Renal Replacement Therapy in the Critically Ill Patient when, how and which modality

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Acute kidney injury (AKI) has a significant association with high mortality in critically ill patients.

Acute renal replacement therapy (RRT) provides supportive management
for patients with severe AKI and multiorgan failure (MOF).

Continuous renal replacement therapy (CRRT), in particular, is utilised for a haemodynamically unstable patient with AKI in an intensive care unit (ICU) setting.

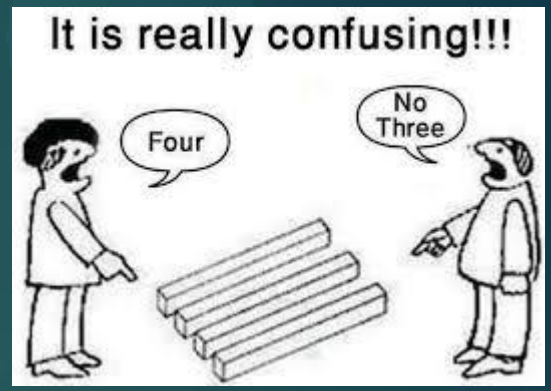
Classification of AKI severity by KDIGO is based on both:
the rate of change in serum creatinine and
change in urine output (UOP).

1- HOSTE EA, CLERMONT G, KERSTEN A, VENKATARAMAN R, ANGUS DC, DE BACQUER D, ET AL. RIFLE CRITERIA FOR ACUTE KIDNEY INJURY ARE ASSOCIATED WITH HOSPITAL MORTALITY IN CRITICALLY ILL PATIENTS: A COHORT ANALYSIS. CRITICAL CARE. 2006;10(3):R73.

2. BAGSHAW SM, LAUPLAND KB, DOIG CJ, MORTIS G, FICK GH, MUCENSKI M, ET AL. PROGNOSIS FOR LONG-TERM SURVIVAL AND RENAL RECOVERY IN CRITICALLY ILL PATIENTS WITH SEVERE ACUTE RENAL FAILURE: A POPULATION-BASED STUDY. CRITICAL CARE. 2005;9(6):R700.

A 66 yo man with history of DM, HTN, underwent laparotomy due to peritonitis. During operation he suffers cardiac arrest, which returns by resuscitation. He admitted to ICU, at that time UO was 300 mL/24Hr and serum creatinine begins to rise (1 to 2 then 3 mg/dL). Serum K is 4 meq/L. his general condition is good, no dyspnea, no fever, and BP is 100/80 mmHg. No urine was increased after administration of frusemide.

The surgeon inserts a CVP line. It was 8 mmHg.



How to manage this case?

1- is it reasonable to start Dialysis or it is better to wait?
2- which kind of dialysis technic must choose for him?
3- in case of beginning dialysis which dose must be considered?
4- if we start dialysis earlier, what impact will it have on the patient's mortality rate over the next 3 months?

1-Timing of RRT

Timing of initiating RRT in critically ill patients with AKI, in the absence of absolute indications, is challenging.

There is a general trend to initiate RRT before a patient develops absolute indications in the ICU setting.

Table 1: Conventional indications for renal replacement therapy.

1.1. Fluid overload resistant to diuretic therapy
1.2. Metabolic acidosis (pH < 7.15) refractory to medical management
1.3. Hyperkalaemia (K > 6.5 mEq/L) refractory to medical management
1.4. Uraemic symptoms or signs (encephalopathy, pericarditis, and bleeding diathesis)
Other important indications for RRT
1.5. Poisoning with a dialyzable drug or toxin
1.6. Hyperthermia refractory to regular cooling techniques
1.7. Life-threatening electrolyte derangements in the setting of acute kidney injury
1.8. Progressive azotaemia or oliguria unresponsive to medical management

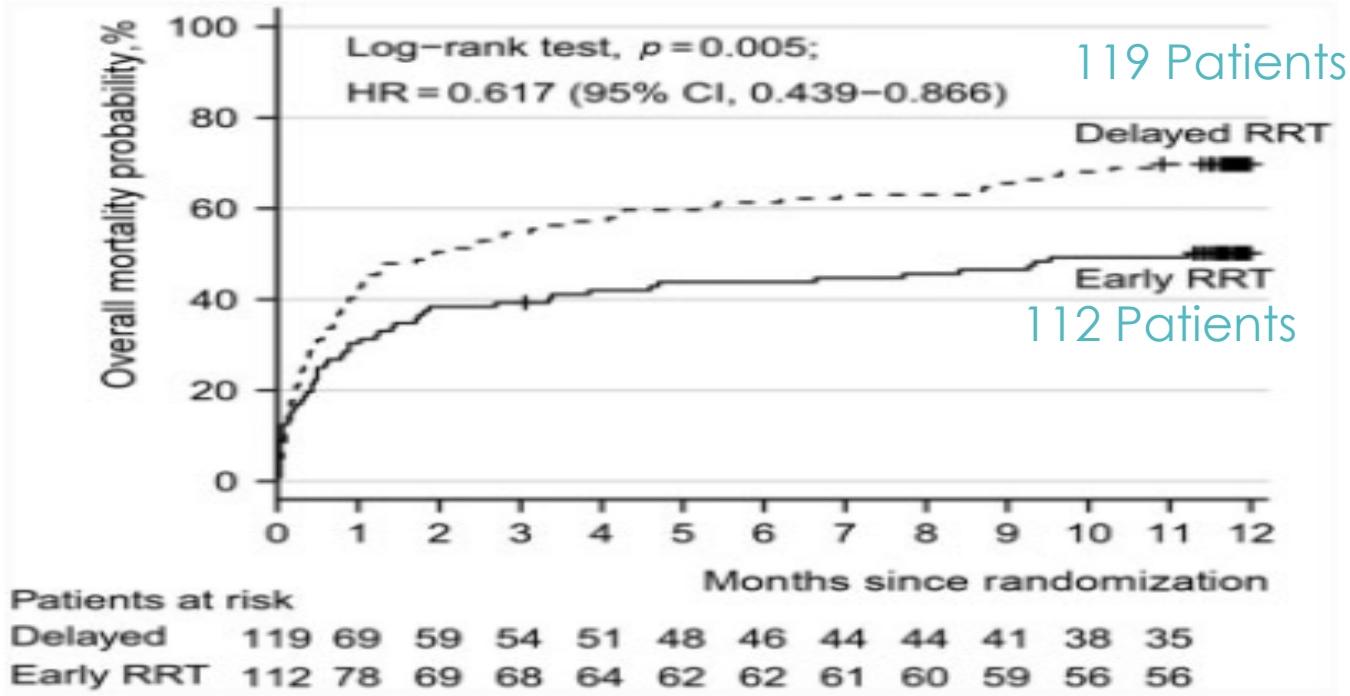


Fig. 1 Kaplan–Meier analysis of overall mortality in the early versus delayed RRT groups in the ELAIN–AKI trial. There was a statistically significant difference showing improved survival in the early versus delayed group.[7] AKI, artificial kidney initiation; ELAIN, effect of early versus delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury; RRT, renal replacement therapy.

12 hr.
CVVHDF

8 hr.
AKI KDIGO
Stage 2

ELAIN study 2016

AKI post surgery KDIGO Stage-II AKI

IACOVELLA GM, KUMAR N, EDITORS.

CONTROVERSIES SURROUNDING RENAL REPLACEMENT THERAPY IN THE CRITICALLY ILL PATIENT. SEMINARS IN RESPIRATORY AND CRITICAL CARE MEDICINE; 2019: THIEME MEDICAL PUBLISHERS.

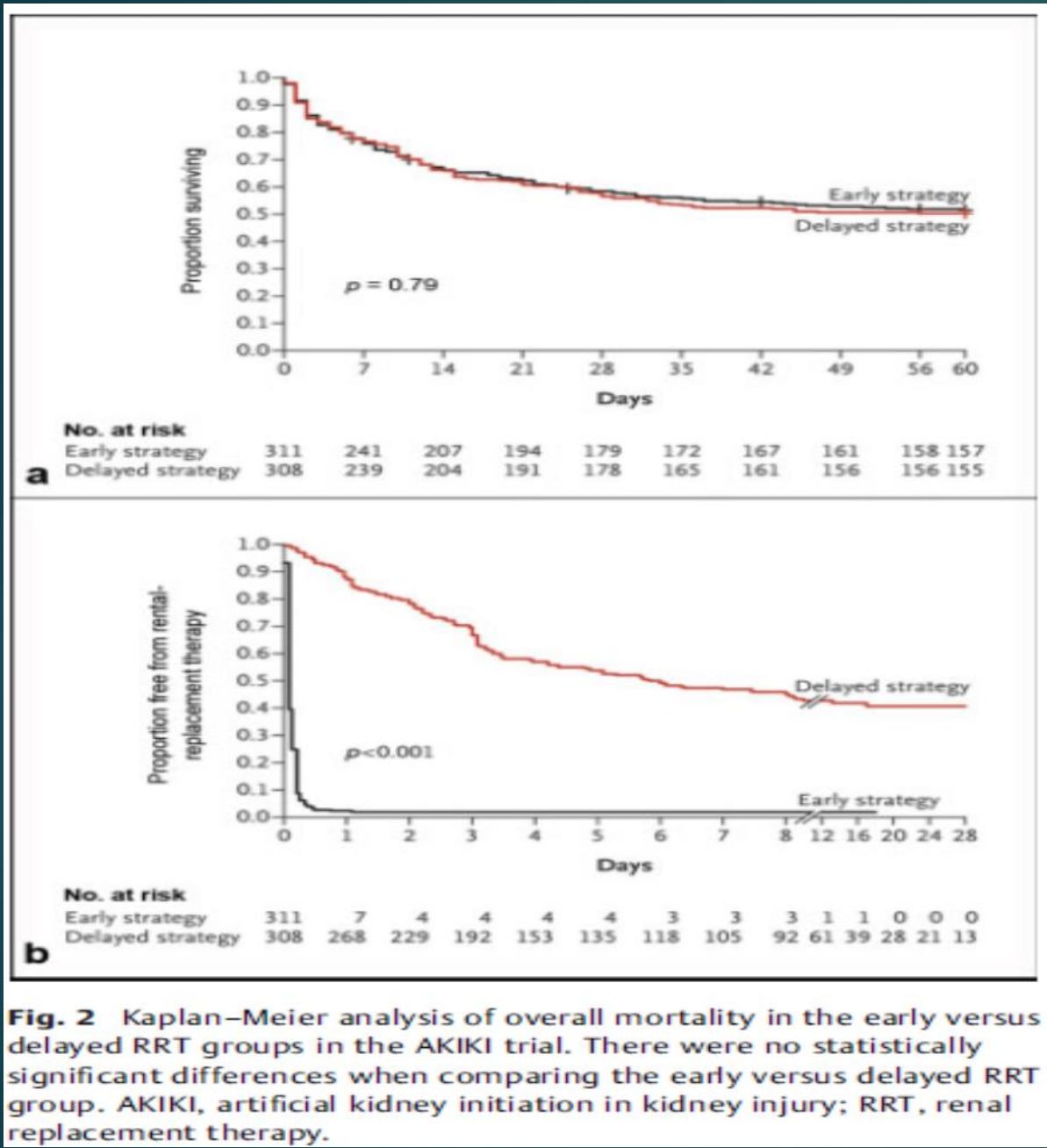


Fig. 2 Kaplan–Meier analysis of overall mortality in the early versus delayed RRT groups in the AKIKI trial. There were no statistically significant differences when comparing the early versus delayed RRT group. AKIKI, artificial kidney initiation in kidney injury; RRT, renal replacement therapy.

AKIKI Study 2016

Non surgical patients

AKI KDIGO stage 3 Following Sepsis

Mechanical Ventilation

Vasopressor

Early group (311 Patients): was defined as initiation of RRT within 6 hours following progression to stage-III AKI.

Late Group (308 patients): 72 hours , stage-III AKI but RRT was only started if any of the following criteria were met: oligoanuria or anuria for >72 hours, serum urea>112mg/dL, serum potassium>6 mmol/L or>5.5 mmol/L despite medical management, pH<7.15 with pure metabolic acidosis or mixed acidosis with PaCO2>50 and the inability to increase ventilation, and acute hypervolemia defined as>5 L/min to maintain SpO2>95% or FIO2>50% via noninvasive or invasive ventilation refractory to diuretics.

There was no mortality benefit demonstrated at 60 days when comparing the early versus delayed strategies for the initiation of RRT (48.5 vs. 49.7%; p value 0.79.

Iacovella GM, Kumar N, editors.
Controversies Surrounding Renal Replacement Therapy in the Critically Ill Patient. Seminars in respiratory and critical care medicine; 2019: Thieme Medical Publishers.

the IDEAL-ICU trial 2018

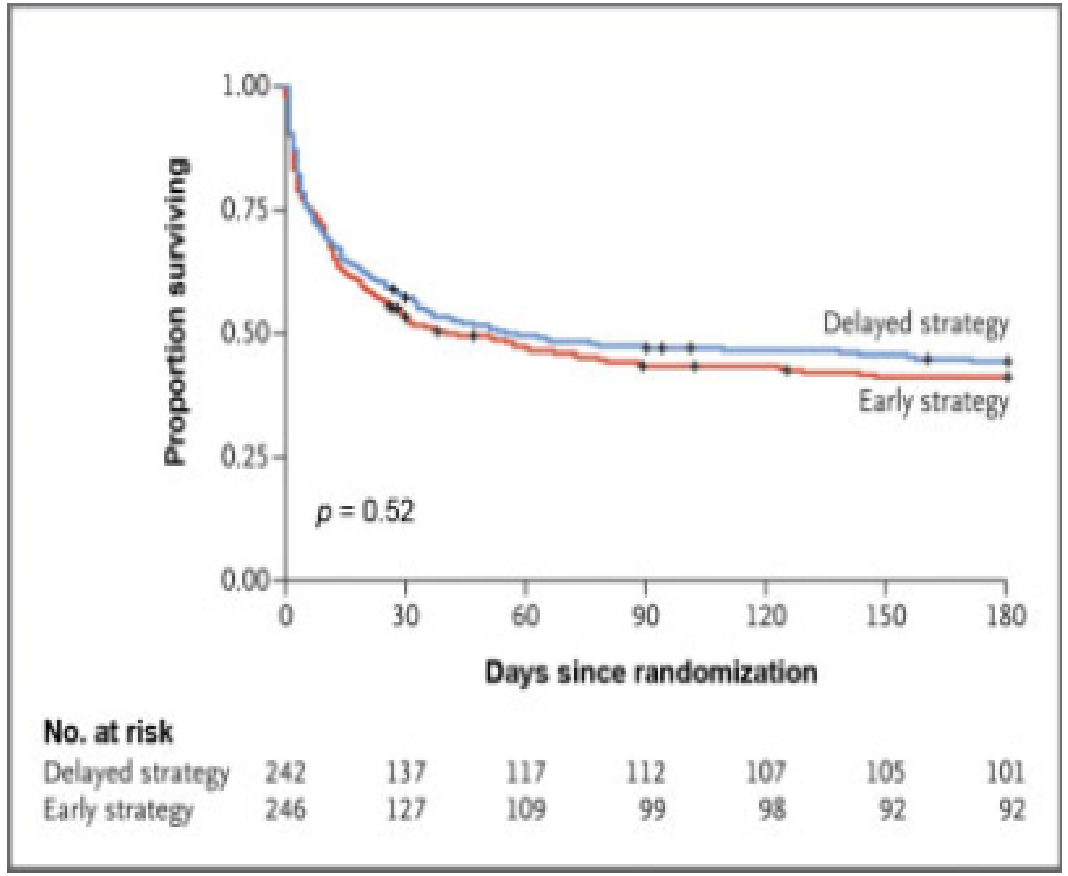


Fig. 3 Kaplan–Meier analysis of overall mortality in the early versus delayed RRT groups in the IDEAL-ICU trial. There were no statistically significant differences when comparing the early versus delayed RRT groups.[10] ICU, intensive care unit; IDEAL, initiation of dialysis in early versus delayed in the intensive care unit; RRT, renal replacement therapy.

AKI due to sepsis in ICU, KDIGO stage-III AKI.
The early group (246) was defined as initiation of RRT within 6 hours of meeting stage-III criteria.
The delayed group (242) was either initiated on RRT after 48 hours or sooner for hyperkalemia (K>6.4 mmol/L), metabolic acidosis (pH<7.15), or hypervolemia with pulmonary edema that was refractory to diuretics.
RRT modality was left to the discretion of the treating physicians.

There were no observed differences in mortality (90 days) between the early versus delayed groups nor any of the secondary endpoints.

The results of the IDEAL-ICU trial were similar to those of the AKIKI trial in that early initiation of dialysis did not confer a mortality benefit. Both trials enrolled patients with varying degree of sepsis in the medical ICU.

Iacovella GM, Kumar N, editors. Controversies Surrounding Renal Replacement Therapy in the Critically Ill Patient. Seminars in respiratory and critical care medicine; 2019: Thieme Medical Publishers.

Table 2: Early versus Delayed RRT strategy: a comparison of ELAIN, AKIKI, and IDEAL-ICU studies.

	ELAIN (23)	AKIKI (24)	IDEAL-ICU (25)
Design	RCT	RCT	RCT
Setting	Single centre	Multicentre (31 ICUs)	Multicentre (29 ICUs)
Population	Predominantly postoperative patients; 47% post cardiac surgery.	Predominantly medical patients with septic shock	Patients with septic shock
(i) Main inclusion criteria	(i) KDIGO stage 2 (ii) NGAL>150 mg/ml (iii) Critical illness including at least one of severe sepsis/ vasopressor support/refractory fluid overload/SOFA score >2.	(i) KDIGO stage 3 (Cr>354micromol/L or anuria for >12 hrs or urine output<0.3 ml/kg/hr for 24 hrs) (i) Critical illness (mechanical ventilation or vasopressor)	(i) Failure stage of RIFLE criteria: Oliguria (urine output <0.3 ml per kilogram of body weight per hour for ≥24 hours), Anuria for 12 hours or more, or a serum creatinine level 3 times the baseline level or ≥4 mg per deciliter (≥350 μmol per litre) (ii) Septic shock <48 hrs of commencing vasopressor support
(i) Main exclusion criteria	Preexisting renal disease eGFR <30 ml/min/1.73m2	Preexisting renal disease CrCl < 30 ml/min/1.73m2	End-stage renal disease and obstructive nephropathy
(ii) No. Of patients	231	620	488
Baseline characteristics			
(i) SOFA score (early vs delayed)	15.6 vs 16	10.9 vs 10.8	12.2 vs 12.4
(i) APACHE II score (early vs delayed)	30.6 vs 32.7	Not available (NA)	NA
Intervention-early RRT	<8 hrs of AKI KDIGO 2	<6 hrs of AKI KDIGO 3 Absolute indications (urea >40 mg/dl, K+>6 mmol/l, pH < 7.15, acute pulmonary oedema, oliguria/anuria >72 hrs)	<12 hrs of failure stage of RIFLE
Control-delayed RRT	<12 hrs of AKI KDIGO 3 or absolute indication		>48 hrs of failure stage of RIFLE criteria or absolute indications developing
RRT requirement in delayed group (%)	91	51	62
Method of RRT	CVVHDF	Multiple modalities: >50% initially on IHD	Multiple modalities: 45% initially on IHD
Primary outcome			
(i) Mortality in early vs delayed RRT	At 90 days: 39.3% vs 54.7%	At 60 days: 48.5% vs 49.7%	At 90 days: 58% vs 54%
(ii) *P* value	0.03	0.79	0.38
Secondary outcome			
(i) Duration of RRT early vs delayed (median days)	9 vs 25	NA	4 vs 2
(ii) Ongoing requirement for RRT	At 90 days: 13% vs 15%	At 60 days: 2% vs 5%	At 90 days: 2% vs 3%
Conclusion	Early RRT compared with delayed initiation of RRT reduced mortality over the first 90 days.	No significant difference in mortality between an early and delayed strategy for the initiation of RRT therapy. A delayed strategy averted the need for RRT in a large number of patients.	No significant difference in 90-day mortality between early and strategy of RRT among septic shock patients.

Ahmed AR, Obiana A, Lappin D. Renal replacement therapy in the critical care setting. Critical Care Research and Practice. 2019;2019.

Bagshaw et al also commented that, in addition to ***decreased urine output*** and ***elevated creatinine***,
the patient's entire clinical scenario needs to be factored in
when debating RRT initiation.

Bagshaw SM, Lamontagne F, Joannidis M, Wald R.
When to start renal replacement therapy in critically ill patients with acute kidney injury: comment on AKIKI and ELAIN. Crit Care 2016;20 (01):245–247

Timing of RRT

In conclusion:

As of now, **there is no uniform recommendation** regarding when RRT should be started and therefore considerable variation among clinicians continues to exist.

Based on limited evidence, when considering the timing of initiating of RRT in **MOF**,

Individual patients ***physiological reserve based on:***

Age

Cardiovascular risk factors,

pulmonary comorbidities,

baseline renal function,

and the trend of inflammatory and renal injury markers should be assessed.

Ahmed AR, Obilana A, Lappin D.
Renal replacement therapy in the critical care setting.
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Controversies Surrounding Renal Replacement Therapy in the Critically Ill Patient. Seminars in respiratory and critical care medicine; 2019: Thieme Medical Publishers.

Li Xiao1, Lu Jia2, Rongshan Li, Yu Zhang, Hongming Ji, Andrew Faramand
Early versus late initiation of renal
replacement therapy for acute kidney injury in
critically ill patients: A systematic review and
meta-analysis, PLOS ONE | https://doi.org/10.1371/journal.pone.0223493 October 24, 2019

Girish Chandra Bhatt1 and Rashmi Ranjan Das
Early versus late initiation of renal replacement therapy in patients with acute
kidney injury-a systematic review & metaanalysis of randomized controlled trials
Girish Chandra
BMC Nephrology (2017) 18:78 DOI 10.1186/s12882-017-0486-9

Timing of RRT

In conclusion:

A ***delayed strategy*** of waiting for 48–72 hrs. after progressing to AKI KDIGO 3 or
Until an absolute indication which arises may be applicable to most medical patients with septic shock.

Patients with low physiological reserve and AKI may benefit from ***"early RRT"*** before absolute indications develop, especially fluid overload.

there may be potential benefits in initiating RRT before absolute indications develop
in AKI associated with **severe burns** or in **postoperative patients**, particularly after cardiac surgery.

Furosemide stress test (FST) can be used in euvolemic patients with acute tubular necrosis and no underlying CKD, where a bolus of furosemide 1–1.5 mg/kg producing less than 200 ml of urine output over 2 hr. reflects an increased risk for progression of AKI and RRT requirement.

The Acute Disease Quality Initiative (ADQI) workgroup on CRRT recommended:
initiating RRT when metabolic and fluid demands exceed total kidney capacity.
however, no specific criteria exist to define excessive demand and low capacity.

Ahmed AR, Obilana A, Lappin D.
Renal replacement therapy in the critical care setting.
Critical Care Research and Practice. 2019;2019.

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2-Dialysis Modality

AKI in the ICU has been associated with both increased morbidity and mortality.
Severe AKI requiring the initiation of dialysis affects approximately 5% of ICU patients and is associated with a mortality rate of up to 60%.

Although there are several dialysis modalities that can be used in this setting, ***iHD*** (since 1940) and continuous renal replacement therapy (***CRRT*** (since 1970, Germany) including CVVH, CVVHD, and CVVHDF) are the most commonly used.

Less commonly used modalities include:
slow, low efficiency daily dialysis ***(SLEDD)*** and peritoneal dialysis ***(PD).***

Nosé Y. Dr. Willem J. Kolff:
the godfather of artificial organ technologies (February 14, 1911–February 11, 2009). Artificial Organs. 2009;33(5):389-402
Iacovella GM, Kumar N, editors. Controversies Surrounding Renal Replacement Therapy in the Critically Ill Patient. Seminars in respiratory and critical care medicine; 2019: Thieme Medical Publishers.

2-Dialysis Modality

CRRT has been considered to be the **preferred dialysis modality** in patients with **hemodynamic instability** due to less fluid shifting, allowing for continued
solute and fluid removal in a slow, protracted manner.
It has also been associated with more efficient removal of small and large metabolites and increasing renal recovery in patients by preventing additional renal injury from rapid fluid shifts.

Several randomized controlled trials (RCTs), meta-analyses, and reviews have been conducted to evaluate the **differences between iHD and CRRT**, and determine whether one is superior to the other. Interestingly, it was concluded that **there was no difference in survival or renal recovery** despite improved volume control and less lowering of the mean arterial pressure in the CRRT group.

Uehlinger DE, Jakob SM, Ferrari P, et al. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. Nephrol Dial Transplant 2005;20(08):1630–1637
Rabindranath K, Adams J, Macleod AM, Muirhead N.
Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev 2007;(03):CD003773

2-Dialysis Modality

Solute removal is another parameter that has been evaluated, and it has been suggested that slower, prolonged Dialysis would facilitate more efficient clearance.

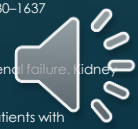
One study compared daily creatinine and urea levels and found they
were lower in patients receiving CRRT versus iHD.

In contrast, other studies did not find any difference in solute clearance.

Uehlinger DE, Jakob SM, Ferrari P, et al. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. Nephrol Dial Transplant 2005;20(08):1630–1637

Mehta RL, McDonald B, Gabbai FB, et al; Collaborative Group for Treatment of ARF in the ICU. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int 2001;60(03):1154–1163

Vinsonneau C, Camus C, Combes A, et al; Hemodiafe Study Group.Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multipleorgan dysfunction syndrome: a multicentre randomised trial. Lancet 2006;368(9533):379–385



2-Dialysis Modality

CRRT has demonstrated an advantage over iHD in certain patient populations,
including those with ***acute liver failure*** or ***elevated intracranial hypertension***.
This has been thought to be attributed to
less hemodynamic shifting and cardiovascular compromise.

CRRT is significantly more **expensive** than iHD. requires utilization of **more ICU resources**, including one-to-one **nursing**. Furthermore, it limits the **patient's mobility** as they are receiving dialysis 24 hours a day. CRRT has also been associated with **increased clotting**, thereby necessitating **anticoagulation** and increasing a **patient's bleeding risk**.

This aspect of CRRT may limit use in certain patient populations that are at increased risk of bleeding and will not tolerate being on anticoagulation.

Iacovella GM, Kumar N, editors. Controversies Surrounding Renal Replacement Therapy in the Critically Ill Patient. Seminars in respiratory and critical care medicine; 2019: Thieme Medical Publishers.

2-Dialysis Modality

Metabolic needs, such as severe hyperkalemia,

Volume overload in stable hemodynamic condition

Poisoning

may be better treated with **intermittent hemodialysis**, as it can be treated more rapidly.

Iacovella GM, Kumar N, editors. Controversies Surrounding Renal Replacement Therapy in the Critically Ill Patient. Seminars in respiratory and critical care medicine; 2019: Thieme Medical Publishers.

2-Dialysis Modality

Extracorporeal Blood Purification beyond AKI in Sepsis:

It is widely believed that **CRRT removes**, or alters the production of, **inflammatory mediators** and thereby might **restore immune homeostasis**.

However, it must be noted that haemofiltration may cause the **removal of both proinflammatory and anti-inflammatory cytokines**.

High cut off (HCO) membranes and high effluent flow rate have been combined with CRRT for cytokine removal in septic patients. Current evidence, however, does not support the routine use of HCO membrane or high effluent flow rate.

HEMOPERFUSION

Iacovella GM, Kumar N, editors. Controversies Surrounding Renal Replacement Therapy in the Critically Ill Patient. Seminars in respiratory and critical care medicine; 2019: Thieme Medical Publishers.

Ahmed AR, Obilana A, Lappin D. Renal replacement therapy in the critical care setting. Critical Care Research and Practice. 2019;2019.

2-Dialysis Modality

Conclusion:

As noted, it is very important to **individualize the dialysis treatment** to the needs (Metabolic, & Hemodynamic status) of the patient.

This may translate into a change in dialysis modality during the course of the patient's illness as their hemodynamic status fluctuates.

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2-Dialysis Modality

Table 4: Comparison of various RRT modalities.

	IHD	SLED	CRRT
Cost	+	++	++++
Duration	4 hrs daily /alternate days	6–12 hrs daily /alternate days	24 hrs (though achieves 16 hrs on avg.) Continuous
Haemodynamic instability	Least suitable	Good	Most compatible
Compatible with extracorporeal life support	No	No	Yes
In raised intracranial pressure	Increases	Can increase	Usually no change
Anti-coagulation	Can be omitted	Can be omitted	Predilution can be utilised to maintain circuit
Serum concentration of renally cleared drugs	Major fluctuations	Some fluctuation	Least fluctuation
Vascular access	AV fistula or nontunnelled or tunnelled catheter	AV fistula or nontunnelled or tunnelled catheter	Nontunnelled or tunnelled catheter
Compatible with supporting large volume infusions (antibiotics, nutrition, etc.)	No	Would need to be daily and longer sessions	Most compatible
Mobilisation	Most compatible	Could be compatible if done at night/rest time	Not compatible—would need to be discontinued.

IHD : intermittent haemodialysis; SLED : sustained low-efficiency dialysis; CRRT : continuous renal replacement therapy.

.Ahmed AR, Obilana A, Lappin D. Renal replacement therapy in the critical care setting. Critical Care Research and Practice. 2019;2019.

3-1 Dialysis Dosing

AKI septic shock and CRRT dose:

The rationale behind very high effluent flow rate (>60 ml/kg/hr) was driven by limited evidence suggesting that removal of inflammatory mediators would improve homeostasis in septic patients.

Initial data suggested survival benefit with relatively higher effluent flow rate (>35 ml/kg/hr).

P. Saudan, M. Niederberger, S. De Seigneux et al., "Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure," Kidney International, vol. 70, no. 7, pp. 1312–1317, 2006.

O. Joannes-Boyau, P. M. Honor´e, P. Perez et al., "Highvolume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial," Intensive Care Medicine, vol. 39, no. 9, pp. 1535–1546, 2013

3- 2 Dialysis Dosing

AKI septic shock and CRRT dose:

The IVOIRE study consisting of 137 patients with septic shock associated AKI compared an effluent flow rate of 70 ml/kg/hr with 35 ml/kg/hr.
There was no significant difference in vasopressor requirement and 28-day mortality between the two groups.

A recent ***Cochrane review*** ***(2017)*** also concluded that there was no mortality benefit with the use of high-volume haemofiltration (HVHF) compared to standard therapy in AKI secondary to septic shock.

O. Joannes-Boyau, P. M. Honor´e, P. Perez et al., "High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial," Intensive Care Medicine, vol. 39, no. 9, pp. 1535–1546, 2013.

E. M. J. Borthwick, C. J. Hill, K. S. Rabindranath, A. P. Maxwell, D. F. McAuley, and B. Blackwood, "High-volume haemofiltration for sepsis in adults," Cochrane Database of Systematic Reviews, vol. 1, no. 1, 2017.

3-3 Dialysis Dosing

AKI CRRT dose:

Ronco et al conducted a randomized control trial of 425 patients examining intensity of **CRRT dosing**, comparing an effluent rate of **20-Low intensity group CVVH versus 35 or 45mL/kg/h**

High intensity group CVVHDF.

They reported a **decrease in mortality from 59 to 43%** in the high-intensity dialysis groups.

There was no mortality difference found between the two higher intensity groups.

The authors concluded that patients should be prescribed a dose of at least 35mL/kg/h.

Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000;356 (9223):26-30

3-4 Dialysis Dosing

Conclusion:

It is important to note that there are **no standardized protocols for prescribing CRRT.**

Based on the cumulative data, in our institution, we typically **prescribe CVVHD with an effluent of 25mL/kg/h** as the evidence behind higher doses of dialysis not being strong.

Furthermore, potential side effects such as **hypophosphatemia**, **worsening hypotension**, and increased vasopressor requirements have been associated with ***higher intensity dialysis***.

3-4 Dialysis Dosing

Conclusion:

It is also important to remember that **prescribed dose** can be very different from **delivered dose**, and each patient should be monitored and their prescription should be tailored and adjusted based on their metabolic and volume needs.

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