When and How I Prescribe CRRT

Ravindra L Mehta  MD, DM; FACP; FRCP; FASN
University of California San Diego
Ravindra L Mehta MD
Speaker
I had a personal financial relationship with commercial entities during the last two years:

- Baxter, AM Pharma, CSL-Behring, Astute Medical Inc. Regulus, Akebia, Intercept, Mallinckrodt, Ferring
- Grants: Relypsy, Fresenius-Kabi; Fresenius, Grifols
CRRT When and How

- CRRT Attributes
- Matching Therapy to Clinical Need
- Prescription and Delivery
CRRT When and How

- CRRT Attributes
- Matching Therapy to Clinical Need
- Prescription and Delivery
The case for CRRT?

How can CRRT be utilized?

- To remove solutes and fluid
- To add solutes and fluid
- For regulation of volume and plasma composition
- To prevent toxicity
RRT Schematic
Blood/Bath Transfer

Dialysate (if used)
Pump (if used)

Arterial or venous access from patient

Solute Fluid Heat Amino Acids Cytokines Replacement Fluid

Filter

Venous Access to Patient

Dextrose

Losses: Protein, Amino acids, Electrolytes, Trace elements, Energy

Additions: Electrolytes, Base, Anticoagulant

Effluent: Ultrafiltrate + Dialysate (if used)
Key Considerations for RRT applications

**Therapeutic Targets**
- Solute Homeostasis
- Fluid Regulation
- Biologic effects
  - Hemodynamics
  - Cytokines
  - Cell function
  - Metabolic control

**Operational Characteristics**
- Solute clearance
  - Electrolytes
  - Acid Base Balance
  - Amino acid removal
  - Drug therapy
- Fluid regulation
  - Space
  - Pressor support
- Modulation of Mediators
  - Removal of toxic factors
  - Adsorption
- Thermal Control
  - Hemodynamic support
  - Cerebral Edema
Specific Features of CRRT

Available time 24 hrs/day
• Provide time for organ failure to resolve
• Treat underlying cause
• Enable dynamic adjustments and control

Organ Support
• Targeted interventions
• Disease modification

Flexibility
• Multiple modalities
• Variation in operational characteristics according to need
• Dissociated fluid and solute control

Multidisciplinary approach
• Interaction to define goals
• Drug management
• Nutritional support
• Trial of therapy
CRRT Modalities

**SCUF**
- No solute clearance;
- Used for fluid removal

**CVVH**
- Solute clearance: convection;
- Operative fluid: RF

**CVVHD**
- Solute clearance: diffusion;
- Operative fluid: dialysate

**CVVHDF**
- Solute clearance: diffusion & convection;
- Operative fluids: RF & dialysate
CRRT Operational Characteristics

Effluent

(Total fluid in waste bag at end of a time period.)

Sieving Coefficient = UF/Plasma concentration of solute
(1 = freely permeable, 0+ not permeable).

Dialysate

Diffusive clearance

Ultrafiltrate

Convective Clearance

Clearance in CRRT = SC or equivalent x effluent volume (UF, dialysate, UF + dialysate) + membrane adsorption

Dialyzer and blood clearance differ based on solute and membrane characteristics
Fluid Management with CRRT

Fluid management

Goals

Circuit integrity
- Anticoagulation
  - None
  - Citrate
  - UF heparin
  - LMWH
  - Other
  - Filtration fraction

Plasma composition
- Type of fluid
- Content
- Site of administration

Fluid balance
- Removal
- Regulation

Precision CRRT to achieve homeostasis

Monitoring
Approaches to Solute and Fluid Homeostasis with CRRT

**Solute homeostasis** is achieved by altering composition of substitution fluid or dialysate.

**Common Strategy**
- Ultrafiltrate
- **Zero fluid balance**
- Na

**Alternate Strategy**
- **UF is Varied**
- Fluid balance is achieved by altering the proportion of substitution fluid to ultrafiltrate

- **-ve fluid balance**
- **+ve fluid balance**

**Key feature of CRRT** is the ability to control solute and fluid balance independently.
What can we do in CRRT?

UF rate > plasma refill rate → hypotension
Higher UF Rate Associated with Death

Higher UF rate $\rightarrow$ death

UF rate 13 mL/h/kg

Flythe et al. Al Kid Int, 2011
Approaches to Fluid Balance with CRRT

Fluid Regulation

Interval Time Assessment
Adjusting fluid removal in 24–8 hours interval

Ultrafiltrate volume limited to match anticipated needs for fluid balance over 8-24 hours.

Net patient balance

IN
BC
Drugs
Nutrition
UO
Drains
IL

Blood Purif 2016;42:266–278
Fluid Assessment and CRRT Prescription

- Ultrafiltrate volume adjusted every hour to achieve targeted patient fluid balance.
- Ultrafiltrate volume adjusted every hour to achieve targeted specific hemodynamic parameters e.g. CVP, PAWA, MAP.

Hourly Assessment

![Diagram showing fluid balance and CRRT process]
Figure 4: Effect of Dialysis Modality on Fluid Balance

Bouchard et al KI 2009;76:422-27
CRRT When and How

CRRT Attributes
Matching Therapy to Clinical Need
Prescription and Delivery
When is CRRT usually considered?

Common scenarios for CRRT

- Oliguric fluid overloaded patient
- Hemodynamic instability
- High intake and difficulty in fluid removal
- Severe acid base disorders
Clinical Indications for CRRT

Organ Support
- Renal
- Cardiac
- Hepatic
- Respiratory
- Neurological
- Nutrition
- Thermal regulation

Disease modification
- Sepsis
- Metastatic Cancer
- Metabolic disorders
CRRT for Renal Support

Impaired Renal Function

• Rationale is to add capacity for solute clearance, fluid removal and achieve electrolyte and acid base homeostasis

• Remove toxins including drugs and metabolites e.g. phenobarbital, methanol, lithium

• Allow time for renal functional recovery
Advantages of CRRT

Steady Clearance of Solutes with more Consistent Metabolic Clearance Without Shifts

Acid Base Balance in CVVH vs EDD

**Fig. 3** Boxplot diagram of pH in arterial blood: before treatment (pre), at 10 h after treatment on day 1, and on days 2, 3 and 4 using EDDf (n = 8) or CVVH (n = 8). No significant differences.

**Fig. 4** Boxplot diagram of bicarbonate in arterial blood: before treatment (pre), at 10 h on day 1, and on day 2, day 3 (p = 0.019), and day 4 (p = 0.039) using EDDf (n = 8) or CVVH (n = 8).

**Fig. 5** Boxplot diagram of base deficit in arterial blood: before treatment (pre), at 10 h on day 1, and on day 2 (p = 0.009), day 3 (p = 0.008), and day 4 (p = 0.033) using EDDf (n = 8) or CVVH (n = 8).
CRRT for Cardiac Support

Cardiac Failure

• Rationale is to remove fluid to restore cardiac function to Starling curve
• Facilitate hemodynamic support with vasopressors and inotropes
• ? Remove myocardial depressant factors
In 88 patients with HF (NYHA class III-IV) we evaluated the effect of CRRT (n = 46) and intravenous diuretics (n = 42) on clinical and instrumental signs of congestion. A clinical score was obtained as the sum of signs and symptoms of HF to estimate the severity of each patient’s clinical condition.

The choice of diuretics or CRRT was guided by renal impairment or diuretics’ resistance.
CRRT for Liver Failure

Key Features of Liver failure

- Hyponatremia, ascites and hypotension
  - Compartment syndrome and hypotension worsen brain edema
- Fulminant liver failure and Hepatic Encephalopathy
  - Brain edema
  - Role of hyponatremia in worsening brain edema
  - Low urea concentration worsens chances of Osmotic Demyelination Syndrome
- Coagulopathy
  - Decreased or increased coagulation?

Stravitz RT CCM 2007;35:2498
Davenport A Contr Nephrol 2007;156:259
Davenport A Hemodial Int 2008;12:307
### Table 3. RCA-CWHD flows and citrate dose at start of treatment and end of observation

<table>
<thead>
<tr>
<th></th>
<th>Normal liver function (bilirubin ≤2 mg/dl)</th>
<th>Mild liver failure (bilirubin 2–7 mg/dl)</th>
<th>Severe liver failure (bilirubin ≥7 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood flow (ml/min)</strong></td>
<td>Start 109 ± 24, End 114 ± 25</td>
<td>Start 109 ± 25, End 117 ± 28</td>
<td>Start 110 ± 24, End 107 ± 20</td>
</tr>
<tr>
<td><strong>Dialysate flow (ml/h)</strong></td>
<td>2144 ± 502</td>
<td>2200 ± 500</td>
<td>2208 ± 402</td>
</tr>
<tr>
<td><strong>Net ultrafiltration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Citrate dose (mmol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 2** Estimated mean ± standard deviation of arterial pH and serum bicarbonate concentrations during regional citrate anticoagulation and continuous venovenous hemodialysis according to liver groups
CRRT for Respiratory Support

ARDS

• Rationale is to optimize fluid status by regulating fluid balance and lung permeability.
• Patients with ARDS and Permissive Hypercapnia
  • Ventilatory support often requires permissive hypercapnia that results in acidemia. Concurrent use of CRRT can allow correction of acidemia without fluid or salt overload.
  • Citrate anticoagulation combined with addition of bicarbonate to dialysate allows compensation for respiratory acidosis

**TABLE 1. Subjects’ characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early CRRT</th>
<th>Late CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50.36 ± 16.97</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>19/8</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2. Comparison of variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early CRRT</th>
<th>Late CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂/FIO₂</td>
<td>121.45</td>
<td>130.23</td>
</tr>
<tr>
<td>PEEP (cm·H₂O)</td>
<td>13.45</td>
<td>14.23</td>
</tr>
<tr>
<td>Plateau pressure (cm·H₂O)</td>
<td>31.85</td>
<td>32.93</td>
</tr>
<tr>
<td>A-a gradient (mm Hg)</td>
<td>46.18 ± 11.12</td>
<td>55.93 ± 12.12</td>
</tr>
<tr>
<td>Cdyn</td>
<td>17.18 ± 11.12</td>
<td>19.09 ± 12.31</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>14.09 ± 3.78</td>
<td>14.78 ± 4.09</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>69.23 ± 25.1</td>
<td>71.15 ± 23.92</td>
</tr>
<tr>
<td>CI (L·min⁻¹·m⁻³)</td>
<td>3.13 ± 1.27</td>
<td>2.95 ± 1.03</td>
</tr>
<tr>
<td>EVLWI (mL/kg)</td>
<td>15.26 ± 5.69</td>
<td>16.07 ± 5.35</td>
</tr>
<tr>
<td>Fluid balance (mL)</td>
<td>163.31 ± 32.67</td>
<td>158.87 ± 32.45</td>
</tr>
</tbody>
</table>

*P = 0.00168

**FIGURE 1. Comparison of duration of CRRT and mechanical ventilation between early initiation of CRRT and late initiation of CRRT groups. CRRT, continuous renal replacement therapy.**

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\(^a\) P < 0.05 compared with early CRRT at the same time point.

\(^b\) P < 0.05 compared with baseline of day 0.

BALF, bronchoalveolar lavage fluid; Cdyn, dynamic compliance; CI, cardiac index; CVP, central venous pressure; EVLWI, extravascular lung water index; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure.
CRRT for Neurological Support

Intracranial Pressure Management

• Rationale is to reduce intracranial pressure following TBI, hemorrhage and stroke
• Manage severe hypo and hypernatremia
• Minimize dialysis diseqilibrium
Pathogenesis of Dialysis Disequilibrium Syndrome

- increased removal of plasma urea
- slower removal from CSF and brain tissue

-> osmotic gradient with passage of water from the relatively hypotonic plasma to the relatively hypertonic brain

-> brain edema.
Intracranial Pressure CRRT vs. IHD

A 59-year-old man with HTN, type 1 diabetes, and ESRD on HD presented after head trauma from a fall while walking.
CRRT for Neurological Support

Patients with intra cranial hypertension or cerebral edema

- Autoregulation is lost!
- Sudden changes in systemic or intra-abdominal pressure change intracranial pressure
  - Patients with abdominal compartment syndrome
  - Patients with fulminant liver failure or acute decompensated liver cirrhosis

Patients with severe azotemia

- Correct azotemia slowly, to avoid dialysis dysequilibrium and worsened brain edema

Patients with hyponatremia

- Correct [Na]p very slowly to avoid osmotic demyelination syndrome
- Urea protects against osmotic demyelination syndrome
CRRT for Nutritional Support

Nutrition

- Create space for nutritional support fluids preventing fluid accumulation
- Provide adequate protein and calories
- Replenish vitamins and trace elements
- permits accurate assessment of nutritional needs and catabolic state
Protein losses with CRRT

- CAVHD
- AN-69 (0.43 m2; PAN membrane)
- BFR MAP dependent (80 mls/min)
- Qd @ 1 l/hr; Quf 340 mL/hr
  - AA losses = 9% of total intake
- Qd @ 2 l/hr; Quf 340 mL/hr
  - AA losses = 12% of total intake

Davies et al, Crit Care Med, 1991

- CVVH and CVVHDF
- Polysulfone membranes
  - (Amicon 20 and Fresenius F-80)
- Qb 100-300 mls/min
- Qd 1000 ml/hr + 600 mL/hr
  - UFR
  - 1.2 - 7.5 gm/day of protein losses


Amino acid and protein losses represent between 10-12% of total delivered nutritional proteins
Glutamine loss accounted for approximately 20% of total AA loss

CRRT for Thermal Regulation

Temperature

• Heat loss across circuit and filter
• Thermal control allows manipulation of core temperature
• Hypothermia reduces metabolic rate
## Continuous Hemofiltration-Related Hypothermia: Influence on Gas Exchange in Sepsis

20 pts CAVH/CVVH, ARF d/t septic shock  
Studied first 30 minutes, subsequent 48 hr CRRT

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Ultrafiltration rate ml/hr</td>
<td>855 +/- 278</td>
<td>1468 +/- 293</td>
</tr>
<tr>
<td>Core Temp Change (C)</td>
<td>37.6 +/- 0.9</td>
<td>34.8 +/- 0.8 p &lt; 0.001</td>
</tr>
<tr>
<td>Hemodynamic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂ (ml/min/m2)</td>
<td>141 +/- 22</td>
<td>112 +/- 22 p &lt; 0.01</td>
</tr>
<tr>
<td>Metabolic rate</td>
<td>7.1% decrease</td>
<td>20% decrease</td>
</tr>
</tbody>
</table>

- **Inverse relationship between ultrafiltration rate/core temperature and VO₂ in septic pts treated with CVVH/CAVH**  
- **Potential beneficial effects in malignant hyperthermia, febrile hypermetabolic, catabolic states**

Calculation of Heat Loss in CRRT

- Hypothermia associated with ↑ mortality
  - Dialysate is warmed by IHD machine
  - CVVHD: dialysate hung like IV bag at room temp
  - CVVH, CVVHDF: UFR solutions also hung like IV bags at room temperature

- Hypothermia is a common problem
  - 36 episodes of hypothermia
  - (core body temp <35.5 C) in 72 CRRT patients
  - Yagi N et al. AJKD 1998;32:1023-30

  - Qb 120 mL/min Quf 1400mL/hr
  - Heat loss = 765 kcal/d
    - blood tubing 26%
    - hemofilter 31%
    - produced UF 43%

- Heating UFR solution to 43 C↓ loss by 72%
  - Take FRF /dialysate out of fridge!
Clinical Indications for CRRT

Organ Support
- Renal
- Cardiac
- Hepatic
- Respiratory
- Neurological
- Nutrition
- Thermal regulation

Disease modification
- Metabolic disorders
- Drug Toxicity
- Sepsis
- Metastatic Cancer
- Combination with apheresis
Patient Selection for Continuous Renal Replacement Therapy

- CRRT/PD
- PIRRT/SLED
- IHD

Hemodynamic stability
Stability of intracranial pressure

Risk of infections
Immobilisation

Rate of fluid removal
Rapidity of metabolic and acid base correction
Risk of osmolar shifts

Speed of small solute clearance, incl. potassium, drugs

CRRT When and How

- CRRT Attributes
- Matching Therapy to Clinical Need
- Prescription and Delivery
Role of CRRT for renal support
How is it Done?

Prescription

- Machine PRISMAFLEX
- Filter HF-1000 filter set
- Mode: CVVHDF
- BFR: 100 ml/min
- Dialysate flow rate: 1000 ml/hr
- Patient fluid removal 1000 ml/hr
- Pre-filter replacement: 500 ml/hr
- Post-Filter dilution 200 ml/hr
- **Effluent volume 2700 ml/hr**

Post-filter replacement: to achieve target fluid balance

Anticoagulation: Regional citrate

- 4% tri-sodium citrate at 180 ml/hr
- Calcium chloride 40 ml/hr
- Monitoring: peripheral and post-filter ionized calcium

Solutions:

- Dialysate: Primsasate
- Pre-filter fluid: 0.9% saline
- Post-filter replacement: Primsasol or 0.9% saline b or or sterile water + 150 meq bicarb or 0.45% saline + 75 meq of bicarb
Machine Programming Components:

Modality: CVVH, CVVHD, CVVHDF

Negative fluid balance desired (Fluid removal rate) (Fld)
Replacement fluid pre vs post filter (RF)
Dialysate flow rate (DF)
Anticoagulant flow rate (AC)

Effluent Pump Speed = RF + DF + AC + Fld removal
San Diego Protocol (CVVHDF)**

**Dialysate:** 5L bag

**B25GK4/2.5:** 5 L bag

- Na⁺ 140 mmol/L
- Cl⁻ 120.5 mmol/L
- HCO₃⁻ 22 mmol/L / lactate 3 mmol/L
- K⁺ 4.0 mmol/L
- Mg 0.75 mmol/L
- Gluc 110 mg/dL
- Ca 2.5 Meq/L

**Rate:** 1000 mL/hr

**Predilution Fluid:** 0.9% NS Rate: 500 mL/hr

**IV Replacement Fluid:** Prismasol with calcium BGK4/2.5/ or BGK 0/2.5

- Rate: 500-750 mL/hr

**Postfilter Fluid:** 0.9% NS

- Rate: 200 mL/hr

**Baxter Prismaflex with M-100 filter**

- Qₐ = Qₐ₁ + Qₐ₂ + Qₐ₄

- 4% Na₃Citrate, 2L bag Rate: 140-220 mL/hr
- 19-29 mmol/hr citrate

- Qₑ = Qₐ₁ + Qₐ₂ + Qₐ₄

- Patient
  - iCa²⁺ 1.12-1.32 mmol/L
  - Rate: 0-40 mL/hr

- Commercial solutions

Av Filter life > 72 hrs

Management of Hyponatremia with CRRT Circuit Adjustments

Management of Hyponatremia with CRRT Circuit Adjustments

When Should We Not Use CRRT?

- Isolated AKI
- High clearances desired over short duration
- Mobility is desired
- Inadequate infrastructure
  - Machines and solutions
  - Nursing support
  - Untrained personnel
  - Protocols
  - Lab
  - Pharmacy
Management of renal replacement therapy in ICU patients: an international survey

When and How for CRRT

Summary

CRRT operational characteristics facilitate its application for organ support

- Solute concentration can be manipulated independent of fluid balance
- Plasma composition can be altered by changing composition of dialysate and substitution fluid
- Fluid regulation can occur concurrently with solute removal to maintain patient fluid balance desired

Flexibility of this technique facilitates its use for a wide variety of indications

Goal should be to use modality for initial therapy in critically ill patients.

Further studies needed to assess effect on outcomes stratifying for timing of intervention, indication and dose.
Renal Replacement in the ICU

The CRRT Safety Net!