Acute Kidney Injury (AKI): the place of Renal Replacement Therapy (RRT)

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content

- Acute kidney injury (AKI) and Renal Replacement Therapy (RRT)
- Definition and staging AKI
- RRT modalities and indications
- Controversies
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- Take home messages

Acute kidney injury (AKI)

- Acute renal failure (also called acute kidney injury) is characterized by abrupt and sustained decline in GFR, which leads to accumulation of urea and other chemicals in the blood.

Acute kidney injury (AKI)

- Pulmonary edema or attack of KHF
- Homeless people with starving and dehydration
- Old (sometimes very) people neglected or assaulted
- Nursing home patients with pneumo of urosepsis, or septic shock
- Rabdomyolizis
- Heatstroke
- Severe diarrhea
- TTP
- ……..

AKI (epidemiology)

- Community-acquired renal failure
  - Prerenal 70%, intrinsic 20%, postrenal 10%
  - Volume depletion, reversible 1% hospital admission
  - Mortality <7%
- Hospital-acquired renal failure
  - After admission
  - Prerenal 20%, ATN 70%, postrenal 10%
  - Toxins, sepsis, MOF
  - Mortality R (15%), I (29%), F (34%)

Acute kidney injury (AKI)

- Pulmonary edema or attack of KHF
- Homeless people with starving and dehydration
- Old (sometimes very) people neglected or assaulted
- Nursing home patients with pneumo of urosepsis, or septic shock
- Rabdomyolizis
- Heatstroke, or other EMS
- Severe diarrhea. GI bleeding
- TTP…….
- Life threatening situations

AKI (a defense mechanism)

- As a part of apoptosis process, whenever our body face a serious hemodynamic or metabolic problem we sacrifice our kidneys first

“LIZARD TAIL LOSS”
autotomy: a defense mechanism

“LIZARD TAIL LOSS” autotomy: a defense mechanism

- “Though this is a natural reaction to what the lizard perceives as a threatening situation, it is still stressful for the lizard, and there are things that **you should do to facilitate proper healing** and, for some species, regrowth”

AKI classification

- RIFLE
- AKIN
- KDIGO

AKI classification systems 1: RIFLE

	GFR criteria	Urine output criteria
Risk	Serum creatinine increased 1·5 times	<0·5 mL kg^{-1} h^{-1} for 6 h
Injury	Serum creatinine increased 2·0 times	<0·5 mL kg^{-1} h^{-1} for 12 h
Failure	Serum creatinine increased 3·0 times or creatinine=355 μmol/L when there was an acute rise of >44 μmol/L	<0·3 mL kg^{-1} h^{-1} for 24 h or anuria for 12 h
Loss	Persistent acute renal failure; complete loss of kidney function for longer than 4 weeks	
End-stage renal disease	End-stage renal disease for longer than 3 months	

GFR=glomerular filtration rate.

Table 1: **RIFLE classification[4]**

AKI classification systems 2: AKIN

Stage	Creatinine criteria	Urine output criteria
1	1.5 - 2 x baseline (or rise $\geq$ 26.4 μmol/L)	< 0.5 ml/kg/hour for > 6 hours
2	>2 - 3 x baseline	< 0.5 ml/kg/hour for > 12 hours
3	> 3 x baseline (or > 354 μmol/L with acute rise $\geq$ 44 μmol/L)	< 0.3 ml/kg/hour for 24 hours or anuria for 12 hours

Patients receiving RRT are Stage 3 regardless of creatinine or urine output

AKI (classification) KDIGO

KDIGO Classification of AKI (2012)

Stage	Serum creatinine	Urine output
1	1.5-1.9× baseline OR >0.3 mg/dL ↑	<0.5 ml/kg/hr for 6-12 hrs
2	2-2.9× baseline	<0.5 ml/kg/hr > 12 hrs
3	3 times baseline OR increase in Cr to ≥4.0 mg/dL OR Initiation of RRT	<0.3 ml/kg/hr > 24 hrs OR Anuria > 12 hrs

KDIGO Clinical Practice Guideline for AKI. Kidney Int 2012

Primary therapeutic goals in AKI

- Optimize hemodynamic and volume status
- Minimize further renal insult
- Correct metabolic abnormalities
- Removal of uremic toxins (RRT)
- Permit adequate nutrition

Standart indication for HD

- Refractory fluid overload
- Severe hyperkalemia (plasma potassium concentration >6.5 mEq/L) or rapidly rising potassium levels
- Signs of uremia, such as pericarditis, encephalopathy, or an otherwise unexplained decline in mental status
- Severe metabolic acidosis (pH <7.1)
- Certain alcohol and drug intoxications

Renal Replacement Therapy (RRT) Modalities

- IHD (Intermittent classical Hemodialisis)
- CRRT (Continuous renal replacement therapy)

Practical comparison of acute RRT modalities

	Intermittent hemodialysis	Sustained low-efficiency dialysis	Continuous renal replacement therapy
Session duration, h	3–5	8–12	24
Blood flow, ml/min	300–400	200–300	100–200
Dialysate flow, ml/min	500–800	200–350	25–40
Anticoagulation requirement	heparin or none	heparin or none	heparin or regional citrate

Fieghen, Nephron Clinical Practice 2009;112:222-229

Continuous vs IHD in AKI: HEMODIAFE study

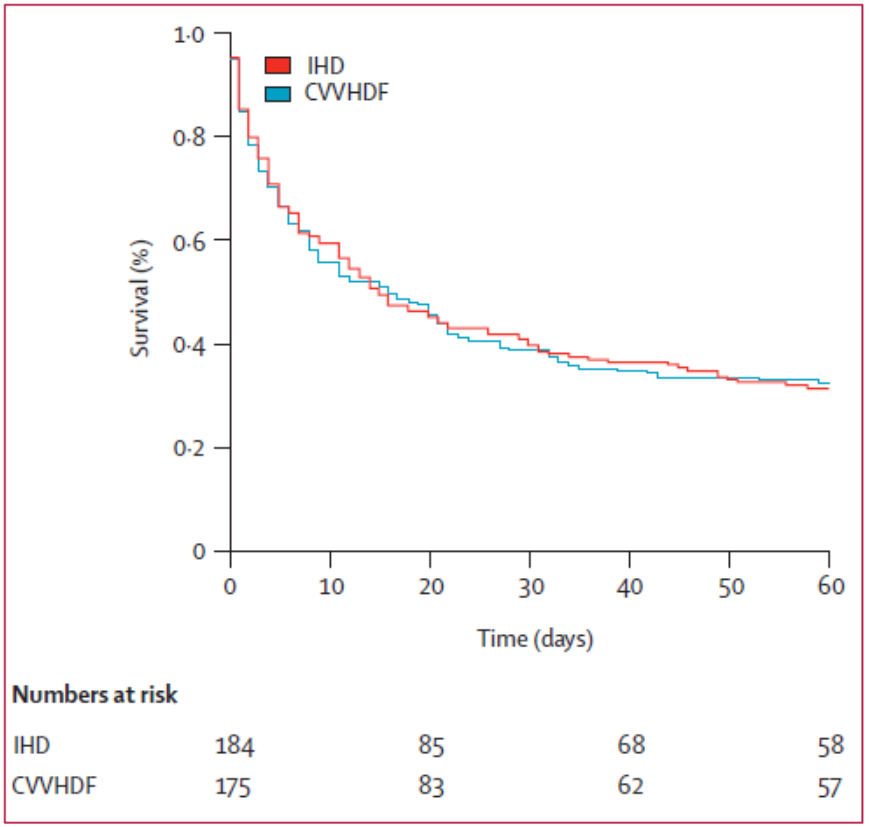


Figure 2: **Estimation of survival rate according to treatment group**
IHD=intermittent haemodialysis, CVVDHF=continuous venovenous haemodiafiltration.

Vinsonneau C, et al. Lancet 2006;368(9533):379-

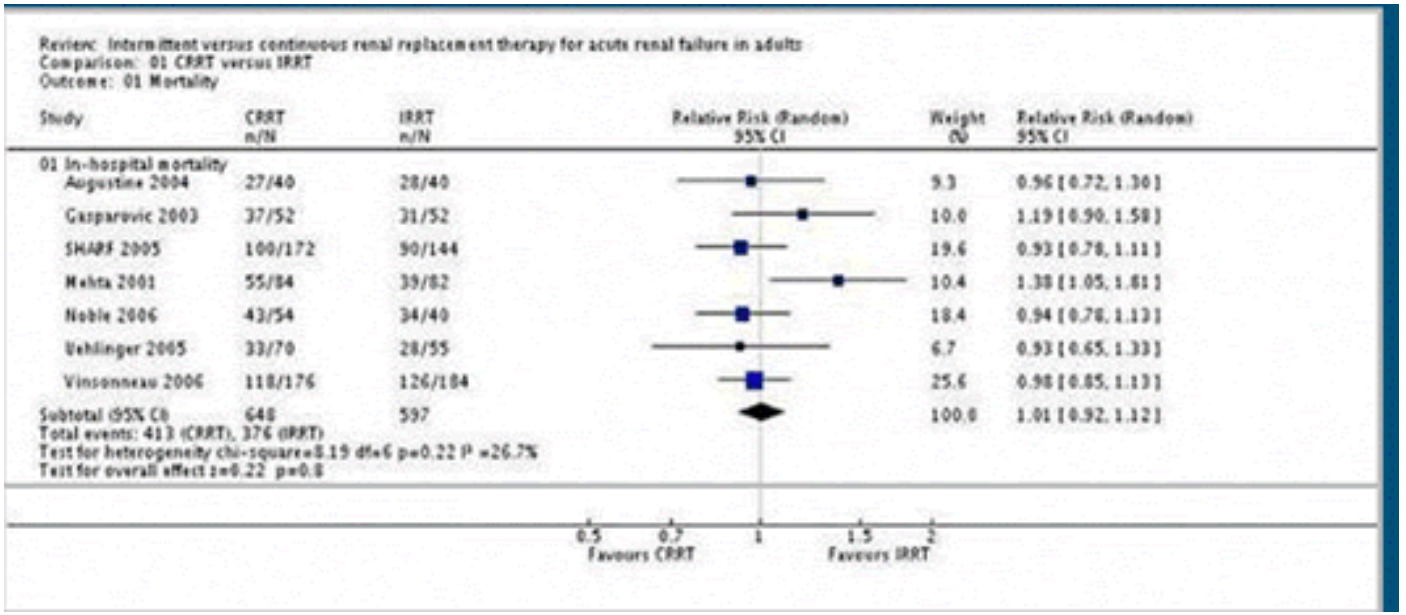
Results of individual RCT's comparing CRRT to IHD

Study	Sample size		Primary endpoint	Mortality, %		Persistent dialysis requirement[a], %	
	CRRT	IHD		CRRT	IHD	CRRT	IHD
Mehta et al. [21]	84	82	ICU mortality	59.5	41.5	14.0	7.0
Augustine et al. [23]	40	40	in-hospital mortality	67.5	70.0	61.5	66.7
Uehlinger et al. [24]	70	55	in-hospital mortality	47.0	51.0	2.7	3.7
Vinsonneau et al. [22]	175	184	60-day mortality	67.4	68.5	1.8	0.0
Lins et al. [25]	172	144	in-hospital mortality	58.1	62.5	16.9[b]	25.5[b]

[a] Defined as dialysis dependence at the time of hospital discharge among survivors.
[b] Glomerular filtration rate <15 ml/min at the time of hospital discharge.

In summary, no survival benefit shown in these trials with CRRT

Meta analysis of studies comparing CRRT and IHD in AKI



Rabindranath K et al.cochrane database syst rev 2007 jul (3)

…so type of treatment (IHD vs CRRT) does not impact survival, but does it impact recovery of renal function?

- So although some studies report better recovery with CRRT these reports only evaluated renal recovery in pts who survived, thereby failing to account for mortality differences b/w groups.

- When analysis combined mortality and non recovery of renal function, both groups showed similar recovery of function

- Randomized studies have also found no such benefit with CRRT

So to Summarize…IHD vs CRRT

- The two principal outcomes that have been examined are **patient survival** and **recovery of renal function.**

- current data suggest that survival and recovery of renal function are similar with both CRRT and IHD.

Timing (early versus late)

- The optimal timing of RRT initiation in critically ill patients with AKI is unknown
- No consensus to guide clinical practice on this issue
- Wide variability in the timing of RRT initiation in this population
- This is an important knowledge gap in the support of critically ill patients with AKI

THE LANCET

JANUARY 21, 1961

OPTIMUM TIME FOR DIALYSIS IN ACUTE REVERSIBLE RENAL FAILURE

Description and Value of an Improved Dialyser with Large Surface Area

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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

Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, PavenstÃ¤dt H, Boanta A, GerÃ, Meersch M.

JAMA 2016 May

- INTERVENTIONS
- **Early** (within 8 hours of diagnosis of KDIGO stage 2;n=112) or
- **Delayed** (within12 hours of stage3 AKI or no initiation;n=119) initiation of RRT.

- MAINOUTCOMES AND MEASURES
- The primary end point
  - Mortality at 90 days after randomization.
- Secondary end points
  - 28 and 60 day mortality,
  - Clinical evidence of organ dysfunction,
  - Recovery of renalfunction
  - Requirement of RRT after day 90
  - Duration of renal support intensive careunit (ICU)
  - Hospital length of stay.

Patients included met the following criteria:

- ages 18-90 years
- intending to receive full intensive care for 3 or more days
- kidney disease classified as KDIGO (Kidney Disease: Improving Global Outcomes) stage 2 (defined as 2 fold increase in serum creatinine from baseline or urine output less than 0.5 ml/kg/hr for greater than or equal to 12 hours after optimal resuscitation)
- plasma neutrophil gelatinase-associated lipocalin (NGAL) > 150ng/mL
- At least one of the following conditions: severe sepsis, use of vasopressors, refractory fluid overload, and development or progression of nonrenal organ dysfunction.

Exclusion criteria included the following:

- pre-existing chronic kidney disease (defined as GFR < 30 mL/min)
- history of renal replacement therapy (RRT)
- acute kidney injury due to permanent occlusion or surgical lesion of renal artery, glomerulonephritis, interstitial nephritis, vasculitis, postrenal obstruction, or hemolytic uremic syndrome or thrombotic thrombocytopenic purpura
- pregnant patients
- AIDs diagnosis with CD4 cell count < 50
- Hematologic malignancy with neutrophil count less than 50
- Prior renal transplant
- Hepatorenal syndrome
- Participation in another interventional clinical trial

Was the assignment of patients to treatments randomized?

- Patients were randomized, but group allocation was not concealed.
- Randomization occurred in a 1:1 ratio using a computer system, stratifying by SOFA score and oliguria.
- The researchers also used block randomization, in blocks of 10.

- All randomized patients were accounted for at the conclusion.
- The trial was not stopped early.
- 11 patients randomized to the delayed RRT group never received RRT for various reasons; 6 never met criteria due to return of renal function or death, 4 violated protocol (reached stage 3 AKI but recovered renal function prior to starting RRT),
- 1 patient never received RRT because a continuous RRT device was not available.

- Patients were analyzed in the groups they were randomized, using intention-to-treat principle.

Were the groups similar at the start of the trial?

- Baseline demographics and characteristics of the groups were similar, including severity of illness scores, presence of comorbid conditions, initial creatinine, NGAL levels, severe sepsis diagnosis, high dose catecholamine treatment, fluid overload, and advanced inclusion criteria.

Aside from the experimental intervention, were the groups treated equally?

- The authors never explicitly ensure that both groups of patients were treated equally other than in reference to RRT technique.
- However, the study took place in a single center, so one may infer treatment was similar between the two groups

How large was the treatment effect?

- For the primary outcome of 90 day all-cause mortality, the early vs delayed treatment group had a hazard ratio of 0.66 (with confidence interval 0.45–0.97), p-value 0.03.
- **The absolute risk reduction was 0.144 (CI 0.01–0.28).**
- In the early RRT group had 39.3% mortality (44 of 112 patient), whereas the late RRT group had 54.7% mortality (65 of 119 patients).

- The early group had reduced **median duration of RRT**, 9 vs. 25 days, HR: 0.69 (CI 0.48–1.00), p-value 0.04
- The early group **had increased recovery of renal function at 90 days**, 53.6% patients vs. 38.7%, OR: 0.55 (CI 0.32–0.93), p-value 0.02
- The early group had decreased **median duration of mechanical ventilation**, 125.5 hours vs. 181.0 hours, p-value 0.002
- The early group had **decreased hospital length of stay**, 51 vs. 82 days, HR: 0.34 (CI 0.22–0.52), p-value < 0.001

- For the primary outcome of 90 day all-cause mortality, the early vs delayed treatment group had a hazard ratio of 0.66 with a 95% confidence interval **0.45-0.97.**
- This confidence interval does not cross one, but the interval if fairly wide, indicating a less precise estimate of the treatment effect.

CONCLUSIONS AND RELEVANCE

- Among critically ill patients with AKI, early RRT compared with delayed initiation of RRT reduced mortality over the first 90days.
- Further multicenter trials of this intervention are warranted.

Earlier versus later initiation of renal replacement therapy among critically ill patients with acute kidney injury: a systematic review and meta-analysis of randomized controlled trials

Tai-Shuan Lai1,2†, Chih-Chung Shiao3,4† , Jian-Jhong Wang5, Chun-Te Huang6, Pei-Chen Wu7, Eric Chueh8, Shih-Chieh Jeff Chueh9, Kianoush Kashani10,11* and Vin-Cent Wu12,13*

Lai et al. Ann. Intensive Care (2017) 7:38
DOI 10.1186/s13613-017-0265-6

Lai et al. Ann. Intensive Care (2017) 7:38 DOI 10.1186/s13613-017-0265-6

- 9 RCTs and 1627 participants
- Mortality (RR) 0.88, 95% (CI) 0.68–1.14,
- ICU and hospital LOS (RR) 0.08 (95% CI 0.26 to 0.09) and 0.11 (95% CI 0.37 to 0.16)
- Earlier RRT was associated with a reduction in the in-hospital mortality among surgical patients
  - RR 0.78, 95% CI 0.64–0.96) (RR 0.80, 95% CI 0.67–0.96).

Lai et al. Ann. Intensive Care (2017) 7:38 DOI 10.1186/s13613-017-0265-6

- Conclusions:
  - Compared with later RRT, earlier initiation of RRT **did not show beneficial impacts** on patient outcomes

BMC Nephrol. 2017 Feb 28;18(1):78. doi: 10.1186/s12882-017-0486-9

- Early versus late initiation of renal replacement therapy in patients with acute kidney injury-a systematic review & meta-analysis of randomized controlled trials.

- A total of 10 RCTs with 1,636 participants were included
- All the trials were open label; six trials have unclear or high risk of bias for allocation concealment while four trials have low risk of bias for allocation concealment.

- Compared to late RRT,
  - There was no significant benefit of early RRT on day
    - 30 day mortality [6 studies; 1301 participants; RR, 0.92;95% CI: 0.76, 1.12)
    - 60 day mortality [3 trials;1075 participants; RR, 0.94; 95% CI: 0.78, 1.14)]
    - 90 day mortality [3 trials; 555 participants; RR,0.94;95% CI: 0.67, 1.33)];
    - Overall ICU or hospital mortality; dialysis dependence on day 90 [3 trials; (RR, 1.06; 95% CI:0.53, 2.12)].

CONCLUSION

- This updated meta-analysis showed no added benefit of early initiation of RRT for patients with AKI.
- The grade evidence generated was of "low quality" and there was a high heterogeneity in the included trials.

Take home messages

- Stable patients with positive indication=HD
- Unstable patients= treat them and make him/her stable, HD
- If you can not=CRRT
- “Early” is good for us (EPs) if they admit patients to hospital for HD (no matter IHD or CRRT)