

Introduction

- Hyperammonemia is a critical metabolic disturbance that is seen in inborn errors of metabolism (IEMs), notably urea cycle defects (UCD) and organic acidemias (OA).
- The initial presentation often includes hypotonia, irritability, somnolence, and metabolic acidosis
 - Secondary symptoms often include hyperammonemia or ketoacidosis
 - Signs and Symptoms include:
 - Poor feeding/refusal to feed
 - Periods of difficulty consoling
 - Periods of difficulty awakening
 - Vomiting
 - Failure to thrive
 - Hypotonia
 - Hypertonia
 - Tachypnea
 - Tachycardia
 - Hypoglycemia
 - Acidosis
 - Dehydration
 - Apnea
 - Seizures
 - Altered mental status
 - Sudden unexplained death
 - Cardiomegaly
 - Arrhythmia
 - Shock
 - Loss of thermoregulation
- Diagnosis is based on the detection of abnormal levels of amino acids or organic acids, or their metabolites, in urine and/or serum specimens.
- The risk of neurologic impairment increases with higher peak ammonia levels and particularly longer durations of hyperammonemia.
- Extracorporeal therapy is often required to achieve a rapid correction of the metabolic disturbance, of which include:
 - Exchange transfusions,
 - Peritoneal dialysis (PD),
 - Hemodialysis (HD), and
 - continuous renal replacement therapy (CRRT).
- The rapid clearance of plasma ammonia levels via CRRT is most often used to treat severe hyperammonemia
- CRRT in IEM:
 - Efficiently removes toxic metabolites to safer levels while diagnostic studies are performed
 - Minimizes the duration of the metabolic derangements which adversely affect long-term outcome.

References

1.Yetimakman AF, Kesici S, Tanyildiz M, Bayrakci US, Bayrakci B. A Report of 7-Year Experience on Pediatric Continuous Renal Replacement Therapy. J Intensive Care Med. 2019;34(11-12):985-989. doi:10.1177/0885066617724339

2.Cavagnaro Santa María F, Roque Espinosa J, Guerra Hernández P. Continuous venovenous hemofiltration in neonates with hyperammonemia. A case series. Uso de Hemofiltración veno-venosa continua en neonatos con hiperammonemia. Serie clínica. Rev Chil Pediatr. 2018;89(1):74-78. doi:10.4067/S0370-41062018000100074

3.Naorungroj T, Yanase F, Eastwood GM, Baldwin I, Bellomo R. Extracorporeal Ammonia Clearance for Hyperammonemia in Critically Ill Patients: A Scoping Review. Blood Purif. 2021;50(4-5):453-461. doi:10.1159/000512100

4.Wong Vega M, Juarez Calderon M, Tufan Pekkuksen N, Srivaths P, Akcan Arian A. Feeding modality is a barrier to adequate protein provision in children receiving continuous renal replacement therapy (CRRT). Pediatr Nephrol. 2019;34(6):1147-1150. doi:10.1007/s00467-019-04211-z

5.Kim HJ, Park SJ, Park KI, et al. Acute treatment of hyperammonemia by continuous renal replacement therapy in a newborn patient with ornithine transcarbamylase deficiency. Korean J Pediatr. 2011;54(10):425-428. doi:10.3345/kjp.2011.54.10.425

6.Symons JM, Chua AN, Somers MJ, et al. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol. 2007;2(4):732-738. doi:10.2215/CJN.03200906

7.Hanudel M, Avasare S, Tsai E, Yadin O, Zaritsky J. A biphasic dialytic strategy for the treatment of neonatal hyperammonemia. Pediatr Nephrol. 2014;29(2):315-320. doi:10.1007/s00467-013-2638-x

8.Ames EG, Luckritz KE, Ahmad A. A retrospective review of outcomes in the treatment of hyperammonemia with renal replacement therapy due to inborn errors of metabolism. Pediatr Nephrol. 2020;35(9):1761-1769. doi:10.1007/s00467-020-04533-3

9.Yetimakman AF, Kesici S, Tanyildiz M, Bayrakci B. Continuous Renal Replacement Therapy for Treatment of Severe Attacks of Inborn Errors of Metabolism. J Pediatr Intensive Care. 2019;8(3):164-169. doi:10.1055/s-0039-1683991

10.Porta F, Peruzzi L, Bonaudo R, et al. Differential response to renal replacement therapy in neonatal-onset inborn errors of metabolism. Nephrology (Carlton). 2018;23(10):957-961. doi:10.1111/nep.13409

11.Lehtranta S, Honkila M, Kallio M, et al. Risk of Electrolyte Disorders in Acutely Ill Children Receiving Commercially Available Plasmalike Isotonic Fluids: A Randomized Clinical Trial [published correction appears in JAMA Pediatr. 2021 Feb 1;175(2):212]. JAMA Pediatr. 2021;175(1):28-35. doi:10.1001/jamapediatrics.2020.3383

Objectives

- Analysis of mortality and risk factors for in the use of RRT to correct metabolic disturbances associated with IEMs

Methodology

- Design:** This is a systematic review on the use of RRT for treating neonates and pediatrics with hyperammonemia caused by an IEM, including prescriptions, prognosis, and outcomes.
- Study Population:** Neonates and pediatrics (<18) with IEM.
- Variables:** Demographic information (sex, age, weight), cause of IEM, ammonia levels upon initiation/ termination of treatment, KRT modality, outcomes, cointervention, and side effects.

Preliminary Results

- A total of 28 studies were included with the data on 1,580 subjects reported.

Incidence of:

- Urea cycle disorders = 27.8%
- Argininosuccinic lyase deficiency = 16.7%
- Argininosuccinic acid synthetase deficiency = 11.1%
- Carbamoyl phosphate synthetase deficiency = 5.6%
- Organic Acidurias = 16.7%
- Isovaleric acidemia = 5.6%
- Idiopathic hyperammonemia = 5.6%

- RRT treatment was complicated by acute renal failure in 48.2% of patients.

- RRT modality of choice:
 - HD = 66.7%
 - Mean duration: 1.7 ± 0.8 days
 - CRRT = 28.6%
 - Mean duration: 3.7 ± 4.6 days
 - PD = 4.8%
 - Mean duration: 2.1 ± 0.3 days

Discussion

- The primary indication for the initiation of RRT is hyperammonemia that fails to improve after the administration of medications allowing for nitrogen excretion via alternative pathways .
- Appropriate nutritional support can inhibit further protein catabolism.
- HD is the most efficient method to reduce plasma ammonia levels; however, hypotension is often cited as a complication and ammonia levels tend to rebound shortly after discontinuation
- Volume removal may be detrimental in patients with metabolic derangements in that it may increase the risk of cardiovascular instability.
 - Strict attention to volume status should be a primary goal and may be achieved by accurately quantifying urine losses by the use of a Foley catheter and by checking intradialytic weight changes during the RRT treatment.
- CRRT can decrease plasma ammonia levels with less risk of hemodynamic instability and less chance of rebound hyperammonemia
- PD remains an option for physicians caring for hyperammonemia neonates who are concerned about the ability to obtain central access in a timely fashion

Conclusion

- Early initiation of RRT should be the standard of care, as continuing with medical therapy that has failed to control the metabolic derangement would be expected to increase the risks for neurologic and developmental morbidity and mortality.

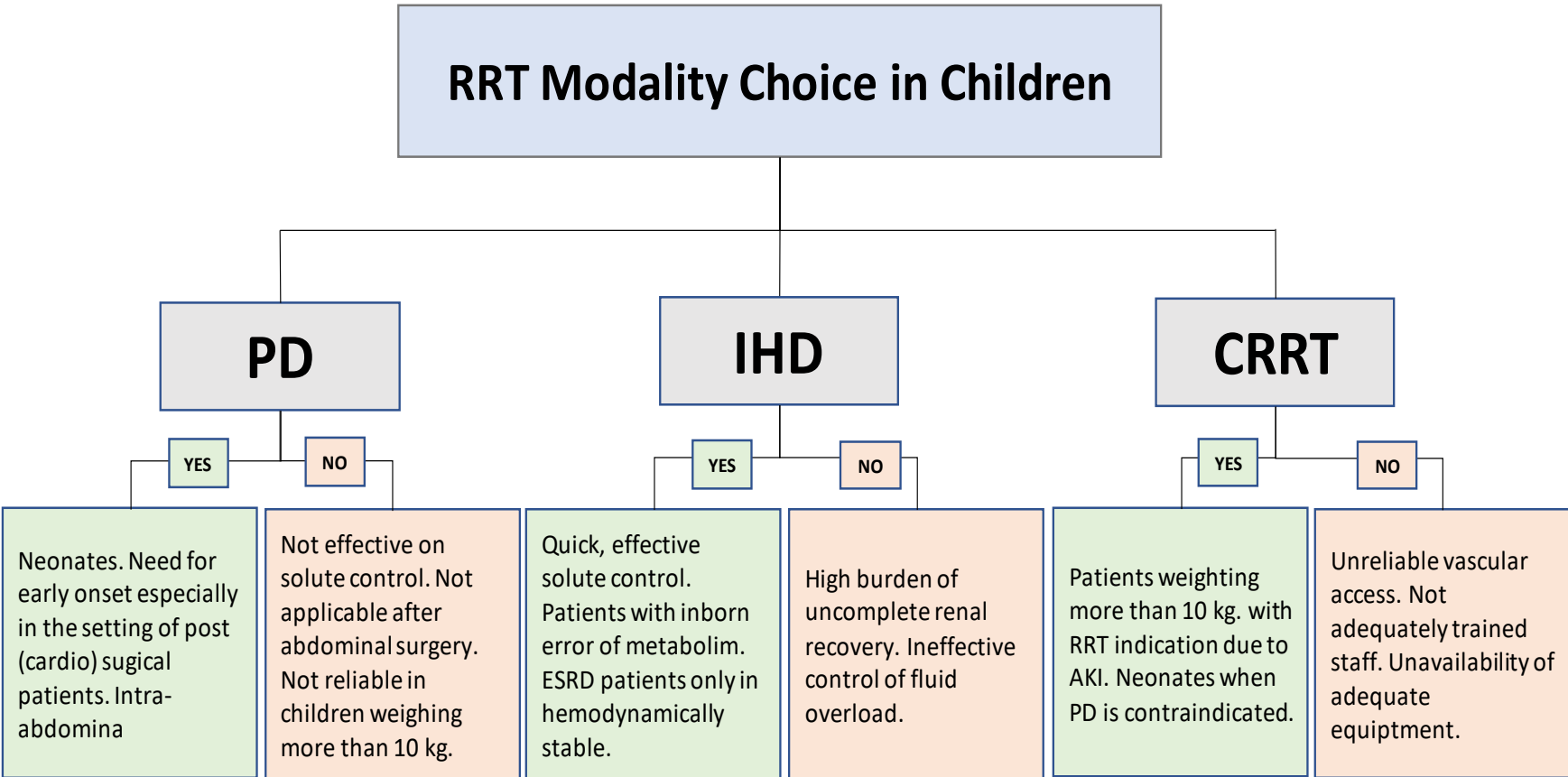


Figure 1: Flowchart depicting the ideal renal replacement modality in children based on relative circumstances.