Choice of CRRT modality

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Disclosure

- ***ERAS ITALIA*** Group (SITI – POIS – SINPE)
- Italian Society of Intensive Care – Secretary General (**SITI**)
- Coordinator European Society of Intensive Care Medicine (**ESICM**) – Next fellowship: Pain, Agitation, and Delirium

Others

Honoraria for lectures and consultancies, support for travel and accomodation (last three years): Baxter, Bbraun, Masimo, Medtronic, MSD, Orion Pharma, Pall Corporation, Vygon – Vytech

Continuous Renal Replacement Therapy
Who, When, Why, and How

CHEST

Modalities of RRT

Multiple modalities of renal support may be used in the management of the **critically ill patient** with kidney failure.

CRRT

Continuous
Renal
Replacement
Therapies

IHD

Intermittent
Hemo
Dialysis

PIRRTs

Prolonged
Intermittent
Renal
Replacement
Therapies

Tandukar S & Palewsky PM. CHEST 2019;155:626-638

CRRT

Continuous
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All of these use relatively similar extracorporeal blood circuits and differ primarily with regard to **duration of therapy** and, consequently, the **rapidity of net ultrafiltration and solute clearance**.

Mechanisms of solute clearance

- = Diffusion
- = Convection

Tandukar S & Palewsky PM. CHEST 2019;155:626-638

CRRT

Continuous
Renal
Replacement
Therapies

CRRT

Continuous
Renal
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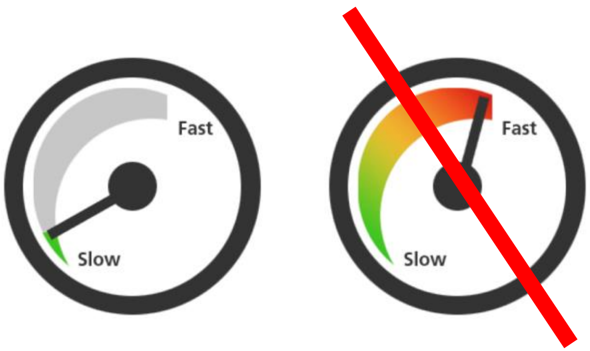


CRRT provides a **slow, gentle**, and **continuous** kidney support → **hemodynamic instability**

More gradual fluid removal and **solute clearance** over <u>prolonged treatment times</u>

Although the **Kidney Disease: Improving Global Outcomes (KDIGO)** Clinical Practice Guideline for AKI recommends the use of <u>CRRT for patients who are **hemodynamically unstable**</u>, the strength of this recommendation is low.

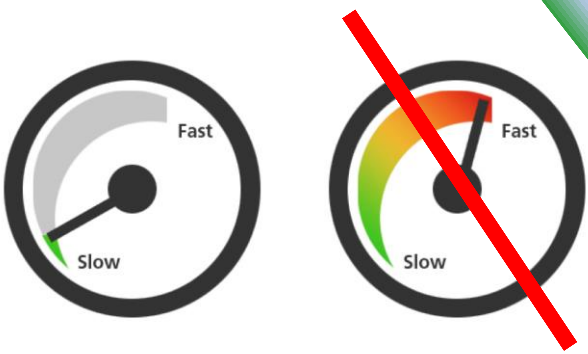
Observational data, however, do suggest that CRRT is more effective in **achieving net** <u>**negative fluid balance**</u> than IHD.

Tandukar S & Palewsky PM. CHEST 2019;155:626-638

CRRT

Continuous Renal Replacement Therapies

- Continuous venovenous hemofiltration (CVVH) – **convection**
- Continuous venovenous hemodialysis (CVVHD) – **diffusion**
- Continuous venovenous hemodiafiltration (CVVHDF) – **diffusion** and **convection**

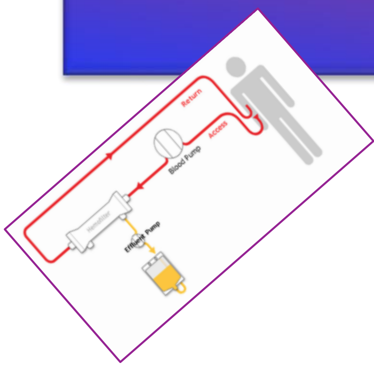


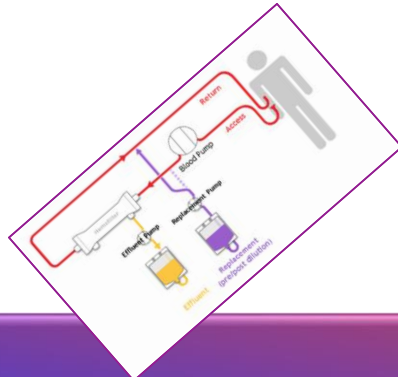
CRRT provides a **slow, gentle**, and **continuous** kidney support → **hemodynamic instability**

More gradual fluid removal and **solute clearance** over <u>prolonged treatment times</u>

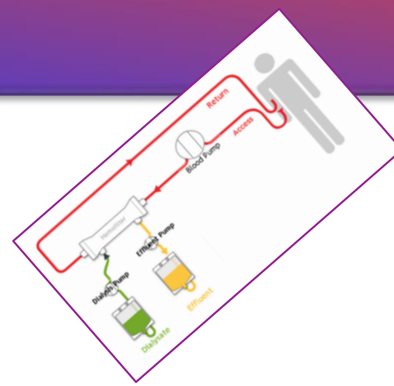
Continuous renal replacement therapy (CRRT)

SCUF

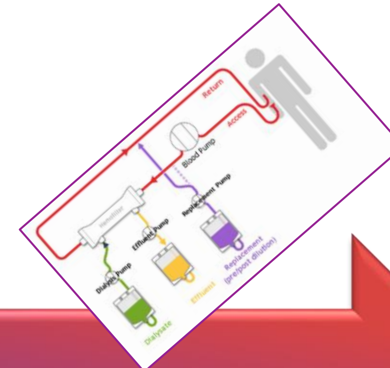




CVVH Post Hep
CVVH Pre Hep
CVVH Pre-Post Hep
CVVH Post-Citrate



CVVHD Hep
CVVHD Citrate



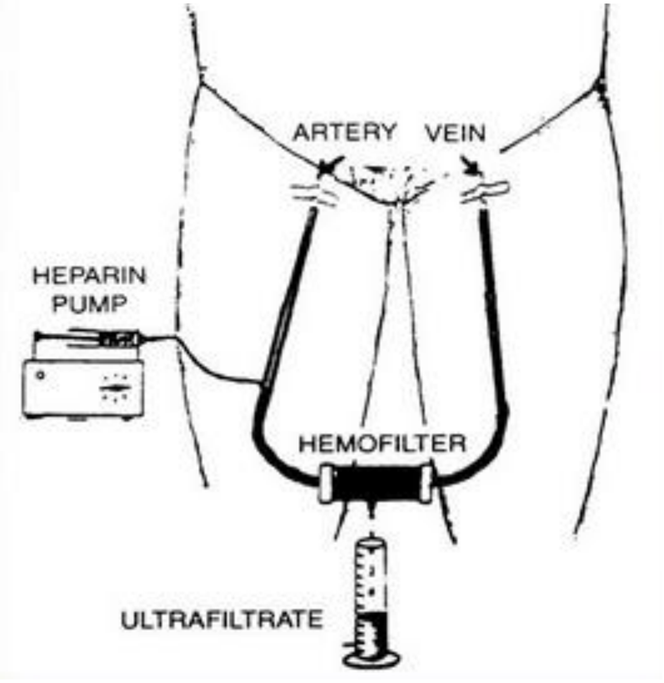
CVVHDF Post Hep
CVVHDF Pre Hep
CVVHDF Pre-Post Hep
CVVHDF Post-Citrate

The modes differ in whether the primary driver of solute removal is **convection**, **diffusion**, or **both,** the **reinfusion** site (pre-post-both) and the **anticoagulation** modality (heparin, citrate → pre).

Selection of CRRT Modality

Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F. [Arteriovenous haemofiltration: a new and simple method fo treatment of over-hydrated patients resistant to diuretics]. *Klin Wochenschr*. 1977 Nov 15;55(22):1121–1122.

- **C**ontinuous **A**rterio**V**enous **H**emofiltration [**CAVH**] - first described in 1977
- Blood flow through the hemofilter is driven by the patient's blood pressure
- However, clearances were low because blood flow was low (often <80 mL/min) and ultrafiltration was low.
- The need to cannulate an artery, however, is associated with **15% to 20% morbidity**.

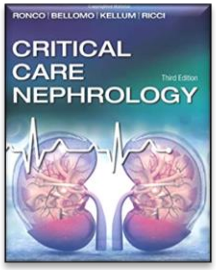


1977

Continuous Renal Replacement Therapy: Modalities and Their Selection

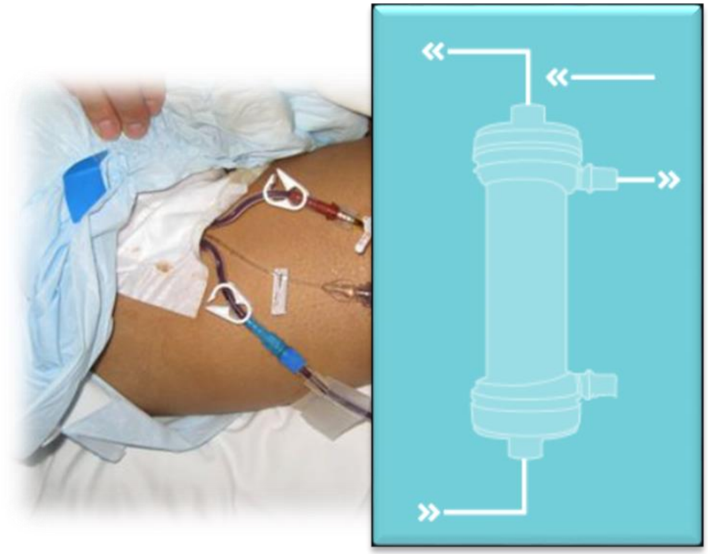
Rinaldo Bellomo and Claudio Ronco

Ronco C, Bellomo R, Kellum JA, Ricci Z.
Critical Care Nephrology, 2018 - 3ED



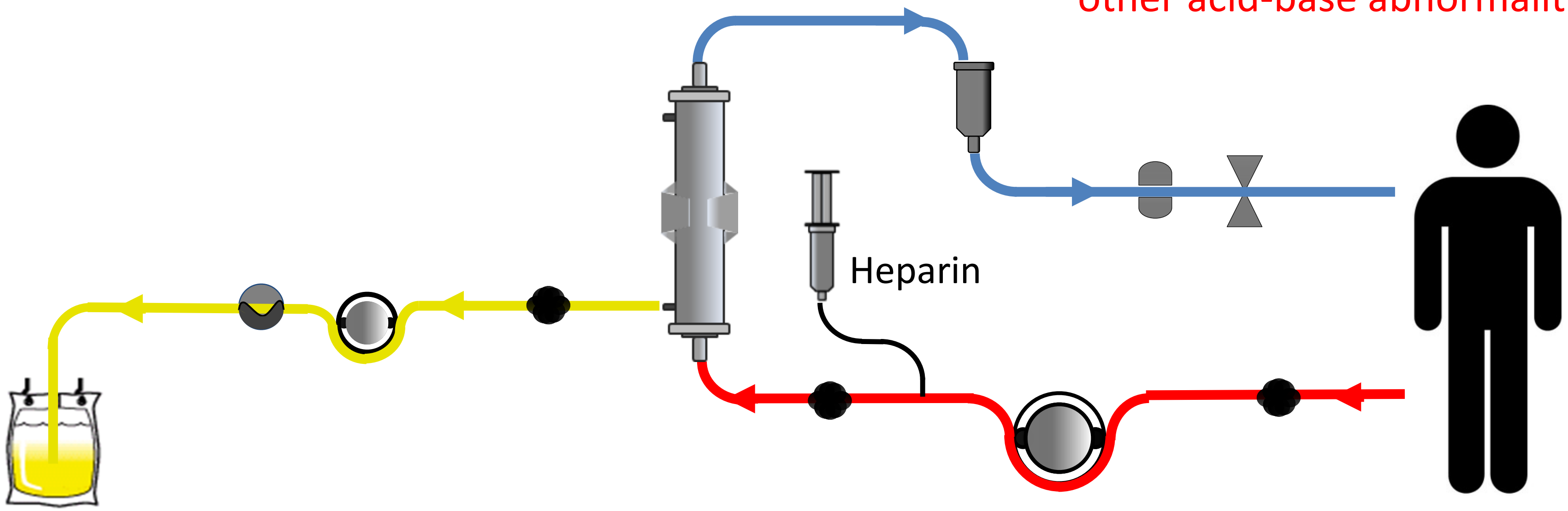
Selection of CRRT Modality

- → Double-lumen catheters and peristaltic blood pumps have come into use with control of ultrafiltration rate.



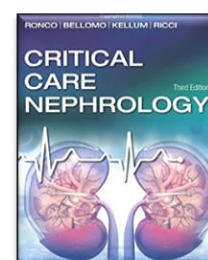
Tandukar S & Palewsky PM. CHEST 2019;155:626-638

Slow Continuous UltraFiltration (SCUF) → Remove plasma **water** in patients without significant electrolyte or other acid-base abnormalities.



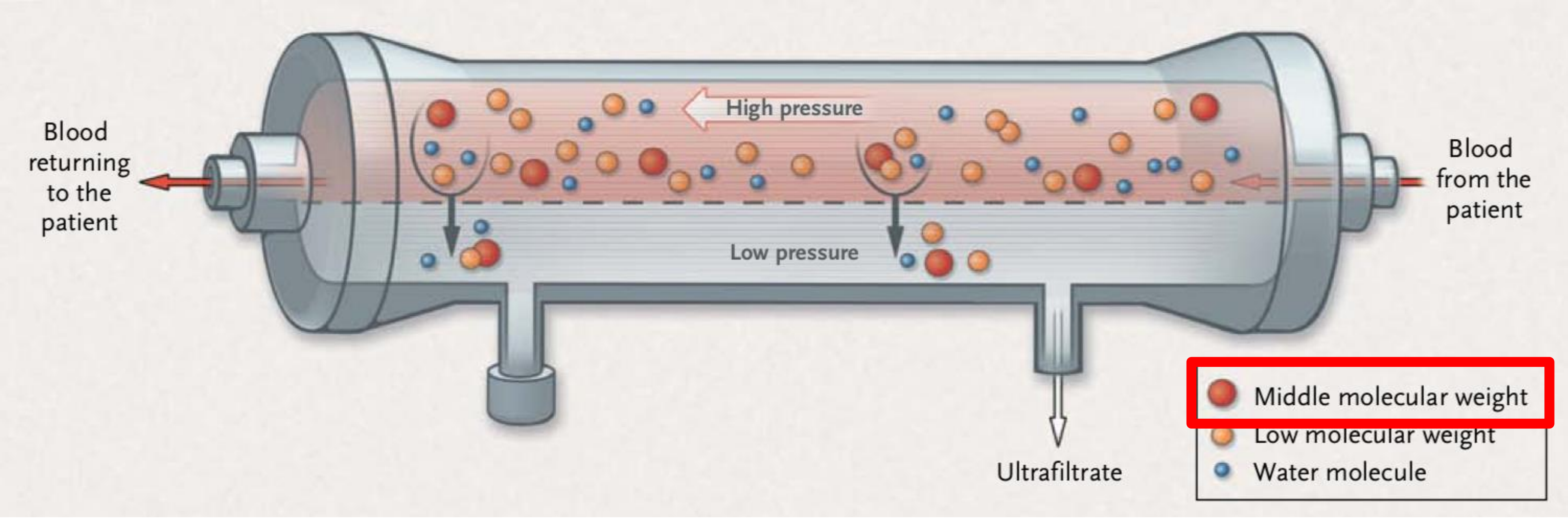
- Ultrafiltration describes the transport of plasma water (solvent) through a semipermeable membrane driven by a pressure gradient between blood and ultrafiltrate compartments.
- An ultrafiltration control system is required to prevent excessive ultrafiltration
- Relative to hemofiltration, low filtration rates (typically 2–8 mL/min) are required
- Very effective for volume reduction but the low filtration rates and lack of substitution fluids → **ineffective** as a blood purification modality.

Ronco C, Bellomo R, Kellum JA, Ricci Z.
Critical Care Nephrology, 2018 - 3ED



Continuous **V**eno**V**enous **H**emofiltration (**CVVH**)

- In **CVVH**, a high rate of ultrafiltration across the semipermeable hemofilter membrane is created by a hydrostatic gradient, and solute transport occurs by **convection**.
- Solutes are entrained in the bulk flow of water across the membrane, a process often referred to as "**solvent drag**".

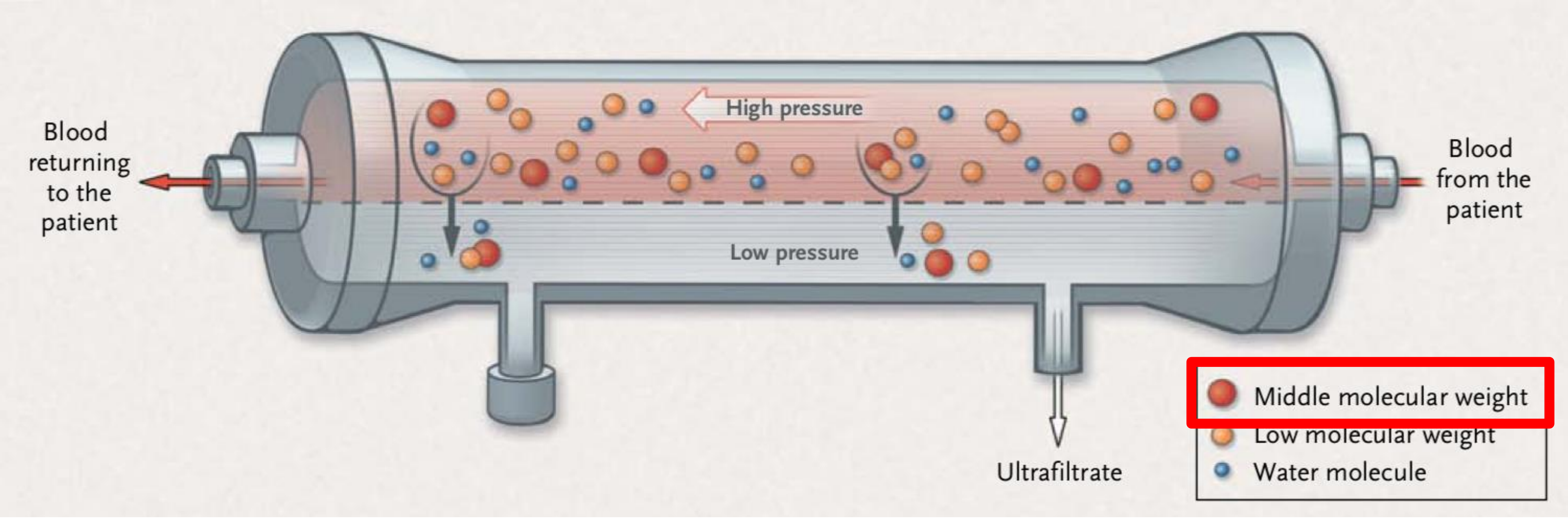


Tolwani A. N Engl J Med. 2012;367(26):2505-2514.

- **High ultrafiltration rates are needed** to achieve sufficient solute clearance, and the ultrafiltrate volume beyond what is required to achieve desired **net fluid removal is replaced with balanced IV crystalloid solutions** (prior the hemofilter = pre-dilution or following the hemofilter = post-dilution).

Continuous VenoVenous Hemofiltration (CVVH)

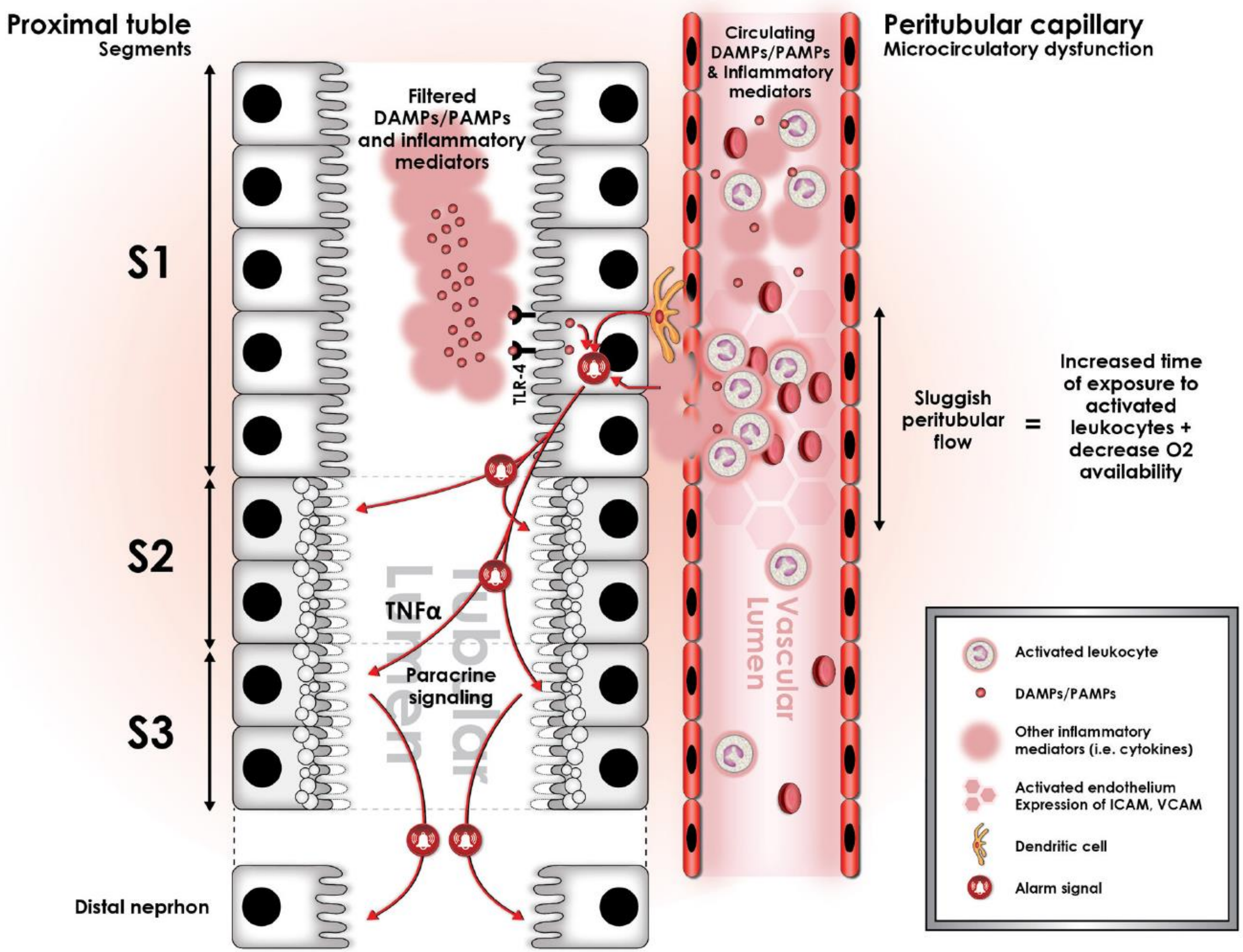
- The porosity of the membrane determines which solutes are removed.
- Small solute molecules, such as urea, and **middle-sized molecules**, such as **inflammatory cytokines**, are cleared.



Tolwani A. N Engl J Med. 2012;367(26):2505-2514.

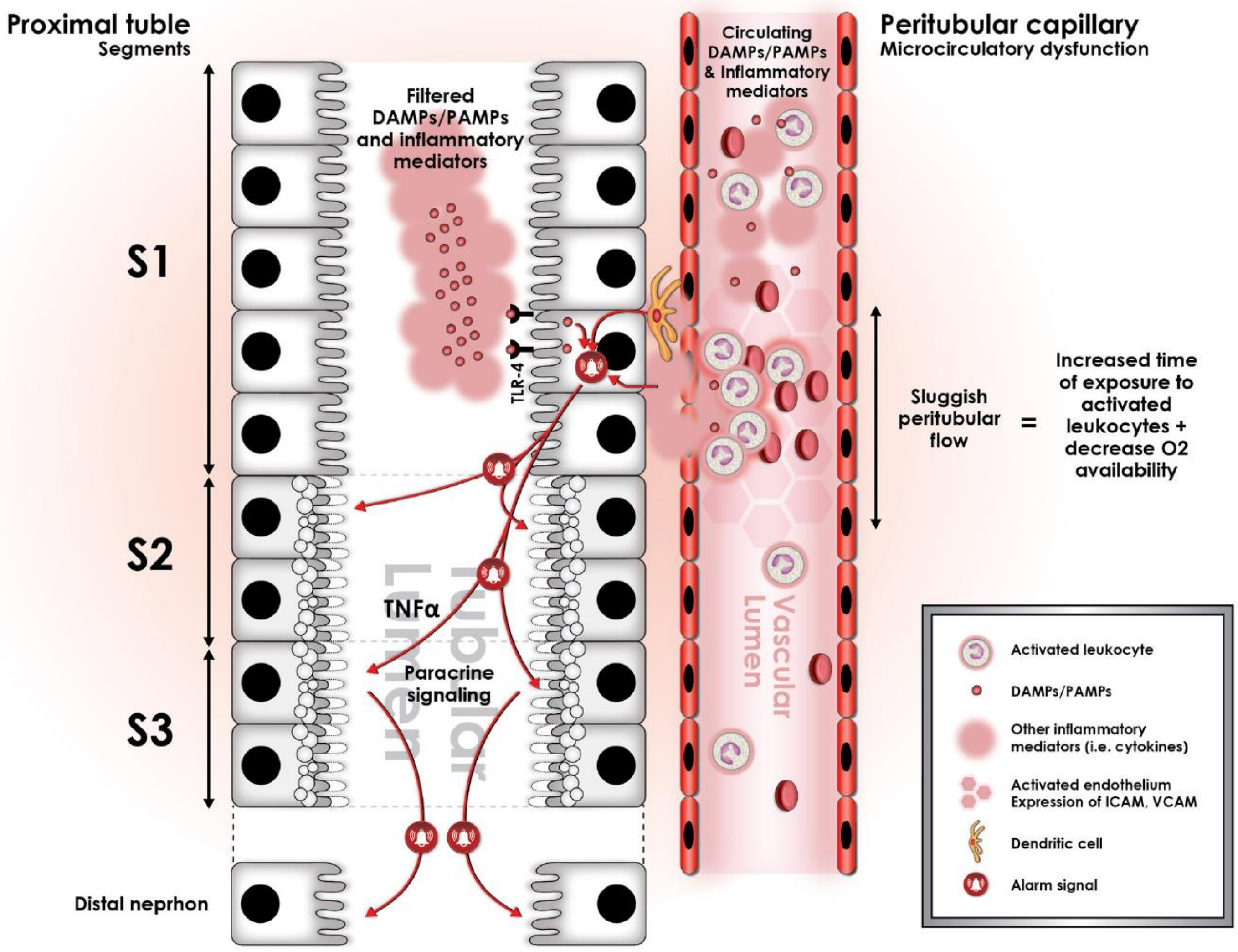
- Post-dilution results in more concentrated blood in the filter and higher solute clearance. Nevertheless, more concentrated blood can lead to a shorter filter lifespan.
- While pre-dilution means lower solute concentrations and clearance, this is offset by a higher ultrafiltration rate and longer filter life.

A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury.

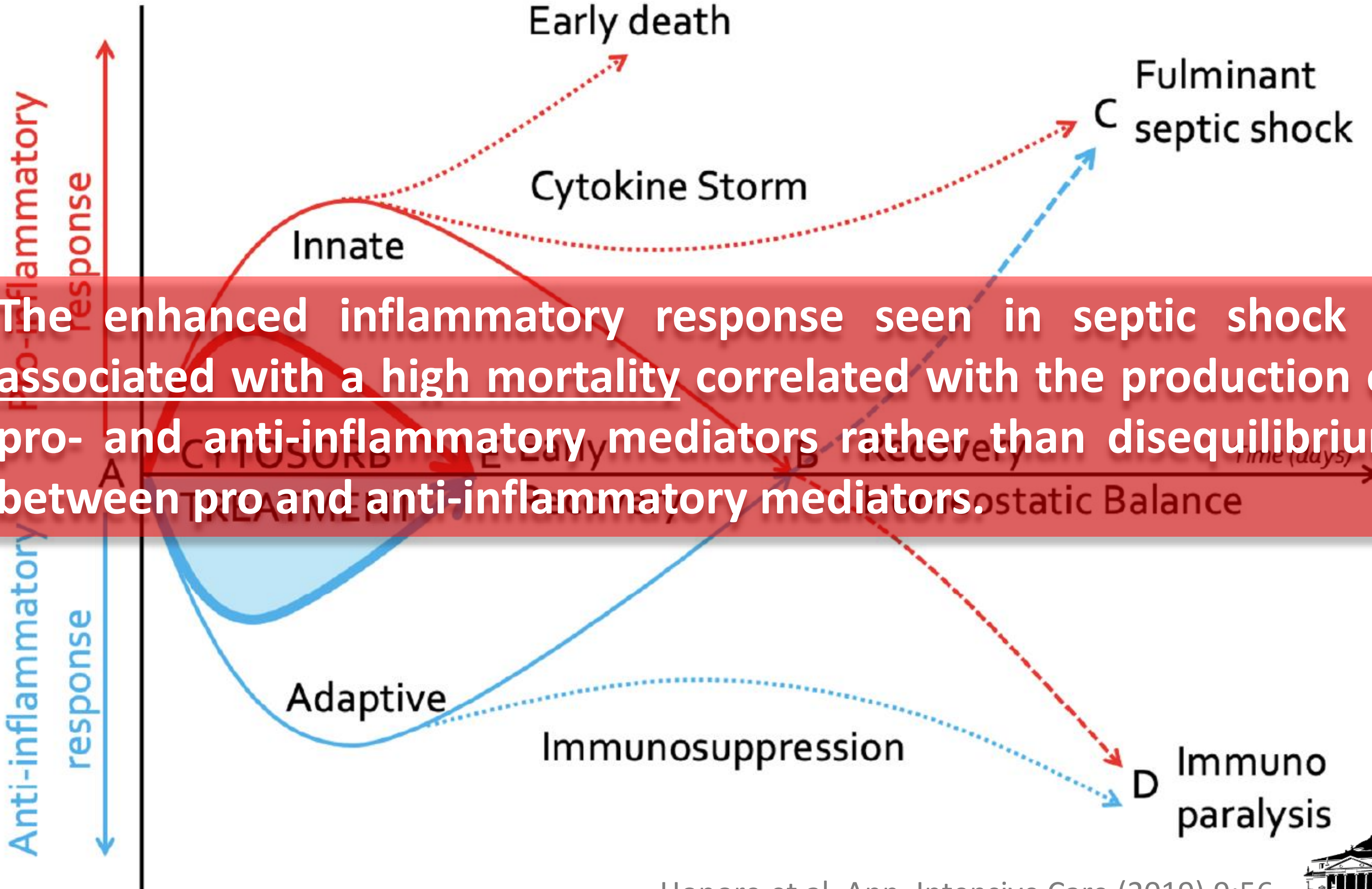


Gomez H et al. Shock. (2014) 41:3-11

During sepsis, inflammatory mediators derived from pathogens and activated immune cells **(i.e. LPS, cytokines, etc. also known as Damage or Pathogen Associated Molecular Patterns or DAMPs/PAMPs)** which prime, signal, alert and guide the immune system to fight infection, also mediate host cellular injury**.**

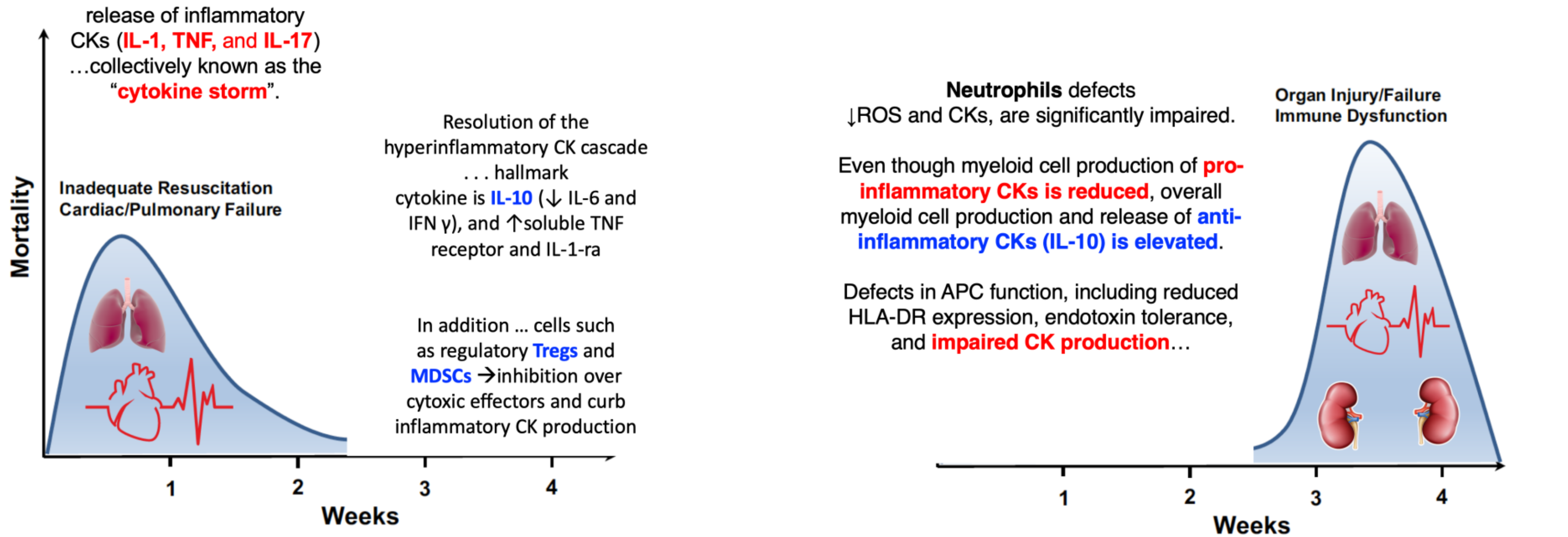


Gomez H et al. Shock. (2014) 41:3-11

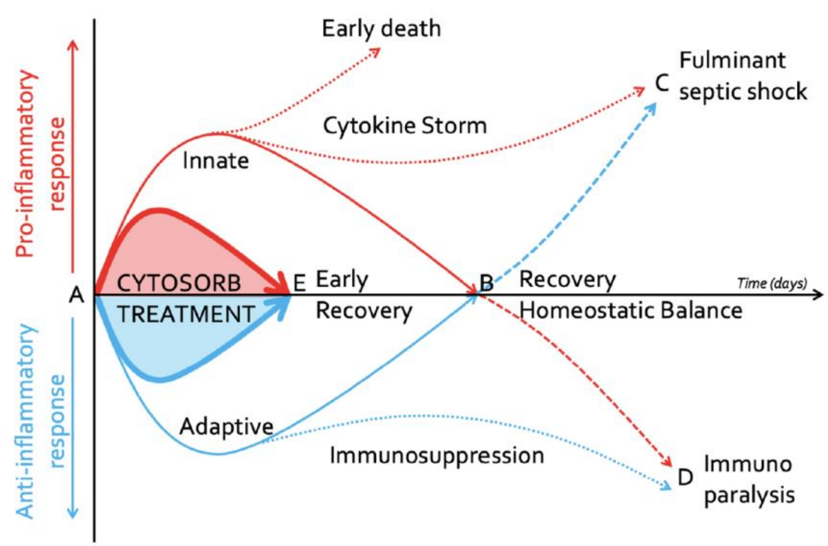


The enhanced inflammatory response seen in septic shock is associated with a high mortality correlated with the production of pro- and anti-inflammatory mediators rather than disequilibrium between pro and anti-inflammatory mediators.

Honore et al. Ann. Intensive Care (2019) 9:56



Delano & Wald Immunological Reviews (2016) 274: 330–353

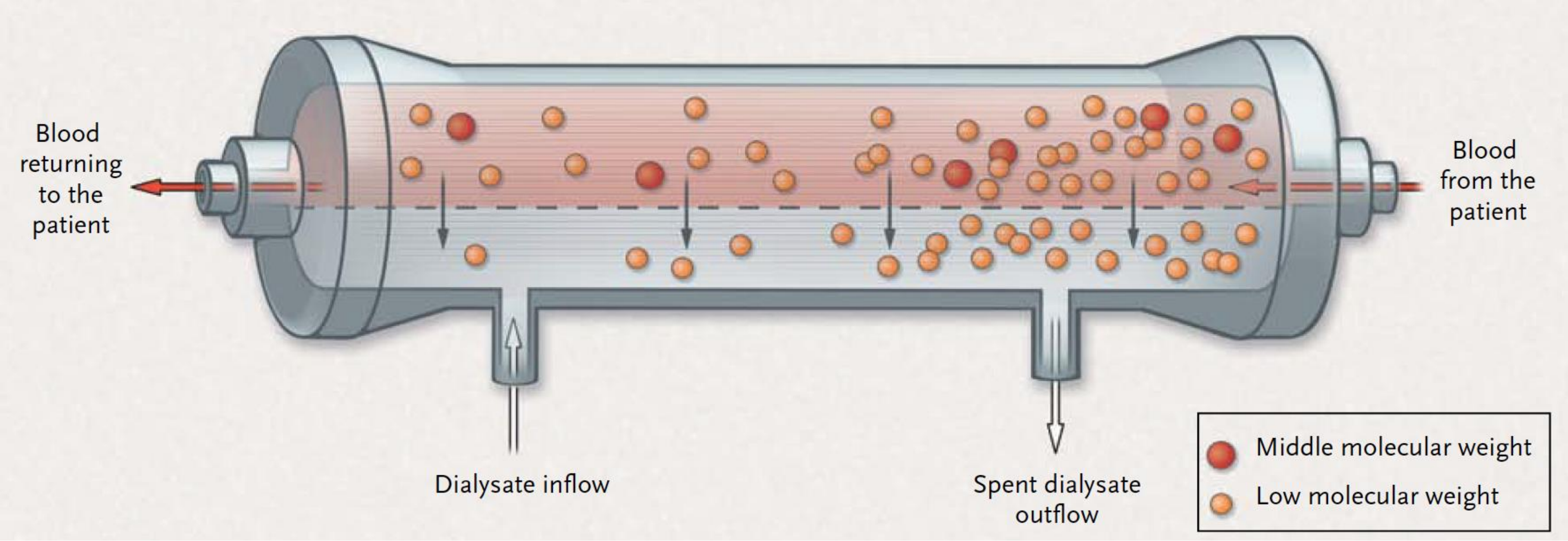


immune homeostasis

Honore et al. Ann. Intensive Care (2019) 9:56

Continuous VenoVenous HemoDfiltration (CVVHD)

- In **CVVHD**, dialysate is perfused across the external surface of the dialysis membrane, and solutes exit from blood to dialysate by diffusion down their concentration gradient.
- Ultrafiltration rates are relatively low compared with those in CVVH, permitting net negative fluid balance without the need for IV replacement fluids.



Tolwani A. N Engl J Med. 2012;367(26):2505-2514.

- Although commonly considered as a **purely diffusive therapy**, unmeasured bidirectional filtration into the dialysate compartment and back-filtration from dialysate to blood (driven by variation in the hemodynamic pressure gradient over the length of the hemodialysis fibers) result in **significant convective solute transport**.

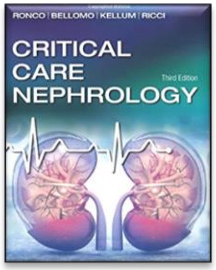
Continuous Renal Replacement Therapy: Modalities and Their Selection

Rinaldo Bellomo and Claudio Ronco

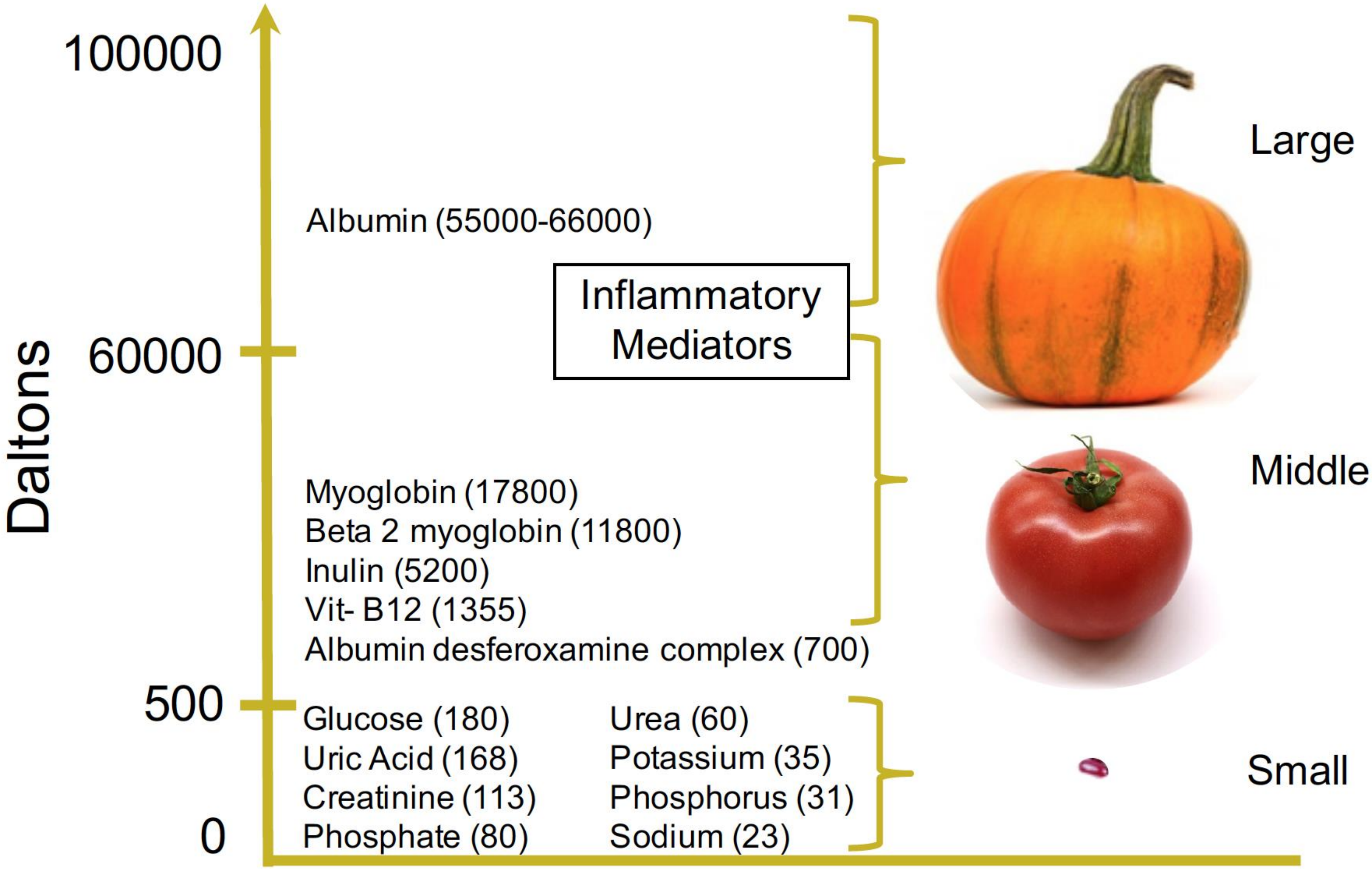
- Purely diffusive clearance is never possible because ultrafiltration is always necessary to **remove some solvent**.

- Accordingly, a degree of ultrafiltration with **convective** clearance always must occur, over a 24-hour cycle, even with **CVVHD.**

Ronco C, Bellomo R, Kellum JA, Ricci Z.
Critical Care Nephrology, 2018 - 3ED



Molecular Weights



Diffusive vs. convective therapy: Effects on mediators of inflammation in patients with severe systemic inflammatory response syndrome

- **CVVH** vs. **CVVHD (24 hr →24 hr)**, in terms of the removal of inflammatory mediators from the blood of patients with systemic inflammatory response syndrome and acute renal failure.

- Randomized crossover, clinical study.
- N=13

- **Convective clearance** (CVVH) or **diffusive clearance** (CVVHD) for the first **24 hrs**, followed by the other modality for 24 hrs.
- All treatments utilized **AN69 hemofilters**.

- **CVVH** was performed with an **ultrafiltration rate of 2 L/hr** and **CVVHD** with a **dialysis outflow** rate of **2 L/hr**.

Kellum AJ et al. Crit Care Med. 1998;26:1995-2000

CVVH was associated with a <u>13% decrease in plasma **TNF-alpha**</u> concentrations compared with a 23% increase while on **CVVHD** ($p < 0.05$).

The <u>clearances</u> for **IL-6** were different between therapies, 1.9 +/- 0.8 (SD) mL/min for **CVVHD** and 3.3 +/- 1.5 mL/min for **CVVH**, ($p < .01$).

Mediator	CVVH	CVVHD	*p* Value
Primary Analysis Only (n = 10)			
TNF-α	0.92 ± 0.12[a]	1.22 ± 0.54[a]	.038
IL-6	1.29 ± 0.50	1.63 ± 1.30	NS
IL-10	1.16 ± 0.39	1.13 ± 0.27	NS
sL-selectin	1.04 ± 0.13	0.99 ± 0.04	NS
Endotoxin	1.12 ± 0.45	1.21 ± 0.11	NS
All Patients (n = 13)			
TNF-α	0.87 ± 0.22[a]	1.23 ± 0.51[a]	.021
IL-6	1.19 ± 0.51	1.57 ± 1.25	NS
IL-10	1.10 ± 0.38	1.11 ± 0.27	NS
sL-selectin	1.03 ± 0.12	0.99 ± 0.04	NS
Endotoxin	1.13 ± 0.43	1.19 ± 0.20	NS

$[CK]_{PL}$

time-weighted mean percent changes

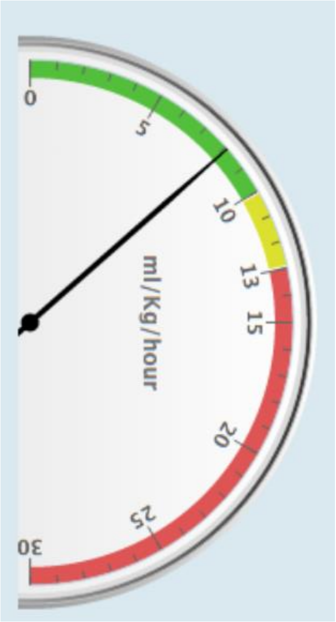
Kellum AJ et al. Crit Care Med. 1998;26:1995-2000

Renal Replacement Therapy With High-Cutoff Hemofilters: Impact of Convection and Diffusion on Cytokine Clearances and Protein Status

- This study compares **diffusive (CVVHD)** versus **convective (CVVH)** **high-cutoff (60 kd)** RRT in terms of *cytokine clearance rates* and effects on plasma protein levels

- **CVVHD**
  - **1** L/h dialysate flow rate
  - **2.5** L/h dialysate flow rate

- **CVVH**
  - **1** L/h ultrafiltration rate
  - **2.5** L/h ultrafiltration rate



Morgera S et al. 2004 Am J Kidney Dis 43:444-453.

Renal Replacement Therapy With High-Cutoff Hemofilters: Impact of Convection and Diffusion on Cytokine Clearances and Protein Status

CVVH achieved <u>significantly greater IL-1ra</u> clearance compared with **CVVHD** (P = 0.0003).

Increasing **ultrafiltration volume** or **dialysate flow** led to a highly <u>significant increase in IL-1ra and IL-6 clearance</u> rates (P < 0.00001).

Conclusion: High-cutoff RRT is a novel strategy to clear cytokines more effectively. **Convection** has an <u>advantage over diffusion</u> in the <u>clearance capacity</u> of IL-1ra, but is associated with greater plasma protein losses.

Morgera S et al. 2004 Am J Kidney Dis 43:444-453.

Renal Replacement Therapy With High-Cutoff Hemofilters: Impact of Convection and Diffusion on Cytokine Clearances and Protein Status

- CVVH achieved significantly greater IL-1ra clearance compared with CVVHD (P = 0.0003)

✓ **CVVH vs. CVVHD**

✓ **Higher dose vs. Lower dose**

…ificant

Co… …kines more effectively. **Convection** has an advantage over diffusion in the clearance capacity of IL-1ra, but is associated with greater plasma protein losses.

Morgera S et al. 2004 Am J Kidney Dis 43:444-453.

Research

Open Access

Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion

Zaccaria Ricci[1], Claudio Ronco[2], Alessandra Bachetoni[3], Giuseppe D'amico[4], Stefano Rossi[4], Elisa Alessandri[1], Monica Rocco[1] and Paolo Pietropaoli[5]

Prospective cross over study in a cohort of critically ill patients, comparing:

- Small (urea and creatinine) and middle (β2 microglobulin) molecular weight solute clearance
- Filter lifespan (polyacrylonitrile filters)

15 CVVH vs. 15 CVVHD

Prescription of 35 ml/kg/h

Ricci Z et al. Critical Care 2006, 10:R67

Research

Open Access

Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion

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- Median filter lifespan was significantly **longer** during **CVVHD** (37 hours, interquartile range (IQR) 19.5 to 72.5) than **CVVH** (19 hours, IQR 12.5 to 28) ($p = 0.03$).

- Median urea and creatinine clearances were **not significantly different** during **CVVH** and **CVVHD** ($p = 0.213$ and $p = 0.917$).

- Median β2m clearance was **higher** during **CVVH** than **CVVHD** ($p = 0.055$).

Ricci Z et al. Critical Care 2006, 10:R67

Renal Replacement Therapy With High-Cutoff Hemofilters: Impact of Convection and Diffusion on Cytokine Clearances

- ✓ CVVH = CVVHD for small molecules
- ✓ CVVH better than CVVHD for middle molecules
- ✓ Filter life is longer in CVVHD than CVVH

red ificant Co ines mo the cle sma protein losses.

Morgera S et al. 2004 Am J Kidney Dis 43:444-453.

1 The pertinent question is whether the differences in solute clearance generate differences in <u>outcomes</u> . . .

2 And which modalities are preferred all over the world?

1

The pertinent question is whether the differences in solute clearance generate differences in <u>outcomes</u> . . .

Optimal Mode of clearance in critically ill patients with Acute Kidney Injury (OMAKI) - a pilot randomized controlled trial of hemofiltration versus hemodialysis: a Canadian Critical Care Trials Group project

- Multicenter pilot **RCT** of **CVVH** vs. **CVVHD** in critically ill patients with AKI

- 35 ml/Kg/h

- The prescribed hourly ultrafiltration rate was **increased above 35 mL/kg/hr** to compensate for the **reduced efficiency of clearance** related to the pre-filter component of the replacement solution volume administered.

Dose = Postfilter RF rate + ((Prefilter RF rate × (Blood flow/(Blood flow + Prefilter RF rate))).

Wald R et al. Critical Care 2012, 16:R205

347 screened

- Inclusion criteria not met (n=31)
- Excluded due to:
- Receipt of RRT in preceding 2 months (n=43)
- Renal obstruction (n=3)
- Indication for intermittent RRT (n=22)
- Kidney transplant (n=3)
- Terminal illness or moribund patient (n=48)
- Enrollment in another ICU study (n=4)
- RRT ongoing for > 36 hrs (n=28)
- Other (n=32)
- Unknown (n=18)

↓

143 eligible

↓

79 patients enrolled

↓ Decision to use non-CRRT modality (n=1)

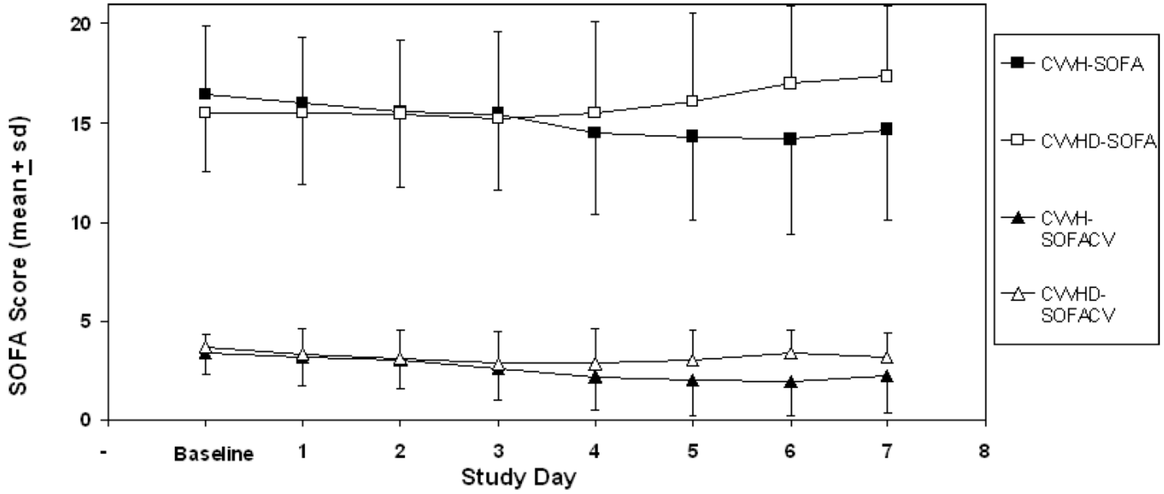
78 patients randomized

39 allocated to CVVH	39 allocated to CVVHD
-35 received CVVH -2 participants died before start of RRT -2 received a different form of CRRT	-38 received CVVHD -1 was withdrawn from trial due to inappropriate randomization
↓	↓
39 included in intention to treat analysis	38 included in intention to treat analysis
↓	↓
35 participants in final feasibility analysis	38 participants in final feasibility analysis

Wald R et al. Critical Care 2012, 16:R205

Clinical outcomes

- All subjects were followed to 60 days, by which point 22/39 (**56%**) and 21/38 (**55%**) of participants assigned to CVVH and CVVHD, respectively, had **died**.
- Over the first week of therapy, the adjusted change in the SOFA score among participants treated with CVVH compared to CVVHD was -0.8 (95% CI -2.1, 0.5). The observed reduction appeared to be driven by a reduction in the **cardiovascular component of the SOFA score**



CVVH	n =	35	35	32	29	24	19	17	12
CVVHD	n =	38	38	37	34	26	19	13	12

Number of participants at risk

Wald R et al. Critical Care 2012, 16:R205

RESEARCH Open Access

Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis

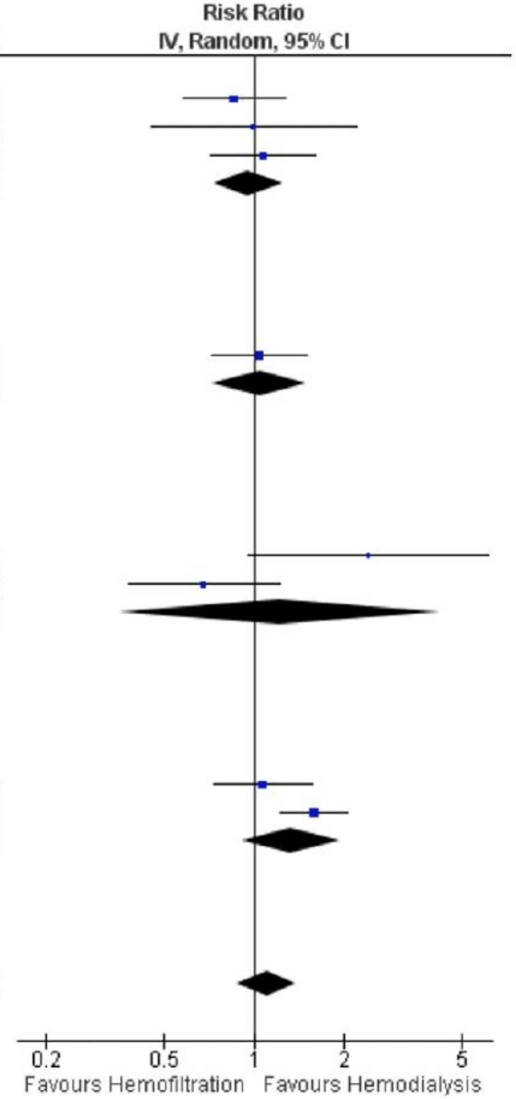
- The objective of this systematic review and meta-analysis was **to determine the effect of RRT**, delivered as hemofiltration vs. hemodialysis, **on clinical outcomes** in patients with AKI.

- 19 RCTs (10 parallel-group and 9 crossover) met inclusion criteria. **16 trials used continuous RRT**.

Friedrich JO et al. Crit Care 2012; 16: R146

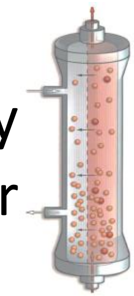
Effect of hemofiltration vs. hemodialysis RRT on mortality

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%						

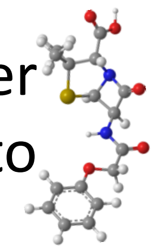


Friedrich JO et al. Crit Care 2012; 16: R146

- They found **no effect** of **hemofiltration** on **mortality** or **other clinical outcomes** (RRT dependence in survivors, vasopressor use, organ dysfunction) compared to **hemodialysis**.



- **Hemofiltration** appeared to <u>shorten time to filter failure</u> (by about five to six hours (or one-third of total mean filter time)



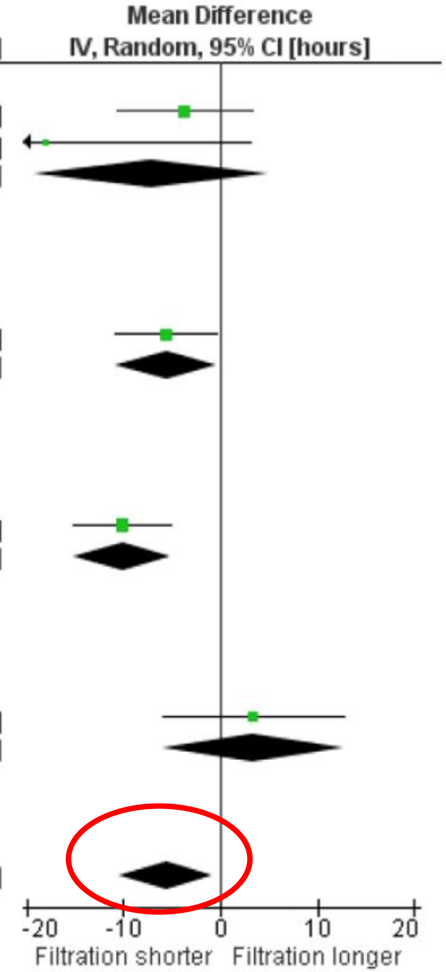
- **Hemofiltration** increased clearance of medium to larger molecules, including inflammatory cytokines, compared to **hemodialysis**.

Conclusions: Data from small RCTs <u>do not suggest beneficial clinical outcomes</u>. Hemofiltration may increase <u>clearance of medium to larger molecules</u>.

Friedrich JO et al. Crit Care 2012; 16: R146

Effect of hemofiltration vs. hemodialysis on filter life.

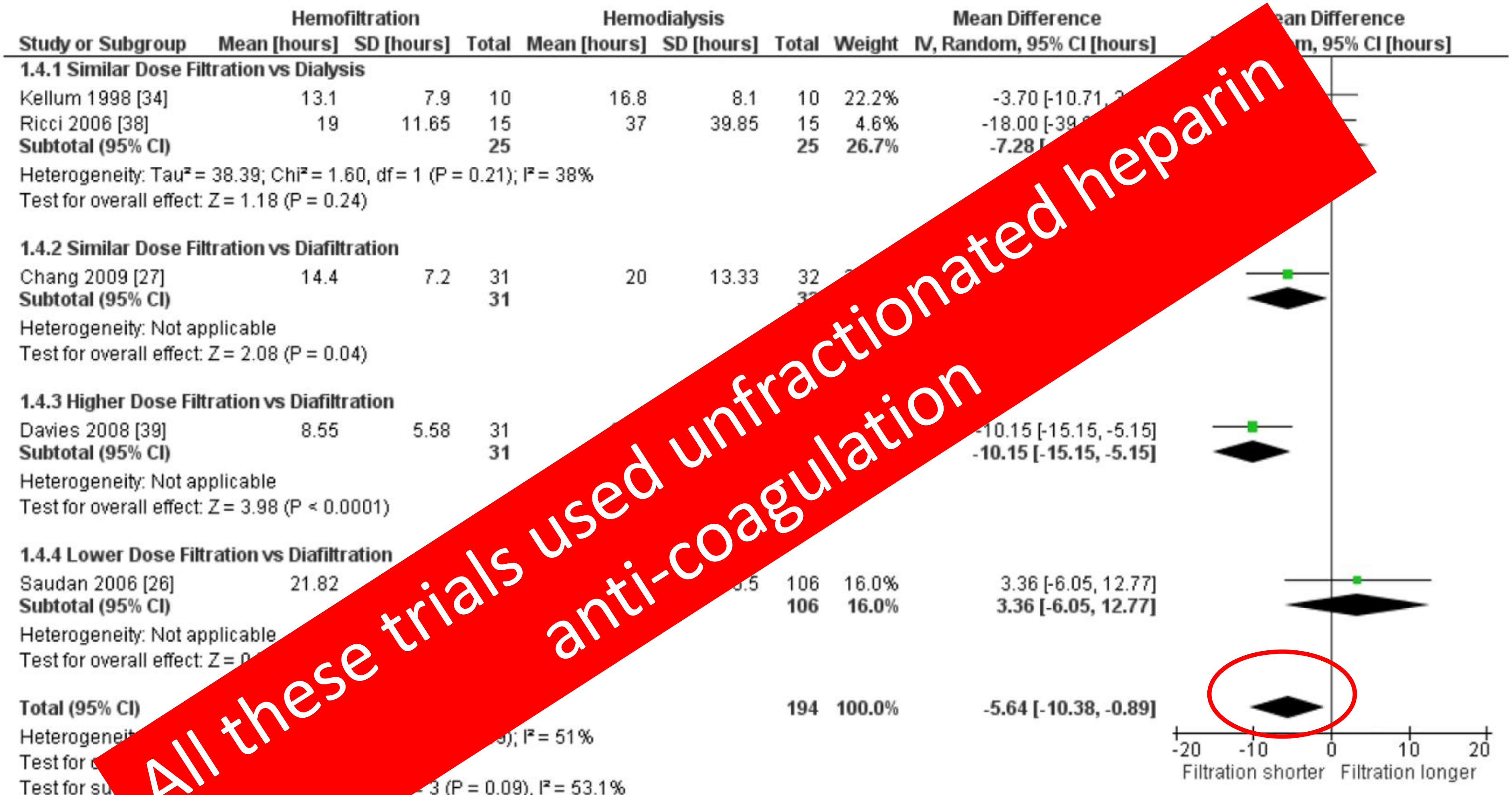
Study or Subgroup	Hemofiltration Mean [hours]	Hemofiltration SD [hours]	Hemofiltration Total	Hemodialysis Mean [hours]	Hemodialysis SD [hours]	Hemodialysis Total	Weight	Mean Difference IV, Random, 95% CI [hours]
1.4.1 Similar Dose Filtration vs Dialysis								
Kellum 1998 [34]	13.1	7.9	10	16.8	8.1	10	22.2%	-3.70 [-10.71, 3.31]
Ricci 2006 [38]	19	11.65	15	37	39.85	15	4.6%	-18.00 [-39.01, 3.01]
Subtotal (95% CI)			**25**			**25**	**26.7%**	**-7.28 [-19.42, 4.86]**
Heterogeneity: Tau² = 38.39; Chi² = 1.60, df = 1 (P = 0.21); I² = 38%								
Test for overall effect: Z = 1.18 (P = 0.24)								
1.4.2 Similar Dose Filtration vs Diafiltration								
Chang 2009 [27]	14.4	7.2	31	20	13.33	32	28.1%	-5.60 [-10.87, -0.33]
Subtotal (95% CI)			**31**			**32**	**28.1%**	**-5.60 [-10.87, -0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.08 (P = 0.04)								
1.4.3 Higher Dose Filtration vs Diafiltration								
Davies 2008 [39]	8.55	5.58	31	18.7	13.05	31	29.1%	-10.15 [-15.15, -5.15]
Subtotal (95% CI)			**31**			**31**	**29.1%**	**-10.15 [-15.15, -5.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.98 (P < 0.0001)								
1.4.4 Lower Dose Filtration vs Diafiltration								
Saudan 2006 [26]	21.82	33.72	102	18.46	35.5	106	16.0%	3.36 [-6.05, 12.77]
Subtotal (95% CI)			**102**			**106**	**16.0%**	**3.36 [-6.05, 12.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
Total (95% CI)			**189**			**194**	**100.0%**	**-5.64 [-10.38, -0.89]**
Heterogeneity: Tau² = 13.63; Chi² = 8.12, df = 4 (P = 0.09); I² = 51%								
Test for overall effect: Z = 2.33 (P = 0.02)								
Test for subgroup differences: Chi² = 6.40, df = 3 (P = 0.09), I² = 53.1%								



- Pooled data from two small crossover trials using similar dose CVVH vs. CVVHD suggest that **hemofiltration may shorten the time to filter failure.**
- This reduction in filter survival time of about one-third is equivalent to a 50% increase in filters required for hemofiltration compared to hemodialysis.

Friedrich JO et al. Crit Care 2012; 16: R146

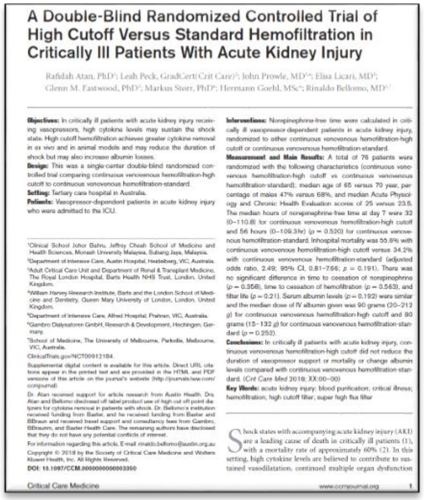
Effect of hemofiltration vs. hemodialysis on filter life.



All these trials used unfractionated heparin anti-coagulation

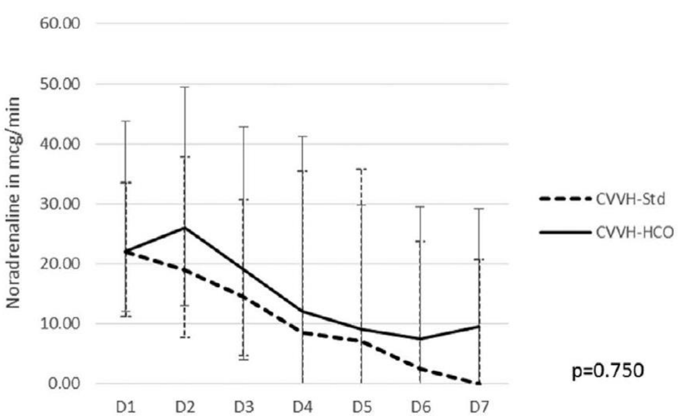
- Poo … om two small crossover trials using similar dose CVVH vs. CVVHD suggest that h … **ofiltration may shorten the time to filter failure.**
- This reduction in filter survival time of about one-third is equivalent to a 50% increase in filters required for hemofiltration compared to hemodialysis.

Friedrich JO et al. Crit Care 2012; 16: R146


A Double-Blind Randomized Controlled Trial of High Cutoff Versus Standard Hemofiltration in Critically Ill Patients With Acute Kidney Injury

- Phase II double blind randomized in critically ill patients with SI-AKI requiring vasopressor support.
- Primary end-point: **hemodynamic impact**.
- **CVVH-Std** or **CVVH-HCO**.

- Median cumulative <u>norepinephrine-free time and the maximum noradrenaline rates</u> of infusion per day were similar for both groups.
- Changes in cytokines levels was shown in a previous publication in which no significant between group differences in plasma levels for each cytokine over the 72 h treatment period were present.



Outcomes	Continuous Venovenous Hemofiltration-High Cutoff, *n* (%)	Continuous Venovenous Hemofiltration-Standard, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
ICU mortality	18 (50)	12 (31.6)	2.17 (0.84–5.58); $p = 0.109$	2.13 (0.69–6.65); $p = 0.191$
Hospital mortality	20 (55.6)	13 (34.2)	2.40 (0.94–6.15); $p = 0.067$	2.49 (0.81–7.66); $p = 0.112$

Atan R et al. Crit Care Med. 2018;46:e988-e994

REVIEW Open Access

Cytokine removal in human septic shock: Where are we and where are we going?

Patrick M. Honore[1*], Eric Hoste[2], Zsolt Molnár[3], Rita Jacobs[4], Olivier Joannes-Boyau[5], Manu L. N. G. Malbrain[4,6] and Lui G. Forni[7,8]

Rationale for cytokine removal

- The enhanced inflammatory response seen in septic shock is associated with a high mortality correlated with the production of pro- and anti-inflammatory mediators rather than disequilibrium between proand anti-inflammatory mediators

(Monneret G et al. Immunol Lett. 2004;95:193–8)
(Frencken JF et al. Crit Care Med. 2017;45:e493–9)
(Kellum JA et al. Arch Intern Med. 2007;167:1655–63)

- This has stimulated much effort towards potential attenuation of this response particularly as early studies suggested that continuous veno-venous haemofiltration (**CVVH**) may reduce cytokine levels.

(De Vriese AS, et al. J Am Soc Nephrol. 1999;10:846–53)

However . . .

early observations have not translated into clinical benefit.

Honore et al. Ann. Intensive Care (2019) 9:56

Given the pivotal role of cytokine production in sepsis, it follows that **removal of these substances**, through such **BPT**, may attenuate the response particularly in the early phase of sepsis.

(Ronco C et al. Artif Organs. 2003;27(9):792–801)

Despite early promise, no multicentre RCT have demonstrated a **survival benefit** including the use of **HVHF** where higher flows may lead to increased cytokine removal were tried

(Lukaszewicz AC et al. Crit Care. 2013;17:159)
(Cole L et al.Intensive Care Med. 2001;27:978–86)
(Honore PM et al. Crit Care Med. 2000;28:3581–7)

Other extracorporeal BPTs also have failed with significant outcome data lacking with no treatment demonstrating a translatable survival benefit in any randomized controlled study.

Joannes-Boyau O et al. Care Med. 2013;39:1535–46.
Clark E et al. Crit Care. 2014;18:R7.
Cavaillon JM et al.Circ Shock. 1992;38(2):145–52.

Honore et al. Ann. Intensive Care (2019) 9:56

1 The pertinent question is whether the differences in solute clearance generate differences in <u>outcomes</u> . . .

2 And which modalities are preferred all over the world?

And which modalities are preferred all over the world?

Continuous renal replacement therapy: current practice in Australian and New Zealand intensive care units

Nigel Fealy, Leanne Aitken, Eugene du Toit and Ian Baldwin

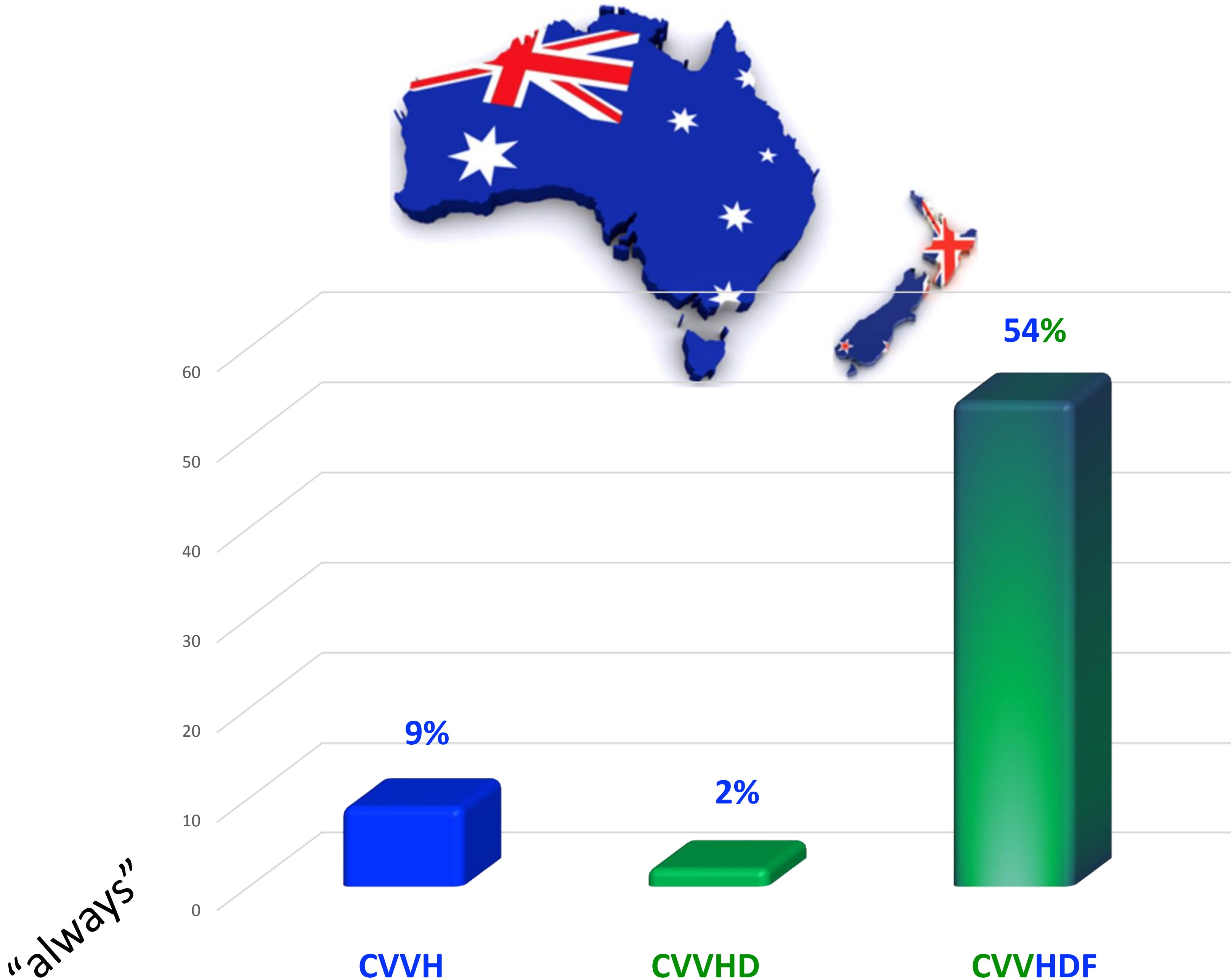
Design and setting:

- A prospective online survey of CRRT practice
- Australian and New Zealand ICUs
- December 2013 to March 2014

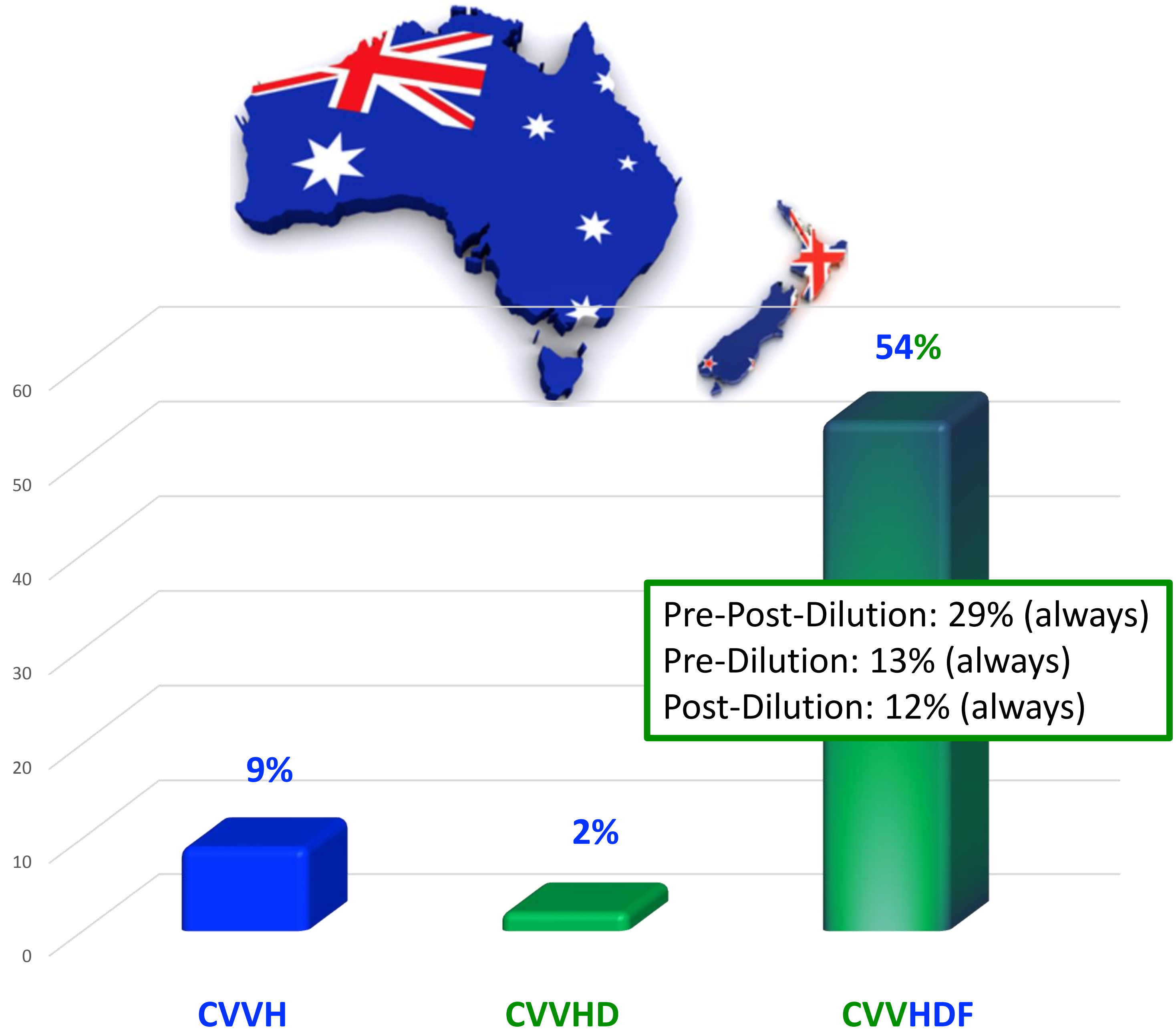
106 ICUs

194 respondents

Fealy et al. Crit Care Resusc 2015; 17: 83–91



Fealy et al. Crit Care Resusc 2015; 17: 83–91



Fealy et al. Crit Care Resusc 2015; 17: 83–91

Continuous renal replacement therapy: A worldwide practice survey

The Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

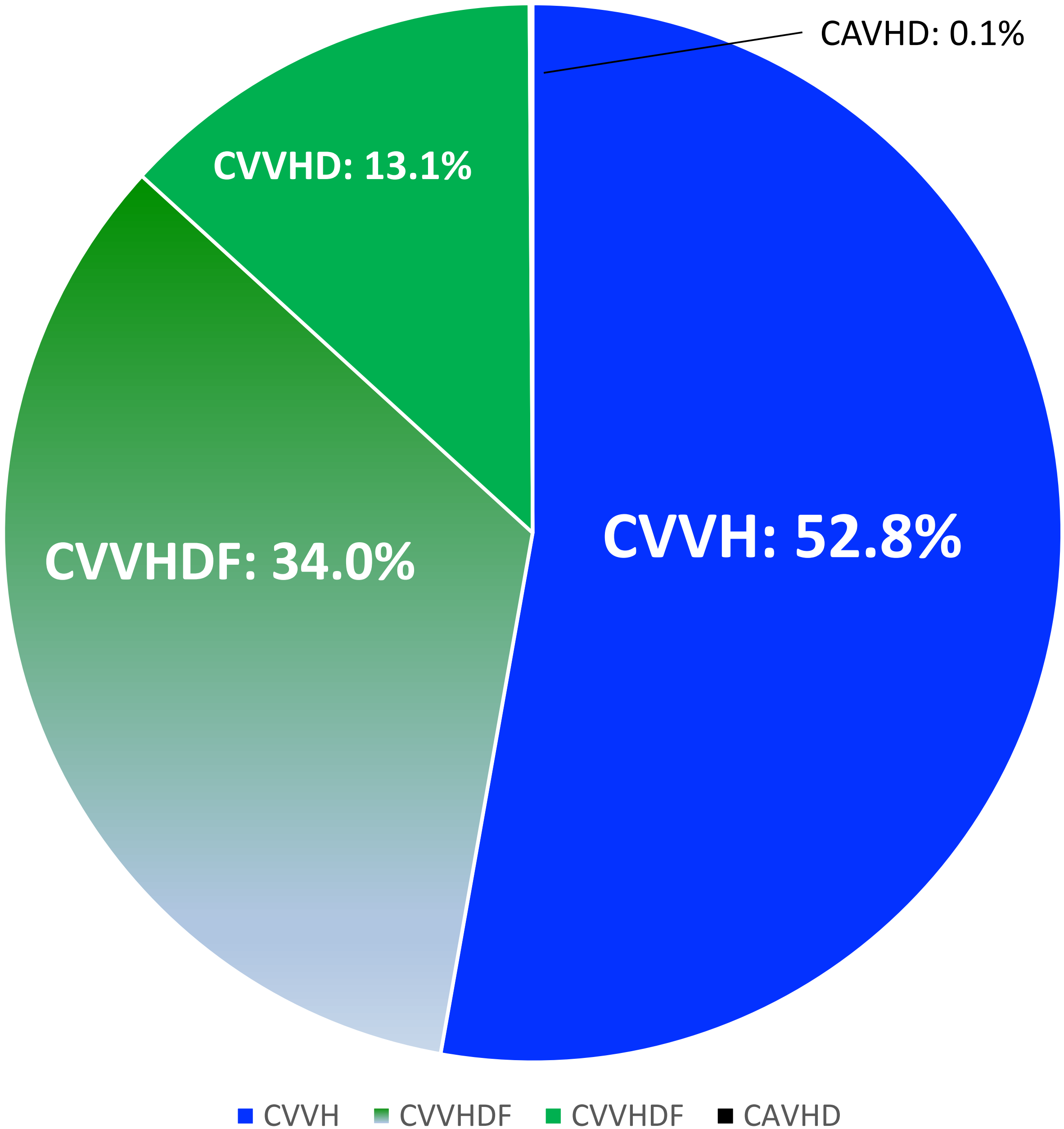
- The **B.E.S.T. Kidney** (**B**eginning and **E**nding **S**upportive **T**herapy for the **K**idney) study is a multicenter, multinational, prospective, epidemiological study that aims to understand multiple aspects of ARF at an international level

- 54 centers in **23 countries** (**2000-2001**) → 1006 subjects treated with CRRT

- We sought to **investigate** several aspects of **CRRT practice** in a multinational, multicenter setting.

- All patients except one were treated with a venovenous technique.

Uchino S et al. Intensive Care Med (2007) 33:1563–1570

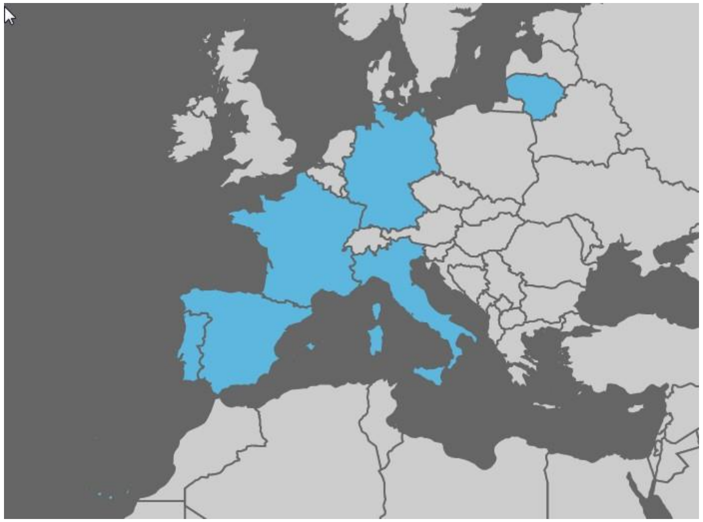


Uchino S et al. Intensive Care Med (2007) 33:1563–1570

The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients

F. Garzotto[1,2*], M. Ostermann[3], D. Martín-Langerwerf[4], M. Sánchez-Sánchez[5], J. Teng[6], R. Robert[7], A. Marinho[8], M. E. Herrera-Gutierrez[9], H. J. Mao[10], D. Benavente[11], E. Kipnis[12], A. Lorenzin[2], D. Marcelli[13], C. Tetta[13], C. Ronco[1,2] and for the DoReMIFA study group

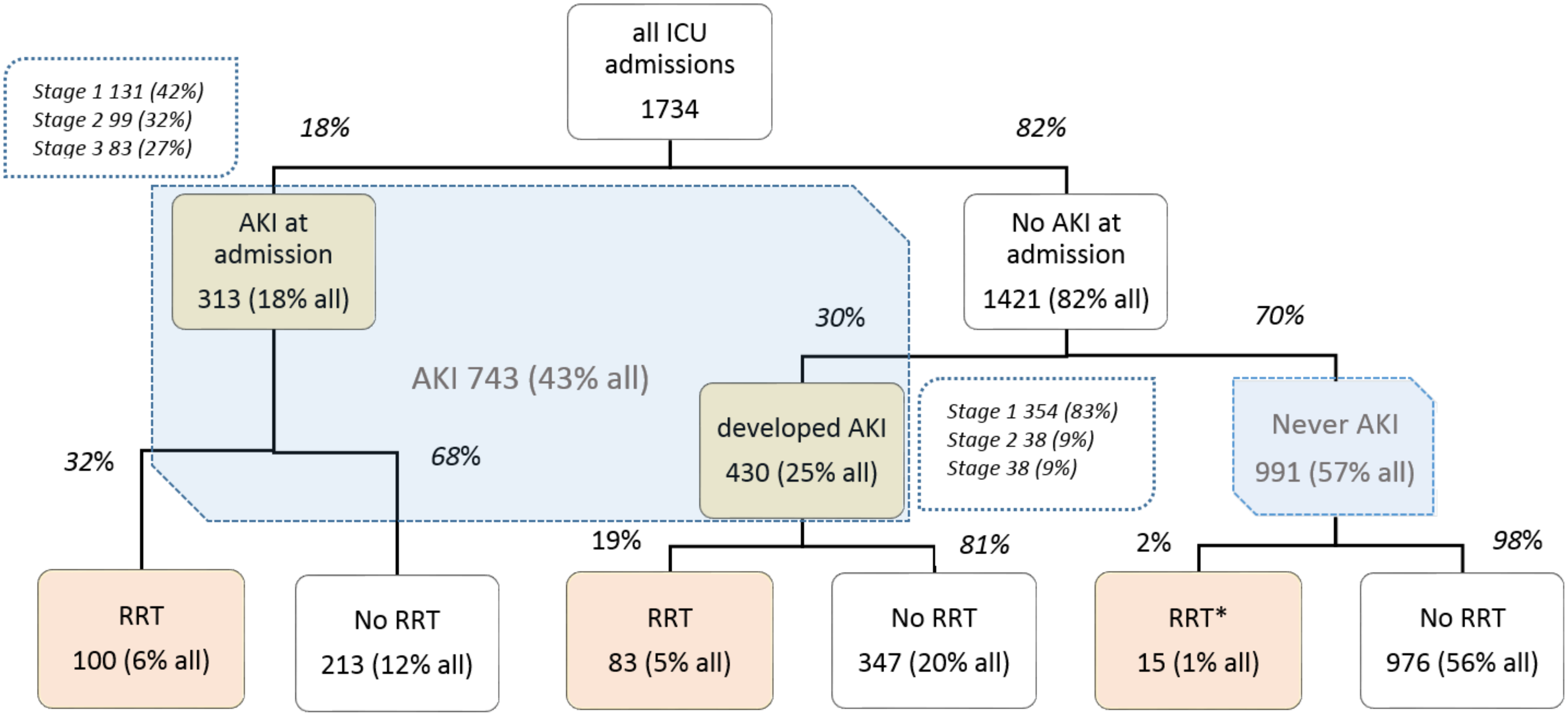
Population: Adult patients admitted to intensive care units (any type) , with anticipated ICU stay >48hrs



1734 patients
21 Centers
10 Countries

Courtesy Prof. Marlies Ostermann & Eng. Francesco Garzotto

Garzotto F et al. Critical Care (2016) 20:196



***Reasons for RRT initiation**
Never AKI 992
AKI 743
Stage 1 485
Stage 2 137
Stage 3 121 * Only for Cr criteria*
AKI wit RRT 183
AKI without RRT 560
RRT 198

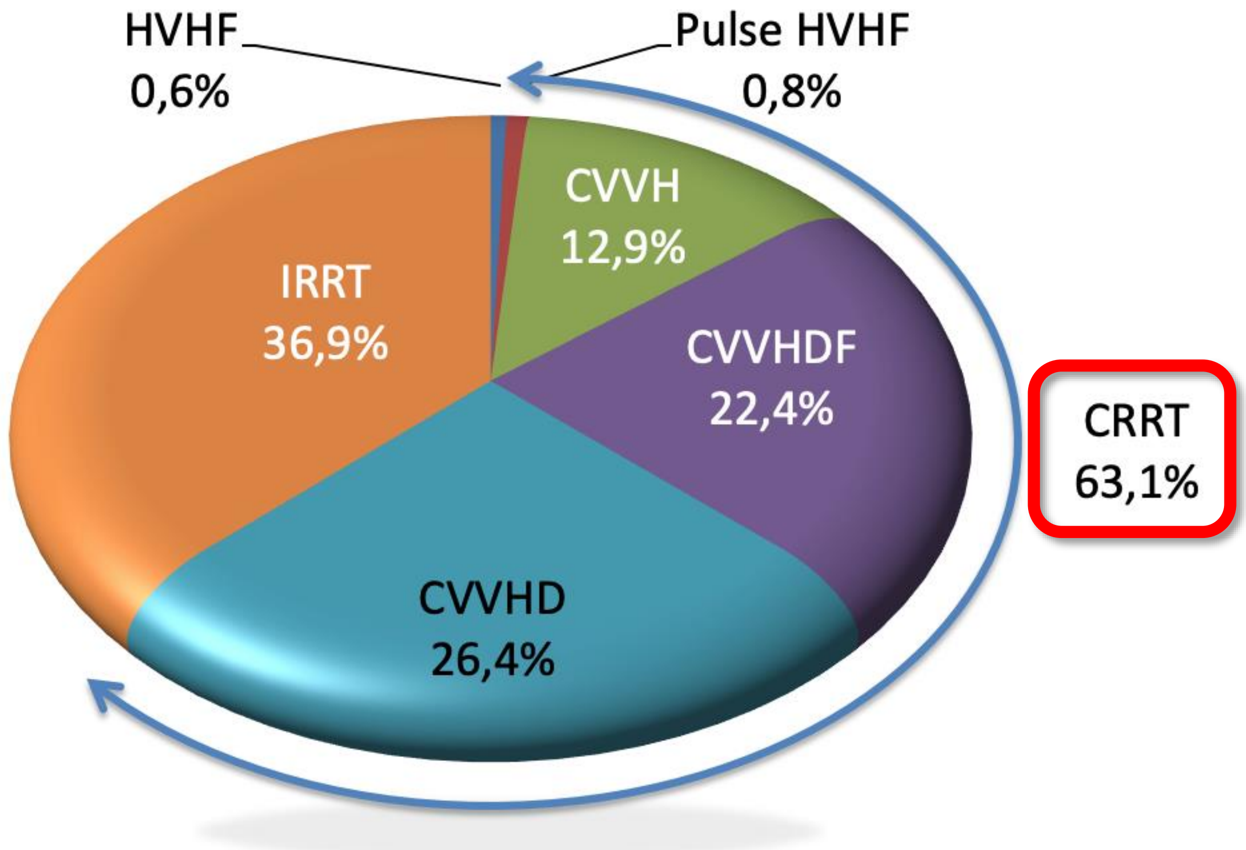
RRT = 198

***Reasons for RRT initiation**
Treatment/ prevention of FO 27%
Azotemia &/or electrolyte imb. 27%
Both 13%
Sepsis 7%
Oligo-anuria 20%
Creatinine/Urea 0
Drugs/Intoxication 0
Other 7%

Courtesy Prof. Marlies Ostermann & Eng. Francesco Garzotto

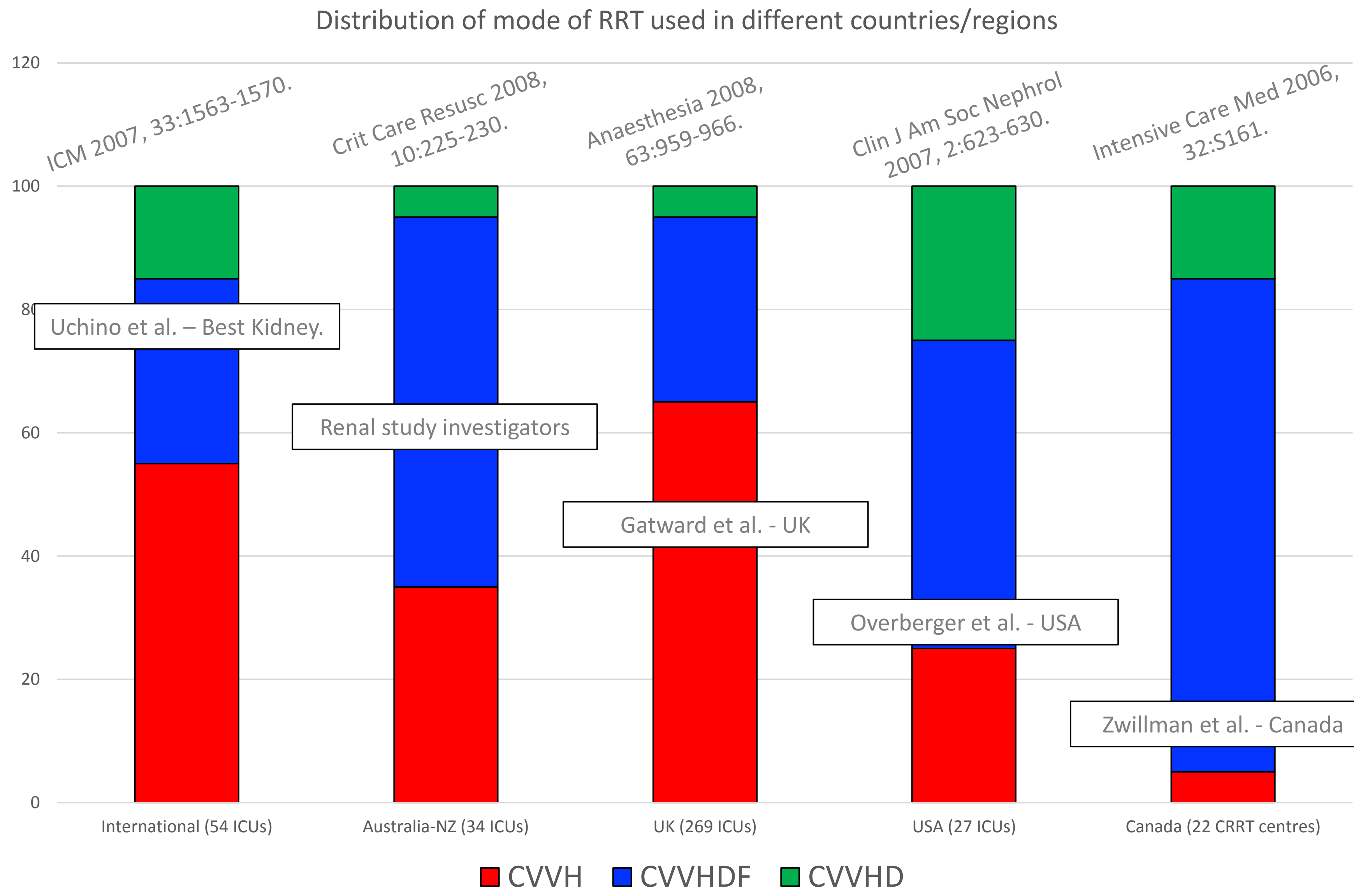
Garzotto F et al. Critical Care (2016) 20:196

Modality of RRT (all sessions)

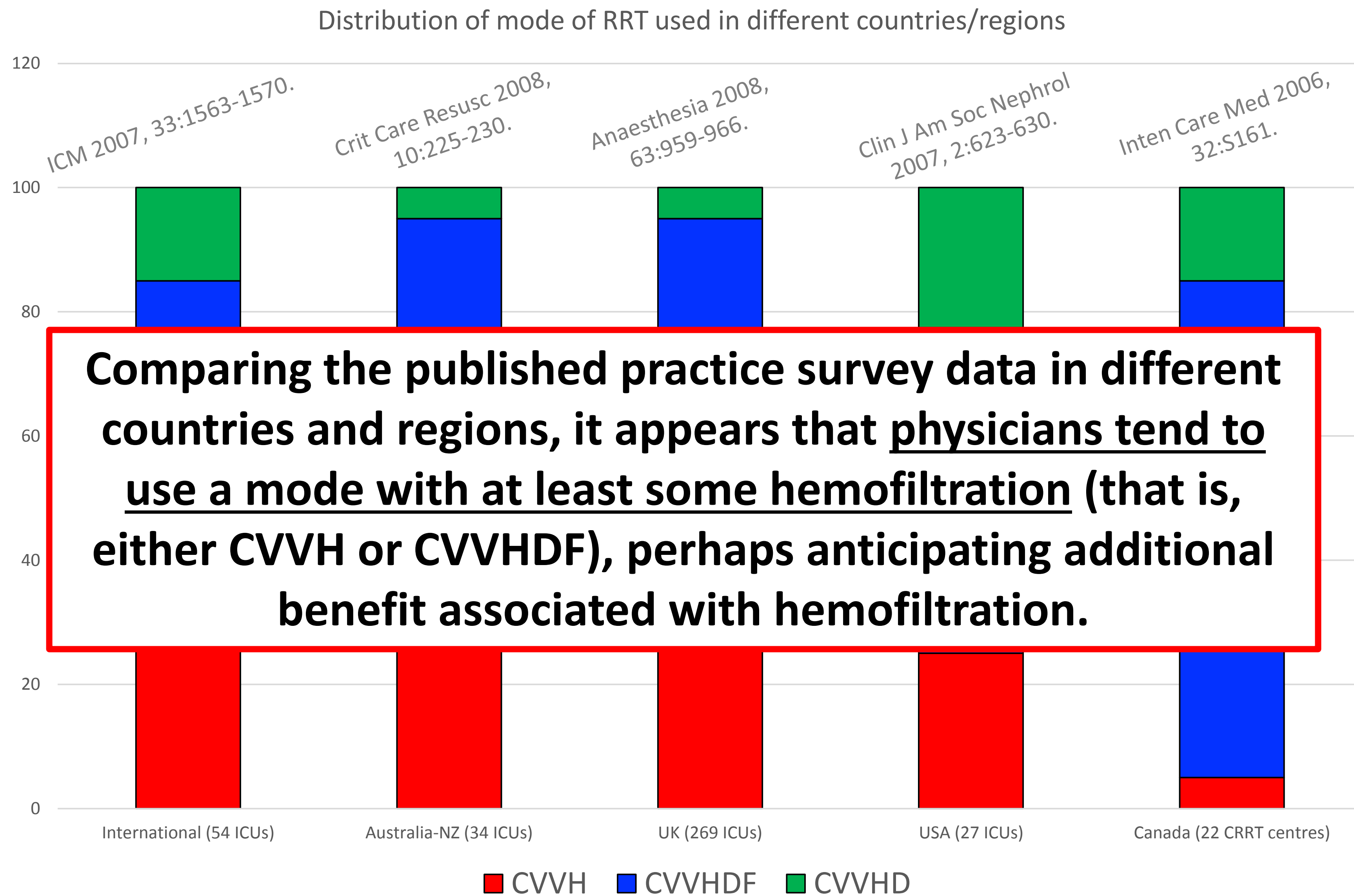


Courtesy Prof. Marlies Ostermann &
Eng. Francesco Garzotto

Garzotto F et al. Critical Care (2016) 20:196



Friedrich JO et al. Crit Care 2012; 16: R146



Comparing the published practice survey data in different countries and regions, it appears that physicians tend to use a mode with at least some hemofiltration (that is, either CVVH or CVVHDF), perhaps anticipating additional benefit associated with hemofiltration.

Friedrich JO et al. Crit Care 2012; 16: R146

The essential conclusions from the meta-analysis are that **we do not have a sufficient database at present to recommend one procedure over the other**.

NHS Evidence Accreditation Mark

‘**choice of RRT modality** should be guided by the individual patient’s clinical status, medical and nursing expertise, and availability of modality’.

However, the question is whether a ‘definitive’ prospective RCT in **unselected** populations with AKI will actually help to resolve this issue.

Jörres A. Critical Care 2012, 16:147

- Moreover, the question of RRT '**dose**' is inextricably linked with the choice of modality.
- If replacement **fluid is added pre-filter** in order to limit hemoconcentration and clotting risk, total treatment volumes must be increased by 20% to 30% to achieve equivalent clearance of small solutes.
- **Anticoagulation** may matter !

More likely, future studies will have to address the question of whether **there are specific subgroups of patients** who might benefit from convective therapies (e.g. myoglobinuric or septic AKI patients in whom the *enhanced removal of myoglobin or cytokines* by hemofiltration might help to improve clinical course and renal recovery).

Jörres A. Critical Care 2012, 16:147

So finally . . . CVVH?, CVVHD?, CVVHDF?

- **SCUF** could be considered in conditions with isolated volume overload, such as heart or liver failure, malnutrition, capillary leak syndromes, or in patients who have become resistant to diuretics.
- Isolated electrolyte abnormalities can be managed with hemodialysis **CVVHD**.

Alvarez G et al. Can J Anaesth. 2019;66:593-604

- Although it has been suggested that the augmented clearance of higher molecular weight solutes (e.g. pro-inflammatory cytokines) provided by **CVVH** might be beneficial, this has not been borne out in clinical practice.

Friedrich JO et al. Critical Care. 2012;16(4): R146
Payen D et al. Crit Care Med. 2009;37(3):803-810.
Joannes-Boyau O et al. Intensive Care Med. 2013;39(9):1535-1546.

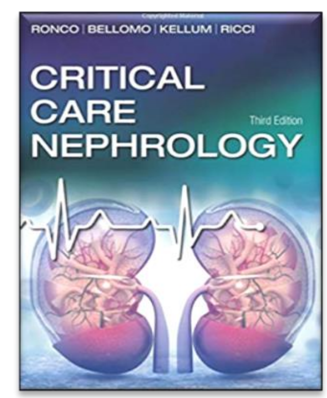
- Thus, choice of CRRT modality (CVVH, CVVHD, or CVVHDF) is primarily **a function of provider preference** rather than patient characteristics or objective outcome data.

Tandukar S & Palewsky PM. CHEST 2019;155:626-638

Continuous Renal Replacement Therapy: Modalities and Their Selection

Rinaldo Bellomo and Claudio Ronco

- No matter what technique is used, the clinician needs to **understand** the solute clearance implications of using one versus the other (**convection-diffusion-combination**) and the solute clearance implications of using so-called **predilution** or **postdilution**.



Ronco C, Bellomo R, Kellum JA, Ricci Z. Critical Care Nephrology, 2018 - 3ED ndt digest

Acute kidney injury: to dialyse or to filter?

Zaccaria Ricci[1,*], Stefano Romagnoli[2] and Claudio Ronco[3,4]

- **Selected patients** (e.g. in the septic shock phase of **hypercytokinaemia**) may actually benefit from aggressive removal of specific solutes, likely better controlled by **continuous haemofiltration**.

- However, compared with **continuous haemofiltration**, **continuous haemodialysis** showed a **decrease in average filter life** (however, most of these studies were conducted in the absence of citrate anticoagulation).

- As a **practical approach**, in order to achieve advantages from both techniques, the **haemodiafiltration modality could be set**.

Ricci Z et al. Nephrol Dial Transplant (2019) 1–3

THANKS!

Stefano Romagnoli, MD, PhD

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Dip. di Anestesia e Rianimazione - AOU Careggi - Firenze

Table 2 Fluids and flows in continuous renal replacement therapy

Flowrate	Symbol	Unit of measure	Definitions and comments
Blood flowrate	Q_B	ml/min	Depends on: - modality - vascular access - hemodynamic stability of the patient
Plasma flowrate	Q_P	ml/min	Approximated as: $Q_P = (1 - HCT) \quad Q_B$ where HCT = hematocrit
Ultrafiltration flowrate	Q_{UF}	ml/h	Total volume of fluid removed in the filter by positive TMP per unit of time: $Q_{UF} = Q_{UF}^{NET} + Q_R$. Depends on: - blood flow rate - filter and membrane design - transmembrane pressure (TMP) - membrane ultrafiltration coefficient and surface area
Net ultrafiltration flowrate (Δ weight flowrate) (weight loss flowrate)	Q_{UF}^{NET}	ml/h	Net volume of fluid removed from the patient by the machine per unit of time
Plasma ultrafiltration flow rate	Q_{P-UF}	ml/h	Total volume of plasma removed in the plasma filter by TMP per unit of time
Replacement flowrate (Substitution flow rate) (Infusion flowrate)	Q_R^{PRE} Q_R^{POST} $Q_R^{PRE/POST}$	ml/h	Sterile fluid replacement can be: - upstream of filter (pre-replacement, pre-infusion or pre-dilution): reduced depurative efficiency but better filter life - downstream of filter (post-replacement, post-infusion or post-dilution): higher depurative efficiency but lower filter life - both upstream and downstream of filter (pre-post replacement, pre-post infusion or pre-post dilution): compromise between the two modalities
Replacement plasma flow rate	Q_{P-R}	ml/h	Replacement of plasma downstream of the plasma filter
Dialysate flowrate	Q_D	ml/h	Volume of dialysis fluid running into the circuit per unit of time
Effluent flowrate	Q_{EFF}	ml/h	Waste fluid per unit of time coming from the outflow port of the dialysate/ ultrafiltrate compartment of the filter: $Q_{EFF} = Q_{UF} + Q_D = Q_{UF}^{NET} + Q_R + Q_D$

Neri et al. Critical Care (2016) 20:318

Table 1 Main disposables and their components with associated color code in a CRRT extracorporeal circuit (modified from [45])

Tubes	
Blood in-flow line (red; previously known as access or arterial line)	Segment connecting the patient's vascular access to the filter
	Segment for pressure measurement (upstream blood pump): segment of the blood in-flow line connected to the in-flow pressure sensor
	Pump segment line: segment inserted between the rotor and the stator of the blood pump
	Blood in-flow air removal chamber: allows removal of light air bubbles before the blood enters the filter
	Segment for pressure measurement (downstream blood pump): segment of the blood in-flow line connected to the pre-filter pressure sensor
Blood out-flow line (dark blue; previously known as return or venous line)	Segment connecting the filter to the patient's vascular access
	Segment for pressure measurement: segment of the blood out-flow line connected to the out-flow pressure sensor
	Blood out-flow air removal chamber: allows removal of light air bubbles before the blood returns to the patient
Effluent/ultrafiltrate line (yellow)	Segment that allows the flow of waste fluids from the filter
	Pump segment line: segment inserted between the rotor and the stator of the effluent/ultrafiltrate pump
	Segment for pressure measurement: segment of the effluent line connected to the effluent/ultrafiltrate pressure sensor
Dialysate line (green)	Segment that allows the flow of incoming dialysate into the filter
	Pump segment line: segment inserted between the rotor and the stator of the dialysate pump
	Segment for pressure measurement (if present): segment of the dialysate line connected to the dialysate pressure sensor
	Heater line: segment of the dialysate line placed in contact with the heater
Replacement line (purple or light blue)	Segment that allows the flow of replacement fluid into the blood in-flow and/or blood out-flow lines
	Pump segment line: segment inserted between the rotor and the stator of the replacement pump
	Segment for pressure measurement (if present): segment of the replacement line connected to the replacement pressure sensor
	Heater line: segment of the replacement line placed in contact with the heater
Pre-blood line (orange)	Segment that allows the flow of specific fluids (mainly regional anticoagulants) into the blood in-flow line before the blood pump
	Pump segment line: segment inserted between the rotor and the stator of the pre-blood pump
	Segment for pressure measurement (if present): segment of the pre-blood line connected to the pre-blood pressure sensor
Anticoagulant and specific antagonists line	Segments connecting the anticoagulant/specific antagonist bag or pump to the main blood circuit
	Citrate line (orange): segment for citrate infusion (i.e., pre-blood line)
	Heparin line (white): segment connecting the heparin syringe pump to the blood in-flow line
	Specific antagonist line (black): segment connecting the specific antagonist syringe pump to the blood out-flow line

	the blood out-flow line
Filter	
Fiber (membranes)	Every fiber, hollow and of cylindrical shape, allows the transport of fluids and solutes through their porous semi-permeable surface
Bundle	Entire number of fibers inside the housing
Housing	Plastic casing containing a single membrane fiber bundle
	Blood in-flow port: entrance port of blood entering into the filter
	Blood out-flow port: exit port of blood leaving the filter
	Dialysate in-flow port: entrance port of fresh dialysate
	Effluent/ultrafiltrate out-flow port: exit port of waste solution
Potting	Polyurethane component fixing the bundle within the housing and embedding the bundle at both ends of the filter

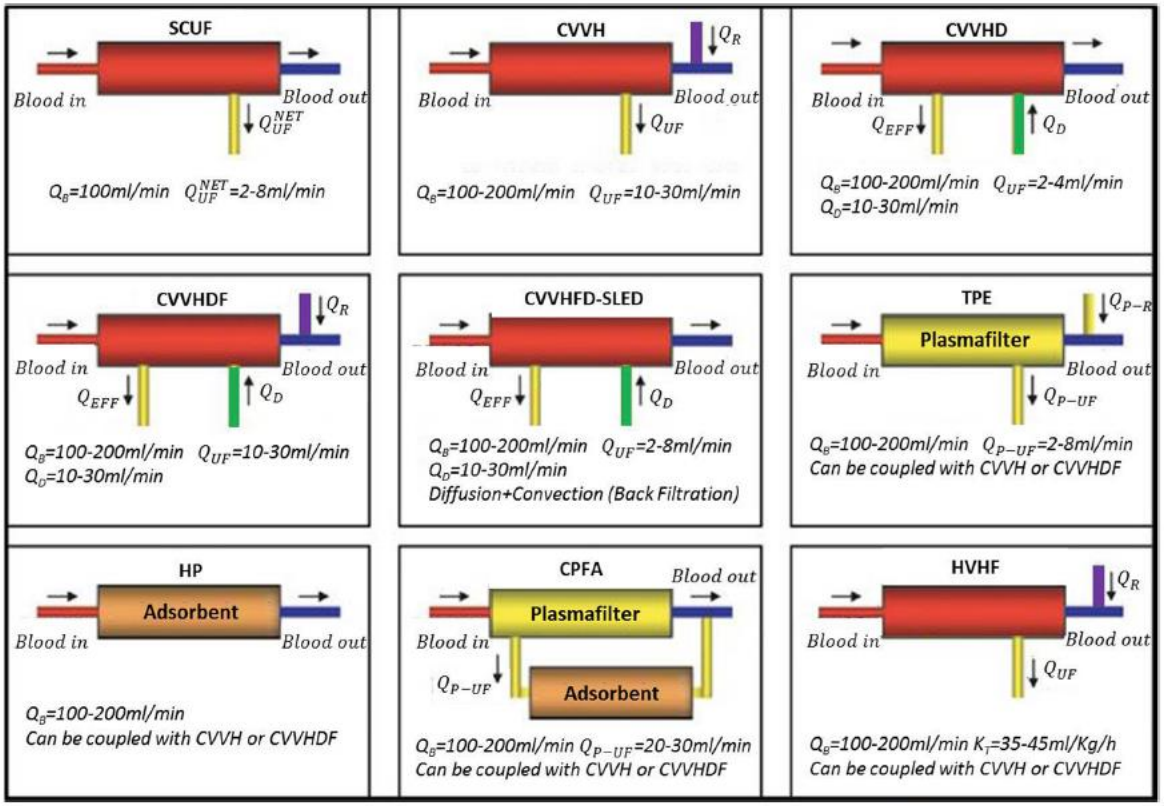

Fig. 2 Main extracorporeal therapies and treatments (modified from [5]) *Abbreviations*: Q_B blood flow rate, Q_{UF}^{NET} net ultrafiltration flow rate, Q_{UF} ultrafiltration flow rate, Q_D dialysate flow rate, Q_R total replacement flow rate, Q_{EFF} effluent flow rate, $Q_{P\text{-}R}$ replacement plasma flow rate, $Q_{P\text{-}UF}$ plasma ultrafiltration flow rate, *SCUF* slow continuous ultrafiltration, *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodialysis, *CVVHDF* continuous veno-venous hemodiafiltration, *CVVHFD-SLED* continuous veno-venous high-flux dialysis–sustained low-efficiency dialysis, *TPE* therapeutic plasma exchange, *HP* hemoperfusion, *CPFA* continuous plasma filtration coupled with adsorption, *HVHF* high-volume hemofiltration

FLOW RATE	SYMBOL	UNIT OF MEASURE
Blood flow rate	Q_B	ml/min
Plasma flow rate	Q_P	ml/min
Replacement flow rate (Substitution flow rate) (Infusion flow rate)	Q_R^{PRE} Q_R^{POST} $Q_R^{PRE/POST}$	ml/h
Net ultrafiltration flow rate	Q_{UF}^{NET}	ml/h
Ultrafiltration flow rate	Q_{UF}	ml/h
Dialysate flow rate	Q_D	ml/h
Effluent flow rate	Q_{EFF}	ml/h