FACULTY OF MEDICINE
AND HEALTH SCIENCES

A KINETICS BASED ALGORITHM TO TREAT ACUTE NEONATAL HYPERAMMONEMIA

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Background

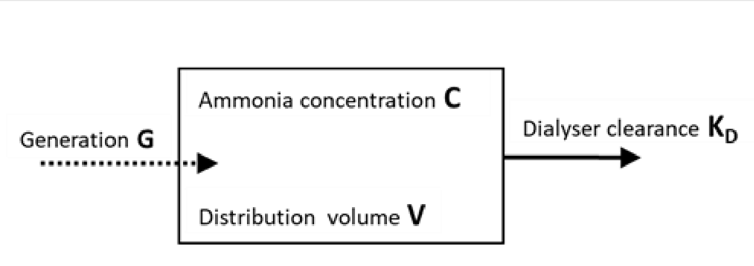
Acute neonatal hyperammonemia due to inborn errors of metabolism (IEM) is associated with poor neurological outcomes and high mortality. As the outcome of these infants is inversely related to the duration and severity of the hyperammonemic coma, prompt management that guarantees a fast decline in serum ammonia is crucial.

We developed, based on kinetic modeling, a user-friendly and widely applicable algorithm to treat acute neonatal hyperammonemia.

Methods

All hemodialysis (n=11) sessions performed in 2019-20 at Ghent University Hospital (Belgium) for acute neonatal hyperammonemia due to IEM were retrospectively reviewed. 4008 Fresenius (dialyzer FXPaed) was used in 5 sessions, and CarpeDiem (co-current flow) with dialyzer 0,15m² (CD015) and 0,25m² (CD025) in respectively 2 and 4 sessions. Dialyzer clearance (K_D) and extraction ratio ($ER=K_D/Q_B$) were derived from the measured ammonia time-concentration curves during dialysis, assuming one-compartmental ammonia kinetics..

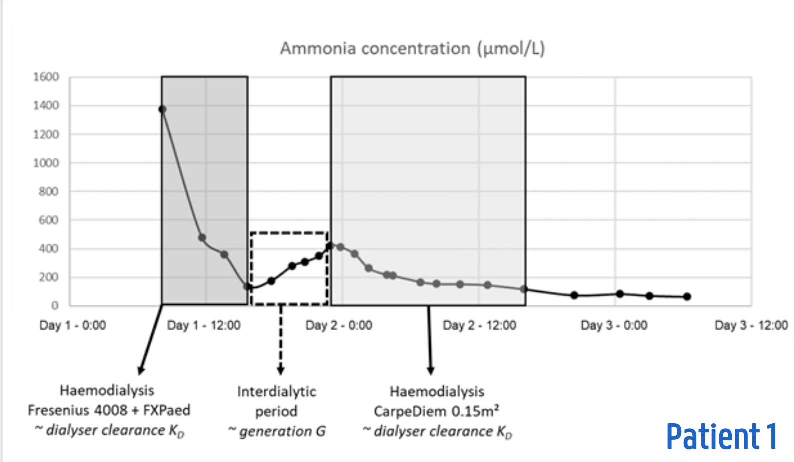
The compartmental volume resembles the distribution volume V of ammonia, which was considered to be total body water, calculated by the formula of Wells et al. (2005) using body weight, height, age, and gender. This compartmental volume is mathematically described having a homogeneous ammonia concentration and different inputs (i.e. generation G) and outputs (dialyzer clearance K_D).



$$C = C_0 \cdot exp\left(\frac{-K_D \cdot t}{V}\right)$$

1-compartiment model

G (µmol/min), i.e. the resultant of the ammonia production and the metabolic medicinal correction, was derived from the ammonia concentration increase during an interdialytic steady state period.



The calibrated single compartmental model was further used to simulate serum ammonia decline in infants (male) of 3 (TBW 72%) and 4 kg (TBW 63%) at age 3-4 days for different ammonia start concentrations (3000, 1500, 800, 400, 200 µmol/L), dialysis machines, dialyzers and settings (Q_B 30-50mL/min).

Results

4 neonates (3.2±0.4 kg; 3/4 males) with acute neonatal hyperammonemia were treated by hemodialysis on the age of 3.0[3.0;3.5] days. Blood flows (Q_B) were 30-35mL/min (4008/FXPaed), 22-35mL/min (CarpeDiem 0.15m²), and 30-34mL/min (CarpeDiem 0.25m²), while dialysate flow was 300mL/min (4008/FXPaed) and 10mL/min (CarpeDiem).

	Patient 1	Patient 2	Patient 3	Patient 4
Patient characteristics at start hemodialysis				
Age (days)	3	3	3	5
Sex (F/M)	M	M	M	F
Body weight (kg)	3.15	3.82	3.02	2.96
Body length (cm)	48	54	52	48.5
Calculated TBW (L)	2.14	2.62	2.23	2.04
Underlying IEM	OTC	OTC	OTC	MMA
Serum ammonium (µmol/L)	1377	729	3017	709
Dialysis prescription				
Vascular access	6.5 Fr dL VJI	6.5 Fr dL VJI	6.5 Fr dL VJI	6.5 Fr dL VJI
Fresenius 4008 (n)	1	2	1	1
Carpe Diem CD015 (n)	2	0	0	0
Carpe Diem CD025 (n)	1	3	0	0

OTC: ornithine carbamoyl transferase deficiency, MMA: methylmalonic acidemia, dL: double lumen, VJI: vein jugularis interna, F: female, M: male, L: liter.

ER were found 45±6% with 4008/FXPaed dialysis, and 13±3% and 15±4% with the CarpeDiem/0.15m² and CarpeDiem/0.25m² dialysis setup. Generation was 0.48±0.32µmol/min, with no observed impact on K_D and ER.

To calculate the time needed to decrease the ammonia concentration from a predialysis start concentration C_{start} to a target concentration C_{target}, accounting for the patient's characteristics and dialysis setup, this algorithm was developed:

	PATIENT DATA	HEMODIALYZER DATA
	Calculation of distribution volume V	*Calculation of dialyzer clearance K*
INPUT	Body weight BW (kg) Body height HT (cm) Age (years) Gender M/F	Ammonia concentration at: Dialyzer inlet - C_{inlet} Dialyzer outlet - C_{outlet}
OUTPUT	$V_{male} = TBW_{male} = exp[-2.952 + 0.551 \cdot LN(BW) + 0.796 \cdot LN(HT) + 0.008 \cdot age]$ $V_{female} = TBW_{female} = exp[-2.952 + 0.551 \cdot LN(BW) + 0.796 \cdot LN(HT) + 0.008 \cdot age - 0.047]$	$ER = \frac{C_{inlet} - C_{outlet}}{C_{inlet}}$ $K = ER \cdot Q_B$

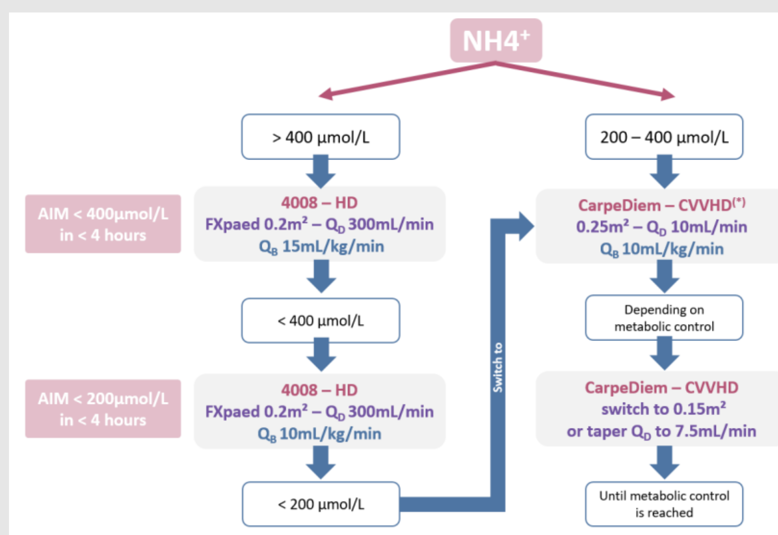
	DIALYSIS SIMULATION
	Calculation of time to target
INPUT	Start ammonia concentration - C_{start} Target ammonia concentration - C_{target}
OUTPUT	$\text{time to target (min)} = \frac{-V}{K} \cdot LN\left(\frac{C_{target}}{C_{start}}\right)$

As visualized in table below, for start concentrations >400-800µmol/L in 3kg child, CarpeDiem was found inadequate to decrease serum ammonia in <4h. Body weight of 4kg resulted in longer time intervals to reach target.

Startconcentration:		3000 µmol/L		1500 µmol/L		800 µmol/L		400 µmol/L		200 µmol/L	
setup	threshold	QB30	QB50	QB30	QB50	QB30	QB50	QB30	QB50	QB30	QB50
4008	400	322	193	211	126	111	66	-	-	-	-
	200	433	259	321	193	221	133	111	67	-	-
	100	546	326	431	259	330	199	221	133	110	65
CD025	400	965	-	632	-	332	-	-	-	-	-
	200	>>	-	965	-	662	-	332	-	-	-
	100	>>	-	>>	-	995	-	665	-	330	200
CD015	400	1112	-	730	-	382	-	-	-	-	-
	200	>>	-	1112	-	765	-	382	-	-	-
	100	>>	-	>>	-	1150	-	765	-	385	230

Time (minutes) needed for the ammonia concentration to reach the threshold concentration in a male infant of 3kg, for different dialysis setups and different blood flows. QB: blood flow (mL/min); CD: CarpeDiem; >>: more than 24h

Derived from these preliminary ammonia kinetics and dialyzer clearances for an infant of 2-4kg, a clinical protocol was proposed.



CONCLUSION: The present kinetic model resulted in a useful algorithm as a tool to concept a center-specific protocol to treat acute neonatal hyperammonemia fitting the patient's characteristics. This tool might be an important chain in the decision-making process, taking into account the availability of dialysis equipment and/or staff, treatment goals and overall condition of the patient, the trend in serum ammonia levels, the response to nitrogen-scavenger therapy and the age and body characteristics of the infant.

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