

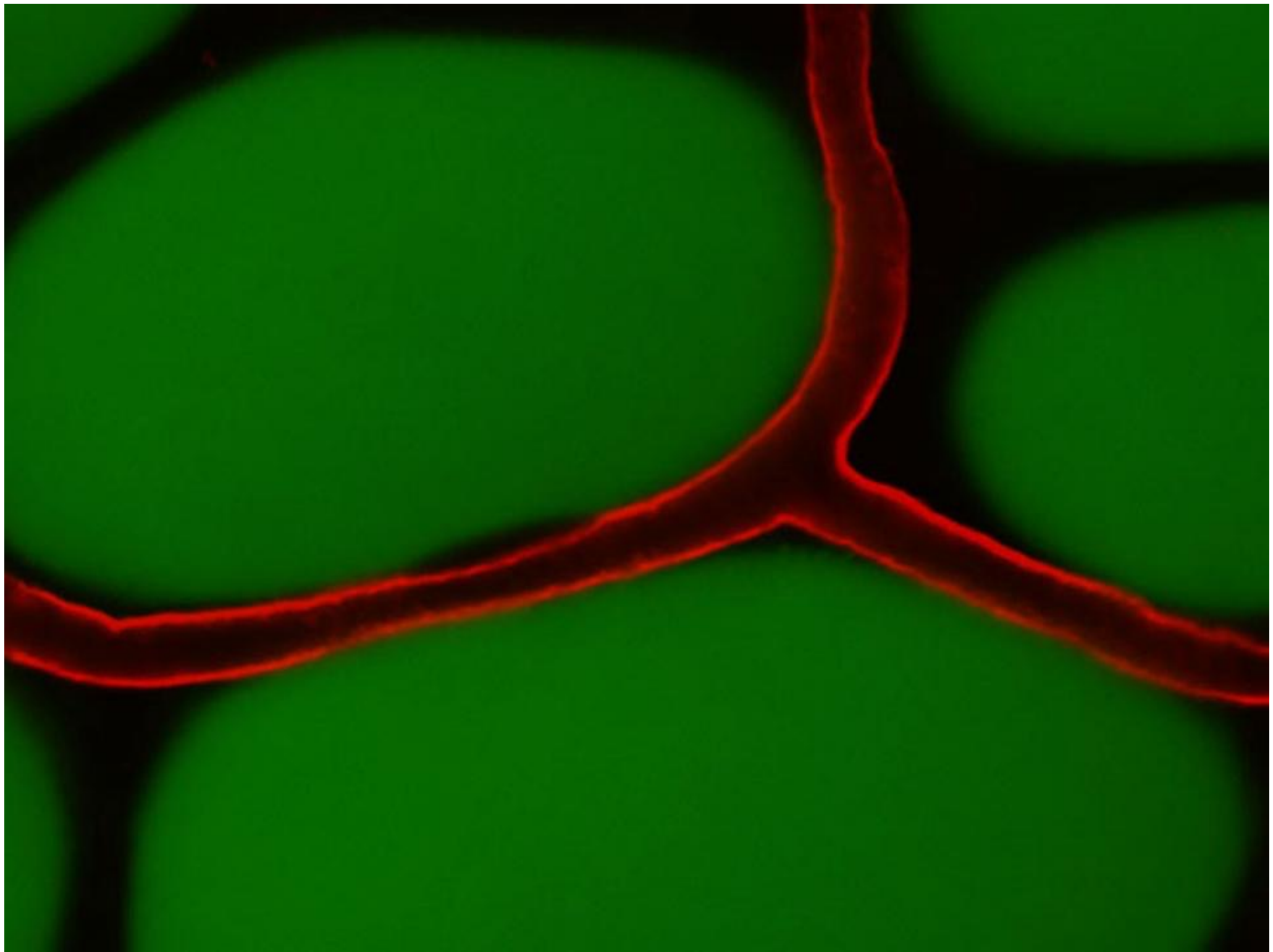


# Renal Replacement Therapy: Choices and Outcomes

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Brigham and Women's Hospital  
Harvard Medical School

# Conflict of Interest Disclosure Slide

I have no financial relationships with commercial entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients relevant to the content I am presenting.







# Primary Therapeutic Goals in AKI

Optimize hemodynamic and volume status

Minimize further renal injury

Correct metabolic abnormalities

Removal of Uremic toxins

Permit adequate nutrition

# Limitations on RRT Delivery in AKI

Hypercatabolic state

Hemodynamic instability

Control of Volume status

# Primary Therapeutic Goals in CRRT

## Solute Removal

Diffusion and Convection

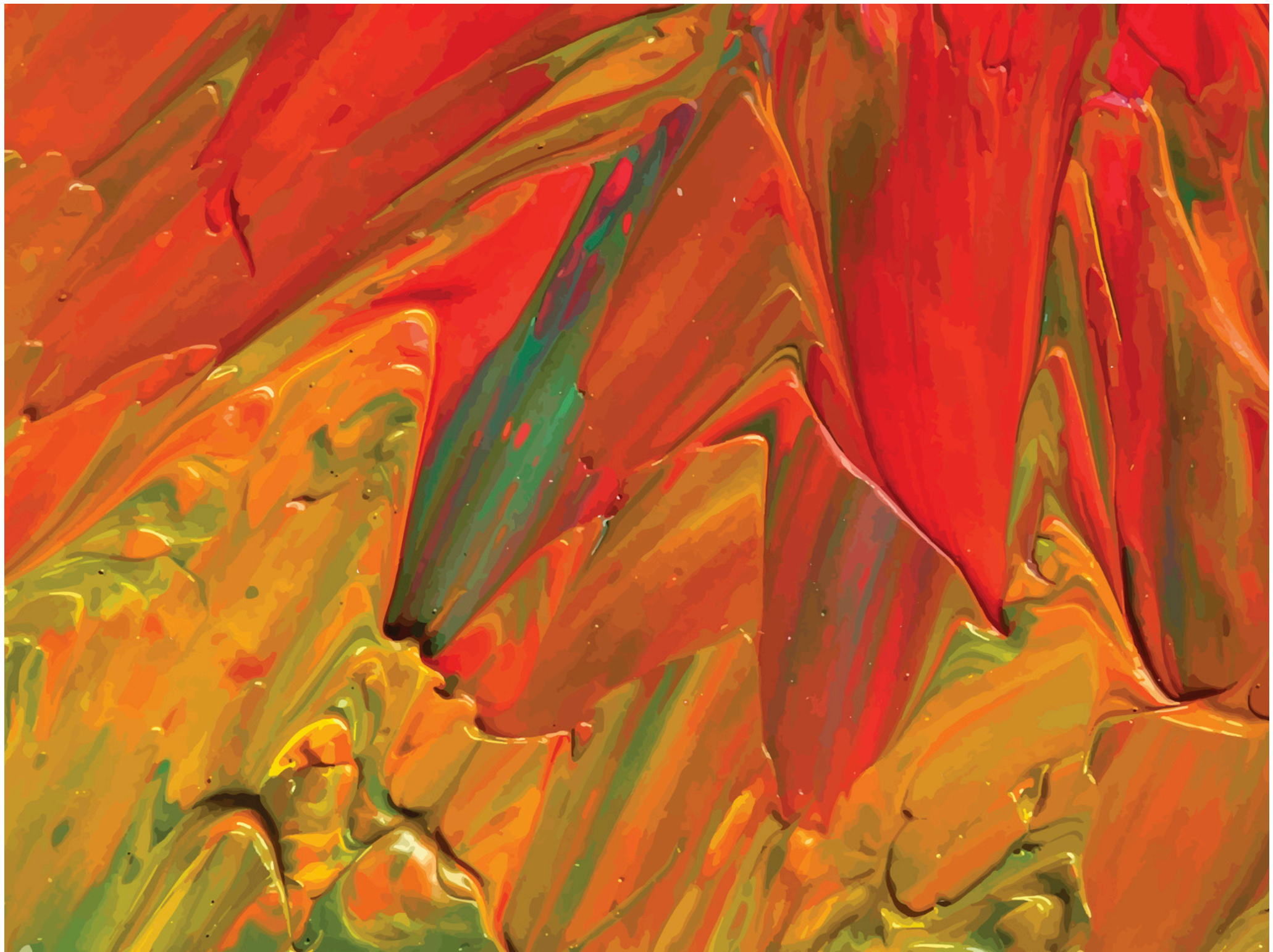
## Solute Addition

Replacement Fluid

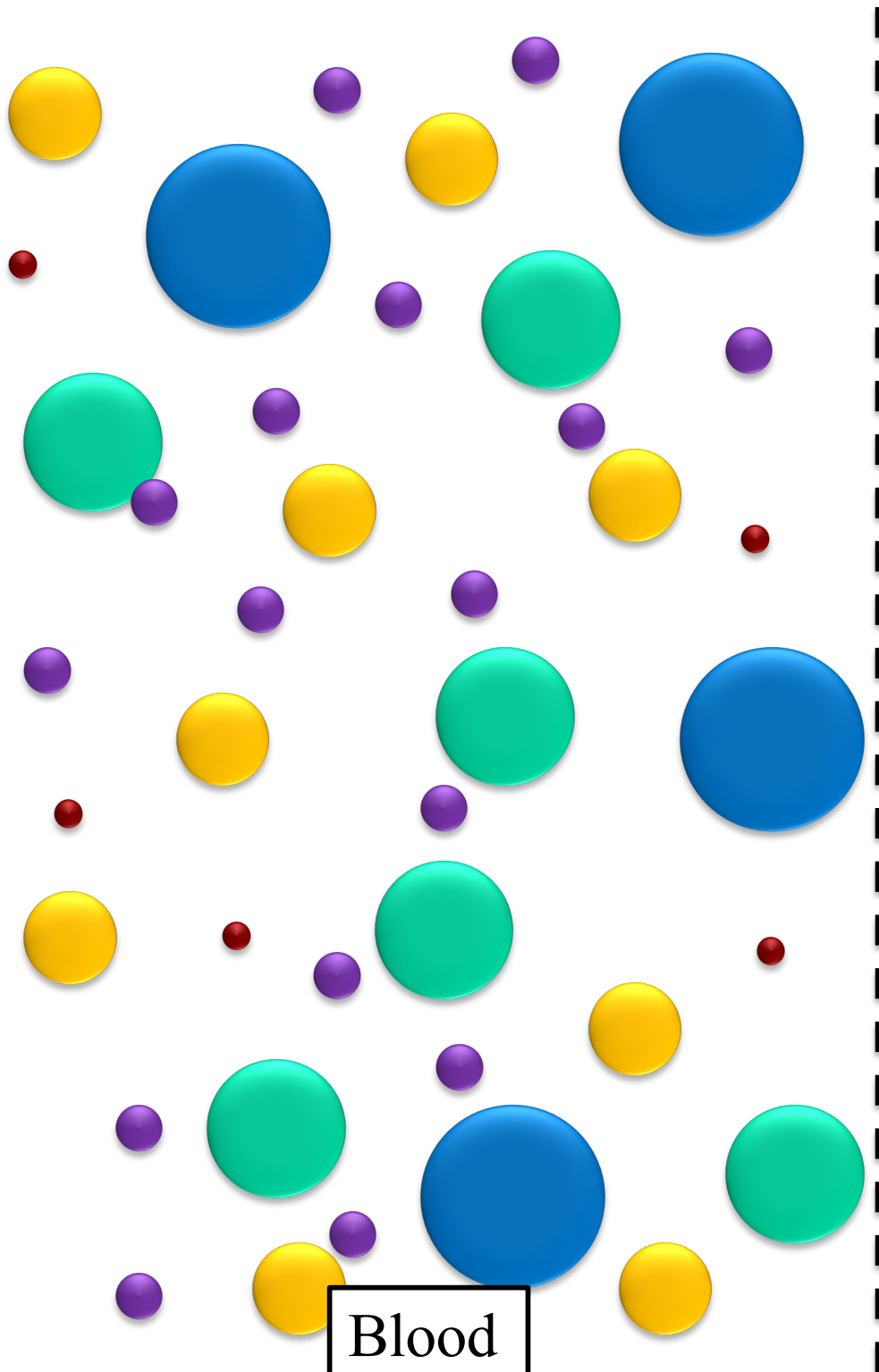
## Fluid Removal

Convection

## Detoxification

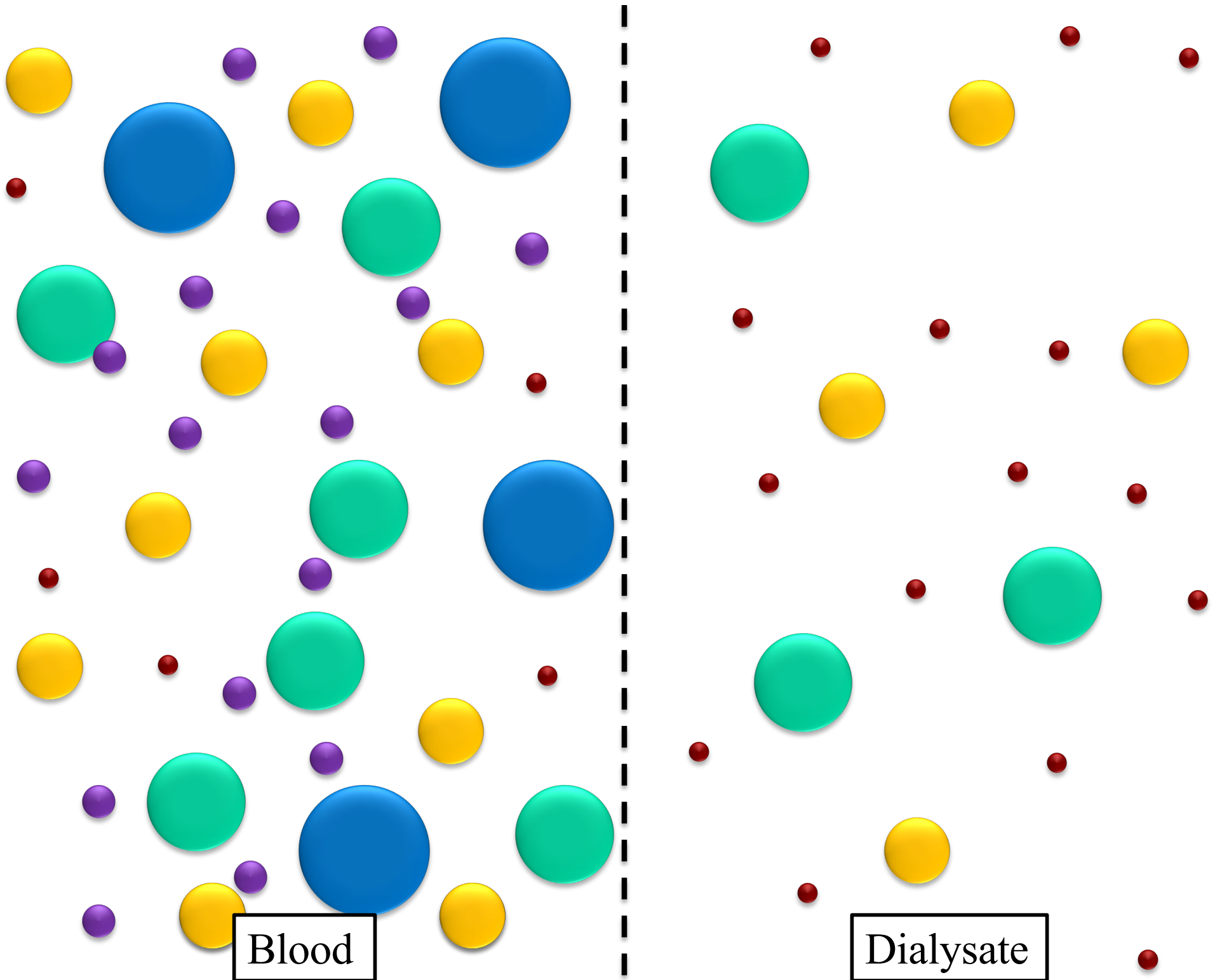






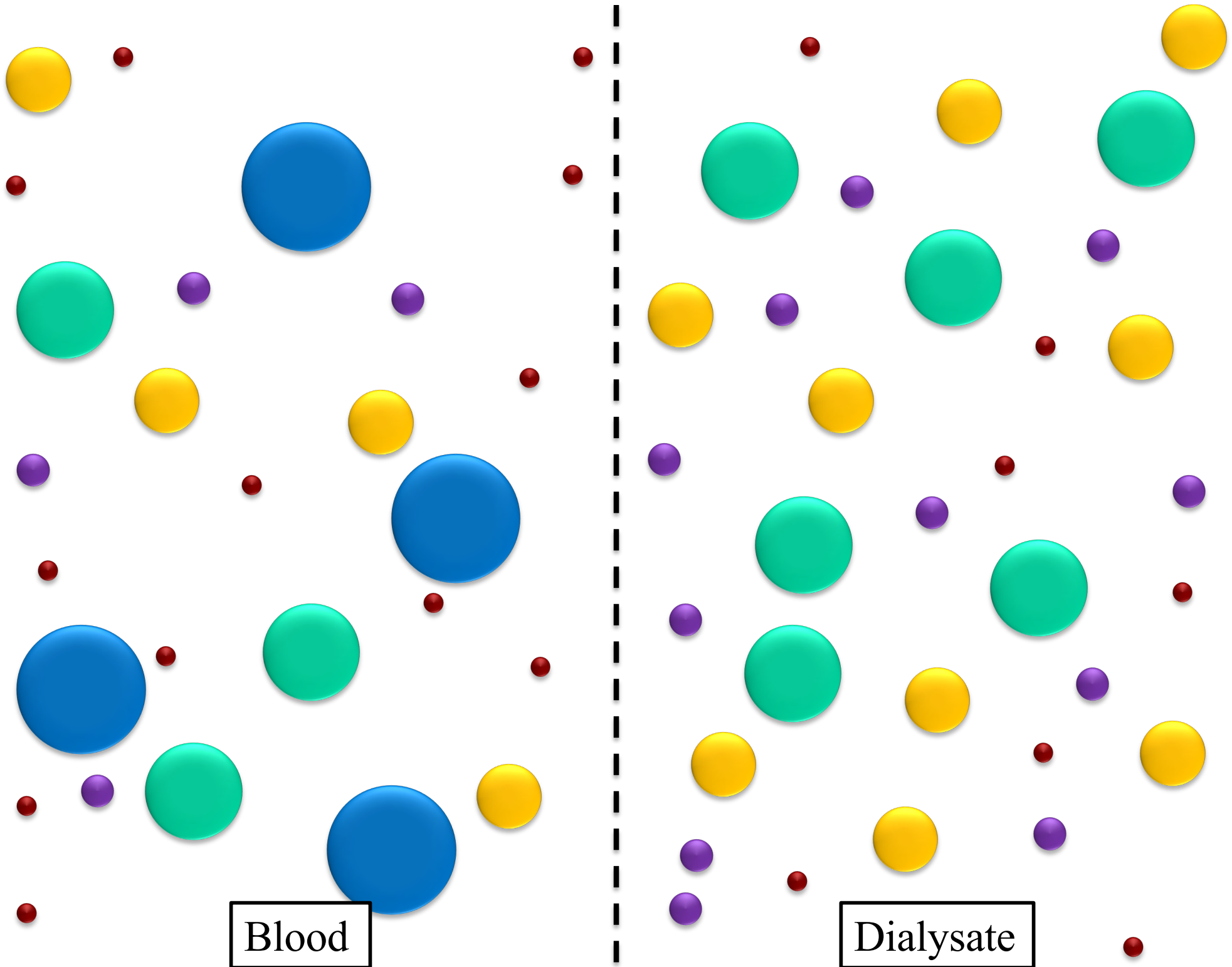
Blood

Dialysate



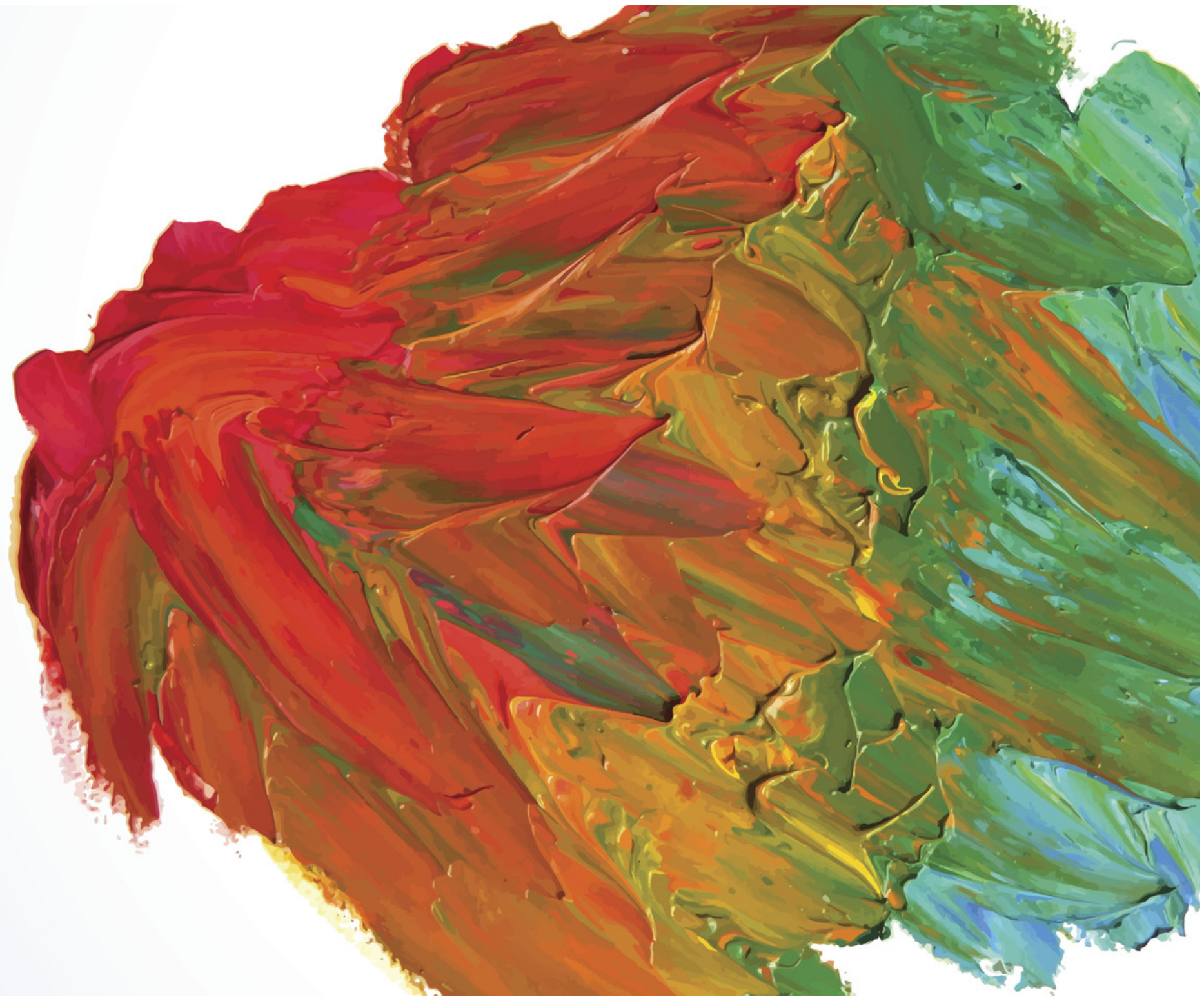
Blood

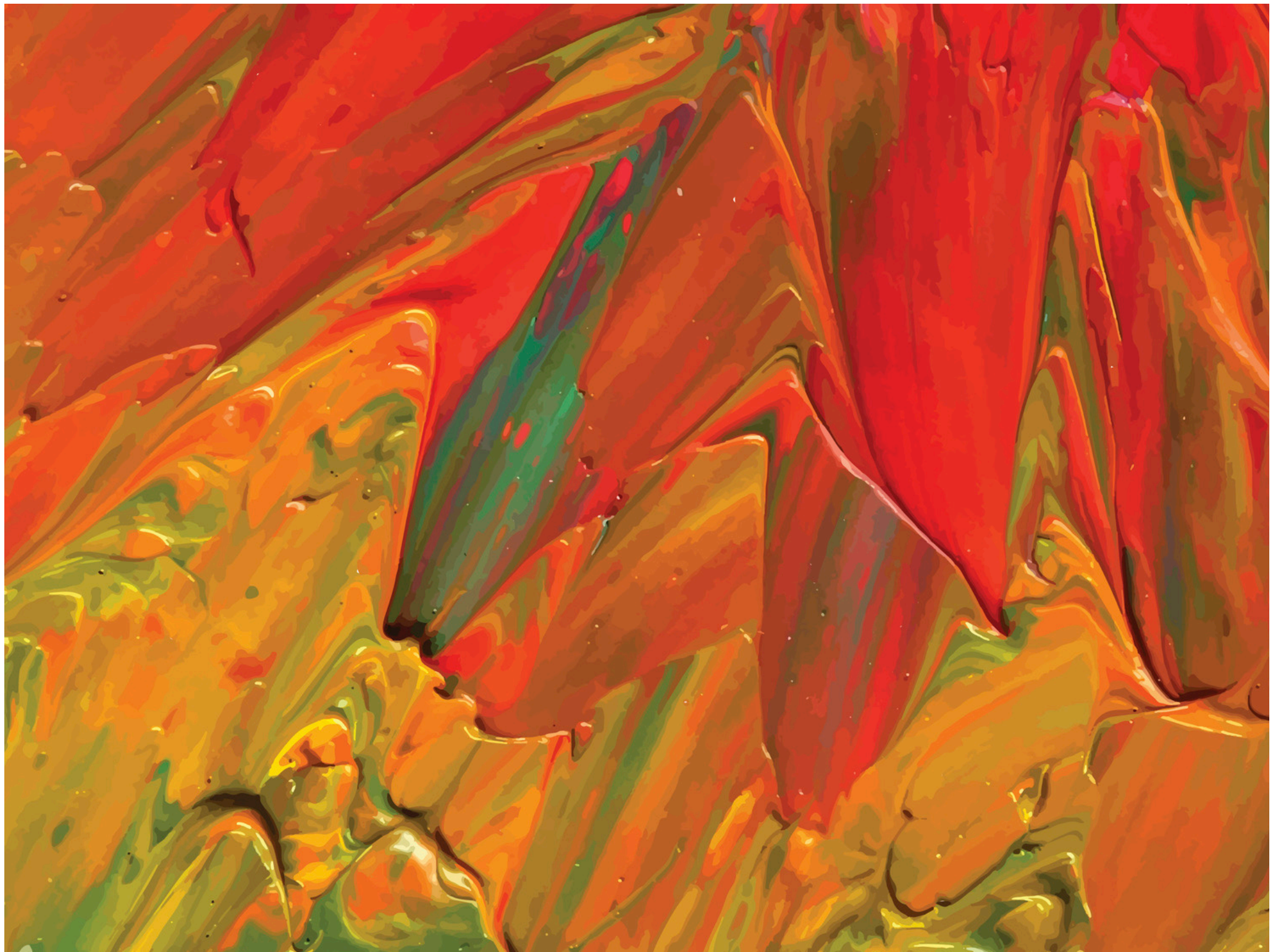
Dialysate



Blood

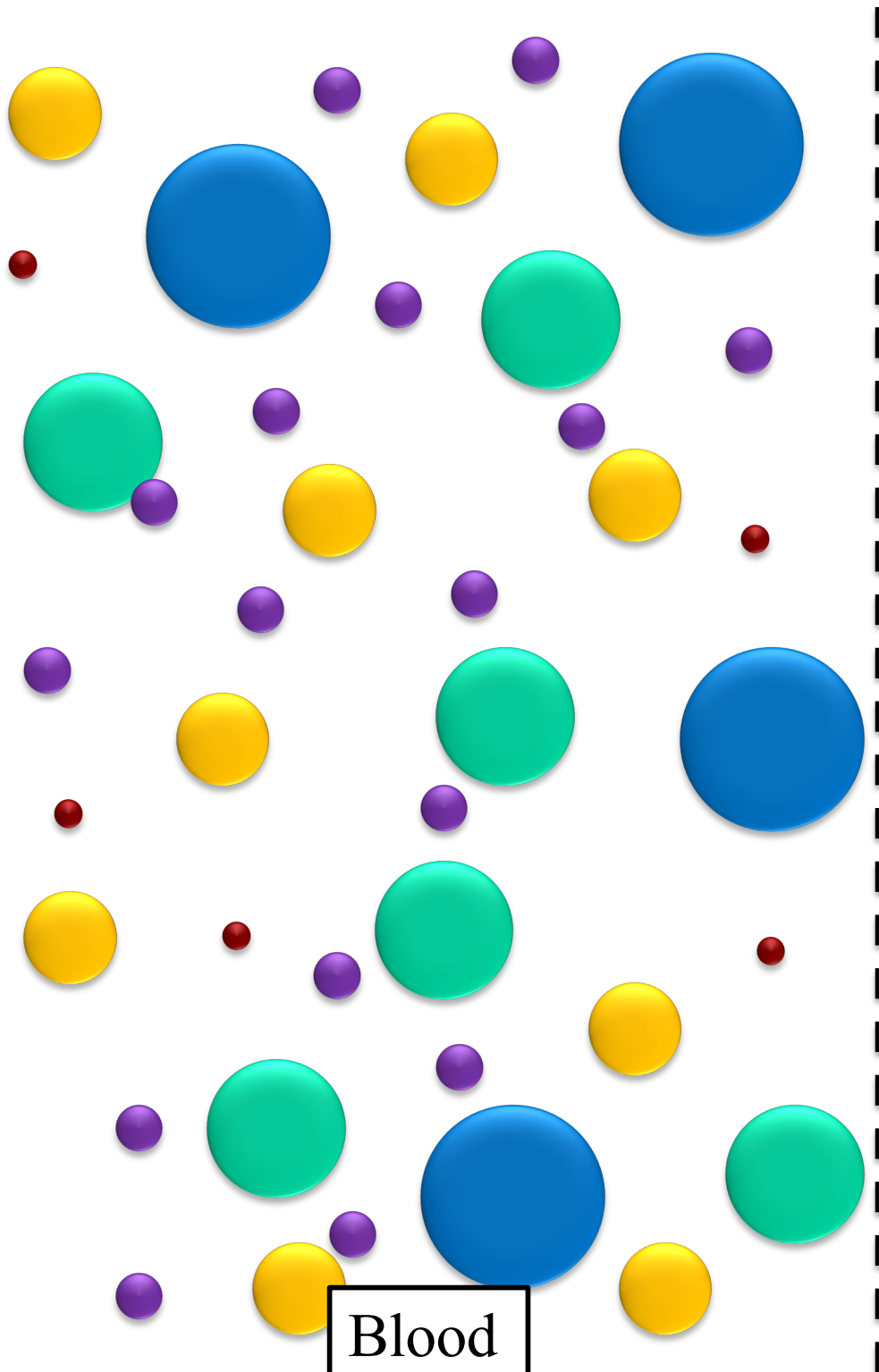
Dialysate





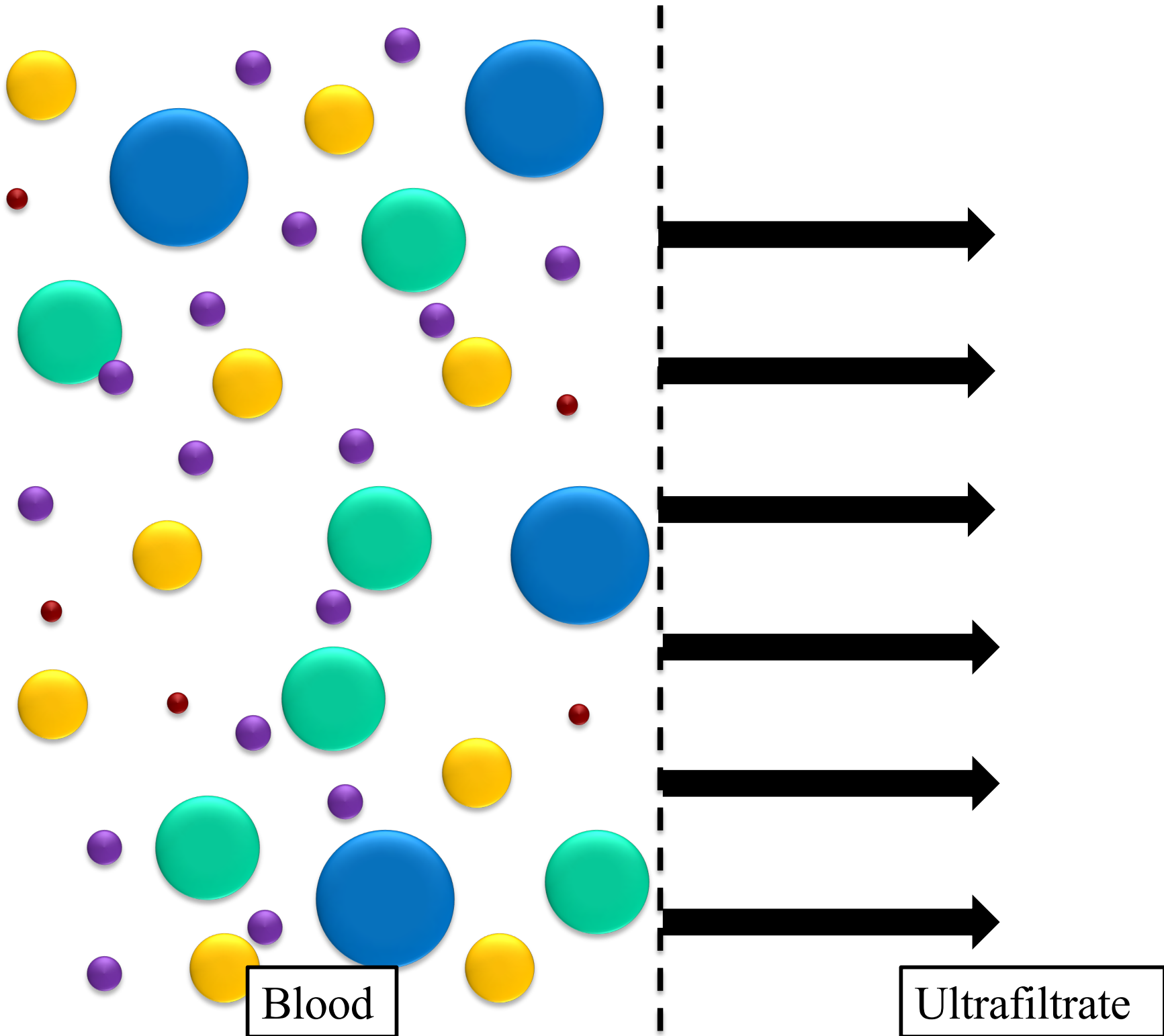






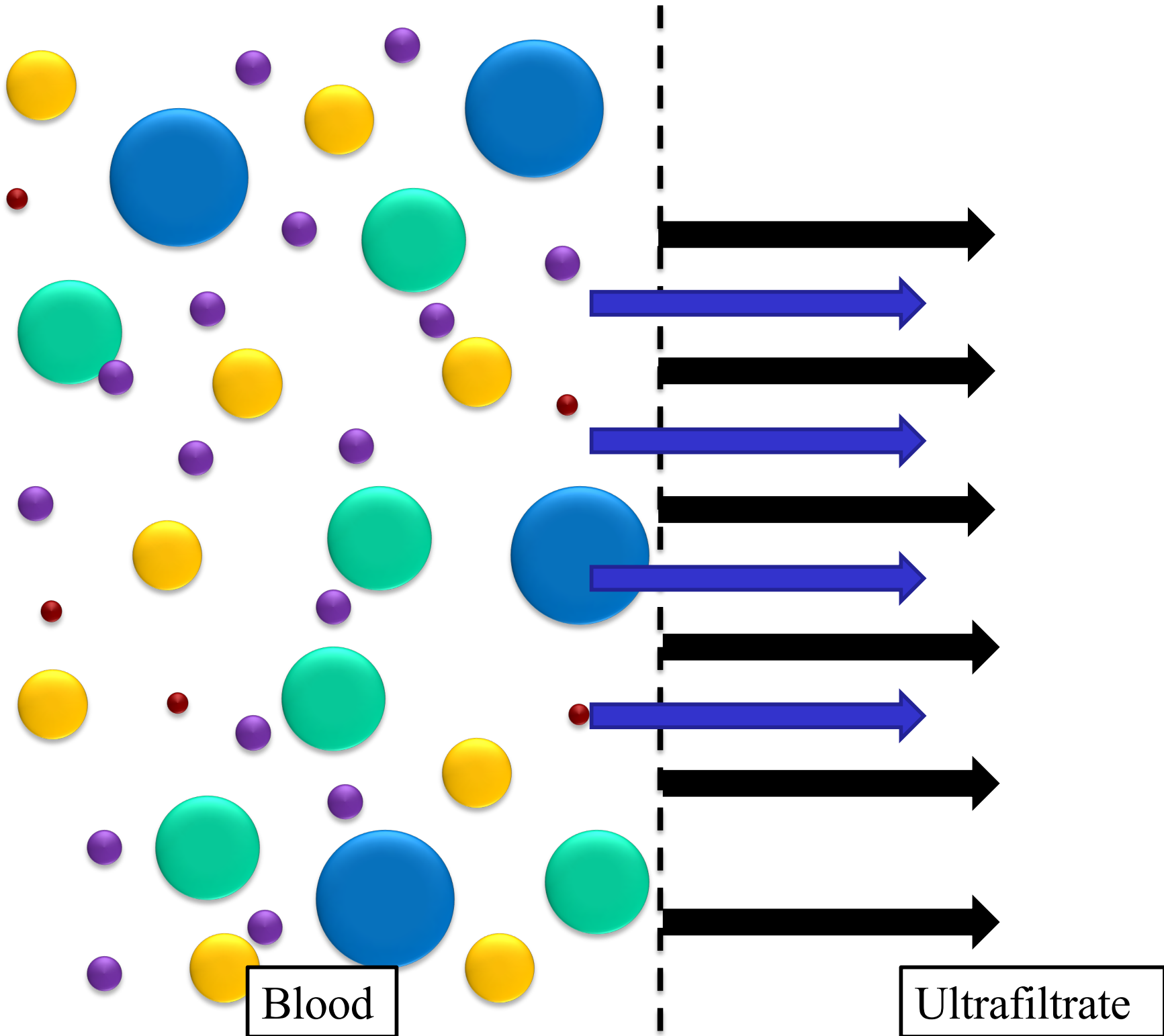
Blood

Ultrafiltrate



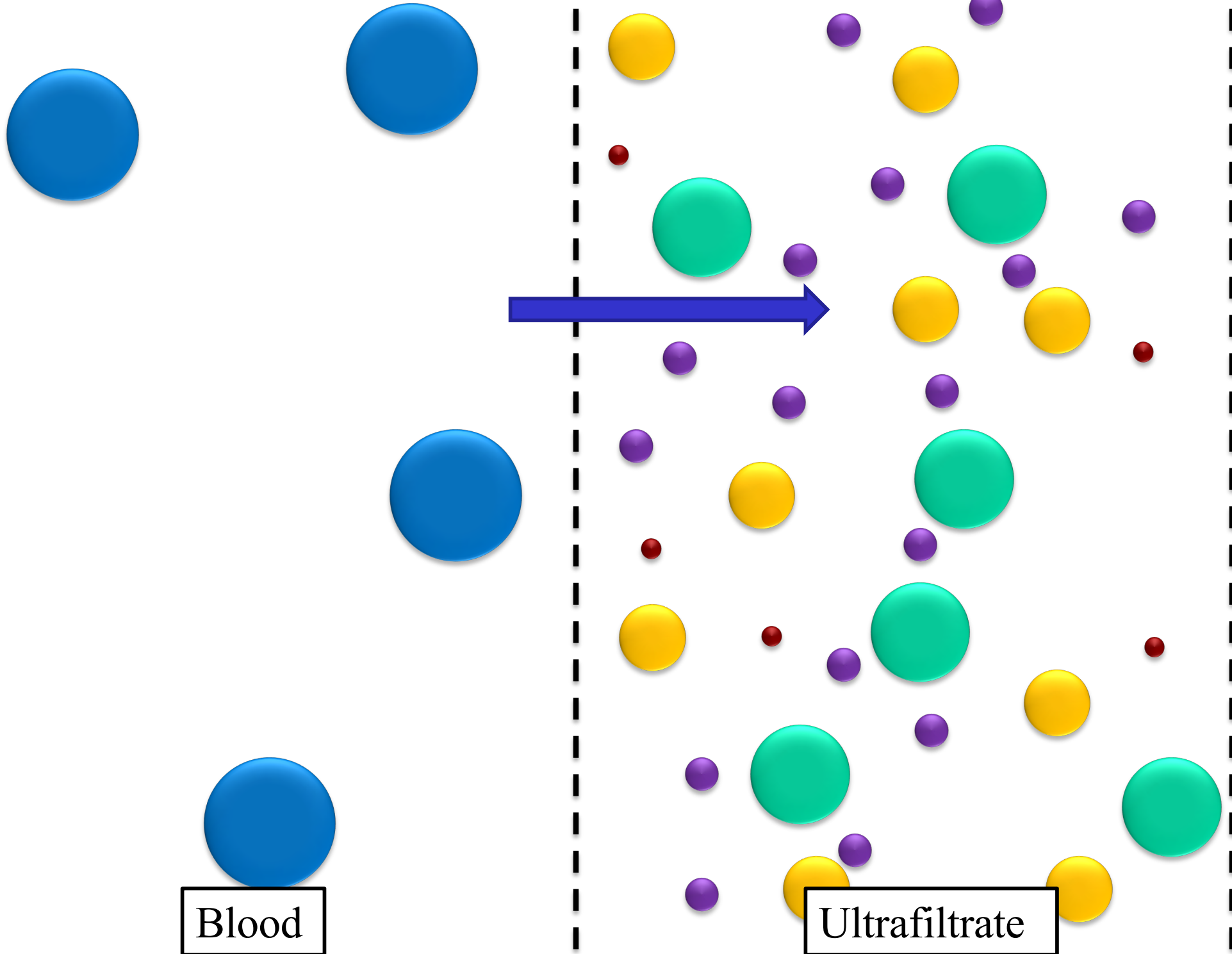
Blood

Ultrafiltrate



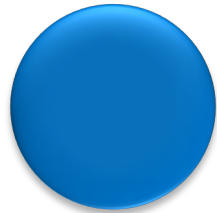
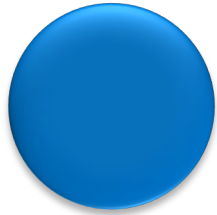
Blood

Ultrafiltrate



Blood

Ultrafiltrate



**4K<sup>+</sup>**  
mEq/L

Break red pin and mix. ↑

**2.5Ca<sup>2+</sup>**  
mEq/L

Replacement Solution for Continuous Renal Replacement Therapy

| Before reconstitution each 1000 mL contains (g) | A    | B     |
|---|------|-------|
| Calcium chloride • 2 H <sub>2</sub> O           | 3.68 |       |
| Magnesium chloride • 6 H <sub>2</sub> O         | 3.05 |       |
| Dextrose anhydrous                              | 20.0 |       |
| (as dextrose monohydrate)                       | 22.0 |       |
| Sodium chloride                                 |      | 6.46  |
| Potassium chloride                              |      | 0.314 |
| Lactic acid                                     | 5.40 |       |
| Sodium bicarbonate                              |      | 3.09  |

Rx only

**A**  
250 mL  
**B**  
4750 mL

After reconstitution, A + B

|        | Calcium Ca <sup>2+</sup> | Magnesium Mg <sup>2+</sup> | Sodium Na <sup>+</sup> | Chloride Cl <sup>-</sup> | Lactate C <sub>3</sub> H <sub>5</sub> O <sub>3</sub> <sup>-</sup> | Bicarbonate HCO <sub>3</sub> <sup>-</sup> | Potassium K <sup>+</sup> | Dextrose    |
|--------|--------------------------|----------------------------|------------------------|--------------------------|---|---|--------------------------|-------------|
| mmol/L | 1.25                     | 0.75                       | 140                    | 113.0                    | 3.0   | 32  | 4.0                      | 5.5         |
| mEq/L  | 2.5                      | 1.5                        | 140                    | 113.0                    | 3.0   | 32  | 4.0                      | (100 mg/dL) |

Theoretical osmolality: 300 mOsm/L      pH: 7.0–8.5

Mix both compartments before use.

See package insert for dosage information and further instructions. Sterile and free from bacterial endotoxins. Confirm the integrity of the packaging. Use only if solution is clear. For single use only. DISCARD ANY UNUSED SOLUTION. Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature]. Do not freeze or expose to excessive heat. As soon as the overwrap is removed, the reconstitution of compartments A and B should be done and the reconstituted solution should be used immediately. After removal of the overwrap, the solution is stable for 24 hours including the duration of the treatment. (See insert for further information.) This product is latex free.

5000 mL

EAN-14: 07332414108663

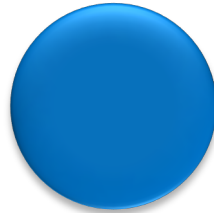
Product# 113923

Batch No. and expiry date are printed on the back of the bag.  
Manufactured by:  
Gamco Renal Products, Inc.  
1845 Mason Avenue, Daytona Beach FL 32117, USA

D07200013 Rev 2010-03/1

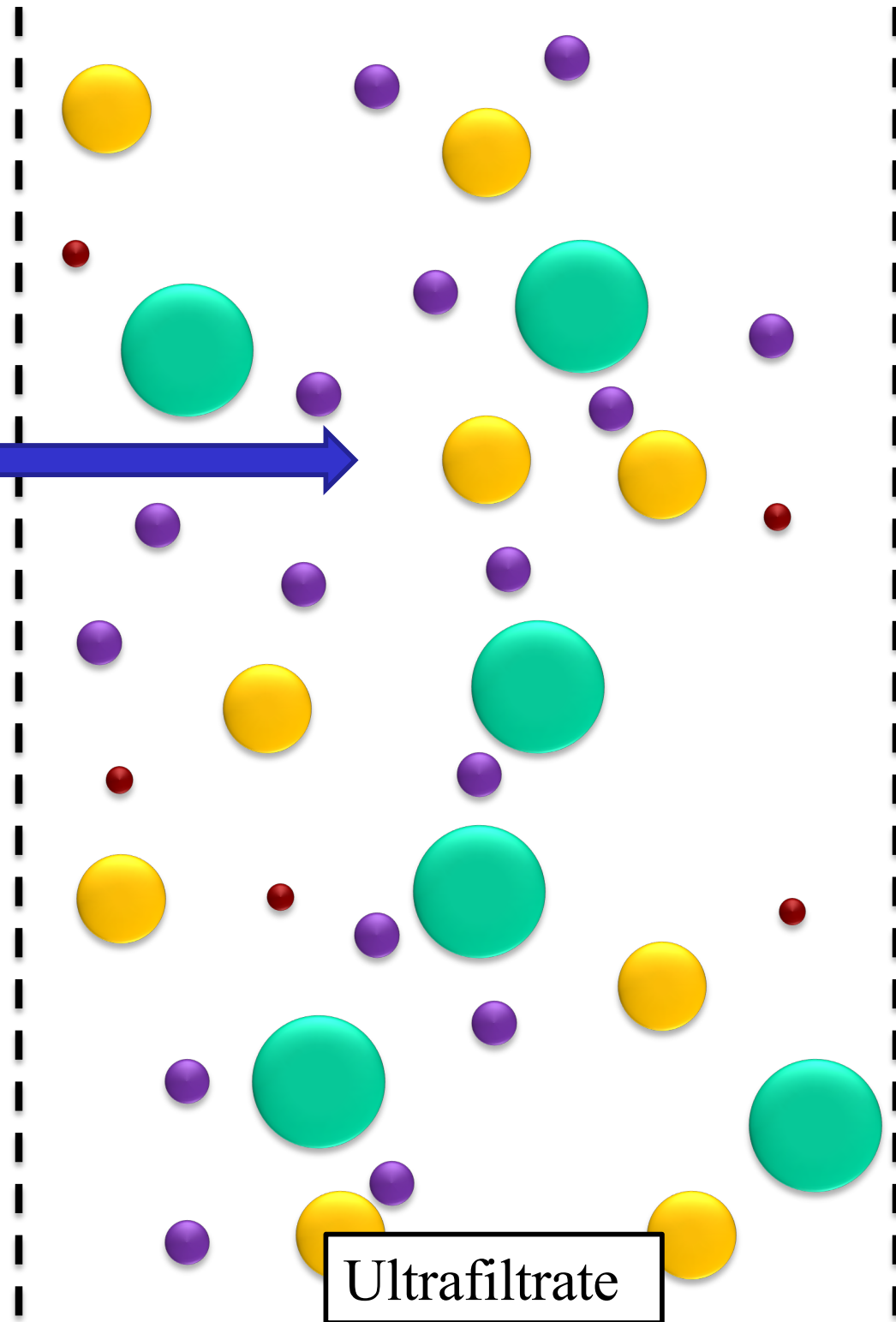
REPLACEMENT

Solution for Continuous Renal Replacement Therapy



Blood

Ultrafiltrate



Break red pin and mix. 

**4K<sup>+</sup>**  
mEq/L

**2.5Ca<sup>2+</sup>**  
mEq/L

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| Dextrose anhydrous<br>(as dextrose monohydrate)            | 20.0<br>22.0 |       |
| Sodium chloride  |              | 6.46  |
| Potassium chloride   |              | 0.314 |
| Lactic acid  | 5.40         |       |
| Sodium bicarbonate   |              | 3.09  |
| Water for injections q.s, Carbon dioxide for pH adjustment |              |       |

Rx only

**A**  
250 mL

**B**  
4750 mL

After reconstitution, A + B

|                                    | Calcium<br>Ca <sup>2+</sup> | Magnesium<br>Mg <sup>2+</sup> | Sodium<br>Na <sup>+</sup> | Chloride<br>Cl <sup>-</sup> | Lactate<br>C <sub>3</sub> H <sub>5</sub> O <sub>3</sub> <sup>-</sup> | Bicarbonate<br>HCO <sub>3</sub> <sup>-</sup> | Potassium<br>K <sup>+</sup> | Dextrose    |
|------------------------------------|-----------------------------|-------------------------------|---------------------------|-----------------------------|--|--|-----------------------------|-------------|
| mmol/L                             | 1.25                        | 0.75                          | 140                       | 113.0                       | 3.0  | 32   | 4.0                         | 5.5         |
| mEq/L                              | 2.5                         | 1.5                           | 140                       | 113.0                       | 3.0  | 32   | 4.0                         | (100 mg/dL) |
| Theoretical osmolarity: 300 mOsm/L |                             |                               | pH: 7.0–8.5               |                             |  |  |                             |             |

**Mix both compartments before use.**  
See package insert for dosage information and further instructions. Sterile and free from bacterial endotoxins. Confirm the integrity of the packaging. Use only if solution is clear. For single use only. DISCARD ANY UNUSED SOLUTION. Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature]. Do not freeze or expose to excessive heat. As soon as the overwrap is removed, the reconstitution of compartments A and B should be done and the reconstituted solution should be used immediately. After removal of the overwrap, the solution is stable for 24 hours including the duration of the treatment. (See insert for further information.) This product is latex free.

**5000 mL**

EAN-14: 07332414108663

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Manufactured by:  
Gambro Renal Products, Inc.  
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**REPLACEMENT**

Solution for Continuous Renal Replacement Therapy

After reconstitution, A + B

|                                    | Calcium<br>Ca <sup>2+</sup> | Magnesium<br>Mg <sup>2+</sup> | Sodium<br>Na <sup>+</sup> | Chloride<br>Cl <sup>-</sup> | Lactate<br>C <sub>3</sub> H <sub>5</sub> O <sub>3</sub> <sup>-</sup> | Bicarbonate<br>HCO <sub>3</sub> <sup>-</sup> | Potassium<br>K <sup>+</sup> | Dextrose    |
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|                  |             |
|------------------|-------------|
| Ca               | 1.25 mmol/L |
| Mg               | 1.5 mEq/L   |
| Na               | 140 mEq/L   |
| Cl               | 113 mEq/L   |
| HCO <sub>3</sub> | 32 mEq/L    |
| K                | 4 mEq/L     |

# Replacement Solution

Replaces the ultrafiltrate removed by hemofiltration and hemodiafiltration.

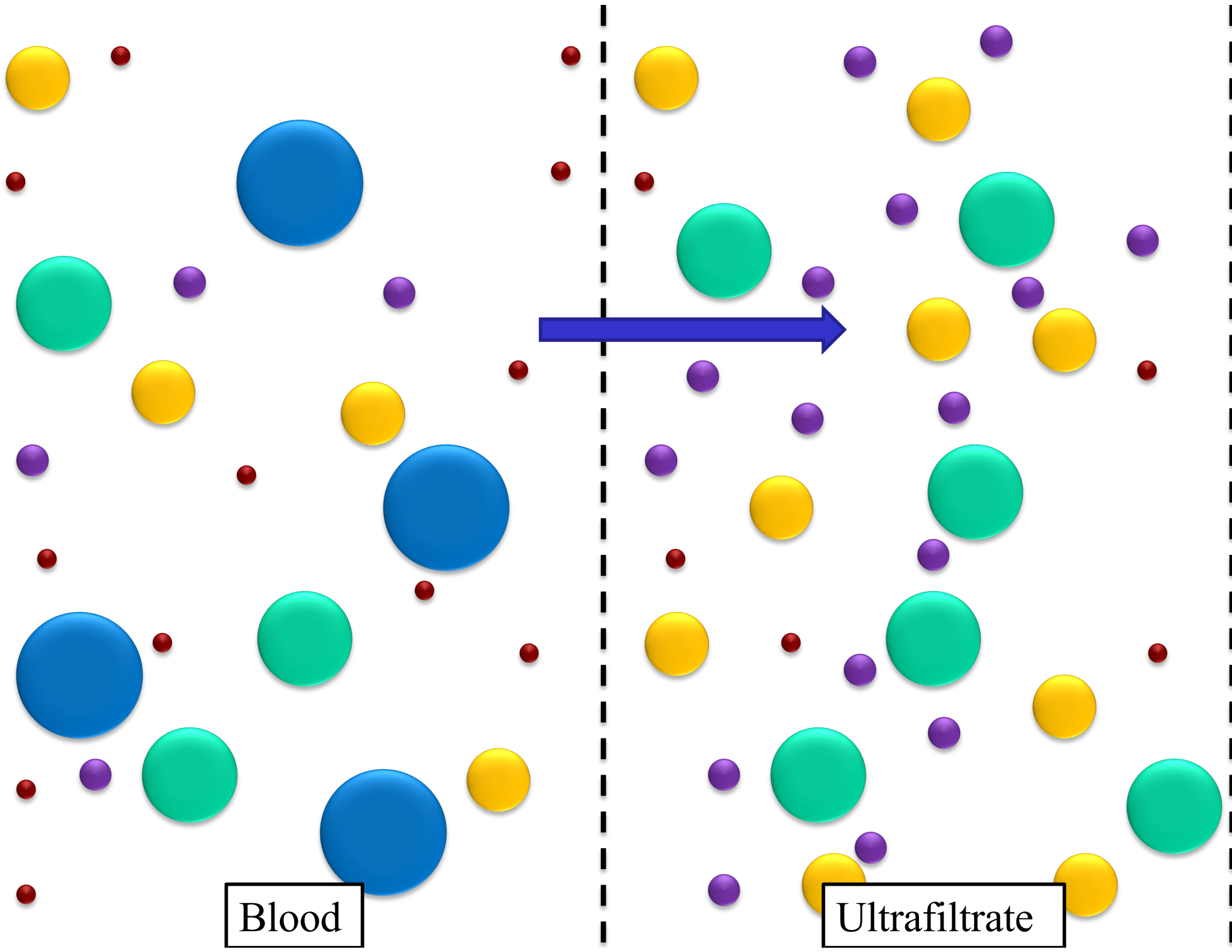
Buffers: Lactate, bicarbonate or citrate

Lactate and Citrate metabolized by liver and muscle to bicarbonate.

Bicarbonate is most easily tolerated  
can be unstable in solution

Citrate

Regional anticoagulation



Blood

Ultrafiltrate



# Continuous Renal Replacement Therapy (CRRT)

**CVVH**      Continuous Veno-Venous Hemofiltration

**CVVHD**      Continuous Veno-Venous Hemodialysis

**CVVHDF**      Continuous Veno-Venous Hemodiafiltration

**SCUF**      Slow Continuous Ultra-Filtration

**SLED**      Slow Low Efficiency Dialysis

# Convection

## Fluid Removal and Solute Removal

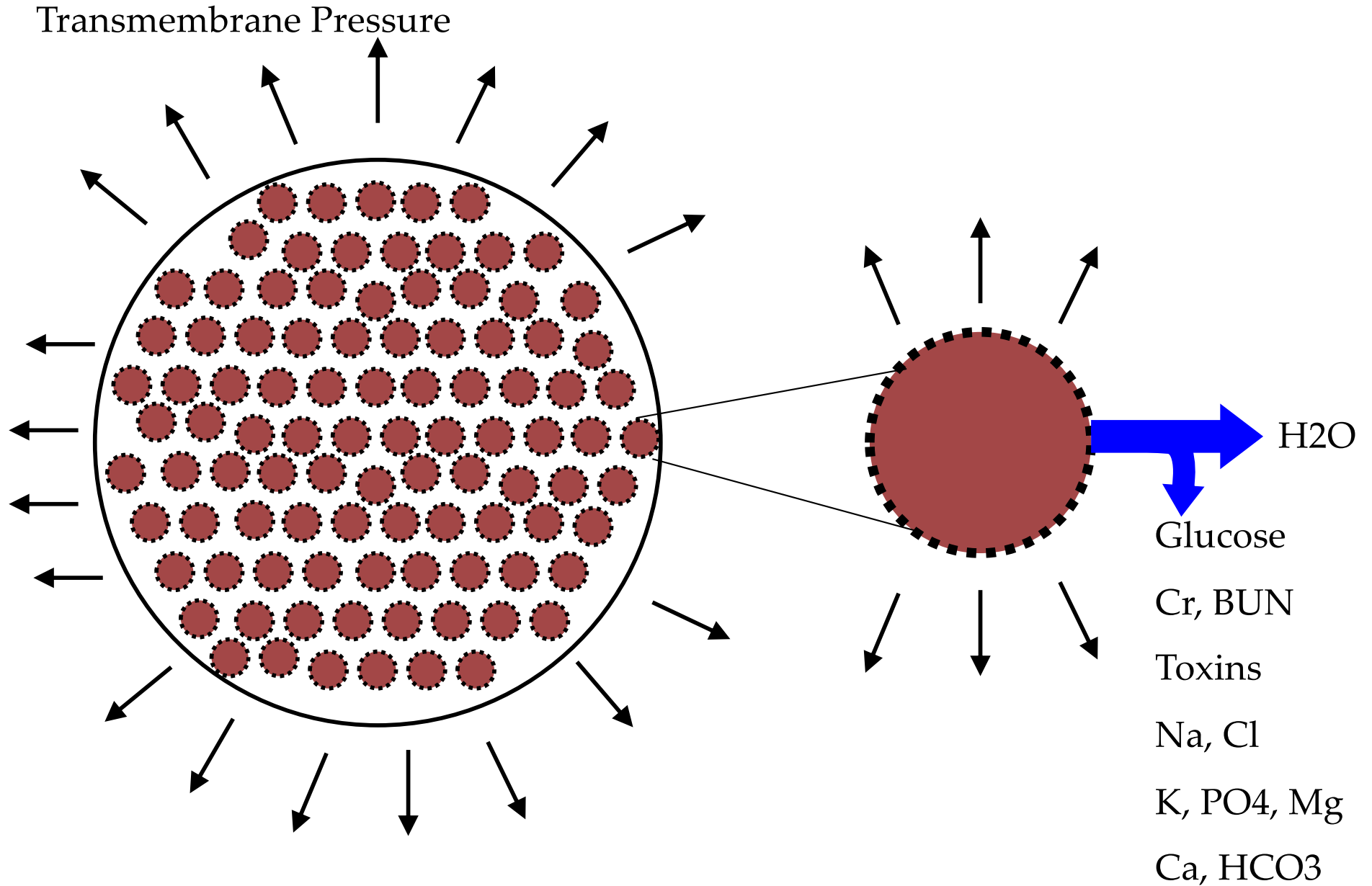
Movement of fluid across the membrane via transmembrane pressure

Water moves across the membrane and carries dissolved solutes with it via solvent drag

Ultrafiltration is fluid removal

Hemofiltration involves partial or total replacement of fluid removed

# Convection



# Diffusion

Movement of solutes down a concentration gradient across a semipermeable membrane.

Solutes cross the membrane from the blood to the dialysis fluid compartment.

Fluid in the dialysis compartment moves in a counter-current direction, thereby maintaining a concentration gradient.

# Diffusion

Diffusive clearance is determined by

Molecular weight of the solute

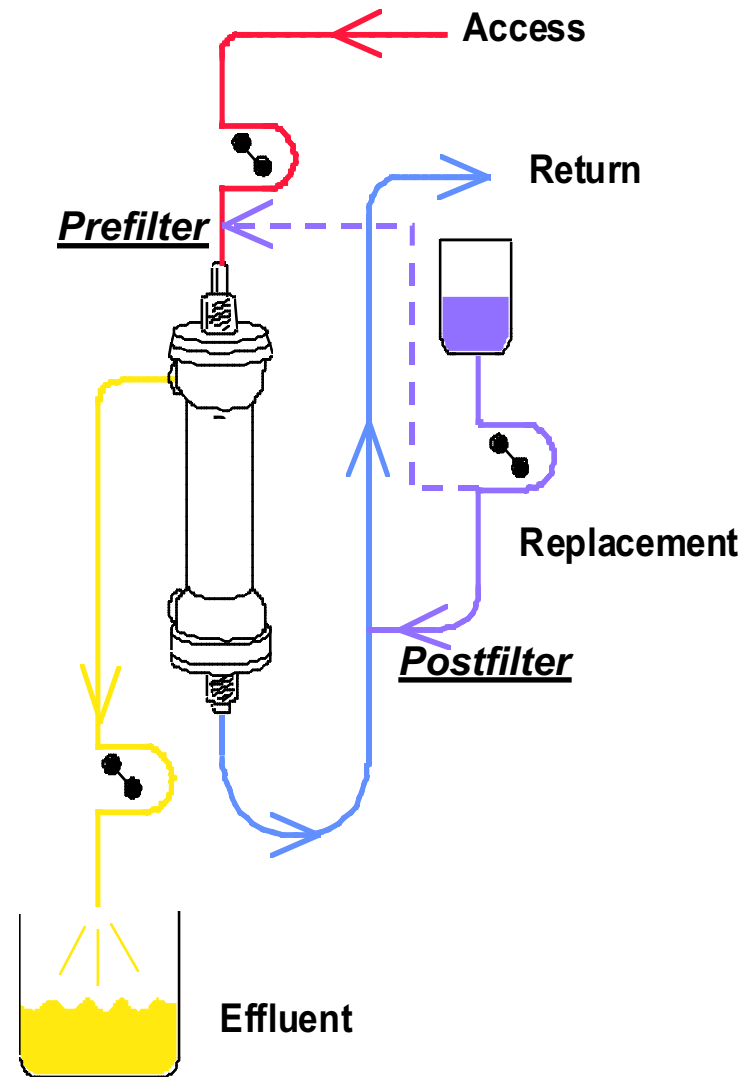
Concentration gradient across the membrane

Membrane surface area

Thickness and pore size

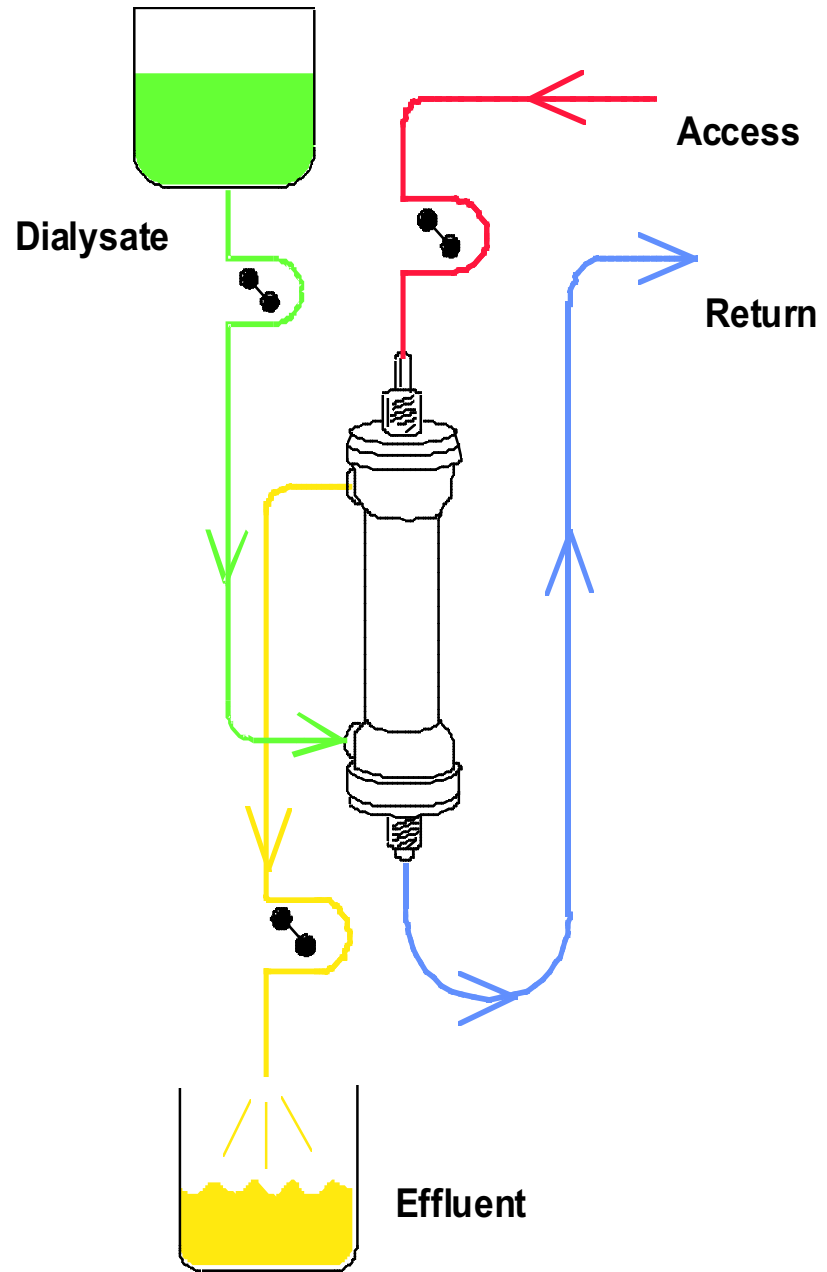
# CVVH

## Continuous Veno-Venous Hemofiltration



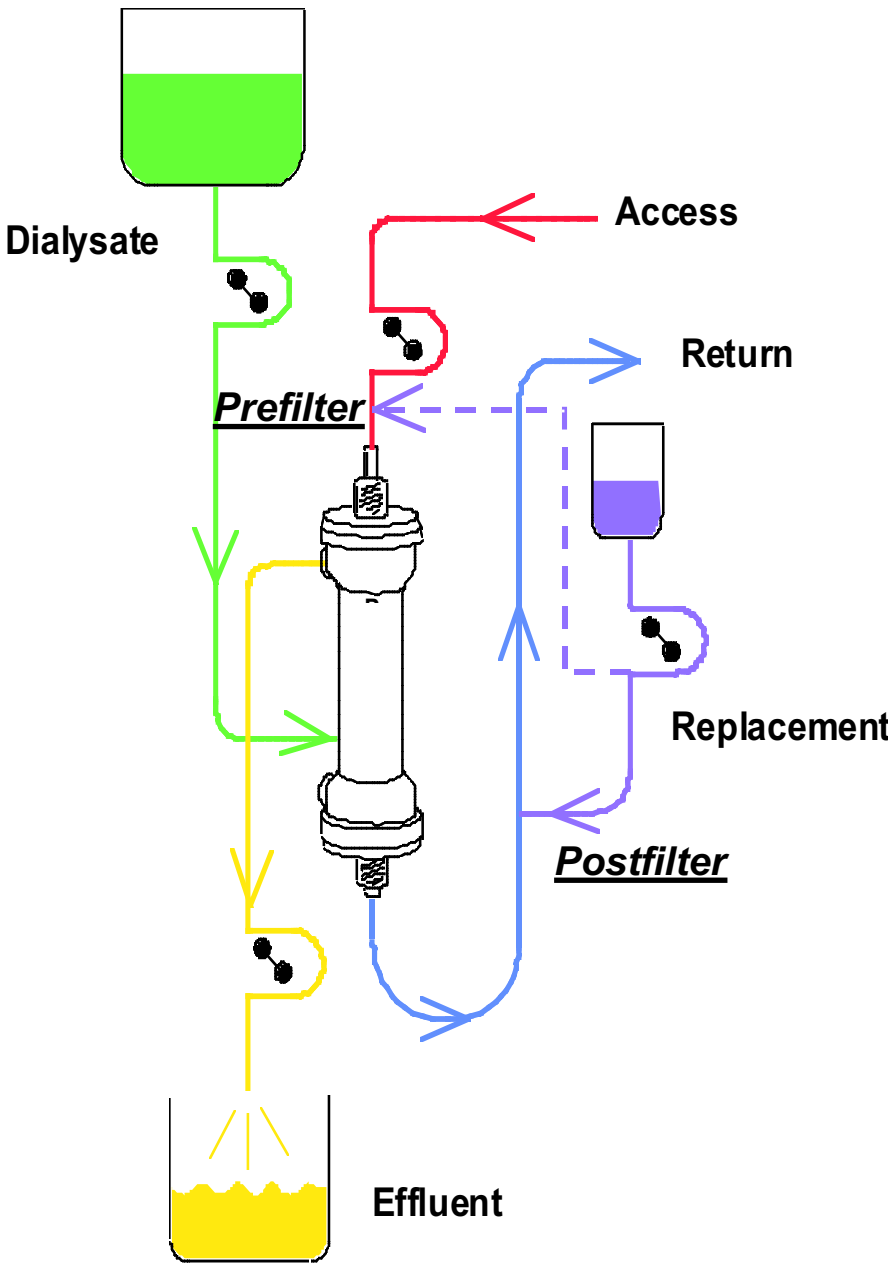
# CVVHD

## Continuous Veno-Venous HemoDialysis



# CVVHDF

## Continuous Veno-Venous HemoDiaFiltration



# Effluent

Represents the end product of the filtration process

CVVH: Ultrafiltrate

CVVHD: Dialysate plus variable ultrafiltrate

CVVHDF: Dialysate plus ultrafiltrate

# Case 1

64 year old diabetic female on Lisinopril

Witnessed PEA arrest

Resuscitated

Progressive volume overload (+15L)

Oliguric, diuretic resistant

BP 100/60 on moderate dose norepinephrine

Mechanically ventilated and sedated

Na 129, K 5.7, CO<sub>2</sub> 14, BUN 69, Cr 4.7

Best Renal Replacement modality?

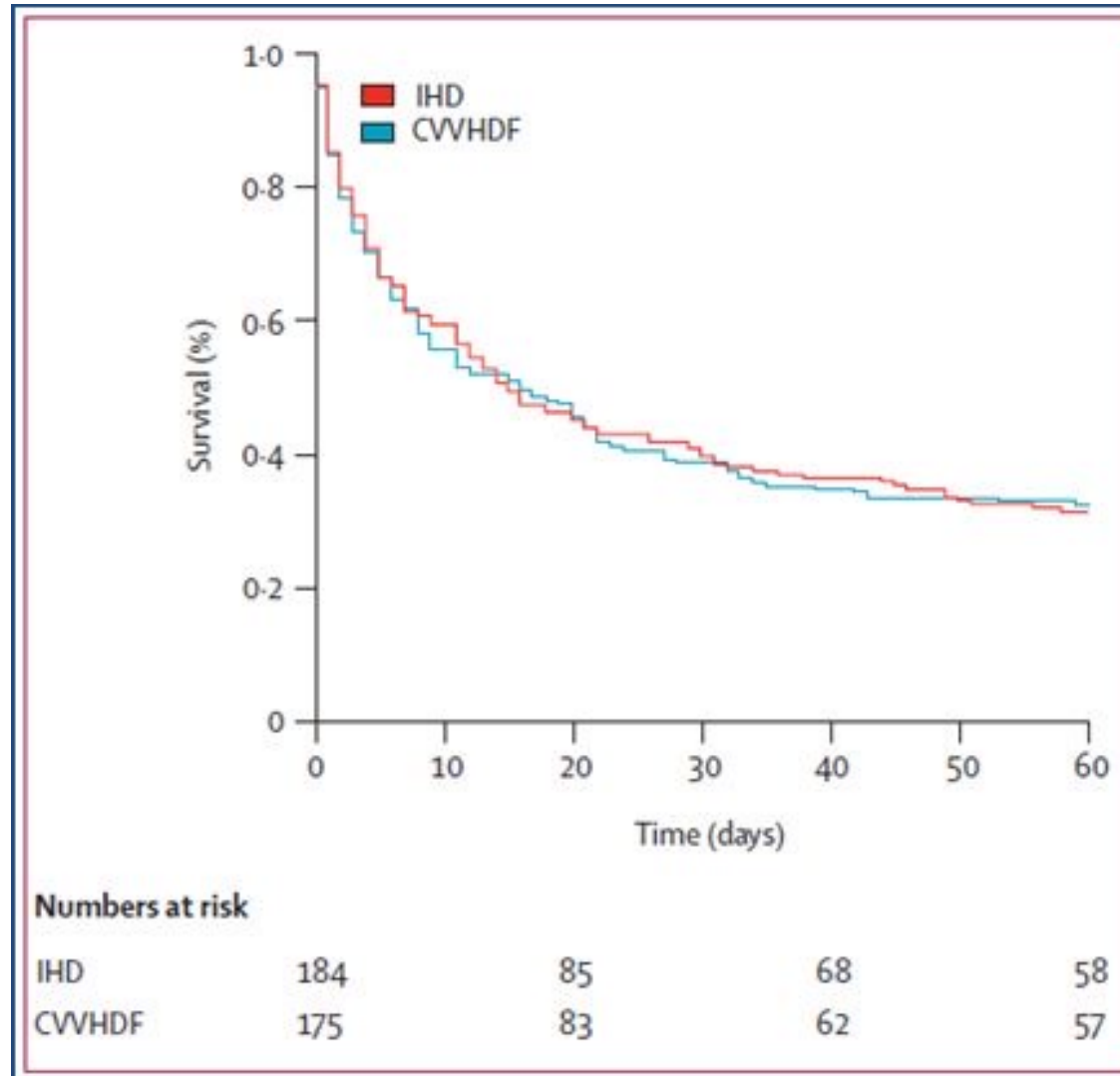
aps

## Case 1

Best Renal Replacement modality?

# CRRT vs Hemodialysis

No difference in survival in RCTs



Vinsonneau et al. Lancet 2006; 368: 379-85

# CRRT vs Hemodialysis

Both methods are complementary

## IHD

- Faster Potassium elimination
- Faster Drug/ Toxin elimination
- Better for overdose

## CRRT

- Regulation of higher calories requirements
- Hemodynamically unstable patients
- Precise adaptable volume control

1 minute

## Case 2

53 year old male with cryptogenic cirrhosis with septic shock and AKI, on CVVH

|     |     |     |     |
|-----|-----|-----|-----|
| 136 | 104 | 32  | 106 |
| 4.3 | 14  | 2.9 |     |

Total Ca 9.6 mg/dl

Ionized Ca 0.8 mmol/L

## Case 2

53 year old male with cryptogenic **cirrhosis** with septic shock and AKI, on CVVH

|     |     |     |     |
|-----|-----|-----|-----|
| 136 | 104 | 32  | 106 |
| 4.3 | 14  | 2.9 |     |

Total Ca 9.6 mg/dl

**Ionized Ca 0.8 mmol/L**

**Anion Gap 18**

# Citrate Toxicity

Low ionized Calcium despite repletion

Elevated total serum Calcium in response to repletion

Exacerbation of serum acidosis

Elevation of anion gap

Decrease Citrate replacement solution rate

Switch replacement solutions

# Citrate Regional Anticoagulation

Citrate causes anticoagulation by chelation of calcium in the extracorporeal system

Systemic anticoagulation does not occur

as ionized calcium level is restored when blood returning from the extracorporeal system is mixed with venous blood

Rapid metabolism of citrate restores bicarbonate level and releases calcium

Patients with severe liver failure and lactic acidosis may have difficulty metabolizing citrate and develop citrate toxicity

# Citrate Replacement solution

**Sodium Citrate = 40 mEq/Liter,**

**Dextrose = 2 gm/Liter,**

**Sodium Chloride = 105 mEq/Liter,**

**Magnesium Sulfate = 1.5 mEq/Liter.**

CVVH with maximum replacement of 2000 cc  
citrate/hour.

CVVHDF add dialysate to improve clearance.

Calcium replacement scales adjusted depending on  
clearance

# Clearance

Clearance is the rate at which solutes are cleared

excretion rate of solute / blood concentration of solute

Solute clearance in CVVH depends on UF Rate

# Strategies to Increase Solute Clearance

Increase Transmembrane pressure

# Strategies to Increase Solute Clearance

Increase Transmembrane pressure

Increase blood flow

CVVHDF

Add dialysis to convection

# Indications for CRRT

Patients with/ at risk for hypotension:

- severe hemodynamic instability

- hepatic failure

- CHF

- sepsis or multiple organ failure

Patients at risk of cerebral complications:

- hepatic failure, stroke or head trauma

- high risk for cerebral edema

# Indications for CRRT

## Increased metabolic needs

massive burns

sepsis

multiple organ failure

## Volume overload

massive volume overload

Patients receiving large amounts of fluids or blood products

When volume management is critical

# Non-renal Indications for CRRT

Lactic acidosis

Ongoing production – removes a little

Crush injury

Myoglobin Removal – a little

Tumor lysis syndrome

Temperature control

Relative hyper or relative hypothermia\*

Massive volume overload without AKI

High  $\text{NH}_3$

# Potential Advantages of CRRT

Increased total solute clearance

Gradual clearance may be better tolerated

- Decreases frequency of hypotension

- Decreases risk of cerebral edema

Continuous clearance may help in removal of toxins  
with high intracellular concentrations

Increased clearance of middle molecules

**Precise adaptable volume control**

# Potential disadvantages of CRRT

Anticoagulation requirement

Lack of rapid fluid and solute removal

Limited role in overdose setting

Relative Hypothermia

Electrolyte Depletion

K, PO<sub>4</sub>, Ca

# Contraindications of CRRT

Life-threatening hyperkalemia

group

## Case 3

35 year old female with aggressive lymphoma (Burkitt subtype) to undergo cytotoxic chemotherapy

|     |     |     |     |
|-----|-----|-----|-----|
| 136 | 104 | 12  | 106 |
| 4.3 | 24  | 1.0 |     |

Total Ca and PO<sub>4</sub> normal

## Case 3

Oncology asks for CRRT prior to cytotoxic chemotherapy to prevent Tumor Lysis Syndrome

Oncology asks how the CRRT will alter the chemotherapy clearance

# Drug Dosage in CRRT

Minimal removal of protein bound drugs  
Some may be removed via membrane adsorption

Drug clearances increased with CVVHDF  
Higher doses may be needed with higher UF rates

GFR = 10 ml/min Low UF rate

GFR = 30 ml/min Medium UF rate

GFR = 50 ml/min High UF rate

Mehta R, Atlas of Diseases of the Kidney 1999

Bugge JF. Acta Anaesthesiol Scand. 2001;45(8):929-34.

# Timing of CRRT

# Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury

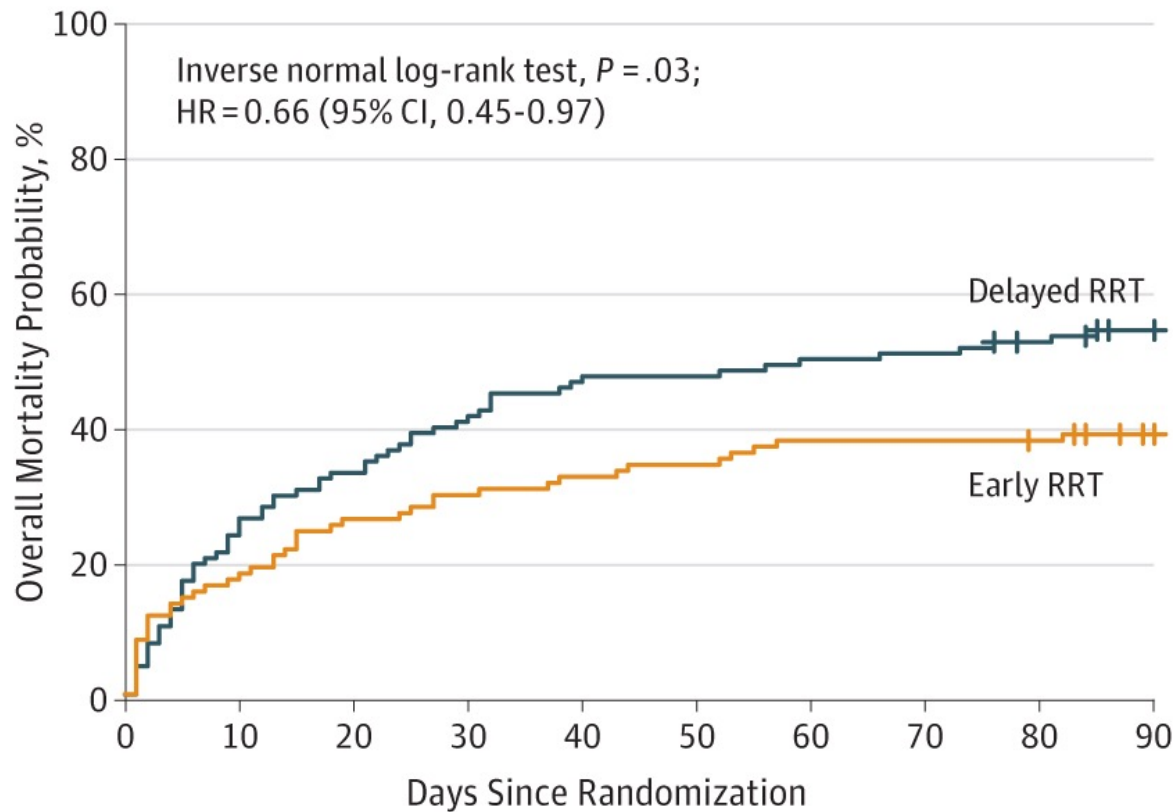
## The ELAIN Randomized Clinical Trial

JAMA. 2016;315(20):2190-2199. doi:10.1001/jama.2016.11111

- Single-center RCT
- 231 patients
- Early RRT was initiated within 8 hours of diagnosis of stage 2 AKI using the KDIGO classification
- Delayed RRT was initiated within 12 hours of stage 3 AKI using the KDIGO classification

# Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury

## The ELAIN Randomized Clinical Trial



| No. at risk |     |    |    |    |    |    |    |    |    |    |
|-------------|-----|----|----|----|----|----|----|----|----|----|
| Early RRT   | 112 | 92 | 82 | 78 | 75 | 73 | 69 | 69 | 66 | 55 |
| Delayed RRT | 119 | 90 | 79 | 70 | 63 | 62 | 59 | 58 | 54 | 48 |

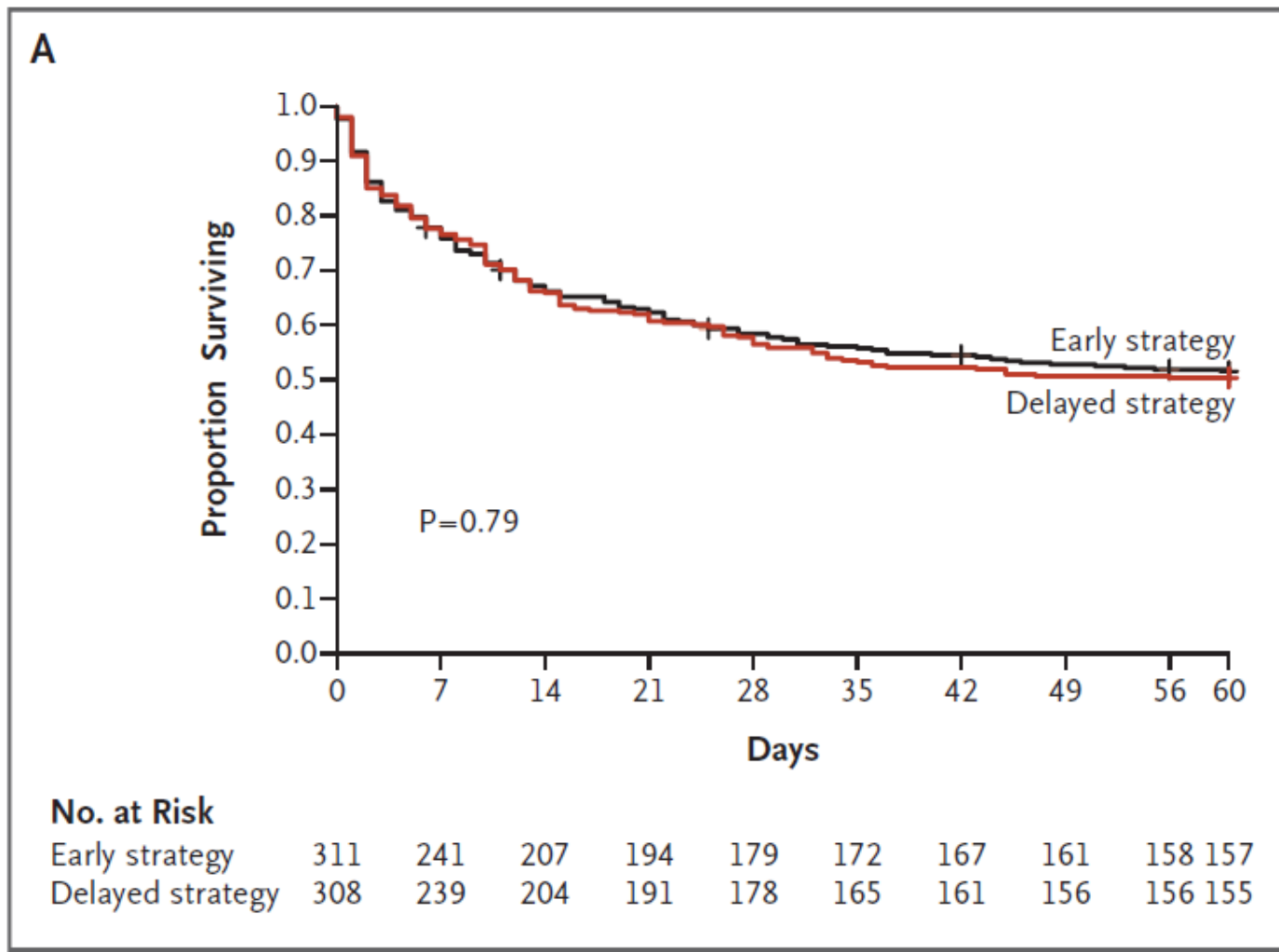
# Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

N Engl J Med 2016;375:122-33.

- Multicenter RCT
- Severe AKI (KDIGO stage 3) on Mechanical Ventilation and/or catecholamines
- 620 patients
- Early strategy - Immediately after randomization
- Delayed Strategy – Severe hyperkalemia, metabolic acidosis, pulmonary edema, BUN > 112 mg/dl or oliguria > 72 hours after randomization

# Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

N Engl J Med 2016;375:122-33.



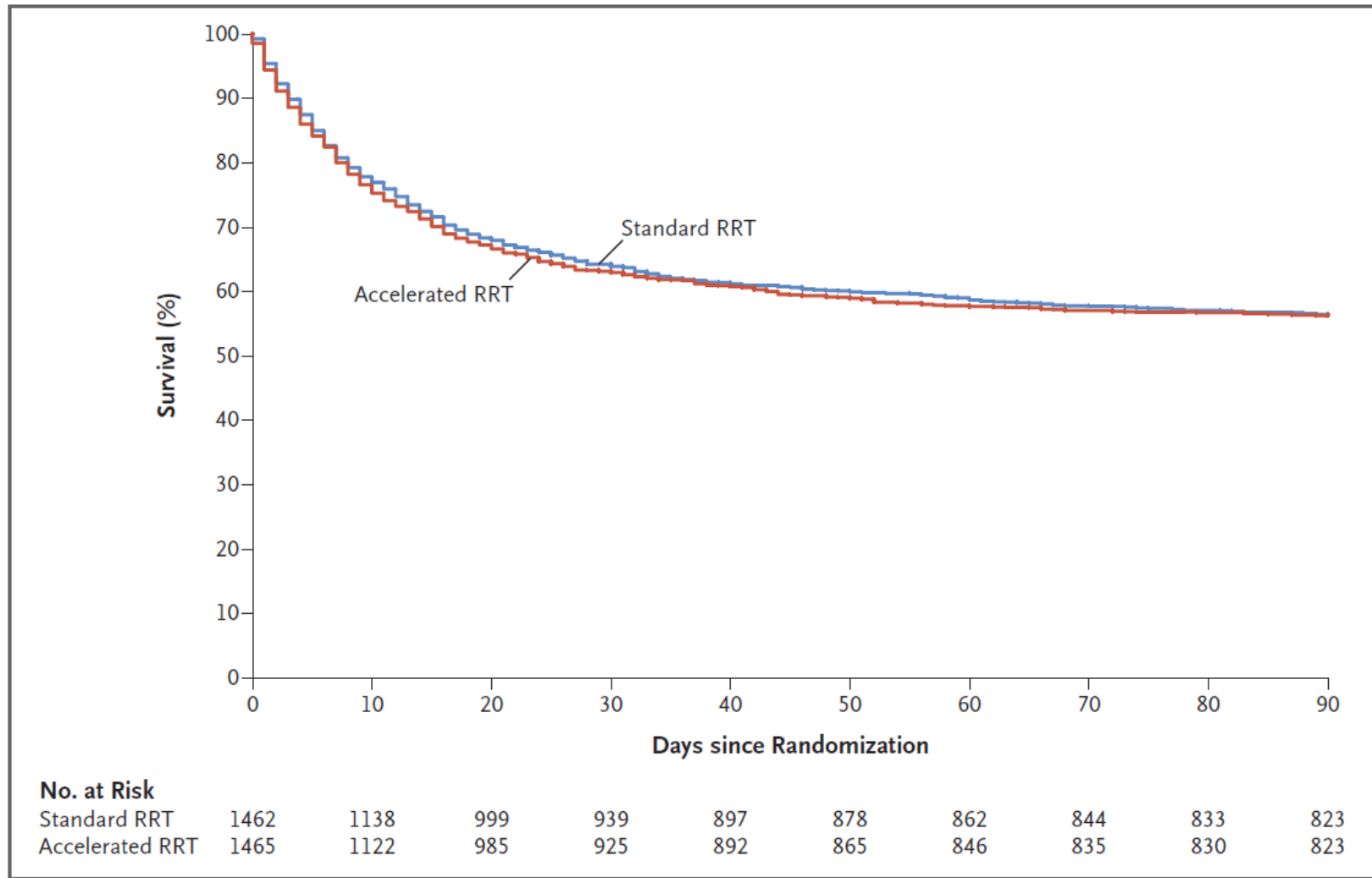
# Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

N Engl J Med 2020;383:240-51.

- Multicenter RCT
- Severe AKI
- 2927 patients
- Accelerated strategy – Within 12 hours
- Standard Strategy – RRT discouraged unless conventional indications developed or AKI persisted > 72 hours

# Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

N Engl J Med 2020;383:240-51.



# Intensity of Renal Replacement

No consistent statistically significant difference in survival regarding intensity

1. The VA/NIH Acute Renal Failure Trial Network. N Engl J Med 2008; 359:7-20
2. Tolwani AJ. J Am Soc Nephrol. 2008;19(6):1233-8.
3. RENAL Replacement Therapy Study Investigators. N Engl J Med. 2009;361:1627-1638

More is **not** better

# CRRT and Sepsis



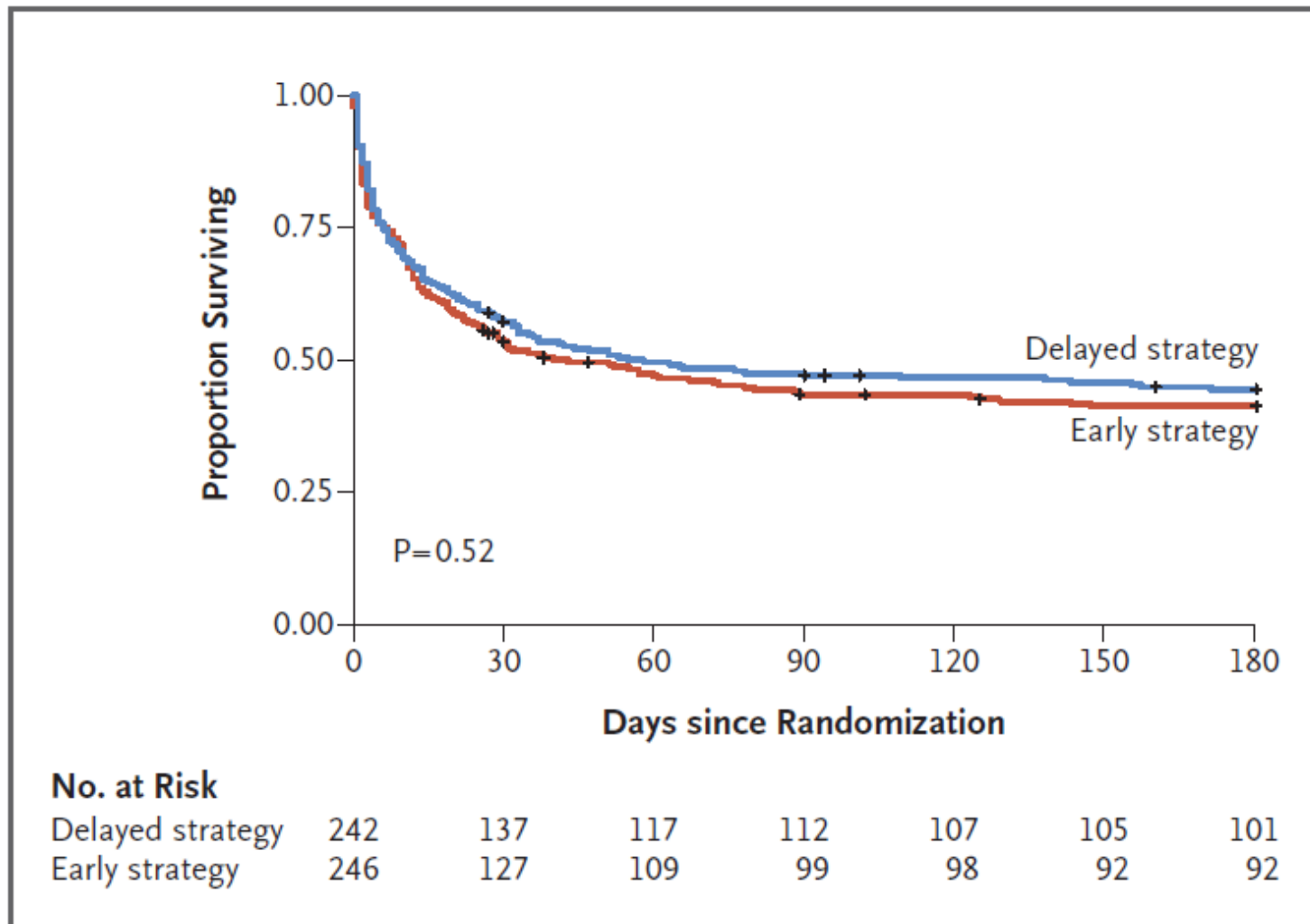
# Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

N Engl J Med 2018;379:1431-42.

- Multicenter RCT
- Early stage Sepsis with RIFLE stage Failure
- 488 patients
- Early strategy – RRT within 12 hours of RIFLE Failure stage
- Delayed Strategy – RRT within 48 hours of RIFLE Failure stage if no recovery had occurred

# Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

N Engl J Med 2018;379:1431-42.



# Cessation of CRRT

All criteria for initiating CRRT are absent

Fluid balance can be kept approximately neutral with current **urine output**

There is a complication related to CRRT

When criteria are fulfilled begin a 12-24 hour period without CRRT

Reevaluate for indications for CRRT

CRRT should be initiated early and ceased late

# Key Take-Home Points

Dialysis utilizes **D**iffusion for clearance

Continuous Renal Replacement utilizes **C**onvection for clearance

No difference in survival between HD and CRRT

HD has much higher clearance per unit time

CRRT not suitable for toxin removal

Life threatening Hyperkalemia is a contraindication for CRRT – CRRT works slowly

CRRT is not effective in improving sepsis

CRRT is more effective in getting patients to euvolemia

# Board Question

Which One Renal Replacement method has the highest probability of in hospital survival?

- A. Intermittent hemodialysis
- B. CVVHDF
- C. Sustained Low-Efficiency Dialysis
- D. CVVH
- E. All are equal

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Which One Renal Replacement method has the highest probability of in hospital survival?

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- C. Sustained Low-Efficiency Dialysis
- D. CVVH
- E. All are equal**

**Survival does not depend on modality of renal replacement in AKI with the exception of peritoneal dialysis (shown to be inferior)**