortality
- Prealbumin renally excreted, may be falsely elevated in AKI
- AKI patients are hypercatabolic
- Protein catabolism markedly increased in CRRT but...
- CRRT allows the clinician to provide adequate nutrition (volume...)
- Consensus recommendations 20-30 kcal/kg/day and 1.5g/kg day protein
- Safety reports of up to 2.5g/kg/day protein on CRRT

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70 year old male with known history of significant cardiovascular disease admitted with gram negative septic shock 2/2 indwelling foley associated UTI.

After 3 days on CRRT which of the following might explain a new leukocytosis in the absence of a fever?

a) Line infection
b) Hospital Acquired Pneumonia
c) Bowel Ischemia
d) All of the above ✅
e) None of the above

Key Concepts

- In patients with AKI requiring RRT, mortality ranges from 50-70%
- Sepsis is the most common cause of AKI in the ICU
- Recognizing standard and alternative indications for initiation of RRT in the critically ill patient
- A continuous modality for RRT (CRRT) is indicated in patients with cerebral edema, acute CNS injury, acute cardiac ischemia and hemodynamic instability
- Fluid overload in patients with AKI is associated with increased mortality
- There is no role for hemofiltration in severe sepsis or septic shock in the absence of AKI
- Understanding how CRRT alters your patient assessment. Remember that CRRT "buffs" your labs...don't be fooled.
Questions are guaranteed in life; Answers aren’t.