Prescription and Dosing Considerations in CRRT

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Case Presentation

A **65-year-old male** with a history of **HTN, IHD, and T2DM**, was admitted to the hospital 48 hours ago with **severe pneumonia** and **septic shock**. He is on **mechanical ventilation** and requires **norepinephrine** for blood pressure support. Over the past 24 hours, his renal function has deteriorated significantly, and his urine output has dropped to less than **20 mL/hour**. On physical examination there is **2+ peripheral edema**. Other findings include:

- Body weight: 70 kg
- Blood pressure: 88/56 mmHg (on norepinephrine)
- Cumulative fluid balance: 6 L (since admission)
- Serum creatinine: 3.5 mg/dL (baseline 1.1 mg/dL)
- HCT: 30%
- Serum sodium: 142 mEq/L
- Serum potassium: 6.8 mEq/L
- Bicarbonate: 14 mEq/L
- pH: 7.08
- Lactate: 5.1 mmol/L
- Chest X-ray: Diffuse bilateral lung infiltration, suggestive of **ARDS**
- Echocardiography: normal

Given the clinical picture of **septic shock** with **multi-organ failure**, including **AKI.** the ICU team consults you for **Kidney replacement therapy** initiation.

Key Considerations in CRRT Prescription and Management

- Considerations prior to CRRT initiation
- Selecting the appropriate CRRT modality
- Components of the CRRT prescription
- Determining the appropriate CRRT dose
- Continuous monitoring and adjusting CRRT performance
- Criteria for discontinuing CRRT

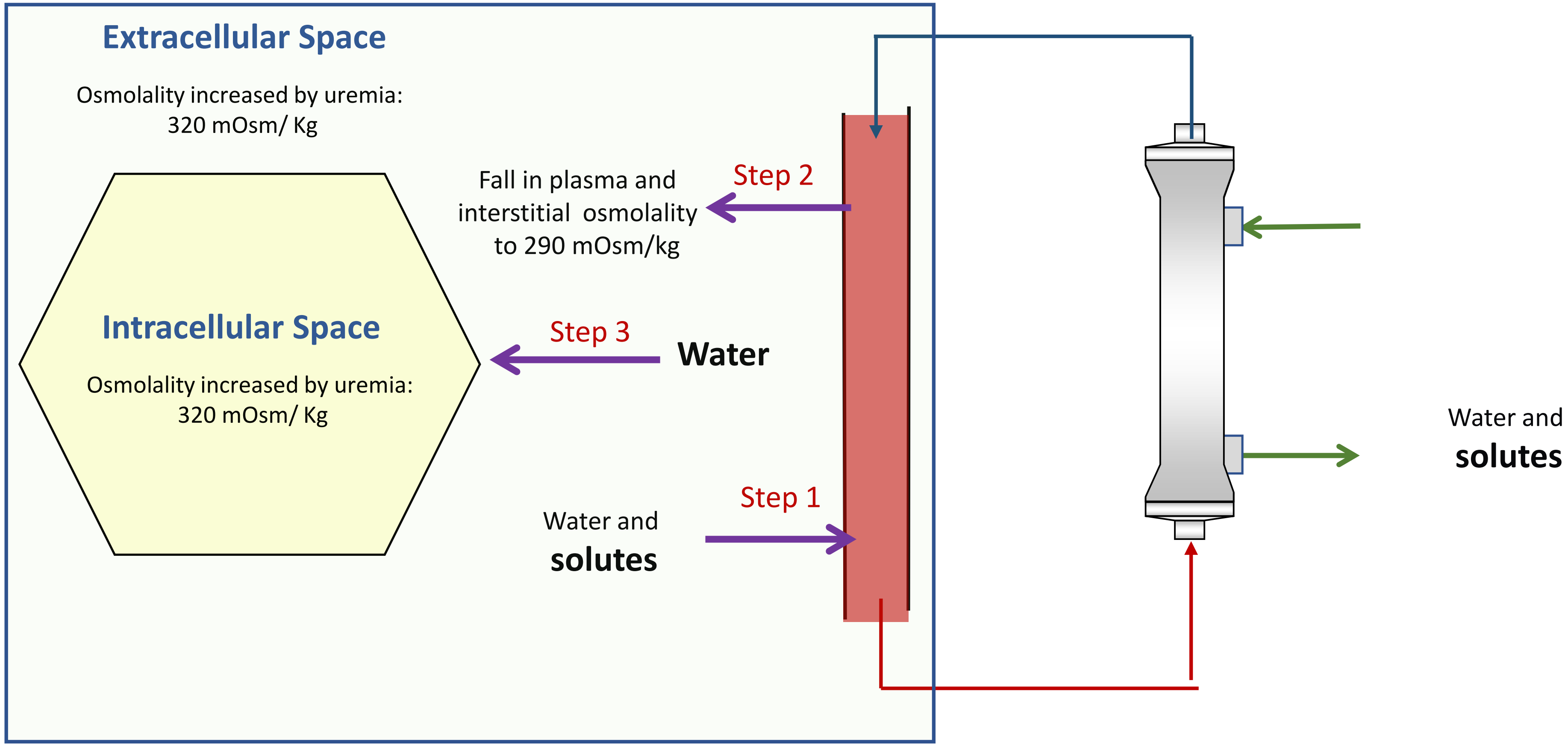
Urgent Indications of Kidney Replacement therapy (KRT)

Patients who meet one or more of these criteria require KRT:

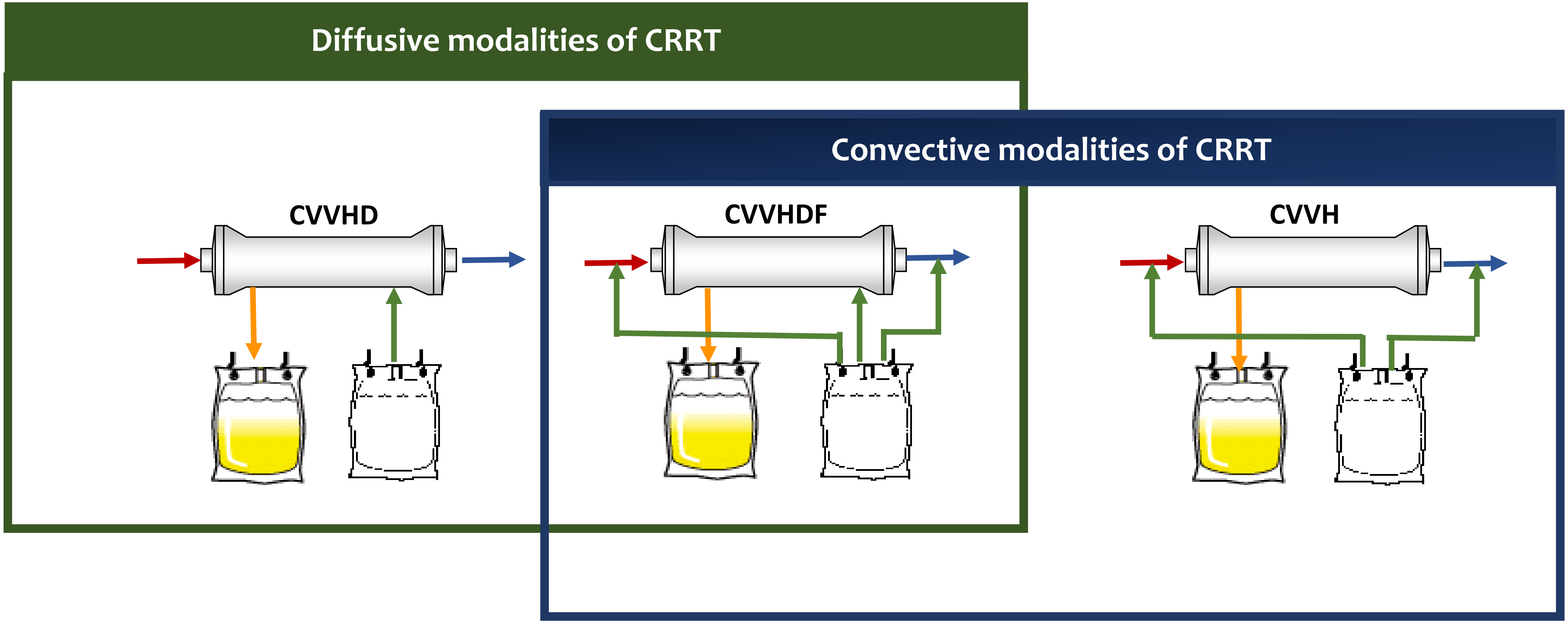
- Fluid overload that does not respond to diuretic treatment
- Significant hyperkalemia (K > 6.5 mg/dL)
- Clear signs of uremia, including pericarditis, encephalopathy, or an unexplained deterioration in mental status
- Severe metabolic acidosis (pH < 7.1) that persists despite medical intervention
- Specific cases of alcohol and drug poisoning

CRRT is too slow for the rapid correction of hyperkalemia; therefore, medical treatment should be initiated as soon as life-threatening hyperkalemia is confirmed.

Intracellular Shift of Water During Conventional Hemodialysis

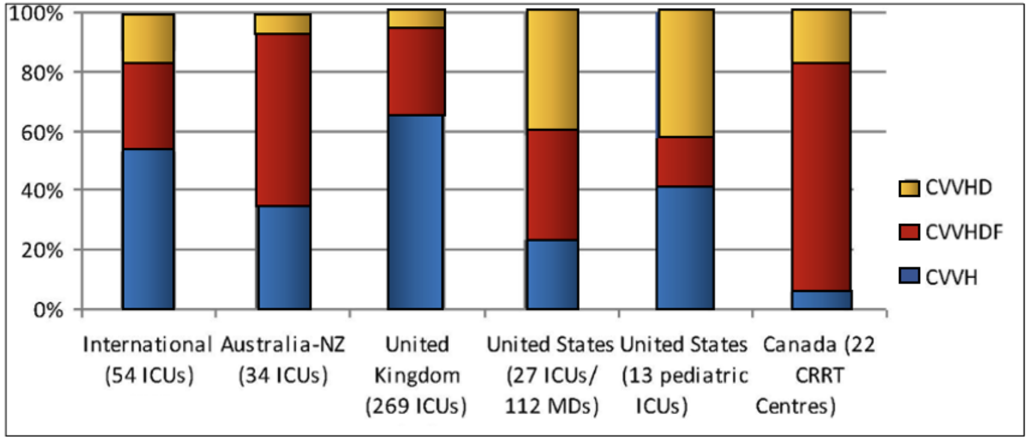


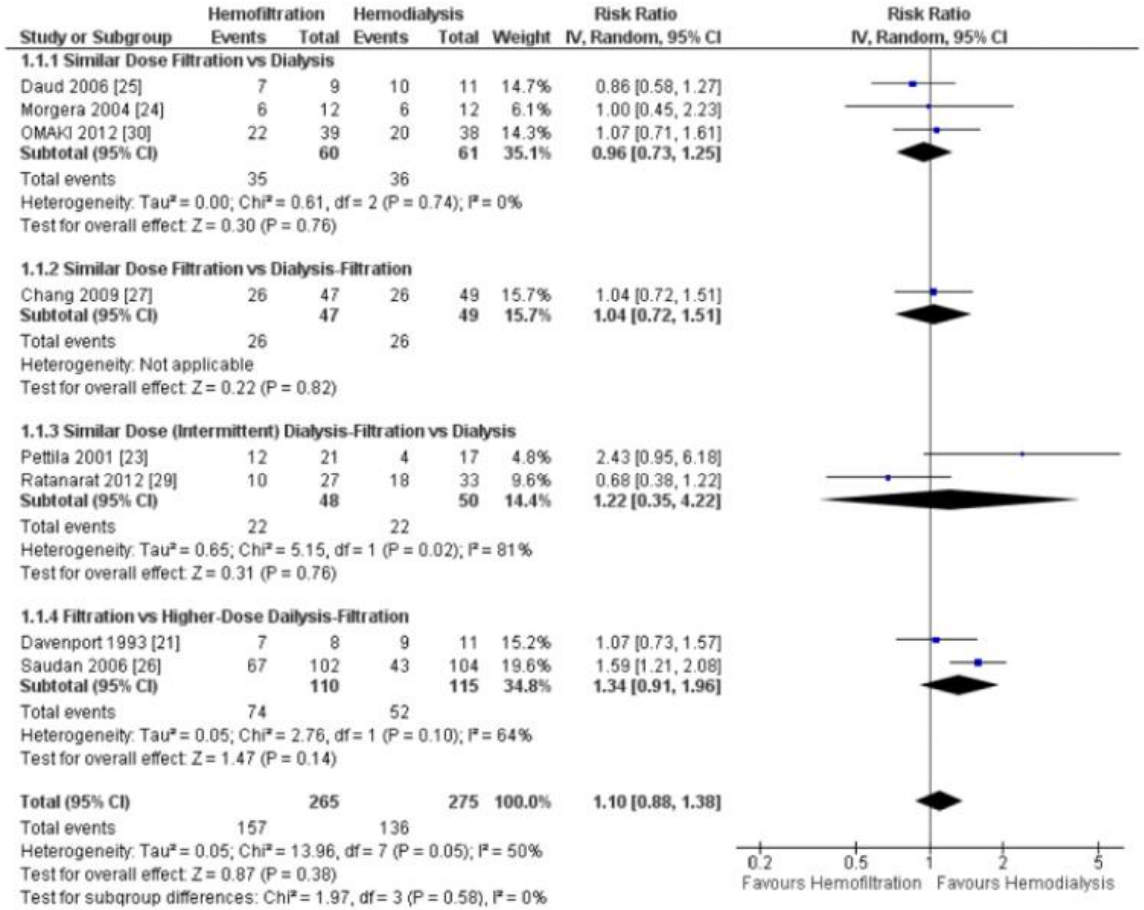
There is no rapid change in osmolality during CRRT. Thus, hypotension is not aggravated by intracellular fluid shift.



Diffusive modalities of CRRT
Convective modalities of CRRT
CVVHD
CVVHDF
CVVH

Hemofiltration Compared to Hemodialysis for Acute Kidney Injury: Systematic Review and Meta analysis





Study or Subgroup	Hemofiltration Events	Hemofiltration Total	Hemodialysis Events	Hemodialysis Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Similar Dose Filtration vs Dialysis						
Daud 2006 [25]	7	9	10	11	14.7%	0.86 [0.58, 1.27]
Morgera 2004 [24]	6	12	6	12	6.1%	1.00 [0.45, 2.23]
OMAKI 2012 [30]	22	39	20	38	14.3%	1.07 [0.71, 1.61]
Subtotal (95% CI)		**60**		**61**	**35.1%**	**0.96 [0.73, 1.25]**
Total events	35		36			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.1.2 Similar Dose Filtration vs Dialysis-Filtration						
Chang 2009 [27]	26	47	26	49	15.7%	1.04 [0.72, 1.51]
Subtotal (95% CI)		**47**		**49**	**15.7%**	**1.04 [0.72, 1.51]**
Total events	26		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
1.1.3 Similar Dose (Intermittent) Dialysis-Filtration vs Dialysis						
Pettila 2001 [23]	12	21	4	17	4.8%	2.43 [0.95, 6.18]
Ratanarat 2012 [29]	10	27	18	33	9.6%	0.68 [0.38, 1.22]
Subtotal (95% CI)		**48**		**50**	**14.4%**	**1.22 [0.35, 4.22]**
Total events	22		22			
Heterogeneity: Tau² = 0.65; Chi² = 5.15, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.1.4 Filtration vs Higher-Dose Dailysis-Filtration						
Davenport 1993 [21]	7	8	9	11	15.2%	1.07 [0.73, 1.57]
Saudan 2006 [26]	67	102	43	104	19.6%	1.59 [1.21, 2.08]
Subtotal (95% CI)		**110**		**115**	**34.8%**	**1.34 [0.91, 1.96]**
Total events	74		52			
Heterogeneity: Tau² = 0.05; Chi² = 2.76, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**265**		**275**	**100.0%**	**1.10 [0.88, 1.38]**
Total events	157		136			
Heterogeneity: Tau² = 0.05; Chi² = 13.96, df = 7 (P = 0.05); I² = 50%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Chi² = 1.97, df = 3 (P = 0.58), I² = 0%						

Effects of hemodiafiltration vs. hemodialysis on mortality

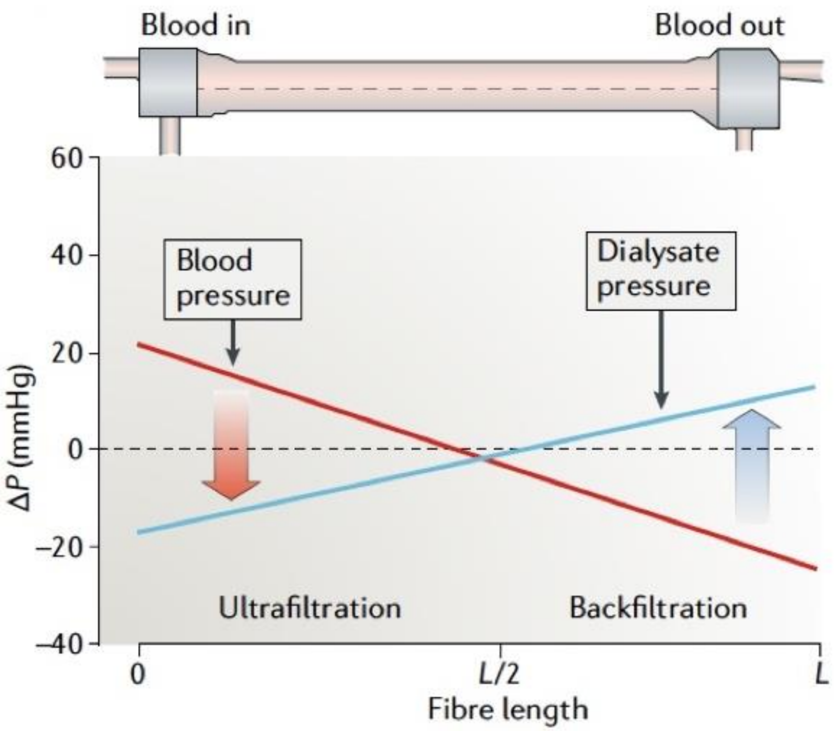
19 RCT (16 continuous RRT)

Friedrich et al. Critical Care 2012, 16:R146

Choosing CRRT Modality

- Practitioners may prefer hemofiltration (CVVH/CVVHDF) due to its higher clearance of larger molecules and inflammatory mediators compared to CVVHD.
- Despite the theoretical advantages, no significant differences in survival, kidney function recovery, vasopressor use, or organ dysfunction have been consistently observed between CVVHD and CVVH/CVVHDF.
- With current CRRT equipment, sufficient solute clearance is attainable through all three modalities.
- The choice of CRRT modality is typically influenced by individual or institutional preference rather than by specific clinical outcomes.

Is CVVHD a Pure Diffusive Modality of CRRT?



While CVVHD often described as a predominantly diffusive therapy, the movement of fluid from blood to the dialysate compartment and the reverse flow from dialysate to blood can happen due to pressure gradient across the high-flux membrane. Therefore, when using membrane with high hydraulic permeability, there is a significant potential for convective transport, allowing the elimination of solutes with larger molecular weight that what would be anticipated through diffusion alone.

Ronco C, and Clark RC. Nature Reviews Nephrology 2018; 14: 394-410

CRRT Prescription Components: Three Different Modalities

Modality: CVVHDF

Duration: ≥ 24 hours ✓
Blood flow rate:
Net UF rate:
Dialysate rate:
Pre-filter replacement fluid rate:
Post-filter replacement fluid rate:
Anticoagulation:

Modality: CVVHD

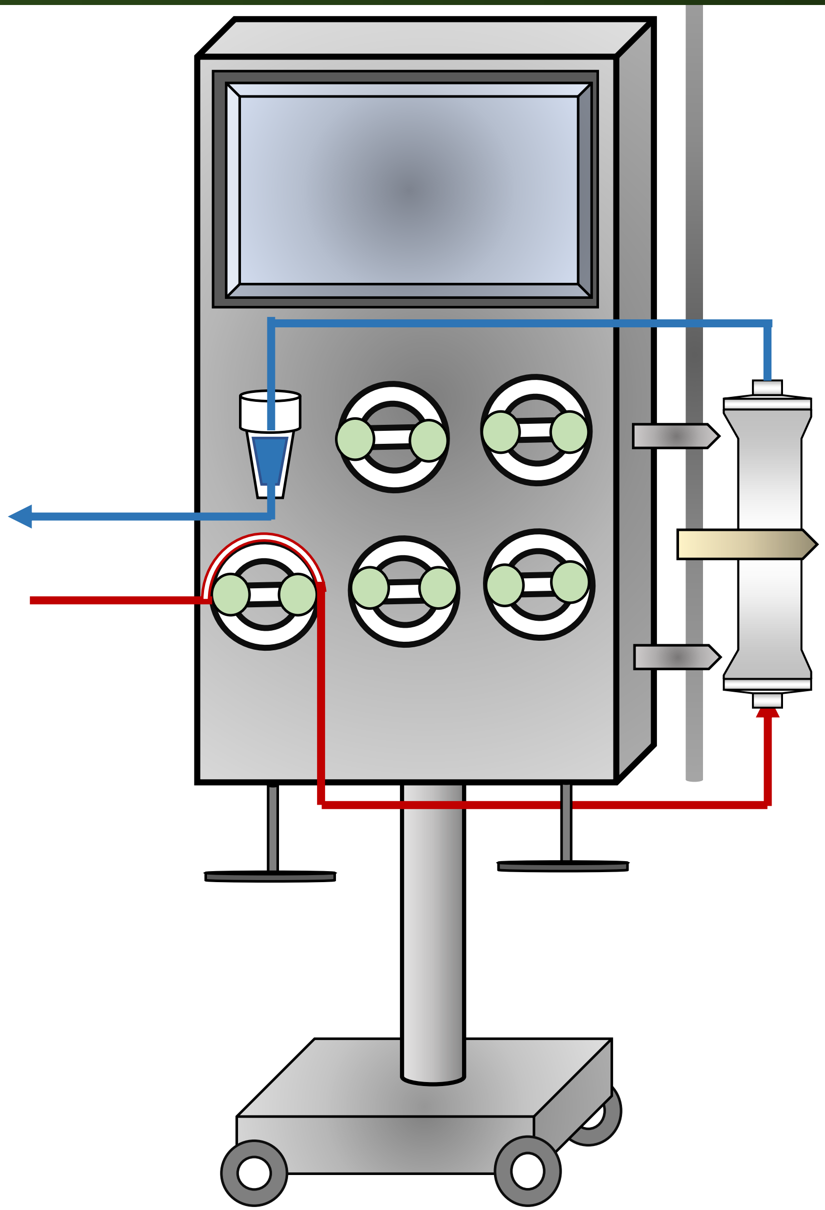
Duration: ≥ 24 hours ✓
Blood flow rate:
Net UF rate:
Dialysate flow rate:
Anticoagulation:

Modality: CVVH

Duration: ≥24 hours ✓
Blood flow rate:
Net UF rate:
Post-filter replacement fluid rate:
Prefilter replacement fluid rate:
Anticoagulation:

Blood Flow Rate in CRRT

While higher blood flow rates during CRRT can sometimes be associated with hemodynamic instability, this effect is often reduced by the low compliance of hollow-fiber membranes, which minimizes significant changes in extracorporeal volume that could affect blood pressure.



The optimal blood flow rate for most patients on CRRT is between 150 and 250 mL/min

CRRT Prescription Components: Three Different Modalities

Modality: CVVHDF

Duration: ≥ 24 hours
Blood flow rate: 150 mL/min
Net UF rate: 100 mL/h
Dialysate rate:
Pre-filter replacement fluid rate:
Post-filter replacement fluid rate:
Anticoagulation:

Modality: CVVHD

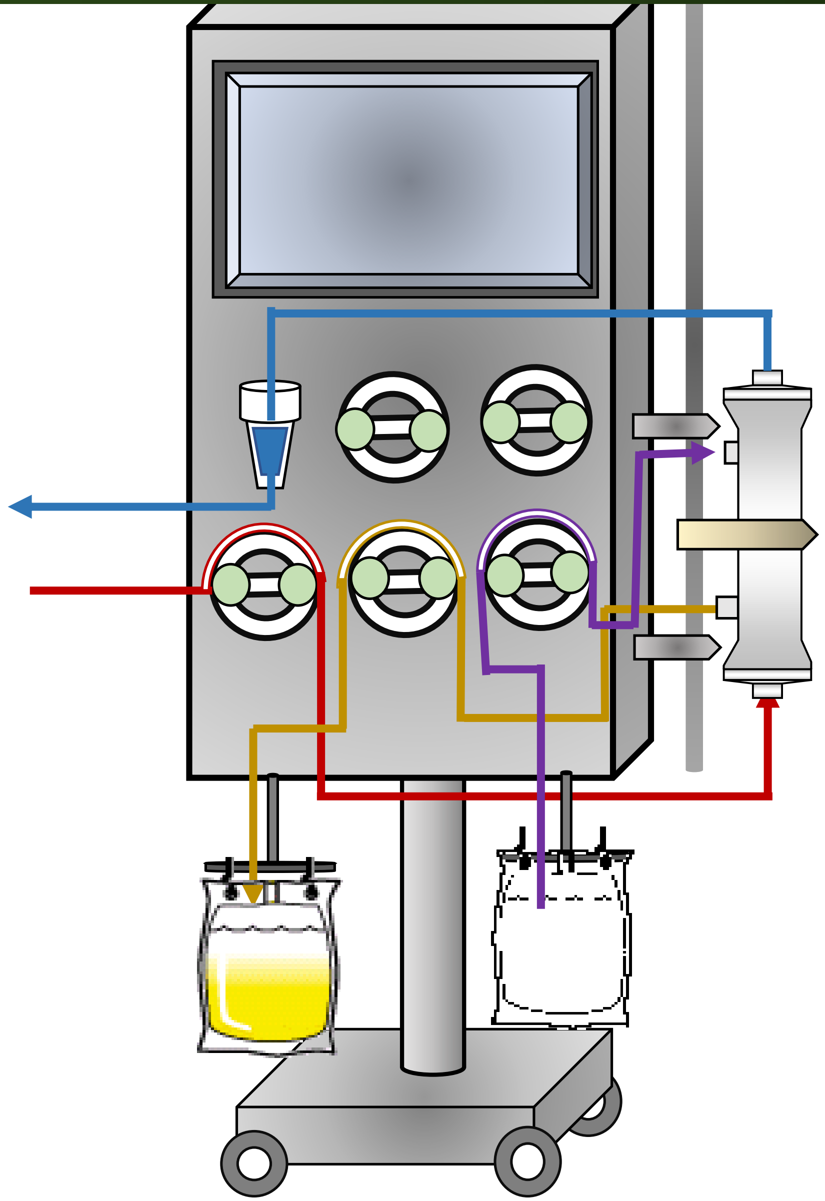
Duration: ≥ 24 hours
Blood flow rate: 150 mL/min
Net UF rate: 100 mL/h
Dialysate flow rate:
Anticoagulation:

Modality: CVVH

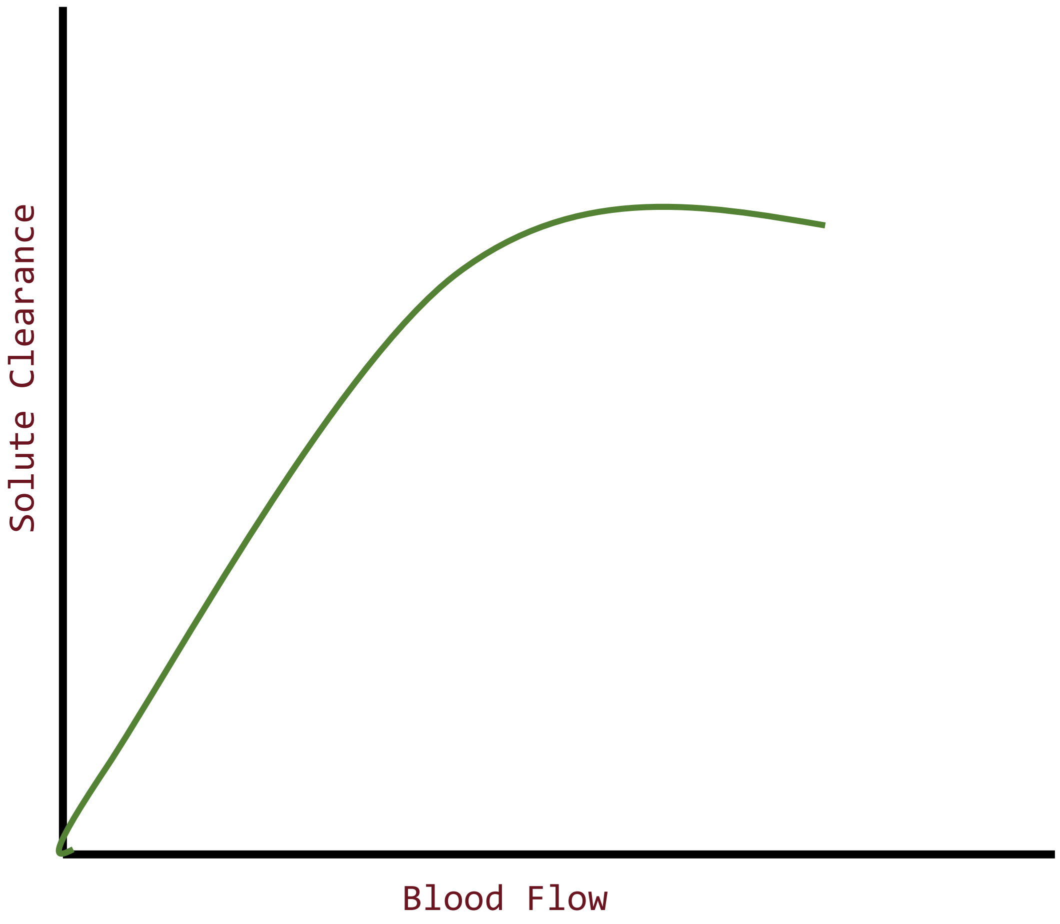
Duration: ≥24 hours
Blood flow rate: 150 mL/min
Net UF rate: 100 ml/h
Post-filter replacement fluid rate:
Prefilter replacement fluid rate:
Anticoagulation:

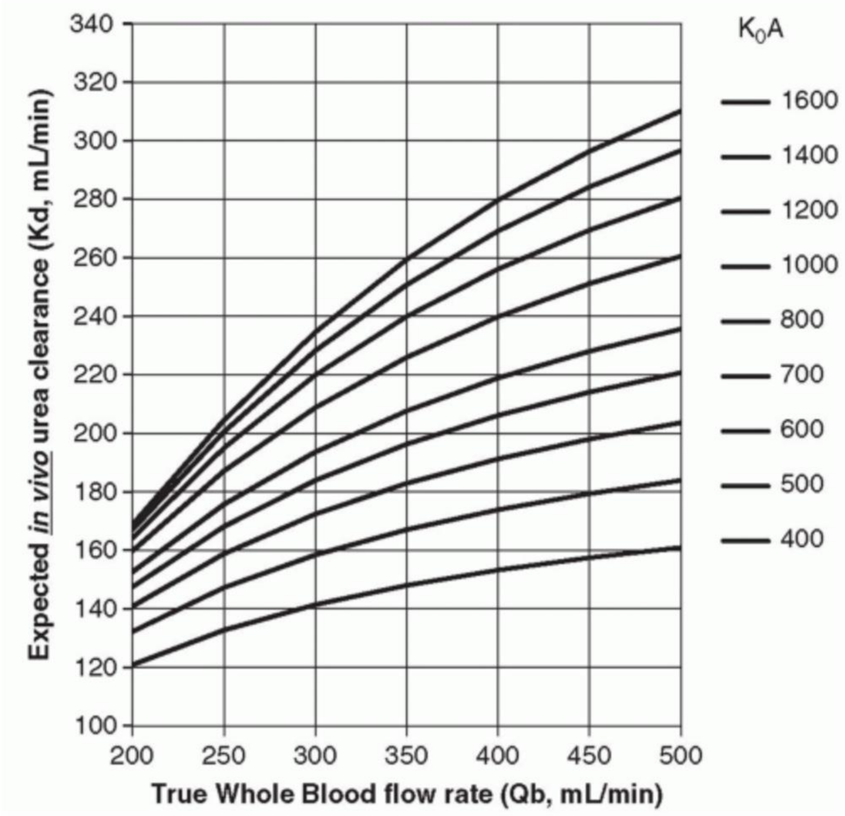
CVVHD

In contrast to conventional hemodialysis, in CRRT, the blood flow rate is much higher than the dialysate flow rate

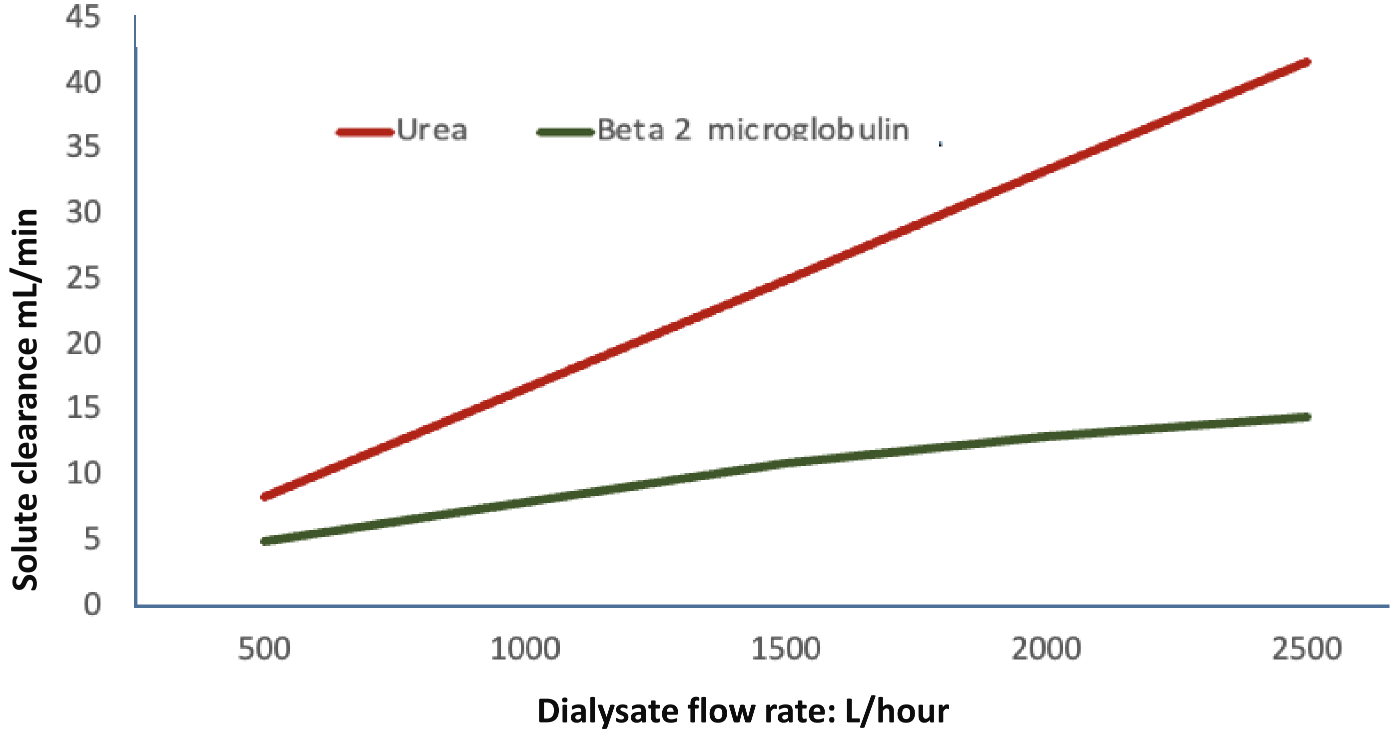


Solute Clearance and Blood Flow Rate During Conventional Intermittent Hemodialysis.





Solute Clearance and Dialysate Fluid Rate in CVVHD



The solute clearance is determined by the dialysate flow rate rather than the blood flow rate in CRRT

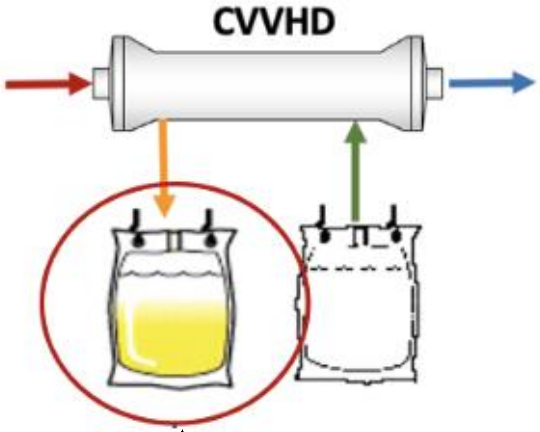
Optimal Blood Flow Rate in CRRT: Reducing Clotting Risks

- Adequate blood flow prolongs circuit life, though it does not enhance solute clearance.
- Low blood flow increases clotting risk, leading to:
  - Reduced solute clearance
  - Loss of filter/lines
  - Increased need for anticoagulation

Solute Clearance in CRRT

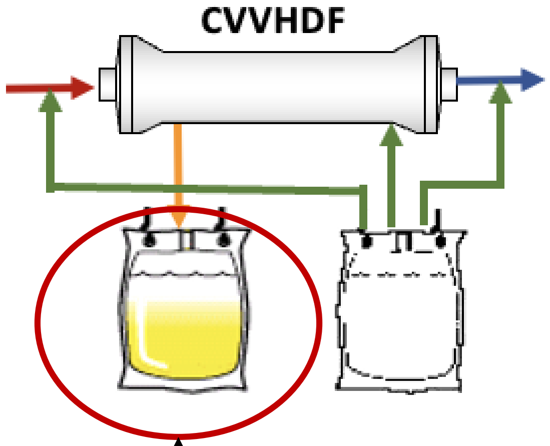
- In CVVHD, the dialysate flow is typically lower than the blood flow, resulting in near-complete equilibrium of low-molecular-weight molecules between plasma and dialysate.
- Similarly, in CVVH, the concentration of low-molecular-weight solutes in the ultrafiltrate closely resembles that in plasma water.
- Therefore, in all CRRT modes, the concentration of low-molecular-weight solutes in the effluent reflects that in plasma water, with clearance of these solutes approximating the effluent flow rate.

Effluent Flow Rate = Clearance of Small Size Molecules



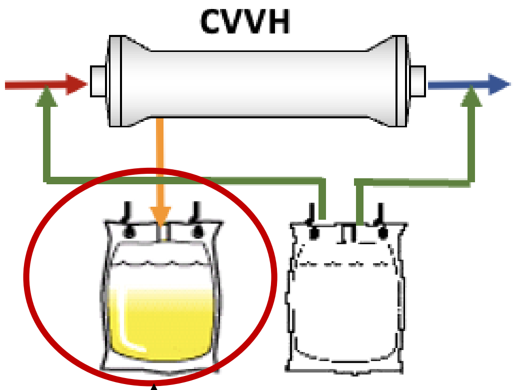
Effluent Flow Rate

Net Fluid removal Rate
+
Dialysate Fluid Rate



Effluent Flow Rate

Net Fluid removal Rate
+
Dialysate Fluid Rate
+
Replacement Fluid Rate



Effluent Flow Rate

Net Fluid removal Rate
+
Replacement Fluid Rate

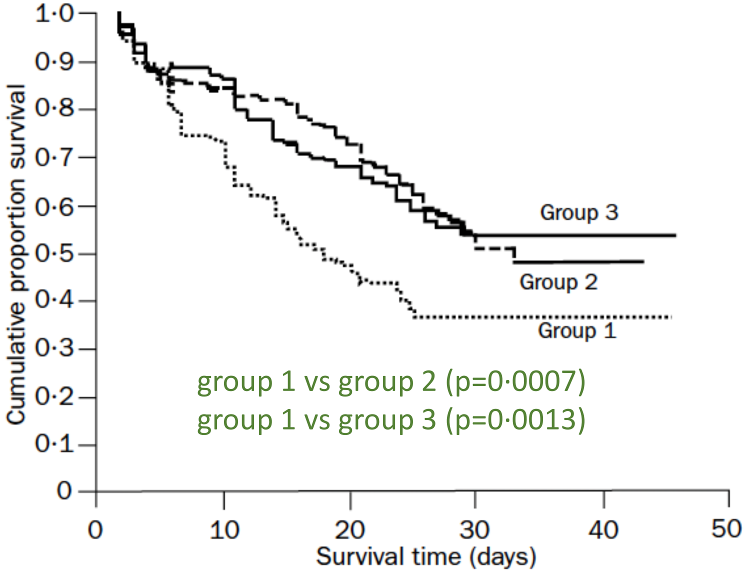
CRRT dose

In CRRT, the dose is typically defined by the clearance of urea, a low molecular weight molecule with a sieving coefficient close to one, and is expressed in mL/kg/h.”

Urea Clearance = Total Effluent rate X Sieving Coefficient of Urea

Sieving Coefficient : Urea Concentration in Effluent / Urea concentration in plasma

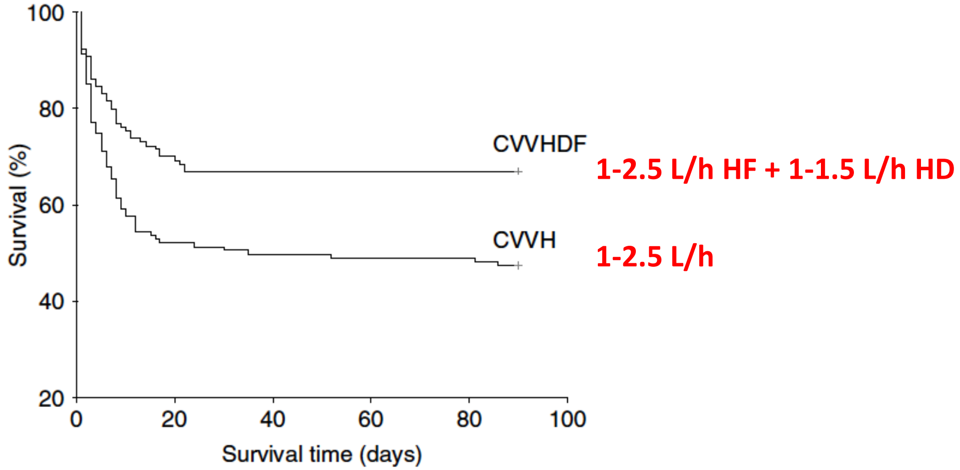
The effect of different doses of CRRT on Outcomes



Number of patients: 425
Patients randomized to 3 groups based on CRRT dose
Group 1: 20 mL /kg/h, 146 patients
Group 2: 35 mL/kg/h, 139 patients
Group 3: 45 mL/kg/h, 140 patients

Modality: CVVH, Post dilution

Ronco C, et al Lancet. 2000; 356: 26–30



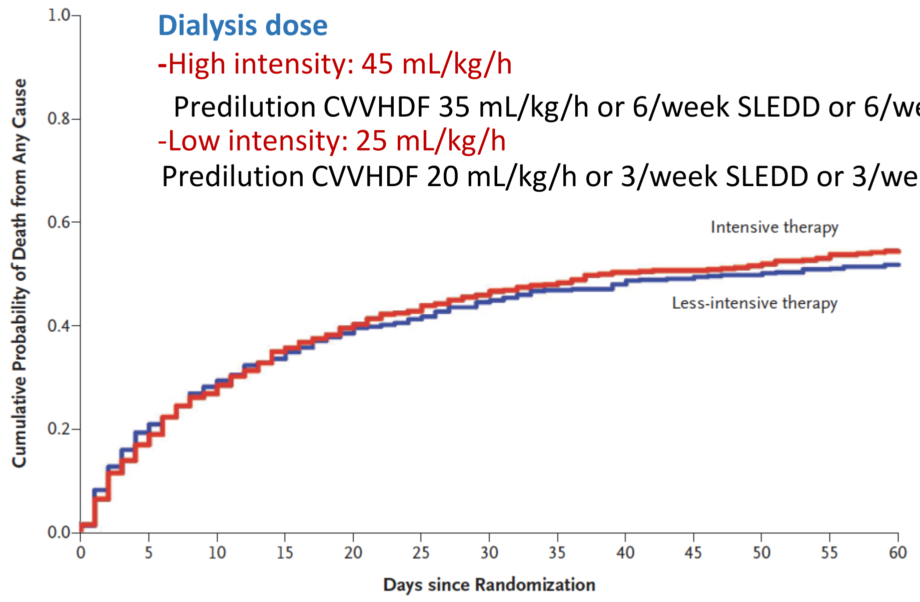
Kaplan–Meier analysis of survival rates in the two groups.

Number of patients: 206

Adding a dialysis dose to CVVH had an impact on mortality in critically ill patients with AKI

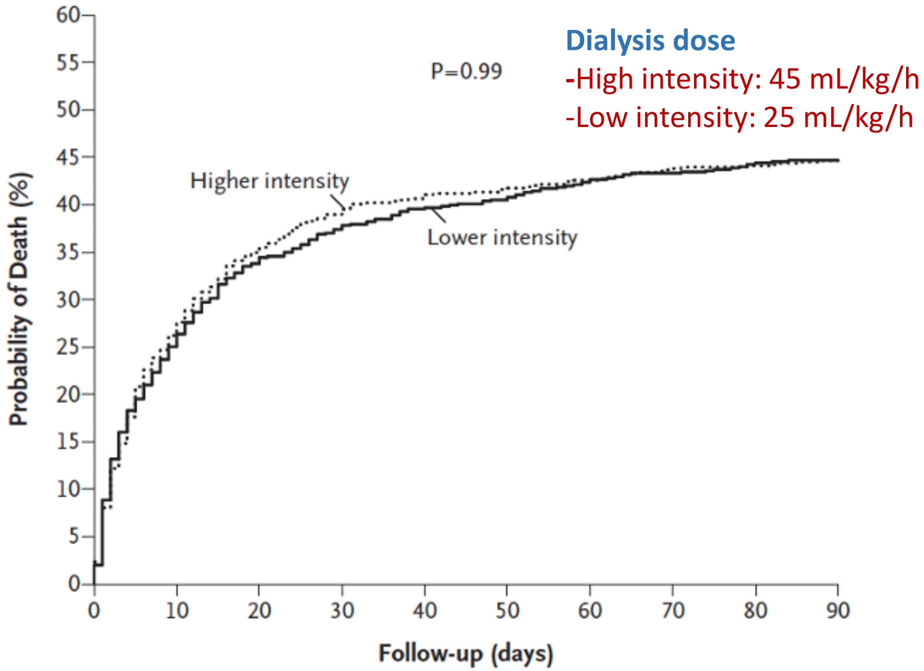
Saudan P, et al . Kidney Int. 2006; 70(7): 1312–7.

The effect of different doses of CRRT on Outcomes



Kaplan–Meier estimate of the probability of death

Type of study: multi center RCT
Participants: 1,124 critically ill patients with AKI
Results: no difference in mortality, recovery of kidney function



Kaplan–Meier estimate of the probability of death

Type of study: multi center RCT
Participants: 1,508 critically ill patients with AKI
Results: no difference in mortality, recovery of kidney function, or dependence on RRT

Acute Renal Failure Trial Network;
Palevsky PM, et al. N Engl J Med. 2008; 359(1): 7–20.

RENAL Replacement Therapy Study Investigators
Bellomo R,et al. N Engl J Med. 2009; 361(17): 1627–38.

Possible adverse effects of high volume ultrafiltration

- Hypophosphatemia
- Hypokalemia
- Loss of nutrients and vital medications
- Increased rate of clotting events

Currently a delivered dose of 20-25 mL/kg/h is recommended for CRRT

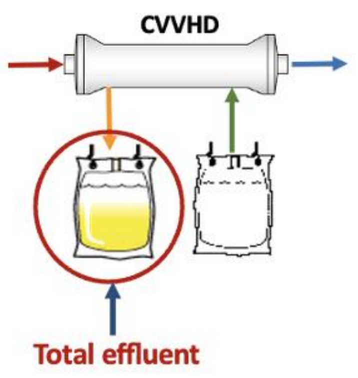
KT/V in CRRT

Prescribed KT/V in a patient with a body weight of 70 kg and an effluent rate of 25 ml/kg/h : 25 x 70 x24=42L/24 h

KT/V= 42/(70x 0.6) = 1

Prescription of CRRT for the presented patient with a body weight of Body weight of 70 kg

- **Duration:** 24 hours
- **Modality:** CVVHD
- **Net UF rate:** 100 ml/hour
- **Dialysate flow rate:** 1500 ml/hour



Total effluent rate = Net UF + Dialysate fluid rate = 100 + 1500 = 1600 mL/h

$$\textbf{Prescribed dialysis dose} = \frac{\textbf{Total effluent rate}}{\textbf{body weight}} = \frac{1600}{70} = 22.9 \text{ mL/kg/hour}$$

Prescribed vs. Delivered Dose of CRRT

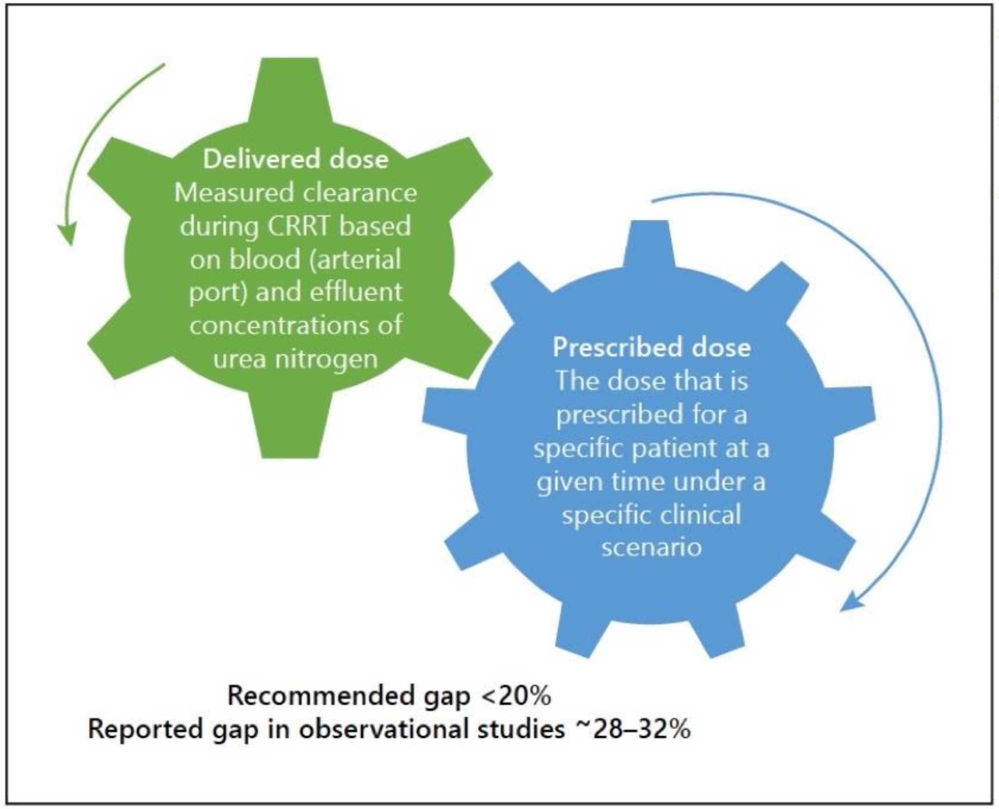
- **After 6 hours, the CRRT staff have to replace filter due to clotting**
- **FUN/BUN: 0.7**

FUN: Fluid urea nitrogen
BUN: Blood urea nitrogen

$$\textbf{Delivered dialysis dose} = \frac{\textbf{FUN}}{\textbf{BUN}} \text{ X Total Effluent Volume} = 0.7 \times 22.9 = 16.3 \text{ mL/kg/h}$$

Common Reasons for Gap Between Prescribed and Delivered Doses of CRRT

- Clotting/Clogging
- Dialysis catheter malfunction
- Bag/Tubing changes
- Replacing filters
- External ICU procedures
- Radiologic investigations and/or surgical procedures
- Machine alarms



Jimenez et al. Nephron 2021

In clinical practice, in order to achieve a delivered dose of 20-25 mL/kg/h, it is necessary to prescribe CRRT in the range of **25-30 mL/kg/h**

Connor MJ Jr,and Karakala N. Chronic Kidney Dis 2017

Modality: CVVHD

Duration: ≥ 24 hours ✓
Blood flow rate: 150 mL/min ✓
Net UF rate: 100 mL/hour ✓
Dialysate flow rate: **1800 mL/hour** ✓
Anticoagulation: ✓
Initial bolus of heparin: 1500 IU
Heparin maintenance dose: 350 IU/hour

$$\text{Prescribed dialysis dose} = \frac{\text{Total effluent rate}}{\text{body weight}} = \frac{1900}{70} = 27.14$$

Recommended doses of heparin during CRRT

Loading dose	Maintenance dose	Target APTT
10-30 IU/kg	5-10 IU/kg/h	1.5-2 times normal

Modality: CVVHD

Duration: ≥ 24 hours ✓
Blood flow rate: 150 mL/min ✓
Net UF rate: 100 mL/hour ✓
Dialysate flow rate: 1800 mL/hour ✓
Anticoagulation: ✓
Initial bolus of heparin: 2000 IU
Heparin maintenance dose: 500 IU/hour

We can increase the heparin dose to prevent filter clotting during ongoing therapy.

Recommended doses of heparin during CRRT

Loading dose	Maintenance dose	Target APTT
10-30 IU/kg	5-10 IU/kg/h	1.5-2 times normal

Continuous Veno-venous Hemofiltration (CVVH)

- In this method, the mechanism of solute transport is convection.
- As the volume of ultrafiltrate is too high, the replacement of ultrafiltrate losses is necessary.
- The replacement fluid can be infused either before the filter (pre-dilution) or after the filter (post-dilution)

Modality: CVVH

Duration: ≥24 hours
Blood flow rate: 150 mL/min
Net UF rate: 100
Post-filter replacement fluid rate: 1800 mL/hour
Prefilter replacement fluid rate: -----
Anticoagulation:

Initial bolus of heparin: 2000 IU
Heparin maintenance dose: 500 IU/hour

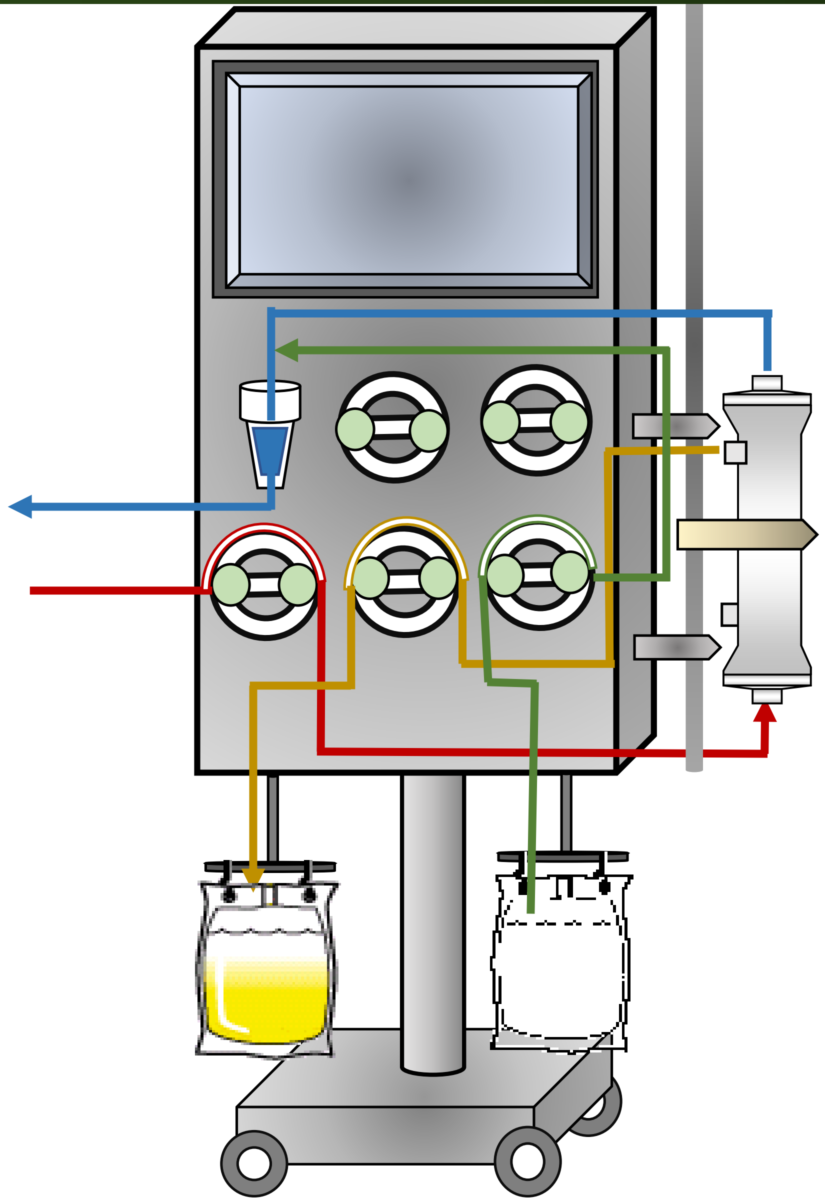
CVVH (Post Dilution)

Advantages:

- Better convective clearance

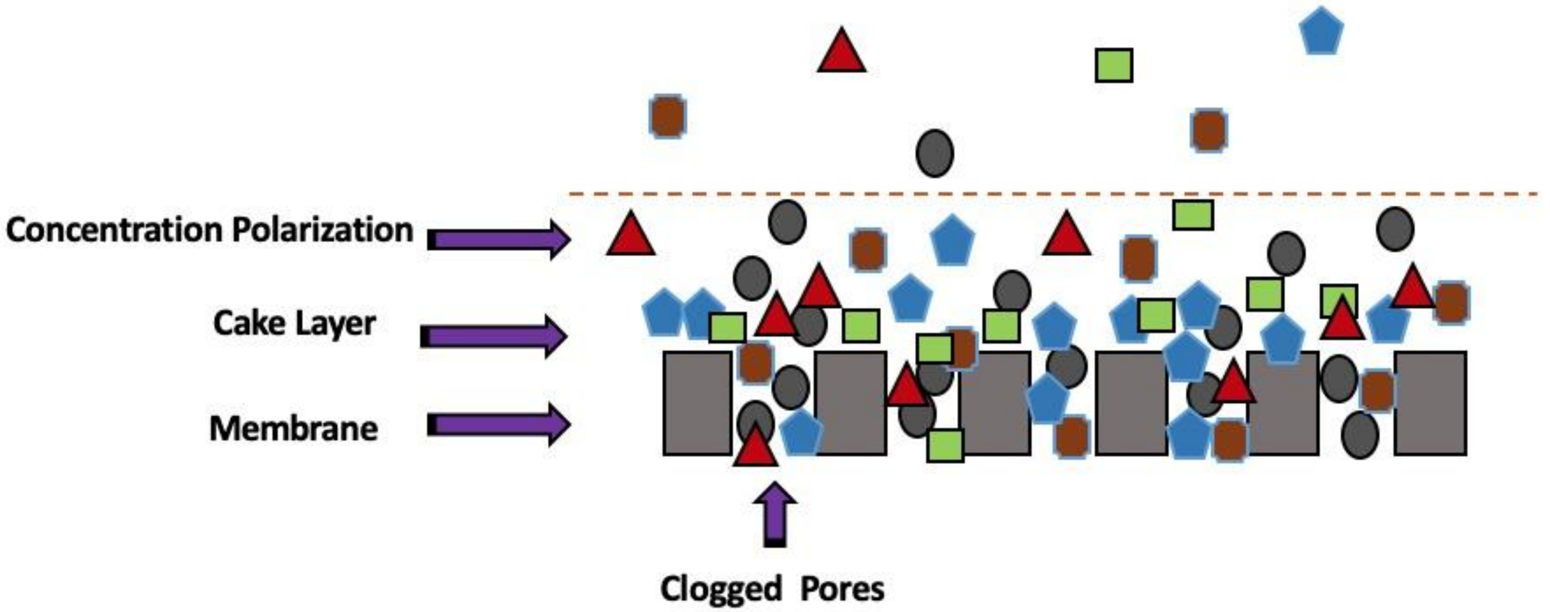
Disadvantage:

- The need to high blood flow rate due to increased rate of filtration fraction
- Increased risk of coagulation
- Lower circuit survival
- Increased rate of concentration polarization, leading to circuit failure



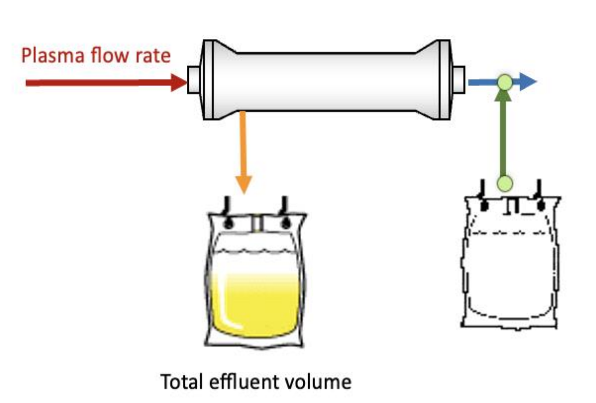
Concentration Polarization in CRRT

In patients with a high effluent-to-plasma flow rate (>30%), concentration polarization may occur, where proteins and cells form a layer on the membrane, reducing its permeability by shrinking pore sizes and numbers.



Prescription of CRRT in a patient with a body weight of Body weight of 70 kg

- **Duration:** 24 hours
- **Blood flow rate:** 150 mL/min
- **Modality:** CVVH
- **Net UF rate:** 100 ml/hour
- **Post filter replacement fluid rate:** 1800 ml/hours
- **HCT:** 30%



Total effluent flow rate = Net UF rate + replacement fluid rate = 1800 + 100= 1900

$$\text{Prescribed dialysis dose} = \frac{\text{total effluent rate}}{\text{body weight}} = \frac{1900}{70} = 27.14 \text{ mL/kg/hour}$$

The CRRT was stopped due to frequent filter alarming and immediate filter clot!!

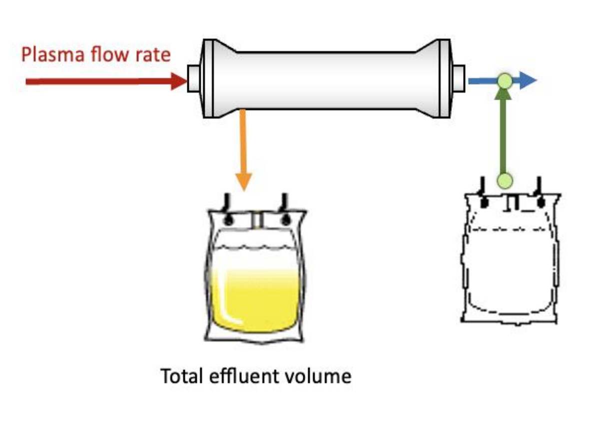
Filtration Fraction in CRRT

- Filtration fraction is the proportion of effluent volume to plasma water entering the filter.

- To prevent clot formation toward the end of membrane and to increase circuit lifespan, filtration fraction should not exceed 20-25%.

Prescription of CRRT in a patient with a body weight of Body weight of 70 kg

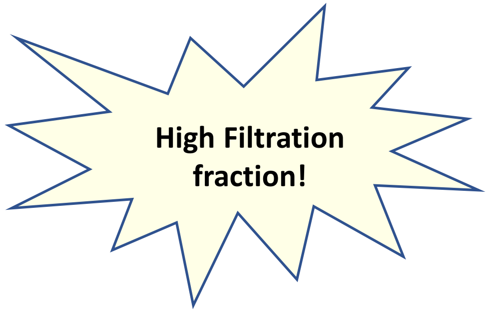
- **Duration:** 24 hours
- **Blood flow rate:** 150 mL/min
- **Modality:** CVVH
- **Net UF rate:** 100 ml/hour
- **Post filter replacement fluid rate:** 1800 ml/hours
- **HCT:** 30%



Total effluent volume = 1800+100= 1900 mL/hour (31.7 mL/min)

Plasma flow rate (ml/min) = blood flow rate x (1-HCT) = 150 ml/min x (1-0.3) = 150 x 0.7=105 mL/min

$$\text{Filtration fraction} = \frac{\text{Total effluent volume}}{\text{plasma flow rate}} = \frac{31.7}{105} = 30.1\%$$



Common Sites of Thrombosis in CRRT

Vascular Access

Venous Chamber

Hemofilter

Consequences of circuit clotting in CRRT

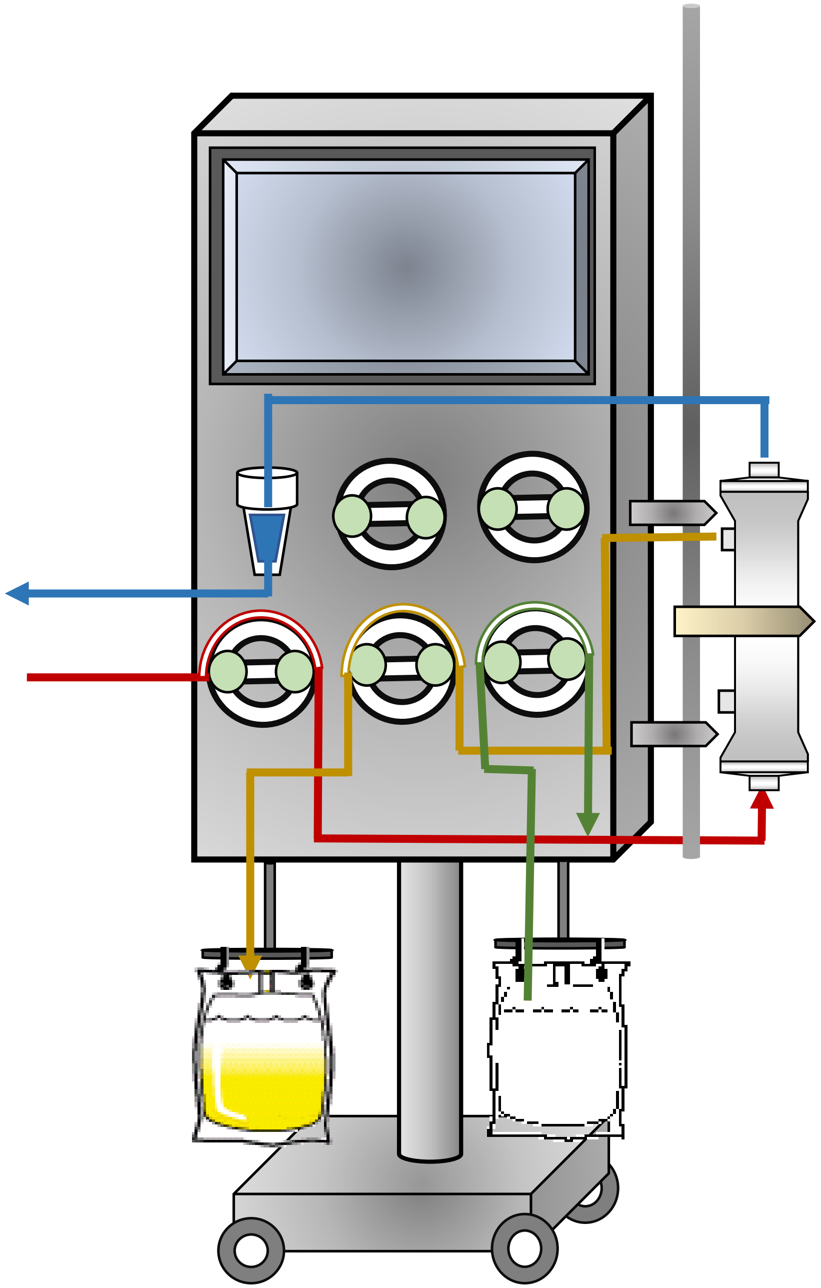
- Reduced solute clearances
- Loss of membrane, tubes, or blood
- Reduced total therapy time
- Increased cost

How to Reduce Filtration Fraction?

- Prescribing a higher blood flow rate (200-250 ml/min)
- Infusing of pre-filter replacement fluid at the expense of reducing CRRT dose

Advantages:

- Reduced risk of coagulation
- Longer circuit survival
- Better membrane performance by reducing protein adsorption and concentration polarization



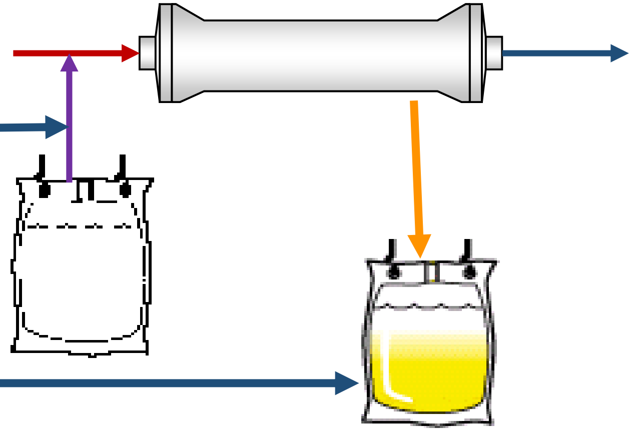
Disadvantage:

- Reduced convective clearance

Modality: CVVH

Duration: ≥24 hours
Blood flow rate: 230 mL/min
Net UF rate: 100
Post-filter replacement fluid rate: --------
Prefilter replacement fluid rate: 2000 mL/hour
Anticoagulation:
Initial bolus of heparin: 2000 IU
Heparin maintenance dose: 500 IU/hour

Plasma flow rate: 161 mL/min (HCT:30%)
Pre-filter replacement fluid rate: 2000 mL/hour or 33.3 mL/min



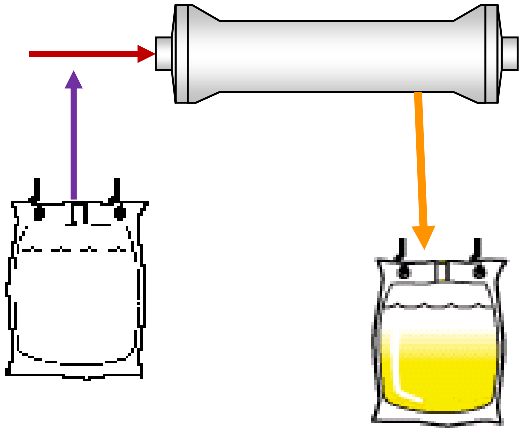
Total effluent rate: 2000+100=2100 mL/hour or 35 mL/min

$$\text{Filtration fraction} = \frac{\text{total effluent rate}}{\text{plasma flow rate + prefilter replacement fluid rate}} = = \frac{35}{33.3+161} = \frac{35}{194.3} = 18\%$$

Dilution Factor

In modalities with pre-filter replacement, the blood entering the dialyzer is diluted and therefore clearance is decreased. In this conditions, the total effluent fluid rate should be multiplied by a dilution factor.

$$\textbf{Dilution factor} = \frac{\text{plasma flow rate}}{\text{plasma flow rate + prefilter replacement fluid rate}} = \frac{161}{161+33.3} = 83\%$$



Modality: CVVH

Duration: ≥24 hours ✓

Blood flow rate: 230 mL/min ✓

Net UF rate: 100 ✓

Post-filter replacement fluid rate: -------- ✓

Prefilter replacement fluid rate: 2000 mL/hour ✓

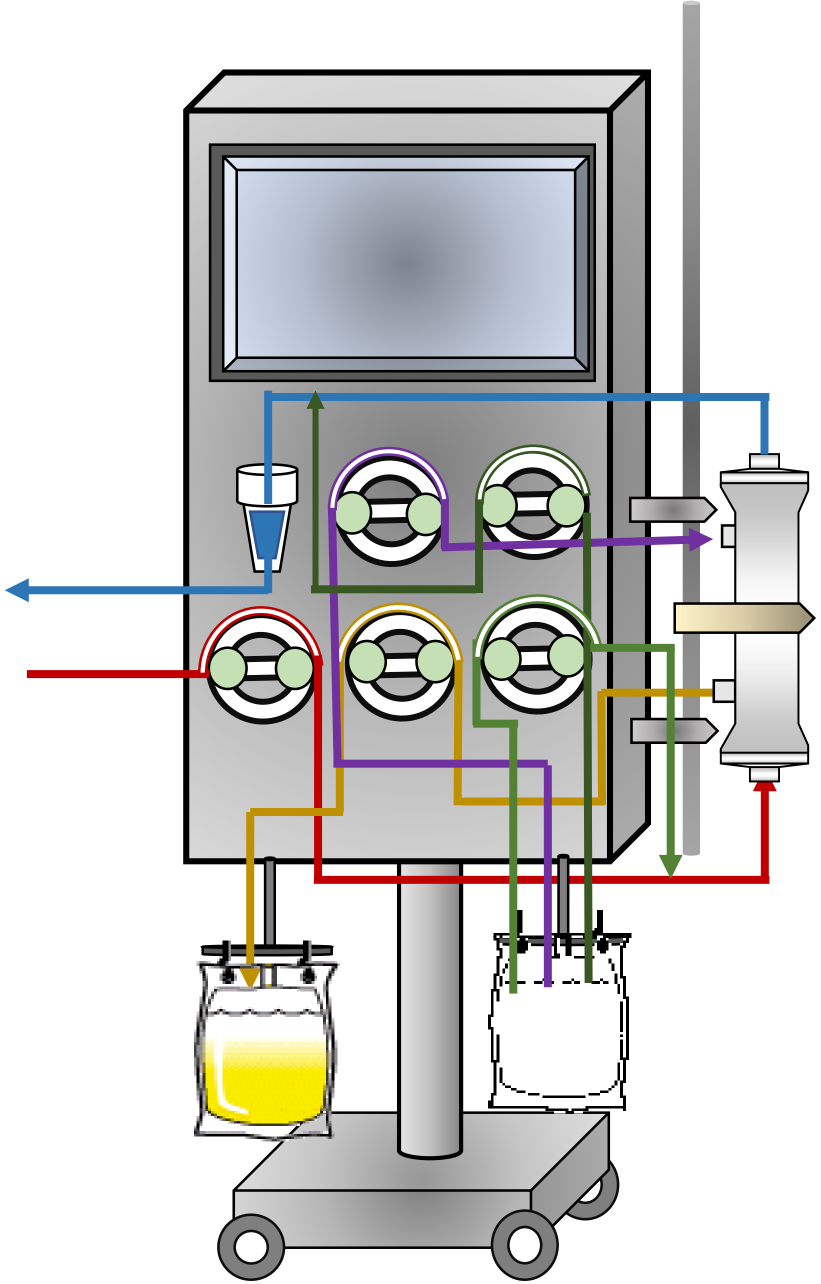
Anticoagulation: ✓

Initial b0lus of heparin: 2000 IU

Heparin maintenance dose: 500 IU/hour

Prescribed dialysis dose with post-filter order: 2100/70= 30 mL/kg/hour

Prescribed dialysis dose with pre-filter infusion = 30 x 83%= 24.9 mL/kg/hour



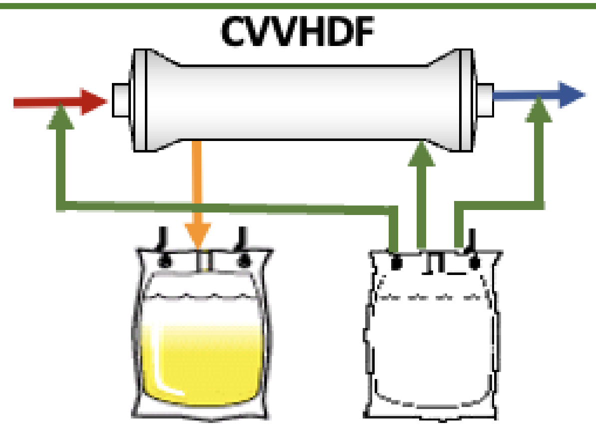
Modality: CVVHDF

Duration: ≥ 24 hours
Blood flow rate: 150 mL/min
Net UF rate: 100 mL/hour
Dialysate rate: 1000 mL/hour
Pre-filter replacement fluid rate: 500 mL/hour
Post-filter replacement fluid rate: 500 mL/hour
Anticoagulation:

- Initial bolus of heparin: 2000 IU
- Heparin maintenance dose: 500 IU/hour

Prescription of CRRT in a patient with a body weight of Body weight of 70 kg

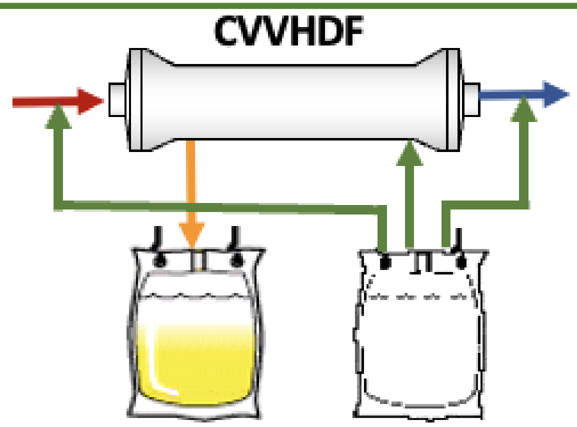
- **Body weight:** 70 kg
- **Blood flow rate: 150** mL/min
- **Dialysate fluid rate:** 1000 mL/hour
- **Post-filter replacement fluid rate:** 500 mL/h
- **Pre-filter replacement fluid rate:** 500 ml/h
- **Net UF rate:** 100 ml/h



$$\text{Filtration fraction} = \frac{\textbf{Total effluent rate}}{\textbf{plasma flow rate + prefilter replacement fluid rate}} = \mathbf{16.2\%}$$

Prescription of CRRT in a patient with a body weight of Body weight of 70 kg

- **Body weight:** 70 kg
- **Blood flow rate: 150** mL/min
- **Dialysate fluid rate:** 1000 mL/hour
- **Post-filter replacement fluid rate:** 500 mL/h
- **Pre-filter replacement fluid rate:** 500 ml/h
- **Net UF rate:** 100 ml/h



Total effluent rate = Net UF + pre-filter replacement rate+ post-filter replacement rate + dialysate rate
= 100+ 500 + 500+ 1000 = 2100ml/h

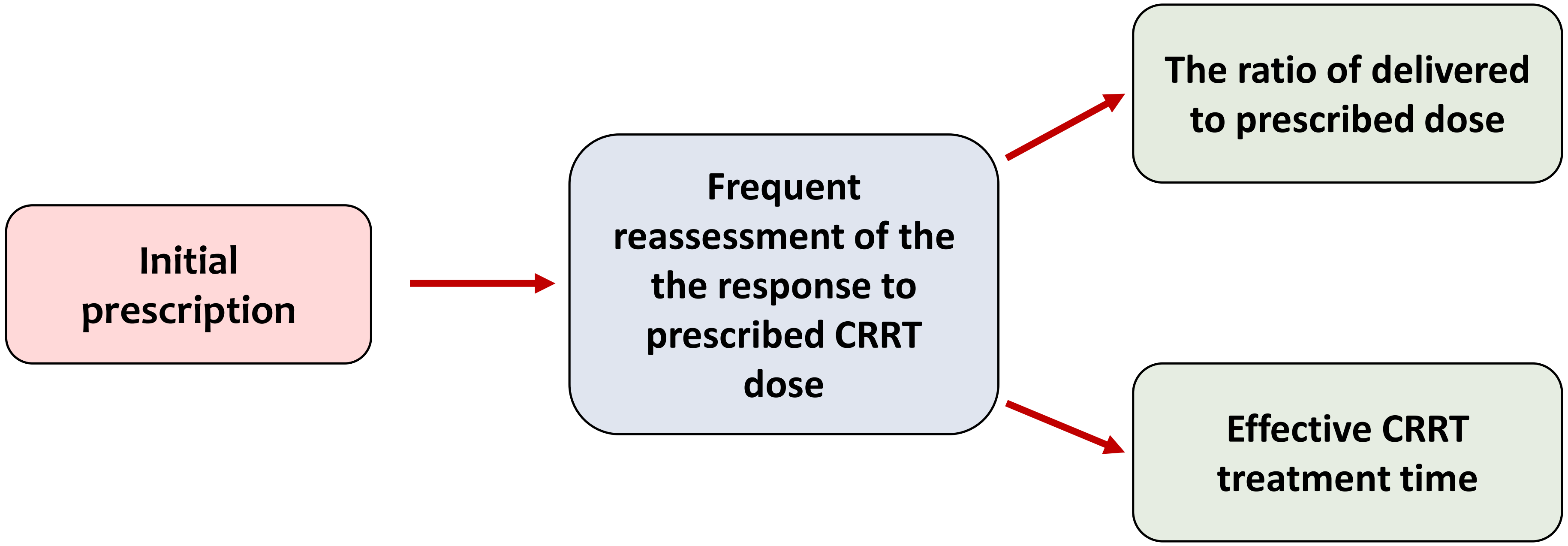
Dilution factor = 92.3%

Prescribed dialysis dose $= \frac{\text{total effluent rate}}{\text{body weight}}$ x dilution factor $= \frac{2100}{70}$ x 92.63%= 30 x 94%= 27.7 ml/kg/hour

CVVHDF was initiated, and after 6 hours, the FUN/BUN ratio reached 1. The patient was then transported out of the ICU for a radiologic evaluation, during which CRRT was paused for 2 hours.

The delivered dose was 27.7 x 22/24 = 25.39

Prescription of CRRT as a Dynamic Process



Conclusion

- ✓ CRRT is generally the most common initial modality prescribed in ICU setting.
- ✓ prescription should be a dynamic process with continuous monitoring of delivered dose with its adjustment based on the patient's condition.
- ✓ RCTs did not find any difference between high intensity and standard intensity CRRT doses and patients' outcomes.
- ✓ A CRRT prescription of 25 to 30 ml/kg/h is recommended to achieve a delivered dose of 20 to 25 ml/kg/h.
- ✓ There is no standard strategy for initiation of CRRT or the selection of its modality.
- ✓ It has been suggested that the restoration of urine output independent of diuretics is the most reliable predictor of successful discontinuation.