

Renal Replacement Therapy in ICU

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Introduction

- Need for RRT in patients with ARF is a common & increasing problem in ICUs
- Leading cause of ARF is sepsis (as a part of MODS)
- Mortality rates of ARF quite high
- The in-hospital mortality rate
 - ~30% in patients with drug induced ARF
 - up to 90% in ARF with severe MODS

- In experimental ARF isolated renal ischemia & reperfusion injury causes injury and dysfunction of distant organs
- Precise effects of 'uremic' toxins is not known in ARF except for severe hyperkalemia
- CRRT in its current form is only a partial solution to the multisystem problems caused by ARF

- For many years, IHD was the only treatment option for patients with ARF
- Still the most frequently used modality

Am J Nephrol 1999; 19:377–382

- Standard IHD could not be used in patients with severe hemodynamic instability
- Led to development of CRRT which was first described by Kramer et al in 1977
- Continuous venovenous hemofiltration (CVVH) was used as an alternative to IHD
 - better tolerated by hypotensive patients
 - continuous regulation of fluid and nutritional support avoided cycles of volume overload and depletion

- In ICU patients AKI is caused by
 - prerenal azotemia (reversible renal insufficiency due to renal hypoperfusion)
 - ATN
- ATN results from combined effect of ischemic & nephrotoxic insults

Critical Care 2004; 8:R204–R212

- Renal hypoperfusion & injury caused by
 - systemic hypoperfusion
 - effects of mechanical ventilation
 - renal vasoconstriction in patients with cirrhosis and sepsis
 - increased intra-abdominal pressure
 - endogenous and exogenous nephrotoxins

- RIFLE criteria (the Risk, Injury, Failure, Loss, and End-stage Kidney) stratified patients into
 - 3 categories of severity (risk, injury, and failure) and
 - 2 outcomes (loss of renal fxn. after receipt of RRT for 4 weeks and permanent kidney failure)

J Am Soc Nephrol. 2003;14(8):2178-2187

- criteria have been simplified to focus only on
 - change in levels of serum creatinine (0.3 mg/dL or a 50% increase)
 - urine output (0.5 mL/kg per hour for longer than 6 hours)

Crit Care. 2007; 11(2):R31

Indications

- AKI requires RRT
 - when there is an acute fall in glomerular filtration rate
 - Developed / at risk of developing clinically significant solute imbalance/toxicity
 - volume overload
- The precise timing of RRT initiation is based on clinical judgment
- The classic indications for dialysis are
 - diuretic resistant pulmonary edema
 - hyperkalemia - refractory to medical therapy
 - metabolic acidosis - refractory to medical therapy
 - uremic complications - pericarditis, encephalopathy, bleeding
 - dialyzable intoxications - lithium, toxic alcohols, and salicylates

Principles

- Water and solute transport through a semi-permeable membrane
→ discarding the waste products
- Ultrafiltration- process by which water is transported across a semi-permeable membrane
- Diffusion and convection are two processes by which solutes are transported across the membrane
- RRT modalities use
 - ultrafiltration for fluid removal
 - diffusion, convection, or a combination to achieve solute clearance

- Ultrafiltration - volume is removal by using a pressure gradient to drive water through a semi-permeable membrane
- Transmembrane pressure gradient - difference between plasma oncotic pressure and hydrostatic pressure
- Determinants of the ultrafiltration rate include
 - membrane surface area
 - water permeability of the membrane
 - transmembrane pressure gradient

- Diffusion - movement of solutes from area of higher solute concentration to area of lower concentration across a semipermeable membrane
- Concentration gradient is maximized & maintained throughout the length of the membrane by running the dialysate counter current to the blood flow
- Solutes with a higher concentration in the blood move across the membrane to the dialysate compartment – Potassium / urea
- Solutes with a higher concentration in the dialysate diffuse into the blood – bicarbonate

- Solute with equivalent concentration in blood and dialysate move very little across the membrane – sodium and chloride
- Smaller solutes & lower molecular weight molecules diffuse more rapidly than larger solutes & are cleared more efficiently than heavier molecules
- The rate of solute diffusion depends on
 - blood flow rate
 - dialysate flow rate
 - duration of dialysis
 - concentration gradient across the membrane
 - membrane surface area and pore size

Modalities

The available modalities of renal replacement therapy include

- Peritoneal dialysis
- Intermittent hemodialysis
- Continuous renal replacement therapies

peritoneal dialysis

- Peritoneal dialysis uses peritoneum as a natural semipermeable membrane for diffusive removal of solutes
- Effective treatment modality in patients with chronic renal failure
- Patient outcomes equivalent to hemodialysis

Kidney Int, 45:1163–9.1994

Kidney Int, 57: 1720–6.2000

peritoneal dialysis

- Peritoneal dialysis is valuable in pediatric critical care
 - challenging vascular access
 - Larger peritoneal surface area
- Acute peritoneal dialysis not widely used in adults
- Requires surgical insertion of a peritoneal dialysis catheter

peritoneal dialysis

- Acute PD complicated by catheter leakage and malfunction
- Limited by
 - Low solute clearance due to Hypercatabolic state
 - potential pulmonary restriction due to expansion of the peritoneal cavity
 - contraindication in postoperative patients who require abdominal surgery or surgical drains
- Comparative study of PD with CRRT in critically ill septic patients with ARF showed more rapid correction of acidosis, solute clearance, and significantly improved survival with CRRT

Intermittent hemodialysis

- Process of solute clearance based on diffusion across the membrane driven by a concentration gradient between the blood and dialysate
- Clearance - amount of solute transported per unit of time depends on
 - the molecular weight of the molecule
 - membrane characteristics
 - dialysate flow
 - blood flow
- Prescribed for 3–6 h per treatment
- Chronic hemodialysis patients are treated three times per week

Intermittent hemodialysis

- Slow efficiency daily dialysis (SLEDD)
- Extended daily dialysis (EDD)
variant of IHD where the
 - duration of dialysis is extended to between 8 and 12 h
 - Low blood flow
 - Gradual fluid removal
 - Slow solute clearance
- SLEDD - less hemodynamic instability than IHD and provides excellent solute control
- Advantages over CRRT w.r.t cost and improved patient mobility

Never been compared directly in a clinical trial

Continuous renal replacement therapies (CRRT)

- CRRT - any renal replacement therapy that is intended to be applied for 24 h per day in an ICU
- Blood purification techniques differ according to
 - the mechanism of solute transport
 - the type of membrane
 - the presence or absence of dialysate solution
 - the type of vascular access
- CRRT provides slower solute clearance per unit time as compared with intermittent therapies
- 24 h may exceed clearances with IHD

CRRT

- Solute removal with CRRT is achieved by
 - convection - hemofiltration
 - diffusion - hemodialysis
 - Combination of both methods - hemodiafiltration
- Hemodialysis most efficiently removes small molecular weight substances → urea, creatinine, and potassium
- Hemofiltration removes middle and larger molecular weight substances

CRRT

- Hemofiltration → hydrostatic pressure causes the filtration of plasma across a semi-permeable membrane
- Solutes are dragged across the membrane along with the plasma resulting in convective transport of solutes in the same direction as water
- Replacement fluid required to prevent iatrogenic acidosis and electrolyte depletion

CRRT

- solutes in the removed filtrate are in the same concentration as those in the plasma
- solute concentration in the remaining plasma is diluted with substitution fluid
- Combining diffusive and convective clearance with hemodiafiltration allows improved clearance of both small and large molecular weight substances
- BUN clearances in the range of 23–30 mL/min can be achieved even in hypotensive patients

CRRT

Commonly applied modalities are

- continuous venovenous hemofiltration (CVVH)
- continuous venovenous hemodialysis (CVVHD)
- continuous venovenous hemodiafiltration (CVVHDF)

Table 1 A comparison of intermittent vs continuous dialysis therapies

	CRRT	IHD
Time	24 hours	4–6 hours
Pump speed	100–180 mL/min	200–500 mL/min
Dialysis membrane	0.9 m ² High flux	1.1–2.1 m ² +/- High flux
Dialysis flow rate	0–2 L/h	500–750 mL/min
Replacement fluid	1–3 L/h	None
Fluid removal	+100 mL/h to –500 mL/h	500–1000 mL/h

Abbreviations: CRRT, continuous renal replacement therapies; IHD, intermittent hemodialysis.

CRRT

- AV modes of CRRT - dialysis access is obtained through the femoral artery and the femoral vein
- Patient's own cardiac output to drive blood through the dialysis circuit
- Fallen out of favor due to
 - high access complication rate
 - development of external circuit pumps

TIMING

- Absence of large RCTs - no firm recommendations for RRT timing in AKI
- Early start may be beneficial in AKI patients with
 - persisting shock
 - poorly recovering functions of other organs
- RRT timing according to renal and nonrenal criteria using
 - ‘RIFLE’ classification
 - severity of other organ failure

Early v/s Late

- Patient outcome can be improved by early or more intensive dialysis to keep the BUN under 80–100 mg/dL
- Bouman et al randomized 106 critically ill patients with ARF to early vs late initiation of dialysis
- Early initiation was started within 12 h of patients meeting the following criteria
 - low urine output (< 30 cc/h) \times 6 h refractory to optimization of hemodynamics and diuretics
 - creatinine clearance of < 20 mL/min

- The late initiation group was started on dialysis when the classic indications for dialysis were met
 - volume overload
 - hyperkalemia,
 - urea greater than 40 mmol/L
- There was no significant difference between the groups in terms of
 - ICU or hospital mortality
 - recovery of renal function

- Randomized trial of 106 patients “early” dialysis was started after 6 hours of urine output of less than 30 mL/h
- No effect on mortality or dialysis dependence in survivors

Crit Care Med. 2002;30(10):2205-2211

- Prospective cohort study reported significantly lower risk of death in patients started RRT with blood urea nitrogen levels of ≤ 76 mg/dL

Clin J Am Soc Nephrol. 2006;1(5): 915-919

- Available literature is inconclusive as regard to indications and timing of renal replacement in ARF

The Acute Dialysis Quality Initiative (ADQI) consensus statement on dialysis treatment makes no recommendations on the timing of initiation of renal replacement therapy beyond those defined by the conventional criteria that apply to chronic renal failure

Kidney Int,2002;62:1855-63

Practical aspects

Vascular access

- Double lumen dialysis catheters
- Inserted in the internal jugular, subclavian, or femoral veins
- Blood recirculation from the venous to the arterial port can reduce the effectiveness of dialytic therapies
- Short (13.5-cm) catheter in the femoral vein may result in up to 23% blood flow recirculation
- Longer catheters (19–25 cms) for femoral vein avoids recirculation

- variable blood flow rates lead to a higher risk of thrombosis
- large bore, small length catheters are preferable for AV procedures to permit a high blood flow rate
- In pumped (venovenous) systems double lumen venous catheters are commonly used
- Size should be selected based on the site of insertion to optimize flow

Membranes

- For hemofiltration high flux membranes designed to provide high water permeability are recommended
- No conclusive evidence to suggest that membrane biocompatibility affects patient outcome
- Synthetic membranes is preferable over cellulose based membranes for the treatment of AKI patients

Replacement/Dialysate solutions

- Dialysate for IHD is generally produced on-line by the dialysis machine from a combination of treated water and various electrolytes
- Water purification is achieved by treatment with reverse osmosis, deionization, and charcoal filters
- Dialysate water is not required to be sterile as there is no contact between blood and dialysate

- All CRRT techniques except SCUF require the use of sterile dialysate/ replacement fluids to compensate for the ultrafiltrate removed
- Due to low blood-side pressures, back filtration of dialysate to blood may occur with high permeability membranes

- Optimal dialysate/replacement solution approximates
 - normal plasma water composition
 - replacing electrolytes and minerals in physiologic concentrations
- Composition can be varied to achieve specific metabolic goals
 - bicarbonate-based solutions can be used to correct acidemia
 - electrolyte content can be altered to correct electrolyte imbalance

- Limitation of using sterile solution for CRRT is that they are acetate or lactate based
- capacity to convert these buffers to bicarbonate may be limited in patients with multiple organ failure
- bicarbonate-based solutions are better tolerated than lactate- or acetate based solutions

Anticoagulation

- Essential component of all blood-based renal replacement therapies
- Passage of blood through an extracorporeal circuit causes platelet activation and induces inflammatory and prothrombotic mediators
- Deposited fibrin on filter membranes affects filter longevity and decrease dialyzer efficacy
- Filtration performance deteriorates and the filter may clot
- Excessive anticoagulation may result in bleeding complications reported to occur in 5%–26% of treatments

- Unfractionated heparin is the mainstay of anticoagulation for IHD and CRRT
- Administered as a bolus → continuous infusion into the arterial limb of the dialysis circuit
- APTT of 1.5–2 × normal is maintained
- Due to renal excretion low molecular weight heparin should not be used without careful monitoring of factor Xa levels

- Systemic anticoagulation is relatively contraindicated in patients at high risk of bleeding
- Heparin dose can be modified but is associated with a high incidence of bleeding and heparin-induced thrombocytopenia
- IHD can be used without anticoagulation
- In heparin-free dialysis
 - blood flows are kept between 250–500 mL/min
 - saline flushes are administered every 15–30 min into the arterial limb
 - minimize hemoconcentration
 - wash fibrin strands from kidney into the bubble trap

- Volume of saline administered with frequent flushing must be removed during the dialysis to prevent hypervolemia
- Associated with only a 2% clotting rate
- Regional anticoagulation of the circuit is preferred in
 - postoperative patients
 - contraindication to systemic anticoagulation

- Regional heparinization uses pre-filter administration of heparin and post-filter protamine infusion
- Citrate anticoagulation may be used with both continuous and intermittent therapies
- Regional citrate anticoagulation is achieved using a continuous citrate infusion through the arterial limb of the circuit
- Chelates free calcium and inhibits the coagulation cascade
- Citrate-calcium complex is removed by a combination of dialysis clearance against calcium-free dialysate and endogenous processes

- Levels of citrate and ionized calcium return to normal values within 30 min of discontinuing a citrate infusion in normal LFT
- Infusion rate of citrate is adjusted to keep the activated clotting time above 160 s
- Regional citrate anticoagulation requires the use of a specialized dialysis solution and frequent monitoring of ionized calcium

- Potential complications from this technique
 - metabolic alkalosis
 - Hyponatremia
 - Hypocalcaemia
 - citrate toxicity in patients with liver dysfunction
- Complication rate associated with this technique is quite low if properly monitored
- Filter longevity in excess of 96 h is common with citrate anticoagulation as compared to 36–48 h patency with heparin

Drug dosing in continuous renal replacement

- Correct drug dosing in ICU patients with CRRT is difficult
 - extracorporeal drug removal superimposed on the disturbed pharmacokinetics induced by critical illness
 - Rapidly changing clinical situation
- Limited literature on the removal of individual drugs with CRRT
- Drug dosing in CRRT patients should be an individualized approach

- Pharmacokinetic changes induced by critical illness are
 - increased volume of distribution of water-soluble drugs due to extracellular volume expansion
 - altered protein binding
 - decreased clearance due to kidney or liver failure
- The hyperdynamic circulation seen in early sepsis may result in supranormal renal clearances

- Effective dosing regimen is consistent with
 - drug's intrinsic pharmacodynamic characteristics
 - pattern of bactericidal activity
 - presence and duration of a postantibiotic effect
- Beta-lactams, glycopeptides and oxazolidinones exhibit time-dependent bacterial killing
- Do not have a postantibiotic effect
- The percentage of the dosing interval that persists above MIC is the major determinant for their efficacy
- Recommend the use of continuous infusions to maximize pharmacodynamic exposure

- Fluoroquinolones and aminoglycosides are concentration-dependent agents with postantibiotic effect
- Efficacy is related to the
 - ratio of the peak plasma concentration to the MIC of the etiologic agent for the aminoglycosides
 - AUC/MIC for the quinolones
- To achieve high peak plasma levels the optimal dosing regimen consists of the administration of high doses with prolonged dosing interval
- Dosing regimens based on pharmacodynamics
 - increase the efficacy of the treatment
 - minimize toxicity and the development of microbial resistance

Drug dosing during CRRT should go through the following steps

- Administration of a
 - loading dose that depends on the target plasma level and V_d
 - drugs with high protein binding and predominant nonrenal elimination requires no further dosage adaptations
- Adaptation of the maintenance dose to the reduced renal function
- Augmentation of the maintenance dose in case of clinically important extracorporeal elimination

- Modern CRRT uses higher volumes & most drugs should be dosed according to a Cl_{creat} between 25 and 50ml/min
- This method of dosing adjustment assumes that drugs only undergo glomerular filtration and therefore will result in
 - overdosing for drugs with important tubular secretion
 - underdosing for drugs with important tubular reabsorption.
- In absence of drug monitoring it is preferred to overdose antibiotic treatment for drugs with low toxicity

CRRT v/s IHD

- CRRT has several theoretical advantages
 - better hemodynamic tolerability
 - more efficient solute clearance
 - better control of intravascular volume
 - better clearance of middle and large molecular weight substances
- Hypotension is most common complications with IHD ~ 20%–30%
- dialysis specific causes
 - excessive or rapid volume removal
 - changes in plasma osmolality
 - autonomic dysfunction
- Several prospective and retrospective studies have demonstrated better hemodynamic stability associated with CRRT

- CRRT - improved efficiency of solute removal
- Urea clearance is more efficient after 48 h than with alternate day IHD
- Fluid restriction compromise adequate nutrition with IHD
- The capacity to adjust fluid balance on an hourly basis in hemodynamically unstable patients is possible with CRRT

- CRRT may also have an immunomodulatory effect
- Association observed between sepsis severity, mortality rate and serum concentrations of various cytokines including TNF, IL1, IL6, and IL8
- Most of these middle molecular weight molecules are water-soluble and are theoretically removable by hemofiltration-based plasma water purification
- Immunomodulatory effects of CRRT remain theoretical at present & have not been shown to affect outcome in human studies

- Despite its apparent advantages over intermittent therapies, superiority of CRRT with respect to mortality or recovery of renal function has not been demonstrated
- In the largest randomized controlled trial to date (n = 166), intermittent hemodialysis was associated with
 - lower in-hospital (48% vs 65%)
 - ICU mortality (42% vs 60%)
- Patients with hypotension were excluded from participating in the study, and there was a significant difference in severity scores between the treatment arms despite randomization

SUMMARY

- Epidemiology of severe AKI in the ICU has changed over the past decade to sepsis and septic shock
- Accompanied by an ongoing evolution in blood purification technology for renal support
- IHD & CRRTs are available and have both advantages and disadvantages depending on the individual clinical situation
- Survival benefit has not been demonstrated for either method
- Nephrologist/intensivist to individualize RRT strategy

SUMMARY

- Adequate RRT results in improved survival in patients with AKI
- Clear guidelines on the dose of RRT and the timing of the initiation are still lacking
- Patients with sepsis and septic shock benefit from
 - early RRT initiation
 - use of increased RRT doses
 - increased removal of mediators

Is debatable