NONRENAL INDICATIONS OF CRRT IN CHILDREN

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- ***Countinious Renal Replacement Therapy(CRRT) :***
- has a positive effect on mortality in high-risk PICU patients. This treatment modality can be used more frequently in pediatric intensive care unit with improved patient outcomes.
- Paralleling the tecnological developments in pediatric critical care medical practice, CRRT has quickly become an essential form of kidney and organ support in the pediatric intensive care unit (PICU), because it allows for slow fluid removal and solute normalization in children with hemodynamic instability.
- Continuous kidney replacement therapy is increasingly being used in the PICU both for kidney and nonkidney indications , particularly in the last decade .

Indications for CRRT :

- Acute kidney injury (AKI)
- Fluid overload and Uremia
- Electrolyte instability
- Acid-base imbalances
- Sepsis (for removal of inflammatory mediators)
- Acute liver failure
- Inborn errors of metabolism
- Drug/toxin removal (intoxications)
- Tumor lysis syndrome
- Rhabdomyolysis
- Pancreatitis

RRT in severe sepsis and septic shock

- ***Phoenix Sepsis Score*** of at least 2 points from a composite four-organ system model that includes criteria for ***respiratory, neurologic, coagulation, and cardiovascular*** dysfunction, with
- ***Septic shock*** requiring at least 1 point in the cardiovascular subscore .
- ***MODS*** including: respiratory, kidney, hematologic

disseminated intravascular coagulation(DIC), hepatobiliary, and neurologic dysfunction

- The proliferation of infammatory mediators, cytokines, and endotoxins that characterize sepsis makes for a target-rich environment for the use of designed RRT filters.

- ***Treatment goals may include:***

- limiting the progression of (MODS)
- reversing (SIRS)
- shortening the duration of organ dysfunction
- shortening the reliance on IMV or inotropic support
- reduction in PICU and hospital length of stay
- improvements in survival and lifelong functioning.

RRT in inborn errors of metabolism (IEM)

- ***Urea cycle disorders, organic acidemias, fatty acid oxidation disorders, and mitochondrial cytopathies*** are metabolic emergencies, and prolonged elevation of **ammonia** or branched-chain amino acids (e.g., leucine) as well as severe **lactic acidosis** can cause profound hemodynamic consequences and irreversible neurological damage .

- Prompt recognition and management of these conditions are crucial.
- A high index of suspicion for metabolic crisis is critical in children of any age with suggestive clinical symptoms .
- Mortality rates remain as high as 25–50%, and non-survivors are likely sicker on admission .
- Even before a defnitive diagnosis is confrmed, emergency procedures for blood purifcation should commence.

Treatment

- aggressive hydration
- Stopping any form of protein
- provision of high-dose dextrose concentration
- As preparations for RRT are underway, it is rational to consider ammonia-scavenging agents (sodium benzoate, sodium phenylacetate, sodium phenylbutyrate, glycerol phenylbutyrate)

- Only limited evidence is available regarding the indication, best methods, and prescription for RRT.
- Several factors infuence the selection of the RRT method, including patient size, severity of enzyme defciency, hemodynamic stability, local expertise, vascular access, and availability of extracorporeal devices.
- The decision for an appropriate RRT should be made jointly by nephrology, metabolic, and critical care teams.

. According to the guidelines, RRT is recommended for patients :

- displaying rapidly deteriorating neurological conditions or cerebral edema, especially when blood ammonia levels surpass 150 µmol/l (256 µg/dl)
- or in the occurrence of moderate to severe encephalopathy .

Specifcally, high-dose CVVHD is the recommended first-line treatment for severe hyperammonemia (blood ammonia level>1000 µmol/l (1703 µg/dl)).

Once ammonia concentrations drop below 200 µmol/l (280 µg/ dl), transitioning to step-down CRRT is recommended .

- During high-dose CRRT, careful attention should be paid to hypophosphatemia, hypokalemia, and hypocalcemia (if using citrate anticoagulation) , replacing certain medications (specifcally antiepileptics such as phenobarbitone, etc.) as well as nutrients and antibiotics which are cleared through dialysis is essential.
- . During the acute crises of IEM, the role of RRT extends beyond just clearing toxic accumulations. It also aids in restoring pH and ensuring adequate caloric need without limiting fuid intake.
- A grave factor complicating the disease process is the increased risk of sepsis and secondary hemophagocytic syndrome. Thus, RRT might also serve an immunomodulatory function, addressing these hyper-infammatory conditions during the acute crises.

RRT in tumor lysis syndrome

• TLS is an oncological emergency and occurs frequently in children and adults with various malignancies such as acute lymphoblastic leukemia and Burkitt's lymphoma although it may also occur spontaneously in highly proliferative tumors or among patients with high tumor burden or sensitivity to chemotherapy

• Rapid Pediatric Nephrology breakdown of cells leads to the release of intracellular contents at a high rate into the blood, thereby disrupting the homeostatic mechanisms and leading to

• Hyperkalemia, hypocalcemia, hyperuricemia, uremia, and metabolic acidosis .

• *Cairo-Bishop criteria*

• is commonly used to diagnose TLS which suggests that laboratory TLS is present if>2 of the following are present within 3 days before or up to 7 days following chemotherapy:

- elevated uric acid (> 8 mg/dl),
- elevated phosphate (> 6.5 mg/dl)
- elevated potassium (>6 meq/l)
- and low calcium (<7mg / dl)
- or the presence of seizures, intracranial bleed, or cardiac arrhythmias

- . AKI, especially AKI requiring dialysis, is an important predictor of adverse outcomes associated with TLS
- Management and outcome data among children is limited .
- ***Initial management includes :***

- close monitoring; vigorous hydration (1.5 to 2 times maintenance rate) to achieve a urine output of around 4 ml/kg/h for infants and 100 ml/m2 /h for older children
- use of rasburicase for hyperuricemia to prevent AKI from uric acid deposition in tubules;
- use of diuretics
- management of hyperkalemia, hyperphosphatemia, and hypocalcemia .
- However, some patients may require RRT due to severe AKI or electrolyte imbalance, and oliguria.

- The choice of dialysis depends on the hemodynamic condition of the patient, fuid status, and presence of multi-organ involvement .
- Due to the expected ongoing lysis of tumor cells and the risk of rebound hyperkalemia and hyperphosphatemia, CRRT is preferred .
- A recent study demonstrated that CRRT is safe among children with hematological malignancies with severe TLS and reverses electrolyte and metabolic abnormalities within 6–12 h.
- However, among children with severe hyperkalemia and hyperuricemia, intermittent HD (or high-dose CRRT) is recommended initially to be switched to standard-dose CRRT. Dialysis should continue until there is sufcient recovery of kidney function and/or urine output and resolution of severe electrolyte abnormalities .
- The role of prophylactic RRT is unclear, and larger studies are needed to assess its benefit.

RRT for Acute liver failure

- Another important non-kidney indication of RRT is in children with liver failure.
- Liver failure can be acute, chronic, or acute on chronic liver failure
- RRT is the most used modality in clinical practice due to the familiarity with the device in pediatric ICUs across the globe.
- Since one of the main causes of mortality in these children is raised intracranial pressure secondary to impaired detoxifcation of toxic molecules, especially ammonia, RRT can be used either as a bridge to spontaneous liver recovery or successful liver transplantation
- although data on its impact on survival in these patients are sparse.

- ***Early use of RRT is recommended for:***
- Hepatic encephalopathy (HE) grades 3 and 4 and hyperammonemia (150 μmol/l (256 μg/dl)
- fuid control, and nutrition.
- decrease the levels of circulating cytokines and other neurotoxic molecules rapidly to decrease systemic infammation and cerebral edema.
- High-volume CRRT removes cytokines such as TNF-α and IL-1β, which are also implicated in the pathogenesis of ALF and HE. But ,must be mindful of the removal of drugs and nutrients while increasing the dose of CRRT.

- Endogenous thrombin generation potential in these patients has been higher than those without ALF.
- Despite deranged coagulation, and high level of INRs, children with liver disease undergoing continuous renal replacement therapy (CRRT) are prone to circuit clotting.
- ***The choices of anticoagulations are:***
- unfractionated heparin, regional citrate anticoagulation with close monitoring for citrate lock and citrate accumulation
- platelet inhibitors like prostacyclin, and nafamostat mesylate.

In the recently published data, use of epoprostenol (a synthetic prostacyclin analog) was shown to be safe , efcacious , and cost efective .

- Another modality in children with ALF is total plasma exchange (TPE)
- High-volume plasma has been shown to improve transplant-free survival by immune modulation leading to amelioration of multi-organ failure .
- TPE and CRRT can be used in tandem during the treatment of PALF .
- Increasingly, CRRT is being used intra-operatively during liver transplant especially in those children who are on CRRT pre-operatively for severe AKI, those with evidence of raised intracranial pressure, and those in multi-organ failure.

RRT in drug toxicity and poisoning

- Another non-kidney indication which can become lifethreatening is the ingestion of drugs or environmental substance.
- Extracorporeal therapies can remove some toxins rapidly, and thus may be urgently utilized to reduce the morbidity and mortality from toxicities.
- When considering extracorporeal therapy for the clearance of intoxications, an understanding of the three inherent properties of the substance is essential.
- First, a substance can be removed with hemodialysis/hemofltration only if it is localized to the intravascular space. A drug's volume of distribution (VD) is the volume in which the substance is distributed within the body's intravascular and extravascular spaces. The lower the VD, the higher its availability for extracorporeal removal [56].
- Second, only the portion of the substance which is not bound to protein can be cleared with dialysis. If a substance has very high protein binding, it is hard to dialyze the large molecular weight drug–protein complex .

- The size of the pores of the flter has an important role in substance removal as only those substances that are smaller than the pore sizes can pass through the flter membrane .
- Typical membranes used in hemodialysis can remove substances that are up to 15 kDa.
- Because convective clearances drag solvents across the membrane, hemofltration mode on a CRRT circuit can remove “middle” molecules (close to 50 kDa) .
- Dialysis has historically been used for lithium, salicylates, and alcohols , carbamazepine, valproic acid, and vancomycin .
- The main drawback to hemodialysis is that once the therapy stops, the drug concentrations may rebound as the substrate within the interstitial and cellular space will then redistribute into the intravascular space.

- To address this rebound, frequent intermittent treatment can be employed. Others choose a two-step approach whereby an intermittent HD treatment is performed to bring the level down rapidly, and then, CRRT is employed to keep the level from rebounding and continuous drug elimination.
- In small children, high-dose CRRT (to bring the levels down quickly) and, then once at the target level, a lower dose that maintains the level can be used to avoid rebound.
- Other potential advantages to CRRT are the ability to use a convection-based approach for higher middle molecule clearance

- ***Therapeutic plasma exchange (TPE)*** has the unique advantage of being able to remove drugs and/or drug-protein complexes of high molecular size.
- TPE that uses centrifuge techniques can remove any drug in the plasma (whether it is protein-bound or not)
- . The pore size of TPE that uses filtration techniques is much higher than standard dialysis membranes which also allows very high clearance of molecules that are highly protein-bound and/or large in size.

RRT in patients with rhabdomyolysis

- In rhabdomyolysis, rapid disruption of skeletal muscle occurs leading to a release of large amounts of myoglobin in the bloodstream.
- ***The causes are*** direct traumatic injury, due to drugs, toxins, infections, electrolyte and metabolic disorders, genetic disorders, crush syndrome, neuroleptic malignant syndrome, and malignant hyperthermia.
- Adults and children are at risk for developing rhabdomyolysis and AKI following a traumatic injury and crush syndrome

- These events can trigger skeletal muscle necrosis wherein intracellular metabolites (e.g., urea, potassium, phosphorus) and proteins (e.g., creatinine kinase and myoglobin) are released into the bloodstream. This response coupled with profuse uncontrolled bleeding, coagulopathy, and/or infection may lead to life-threatening multisystem organ failure and severe kidney dysfunction .

- Rapid fluid replacement therapy is necessary to avoid hypovolemia.
- it is crucial to keep a positive fuid balance.
- urine alkalization and maintain urine pH at≥6.5 to avoid the formation of uric acid crystals and increases dissolution of myoglobin and avoids further deposition.

Multiple studies suggest that early initiation of CRRT may have a favorable impact on survival outcomes for traumatized adult patients with AKI.

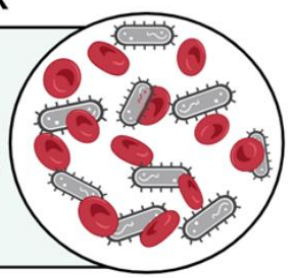
Unfortunately, pediatric data describing trauma-induced AKI and the utility of CRRT are scarce and needFuture work .

- Early initiation of CRRT may be useful in eliminating toxic substances, managing fuid overload, and preventing further fluid accumulation, all of which can further exacerbate an already severely compromised state.
- .

Pediatric CRRT and Diverse Indications

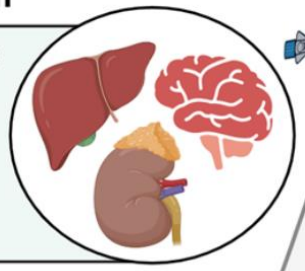
Severe Sepsis/ Septic Shock

- New filters being tested for their ability to remove cytokines and endotoxins(e.g., polymethylmethacrylate (PNMA) filter, oXiris, CytoSorb®)
- Limited pediatric data



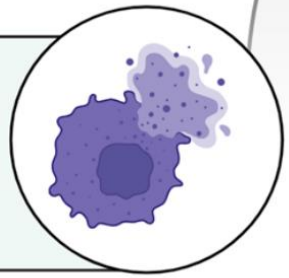
Inborn Errors of Metabolism

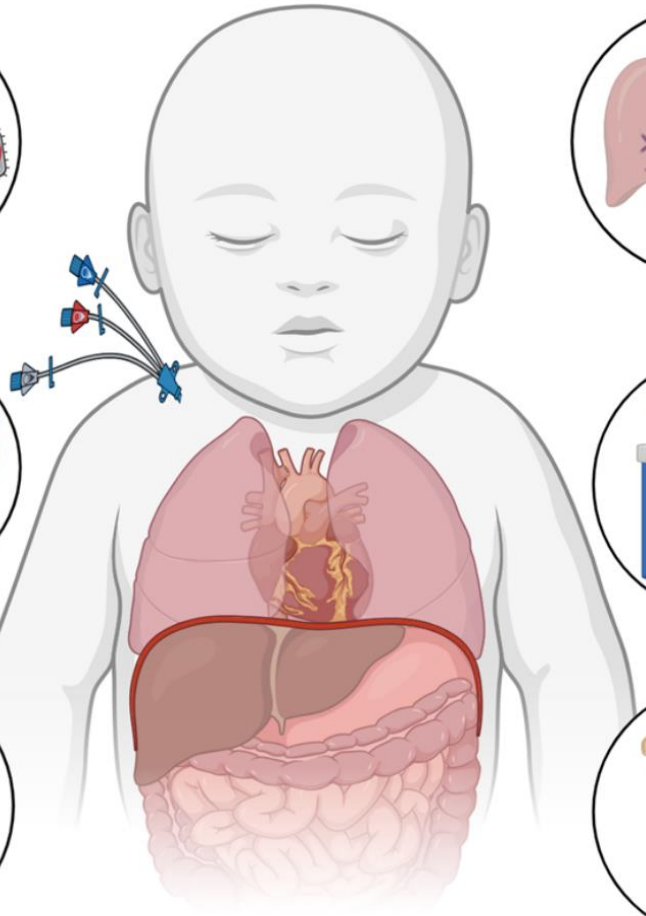
- Prompt supportive treatment to prevent adverse outcomes
- Early CRRT very useful to lower ammonia levels
- High-dose CVVHD preferred initially



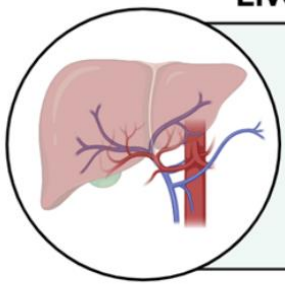
Tumor Lysis

- Early recognition and prompt treatment necessary
- CRRT preferred over HD to prevent rebound
- Role of prophylactic CRRT and PD unclear



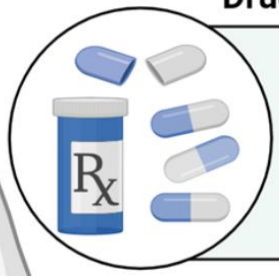


Liver Failure



- Hyperammonemia and encephalopathy require early CRRT
- CRRT aids in removal of cytokine/ neurotoxic molecules
- Careful monitoring for circuit clotting required

Drug Toxicity and Poisoning



- Timely CRRT highly beneficial
- V_D, size of molecule and protein bound status essential to CRRT plan
- HD preferred to achieve high clearance

Rhabdomyolysis

- Rapid initiation of fluid and supportive treatment required
- CVVH more effective to remove myoglobin
- Role of extracorporeal myoglobin removal not well established

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Acute Solution:

DPMAS for Liver Failure

- Specifically adsorb bilirubin and bile acid.
- Remove middle molecular toxins induced by liver disorder, such as inflammatory mediators, ammonia, phenol, mercaptan, etc.

Indications:

- Liver failure & Complications
- Pre & Post Liver Transplant
- Hepatitis
- Jaundice

Recommended regimen

2~3 times/week, 2~3h/session,

3~5 times each patient

*2-5 treatments for the first two weeks, 1-2 treatment per week after the third week, average 3-5 treatments per patient.

JaFron

Acute

ICU/Cardiac

HA330/HA380

Liver Failure

DPMAS(BS330+HA330-II)

Poisoning

HA230

Chronic

ESRD

HA130

Children Care

HA60
BS80


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هوالشافی

باياری خداوند متعال مرکز آموزشی، پژوهشی و درمانی زهرا مردانی آذری در مرداد ماه ۱۴۰۰ در زمان ریاست جمهوری جناب آقای دکتر روحانی و ریاست دانشگاهی جناب آقای دکتر محمدحسین صومی بهبهره برداری رسید.

این پروژه عظیم با تلاش بی دریغ خیر برزگوار

جناب آقای حاج کریم مردانی آذری و همکاری

دانشگاه علوم پزشکی تبریز و شهرداری کلانشهر

تبریز همکان یابی، طراحی و اجرا شد.

خداوند به تمامی دست اندرکاران اجر و پاداش عنایت فرماید.