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RENAL REPLACEMENT THERAPY IN INBORN ERRORS OF METABOLISM

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Bambino Gesù
OSPEDALE PEDIATRICO

Health-e-Child

Comune di Roma

Information Society Technologies

OUTLINE

- ***WHY:*** RRT is useful in IEM
- ***WHEN:*** intervention timing of RRT in IEM
- ***HOW TO PERFORM :*** RRT in IEM
- ***HOW TO GET INFORMATION:*** about the disease from response to RRT and kinetic models
    - *HYPERAMMONEMIA*
    - *MSUD*
    - *OXALOSIS*

"SMALL MOLECULES" DISEASES INDUCING CONGENITAL HYPERAMMONEMIA

INCIDENCE

- Overall: 1:9160
- Organic Acidurias: 1:21422
- Urea Cycle Defects: 1:41506
- Fatty Acids Oxidation Defects: 1:91599

AGE OF ONSET

Neonate: 40%

Infant: 30%

Child: 20%

Adult: 5-10% (?)

Dionisi-Vici et al, J Pediatrics, 2002.

KEY POINTS OF NEONATAL HYPERAMMONEMIA

- hyperammonemia is extremely toxic (*per se* or through intracellular excess glutamine formation) to the brain causing astrocyte swelling, brain edema, coma, death or severe disability,

thus:

- emergency treatment has to be started even before having a precise diagnosis since prognosis may depend on:

✓ coma duration (total and/or before treatment)

(Msall, 1984; Picca, 2001; McBryde, 2006)

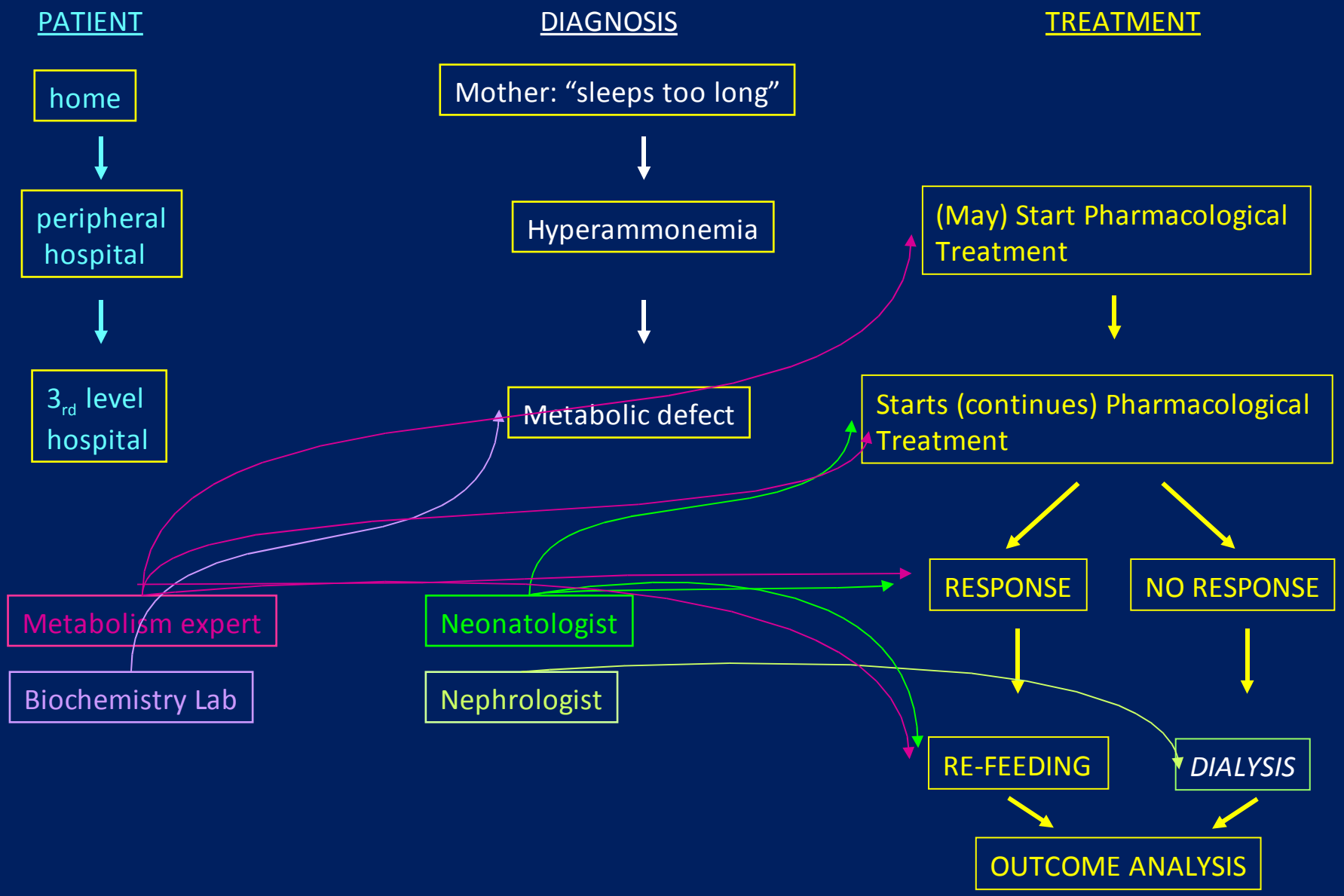
✓ peak ammonium level

(Enns, 2007)

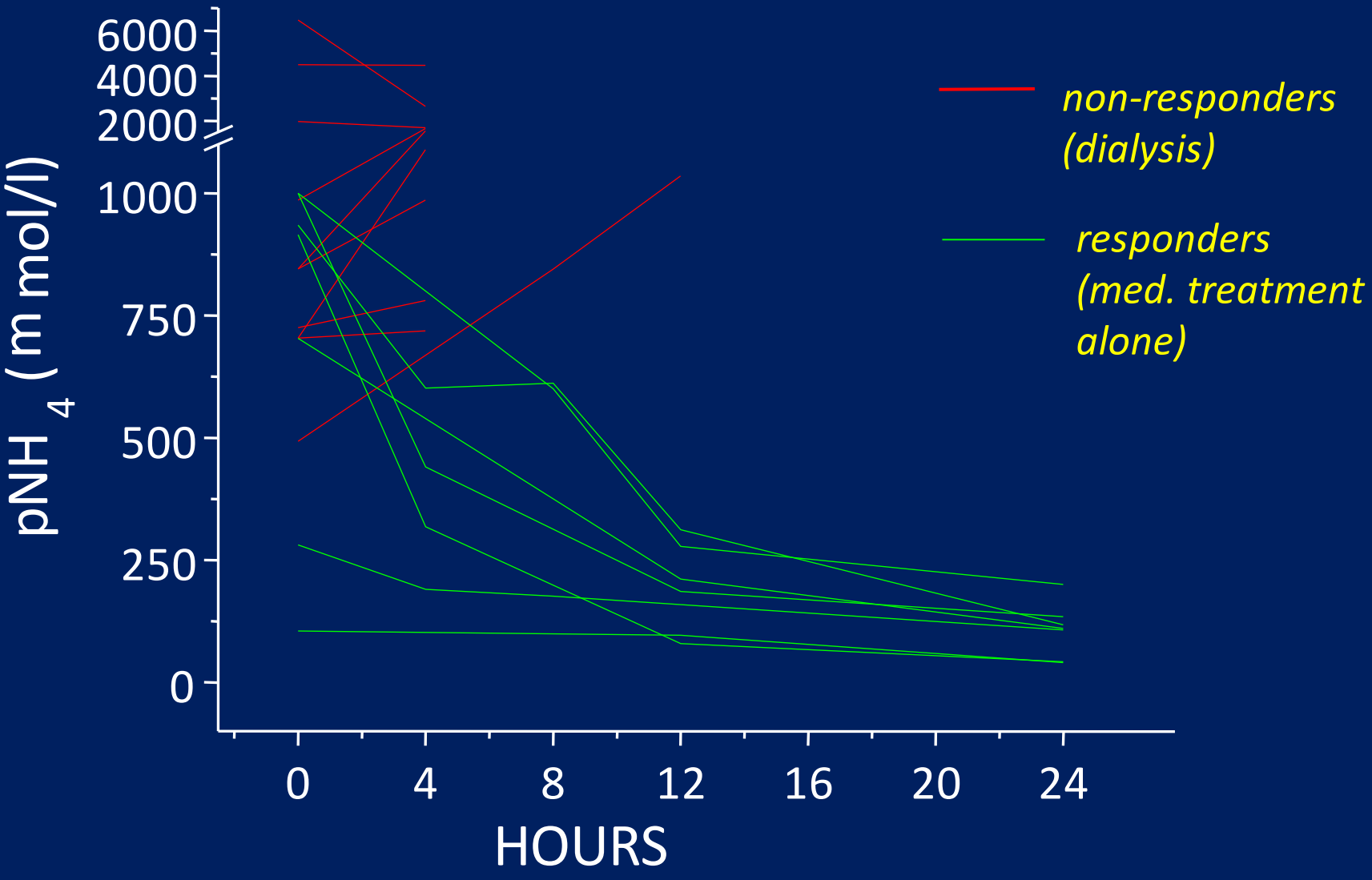
✓ detoxification rapidity

(Schaefer, 1999)

THE USUAL COURSE OF NEONATAL HYPERAMMONEMIA



0-4 HOURS MEDICAL TREATMENT IN NEONATAL HYPERAMMONEMIA



Picca, 2002, unpublished

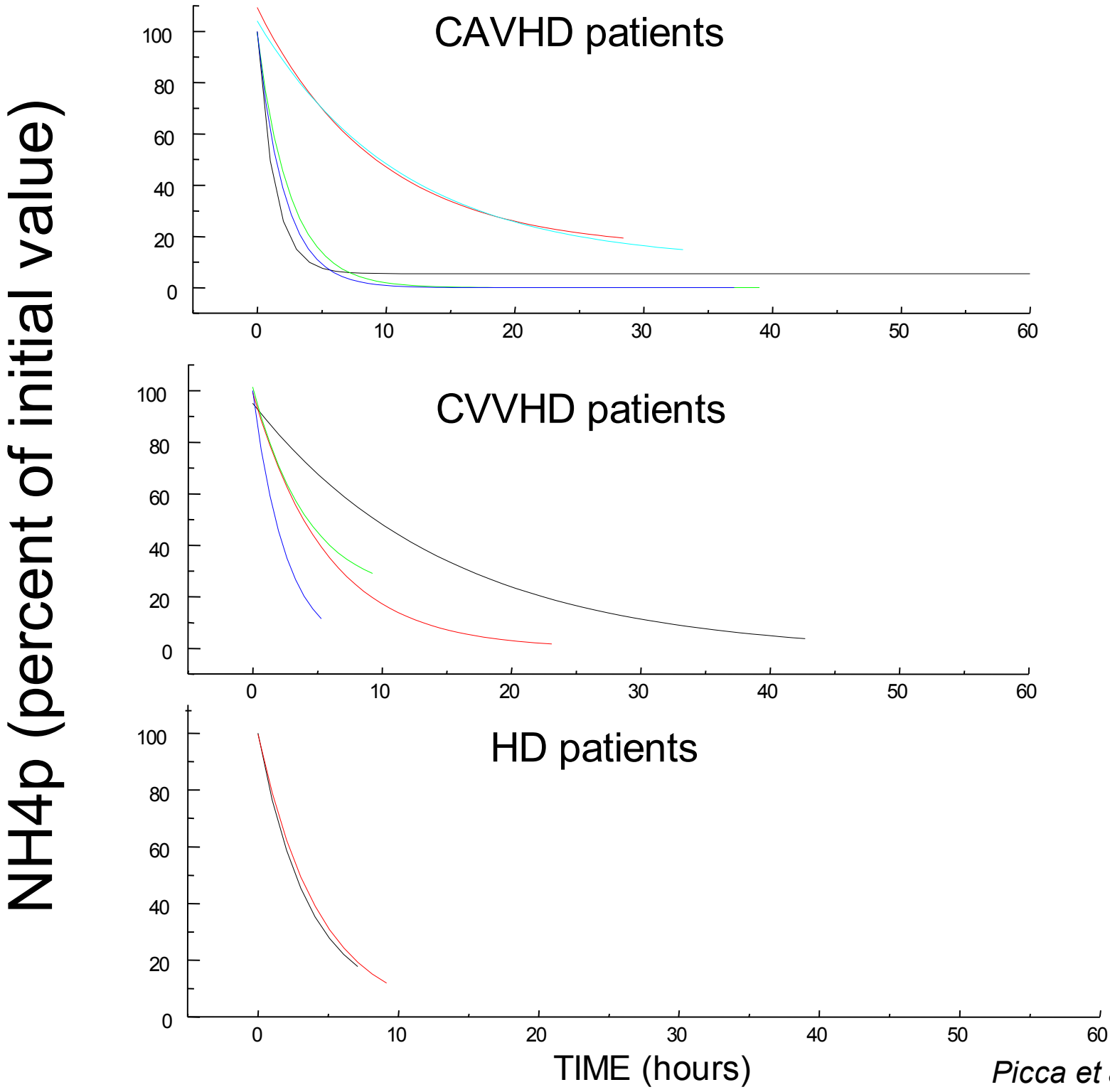
AMMONIUM CLEARANCE AND FILTRATION FRACTION USING DIFFERENT DIALYSIS MODALITIES

Patient (n)	Type of Dialysis	Qb (ml/min)	Qd (ml/min)	Ammonium Clearance (ml/min/kg)	Ammonium Filtration Fraction (%)
3	CAVHD	10-20	8.3 (0.5 l/h)	0.87-0.97	12.5-14.3
3	CVVHD	20-40	33.3-83.3 (2-5 l/h)	2.65-6.80	53.0-58.0
2	HD	10-15	500	3.95-5.37	95.0-96.0

Picca et al., 2001

Patient (n)	Type of Dialysis			Ammonium Clearance (ml/min)	
4	PD			0.48-2.7 (1.4±1.1, about 0.48 ml/min/kg)	

Arbeiter et al., 2009

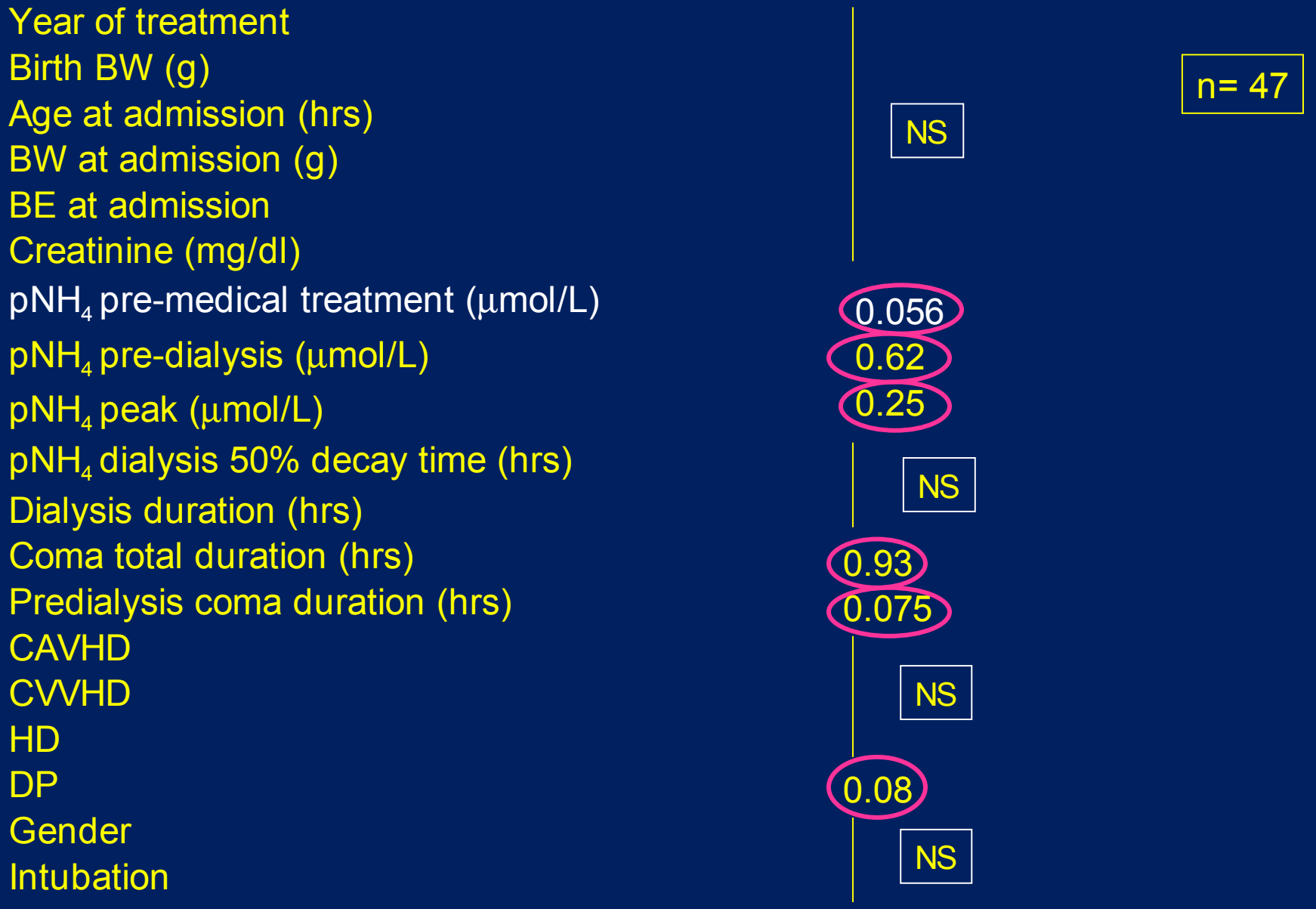


Picca et al. Ped Nephrol 2001

PROGNOSTIC INDICATORS IN DIALYZED NEONATES: SURVIVAL

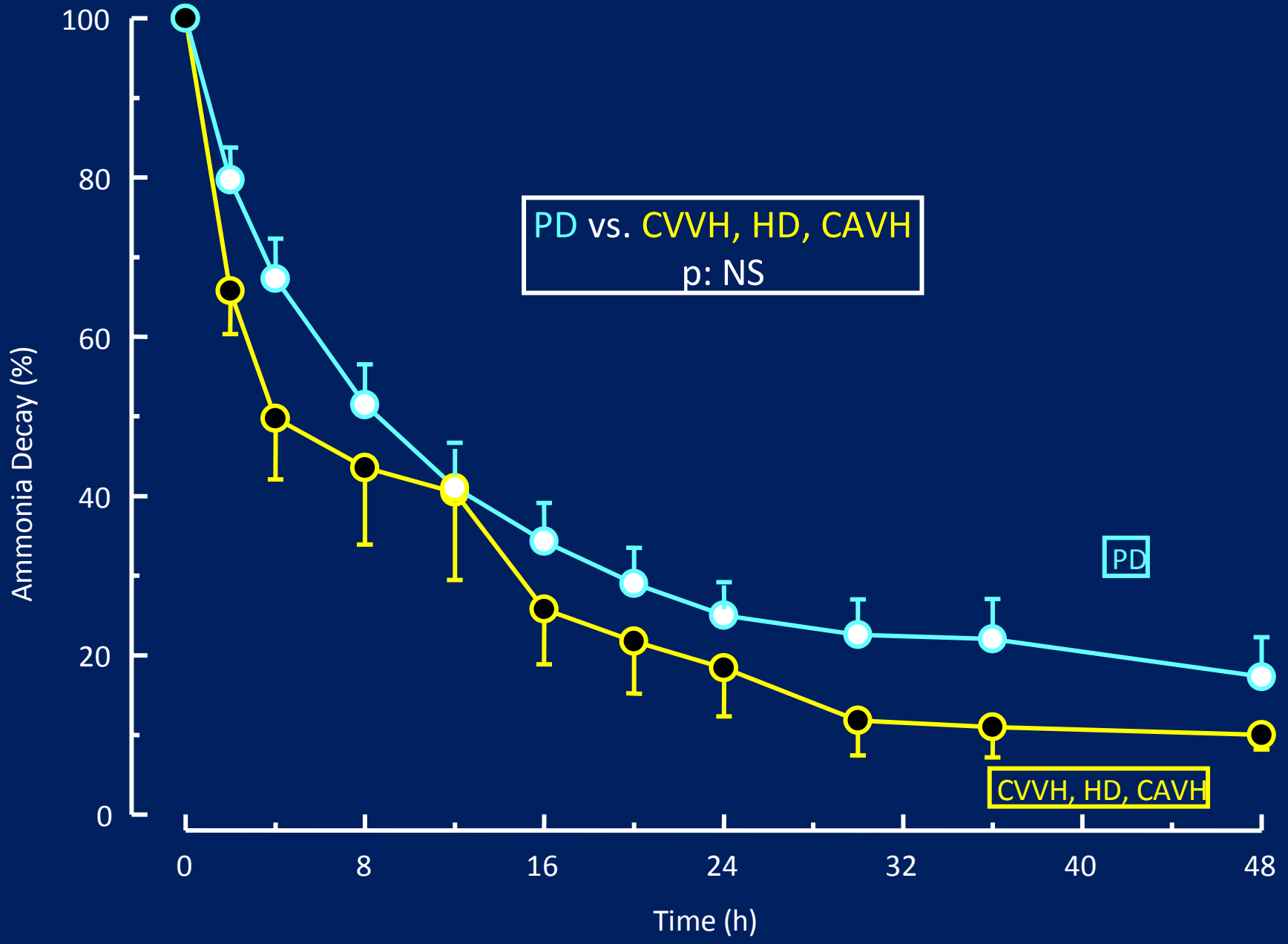
McBryde, 2006	•pNH_4 at admission<180 μmol/L •Time to RRT<24 hrs •Medical treatment<24 hrs •BP> 5%ile at RRT initiation •HD initial RRT (trend)
Schaefer, 1999	•50% pNH_4 decay time < 7 hrs •(catheter > 5F)
Picca, 2001	•pre-treatment coma duration < 33 hrs (no influence of post-treatment duration) •responsiveness to pharmacological therapy
Pela, 2008	• pre-treatment coma duration < 10 hrs

DEP. VARIABLE 1: SURVIVAL AT DISCHARGE



Picca, unpublished, 2009

EFFICIENCY OF PERITONEAL VS. EXTRACORPOREAL DIALYSIS ON AMMONIUM DECAY



CONCLUSIONS- RRT in HYPERAMMONEMIA

- ***WHY:***
- ➢ RRT induces rapid decrease of ammonium levels
- ***WHEN:***
- ➢ Four hours seem a reasonable time for pharmacological treatment before RRT initiation
- ***HOW TO PERFORM:***
- ➢ CVVHD with high dialysate flow seems the best available option
- ➢ However, PD induces similar plasma ammonium decay in the face of lower ammonium clearance (glucose utilization → anabolism? shorter predialysis coma duration?)
- ***HOW TO GET INFORMATION:***
- ➢ Severe hyperammonemia can be reversed also by pharmacological treatment alone
- ➢ Response to dialysis can be useless if coma duration before treatment is too long

KEY POINTS OF MSUD (LEUCINOSIS)

- In Maple Syrup Urine Disease (MSUD), leucine is the main neurotoxic compound that accumulates in cells and body fluids during proteolytic stress (“crises”)
- These crises present with lethargy and/or coma and are potentially associated with a high risk of cerebral edema and death
- Leucine is a free solute (MW 131) and it easily diffuses through dialysis membranes

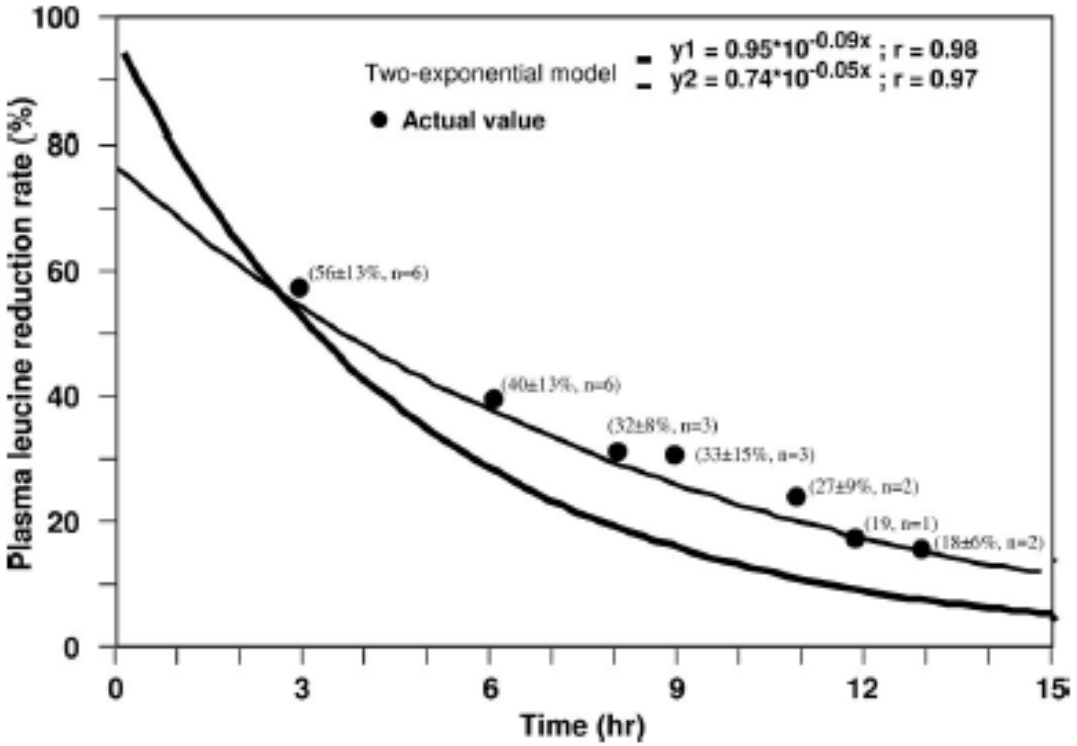


Figure 1. Leucine plasma kinetic modeling obtained from seven neonates with severe acute-onset MSUD treated with CECRT and with specific nutrition. The number of patients, the mean plasma leucine level decrease, and the SD (percentage of initial plasma leucine level) are provided for each value plotted. The leucine reduction rate is correlated with a bicompartmental model. The first 3-h period corresponds to an exponential curve: $[Leu]_t = [Leu]_i \times 0.95 \times 10^{-0.09t}$ ($r = 0.98$); and the period from the h 4 to the end of CECRT corresponds to a second exponential curve: $[Leu]_t = [Leu]_i \times 0.74 \times 10^{-0.05t}$ ($r = 0.97$), where $[Leu]_t$ is the leucine plasma level (μmol/L), t (h) is CECRT duration, and $[Leu]_i$ is the initial plasma level.

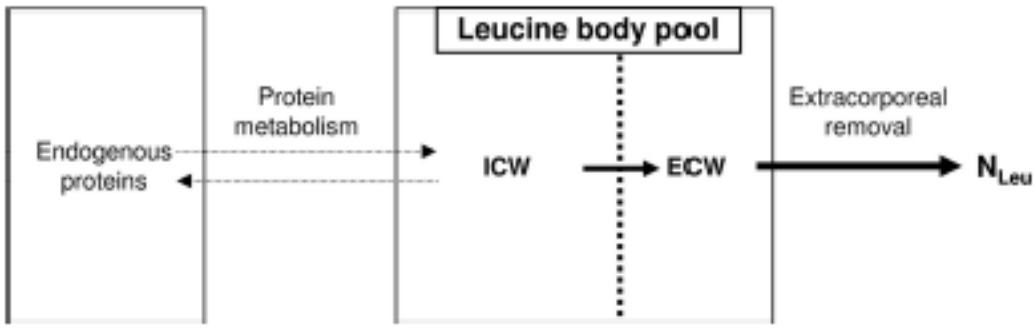
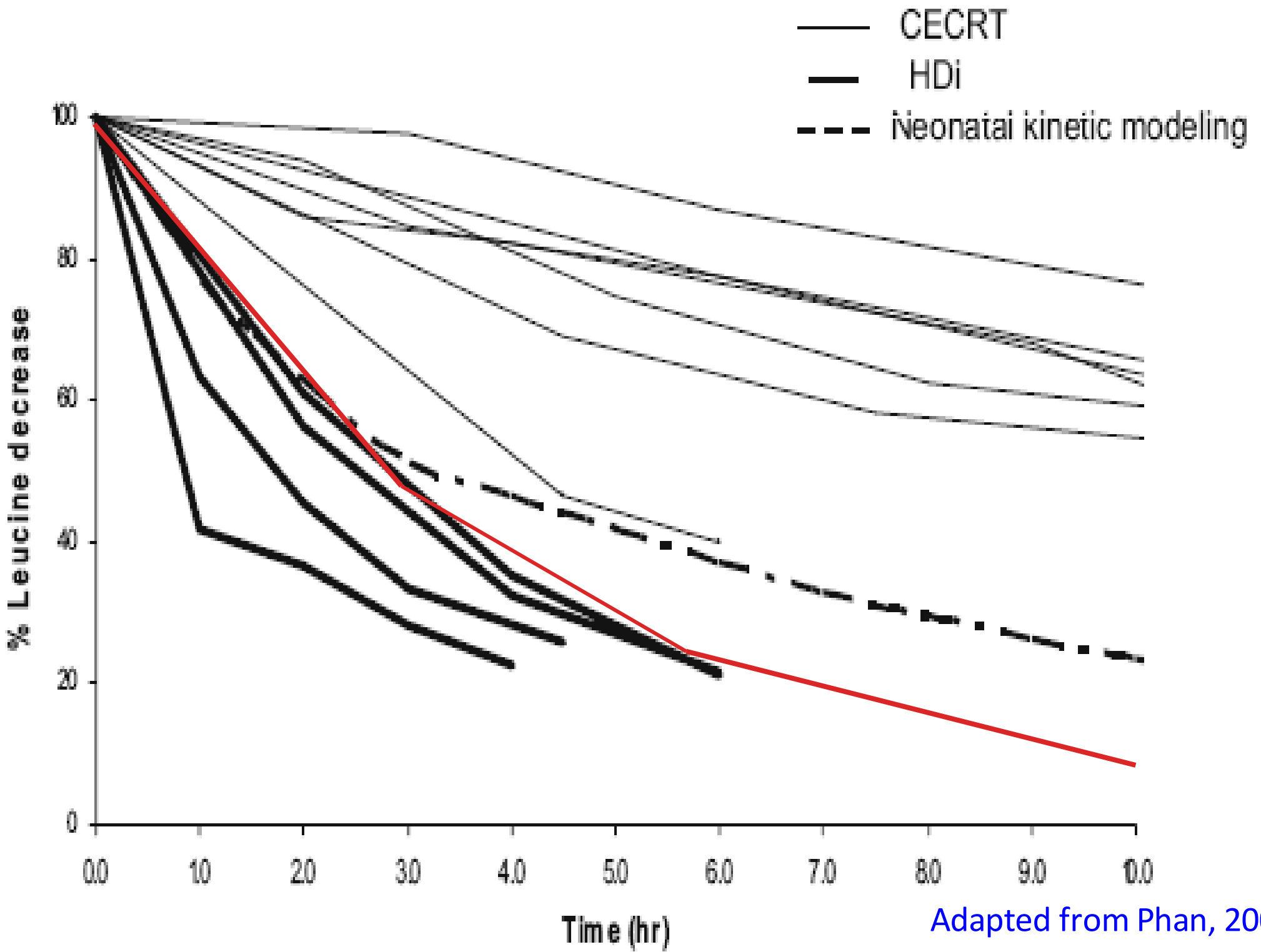


Figure 3. Schema of the bicompartmental model of leucine fluxes in MSUD. *ICW*, intracellular water space; *ECW*, extracellular water space; N_{Leu}, leucine mass removed by continuous extracorporeal removal therapy.

i.e.: 6-8 hrs of RRT with 35 ml/min/1.73 m² can induce
a 60% leucine plasma level decrease (~ 4 ml/min in a neonate)

Jouvet, 2005



Adapted from Phan, 2006

Table 1. *Kinetic modeling of leucine plasma concentration changes derived from data obtained from seven neonates with acute phase maple syrup urine disease treated with CECRT*

			CECRT				Leucine plasma level		Leucine			
Patient	BW (kg)	Age at treatment (days)	T (hr)	QS	QD (ml/min)	QF	initial (μM)	final (μM)	mass removal (mmol/session)	Cl (ml/min)	Vd1 (% BWt)	Vd2 (% BWt)
1	3.7	12	12	20	0	2.0	2186	1131	2.0	1.7	37	42
2	2.9	11	11	20	16	1.0	3818	1275	6.6	4.3	45	95
3	2.0	22	12	20	25	0.0	2536	488	3.5	3.9	42	89
4	3.2	16	13	30	0	7.4	3117	679	5.1	3.5	25	75
5	3.1	12	12	40	0	8.7	2226	305	4.0	4.1	29	68
6	3.2	13	11	40	0	9.5	3189	196	6.2	4.8	24	60
7	2.4	12	8	30	27	0.0	1629	496	2.3	2.8	36	76
Mean ± SEM										3.6 ± 0.4	34 ± 3	72 ± 7

Jouvet, 2005

BW (kg)	Time (hrs)	Qb (ml/min)	Qd (ml/min)	Initial (μmol/l)	At 3 hrs (μmol/l)	Final (μmol/l)	Mass removal (μmol)	Cl Leu (ml/min)
3.6	14	**34-40**	**50**	**1190**	**571**	**94**	**5.063**	**8.8**

Picca, unpublished, 2010

CONCLUSIONS- RRT in MSUD

- ***WHY:***
  - RRT induces rapid decrease of leucine levels
- ***WHEN:***
  - Plasma leucine levels > 1000 µmol/l are associated with highest neurological risk and make indication to RRT mandatory
- ***HOW TO PERFORM:***
  - Leucine is best removed by diffusion (HD, CVVHD)
  - In CVVHD, dialysate flow ≥ 3 l/h seems indicated
- ***HOW TO GET INFORMATION:***
  - RRT provides info about leucine bicompartimental distribution volume
  - This allows therapy targeting

KEY POINTS OF OXALOSIS

- Oxalosis is the accumulation of insoluble oxalate throughout the body (mainly bone, kidney, heart and liver) occurring in hyperoxaluria type 1 (PH1), a rare autosomal recessive disorder (1:120,000 live births) caused by the defect of liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- In early expressed phenotype, oxalosis can lead to ESRD even in neonatal age
- In these patients, combined liver-kidney transplantation is presently the therapeutic gold standard
- No form of chronic dialysis is recommended in oxalosis but dialysis is needed:

5. awaiting transplantation
6. when small patient size does not allow transplantation
7. right after combined transplantation to prevent oxalosis relapse

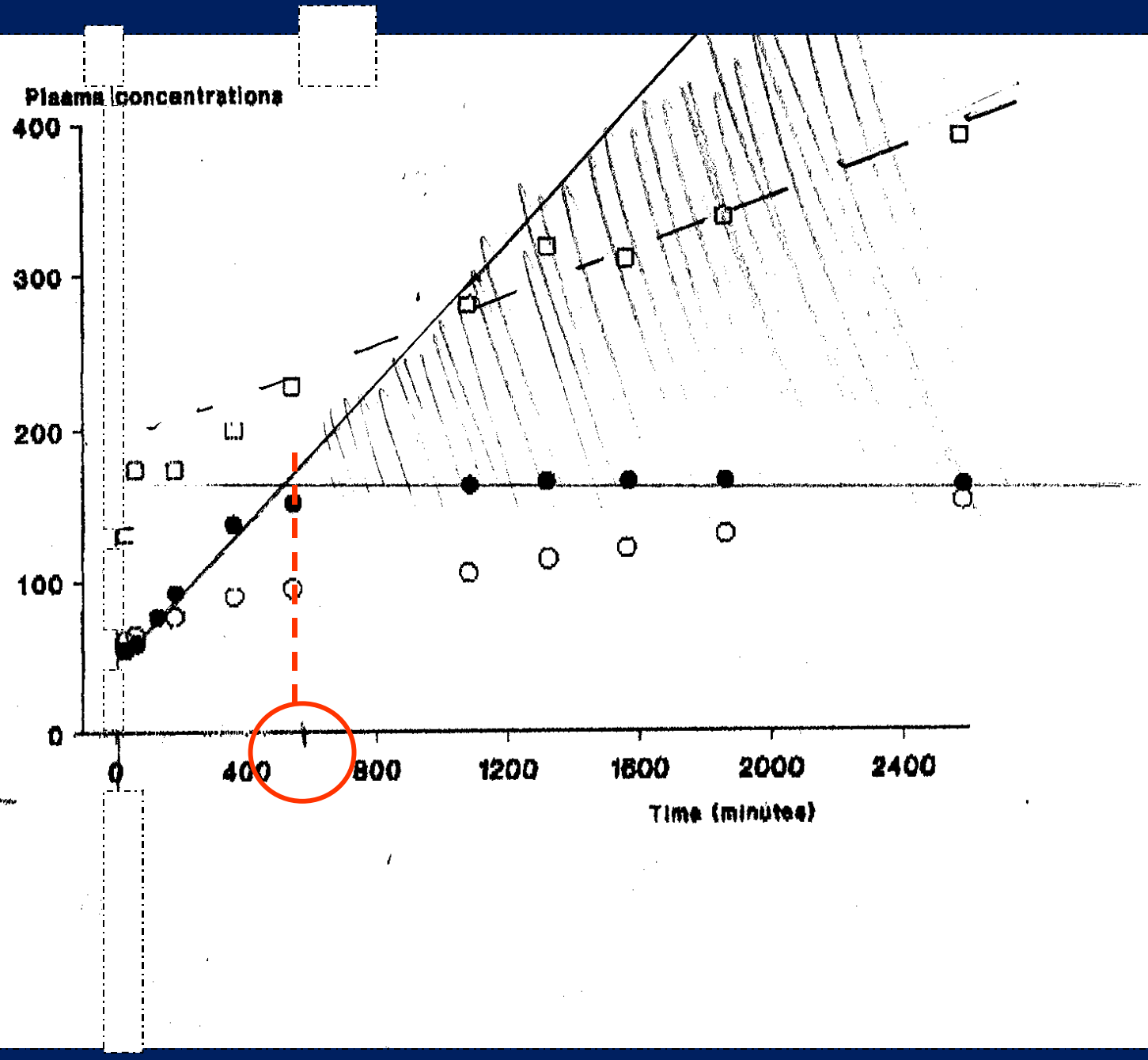


Fig 1. Profiles of plasma concentrations of urea (mg/dL, ○), glycolate (μmol/L, □), and oxalate (μmol/L, ●) over the entire interdialytic time, in one patient with type I primary hyperoxaluria.

From Marangella M et al, 1992

Table 3 | Oxalate kinetics

Patient	BSA (mean) (m^2)	$Oxalate_{Plasma}$ (mean) (μmol/l)	Diuresis (mean) (ml/day)	Mode of elimination	$Clearance_{Oxalate}$/ $Dialysance_{Oxalate}$ (mean) (l/week/1.73 m^2)	$Removal_{Oxalate}$ (mean) (mmol/week/1.73 m^2)	
A	0.56	51	1900	Urine	138	5.6	→ 55%
				CCPD	103	4.5	
					Σ 241	Σ 10.1	
B	0.80	117	0	HD	444	24.1	
C	0.47	82	0	HD	158	12.4	
D	0.54	132	0	HD	342	20.2	
E	1.47	137	3140	Urine	95	12.4	
				HD	164	10.6	
					Σ 259	Σ 23.0	
F	0.47	111	630	Urine	88	6.6	→ 34%
				CCPD	66	5.7	→ 29%
				HD	222	7.3	→ 37%
					Σ 376	Σ 19.6	

Illies, 2006

PATIENTS

#1. F, 4.4 kg.

2 null mutations (no protein expected)
c.33delC + IVS9+2 G>T

2 months

- Anuric. Hyperechoic kidneys, flecked retinopathy.
- PD start.
- Severe Candida Alb. peritonitis, PD stopped, HD started.

4 months

- rhGH started

16-27 months

- hyperparathyroidism (270 → 1040 pg/ml) with hypercalcemia. Cinacalcet and PTH reduction. 5 fractures of one single translucent band in four different long bones.

27-36 months

- femoral and tibial bowing
- Worsening of retinal deposits

36 months

- combined liver-kidney transplantation

#2. M, 6.1 kg.

2 missense mutations (D201E)

6 months

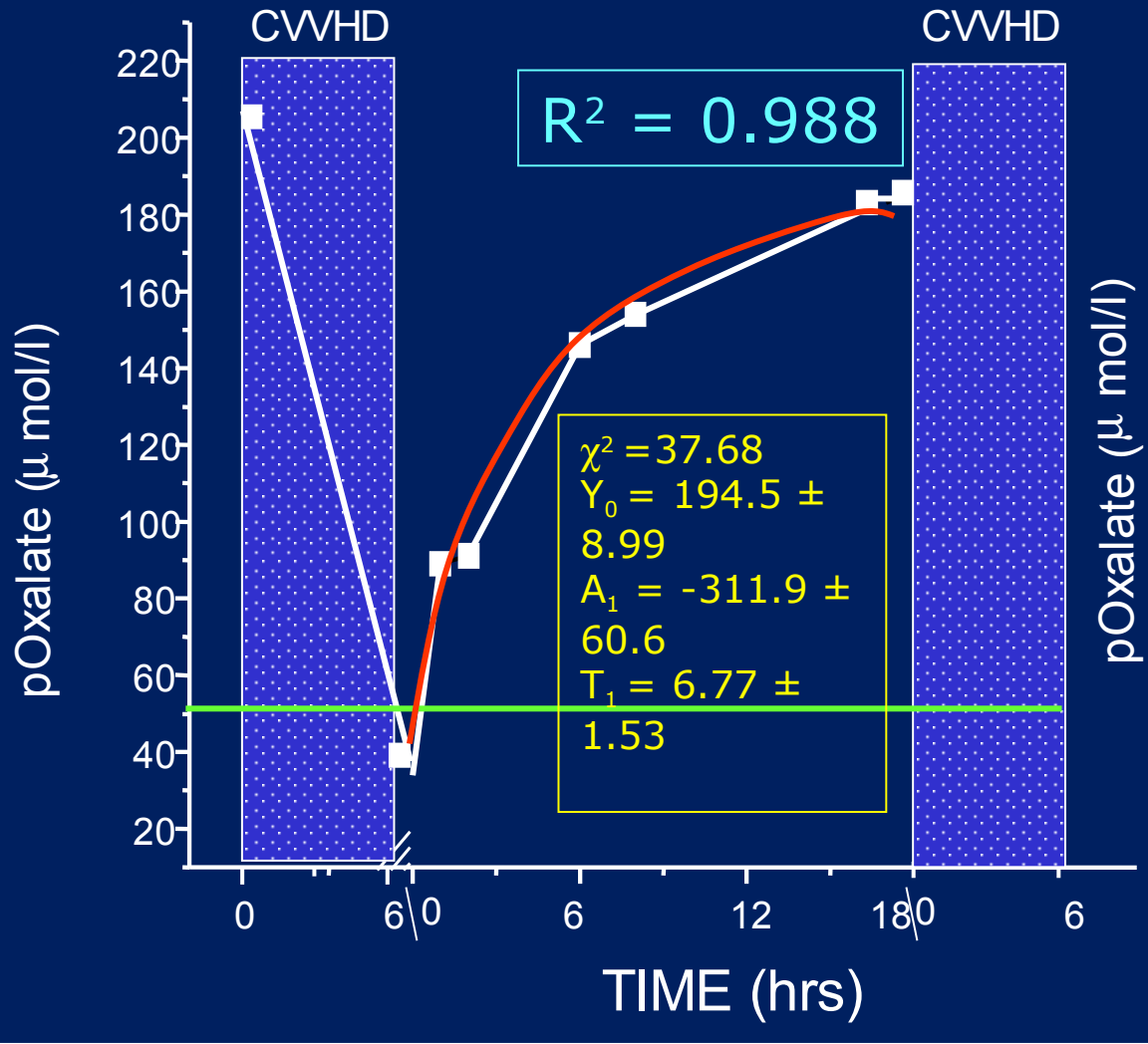
- Anuric. Hyperechoic kidneys, flecked retinopathy.
- PD start.
- Severe Candida Alb. peritonitis, PD stopped, HD started.

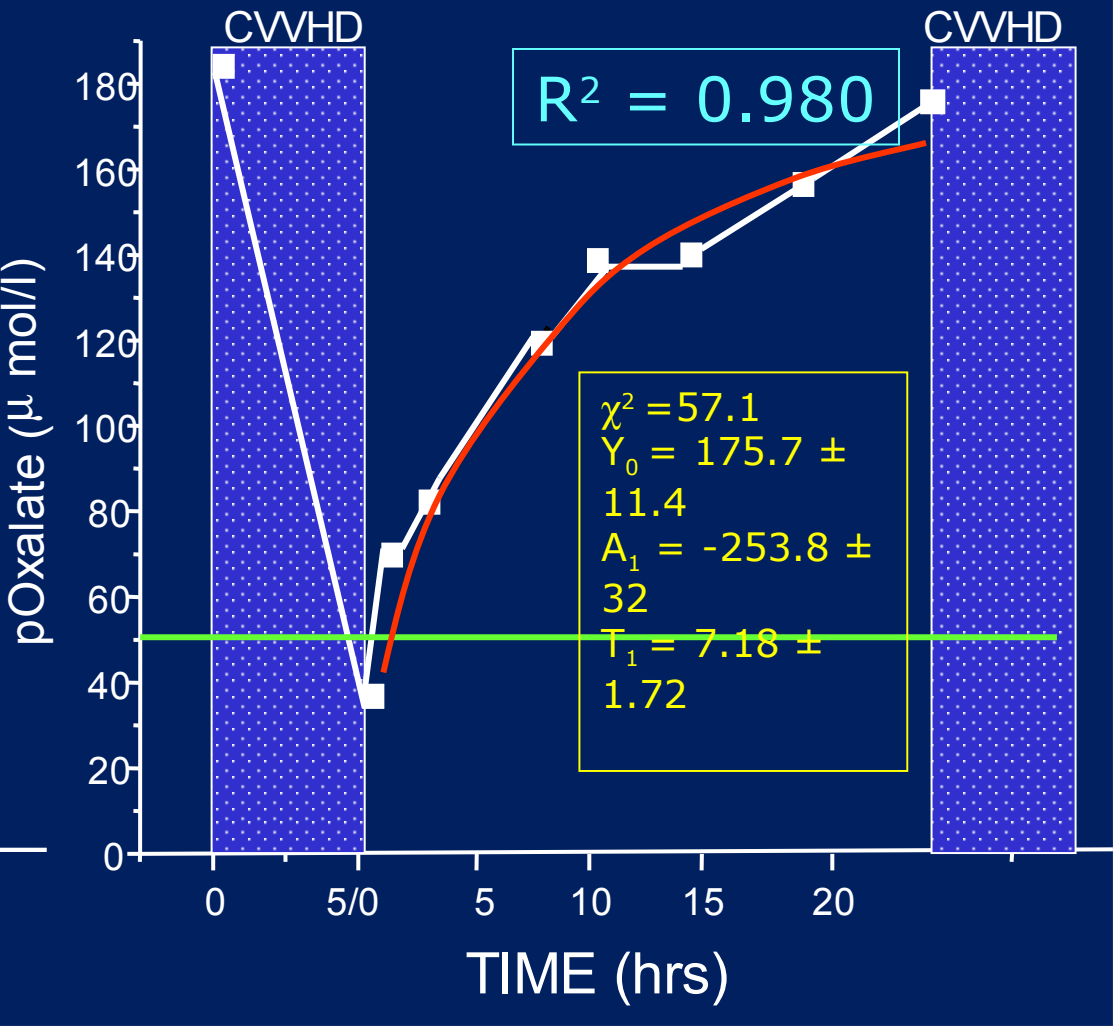
12 months

- On chronic HD, awaiting combined LK tx

Pt #1

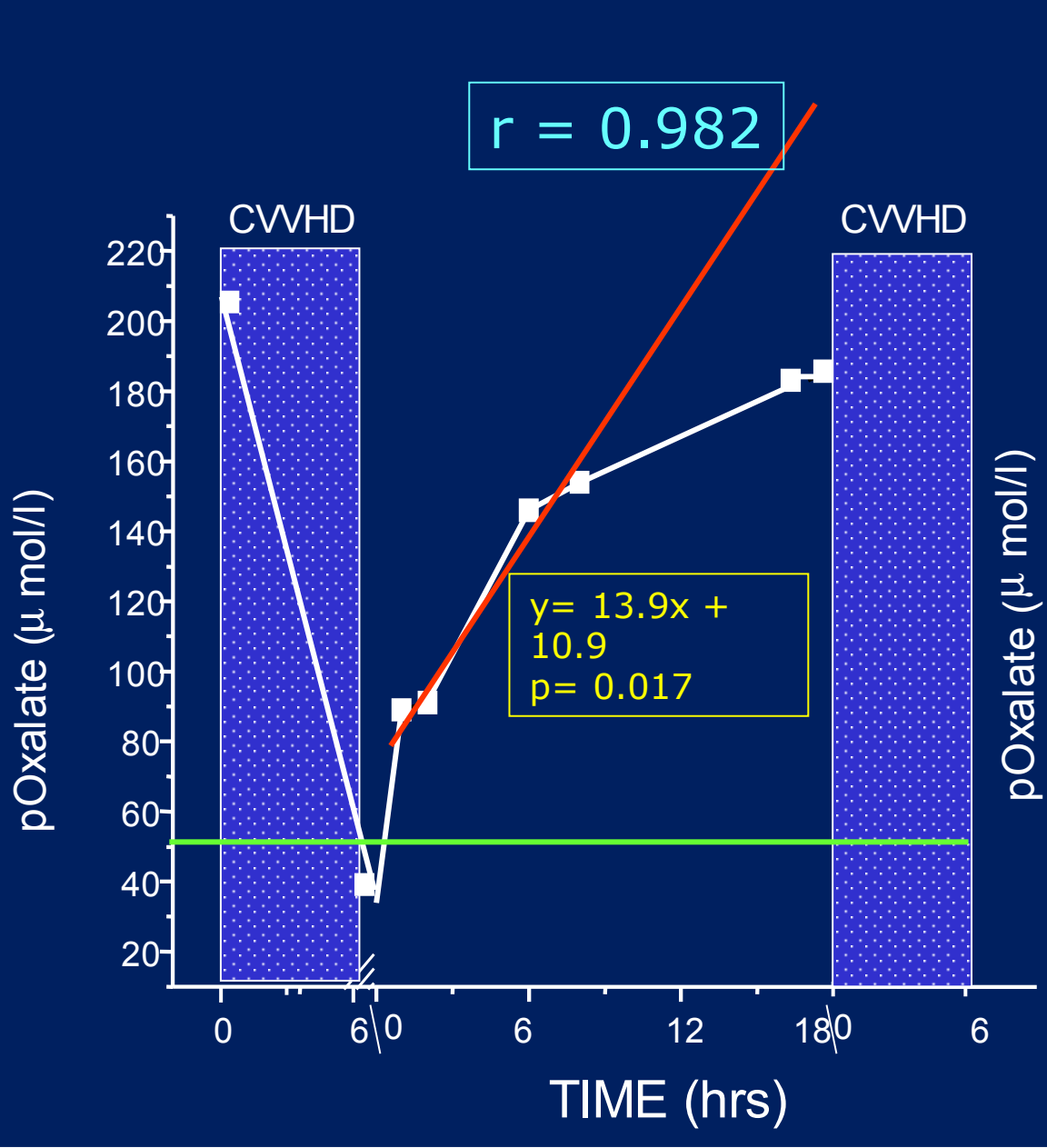
INTERDIALYSIS pOXALATE INCREASE

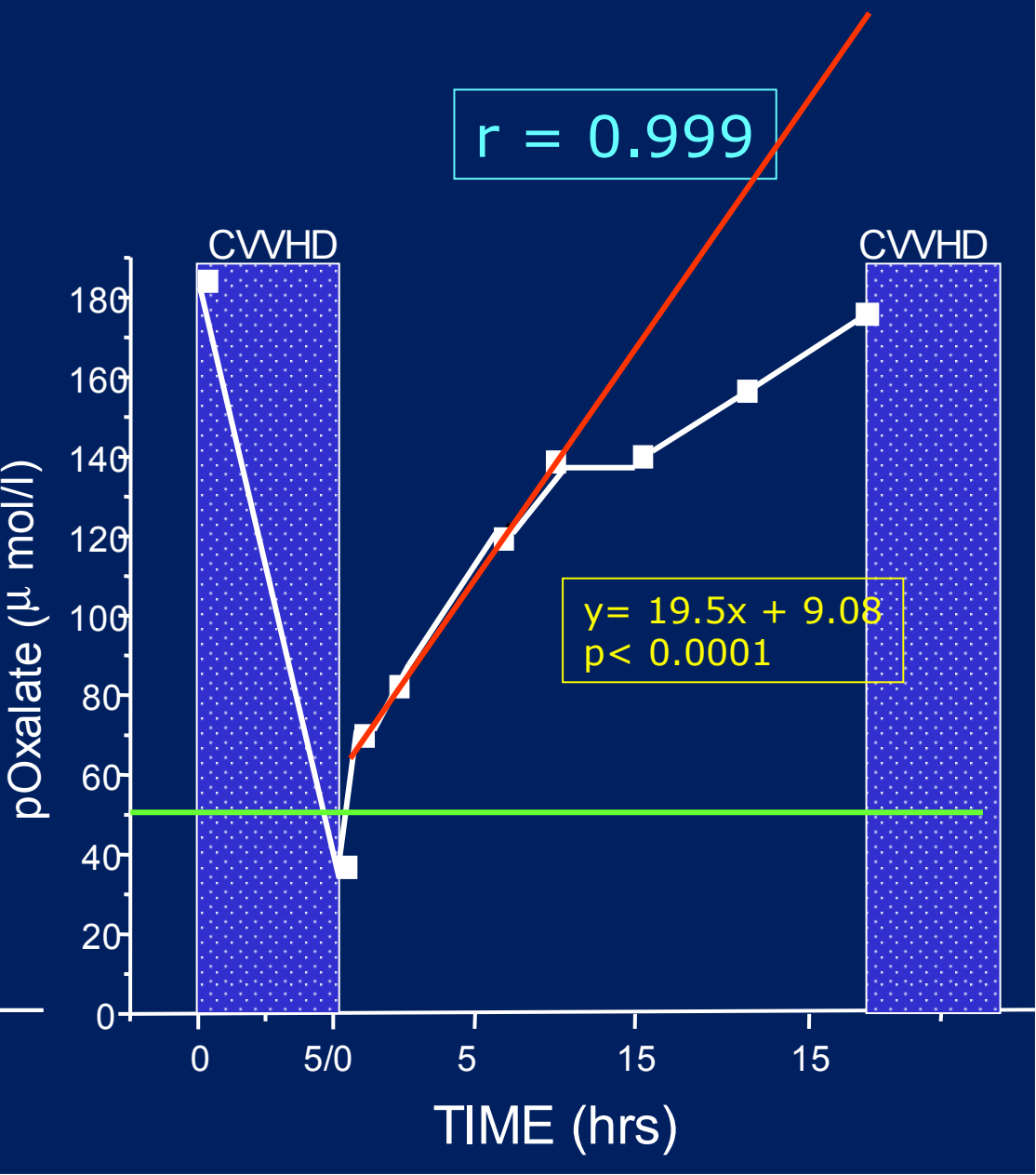




Pt #1

INTERDIALYSIS pOXALATE INCREASE





PATIENT #1

Patient age, body weight HD setting, blood flow	*Plasma Oxalate, µmol/l*	*Mass Removal, µmol*	*Generation Rate, µmol/l/h*	*Distribution Volume, L (% of BW)*	*Tissue Deposition, µmol/24h/kg*	*Oxalate clearance, l/week/1.73 m²*
6 months, 5.0 kg daily CVVHD, Qb 40 ml/min	PreHD: 205 PostHD: 31	644	10.0	2.84 (56.8)	5	228
8 months, 6.5 kg daily CVVHD, Qb 50 ml/min	PreHD: 178 PostHD: 41	615	9.14	3.68 (56.7)	19	167
16 months, 9.5 kg HDx6/week, Qb 70 ml/min	PreHD: 162 PostHD: 41	874	-	-	-	213
18 months, 9.9 kg HDx6/week, Qb 90 ml/min	PreHD: 140 PostHD: 33	590	-	-	-	141
30 months, 12.3 kg HDx6/week, Qb 110 ml/min	PreHD: 102 PostHD: 28	812	4.81	8.28 (67%)	12	185

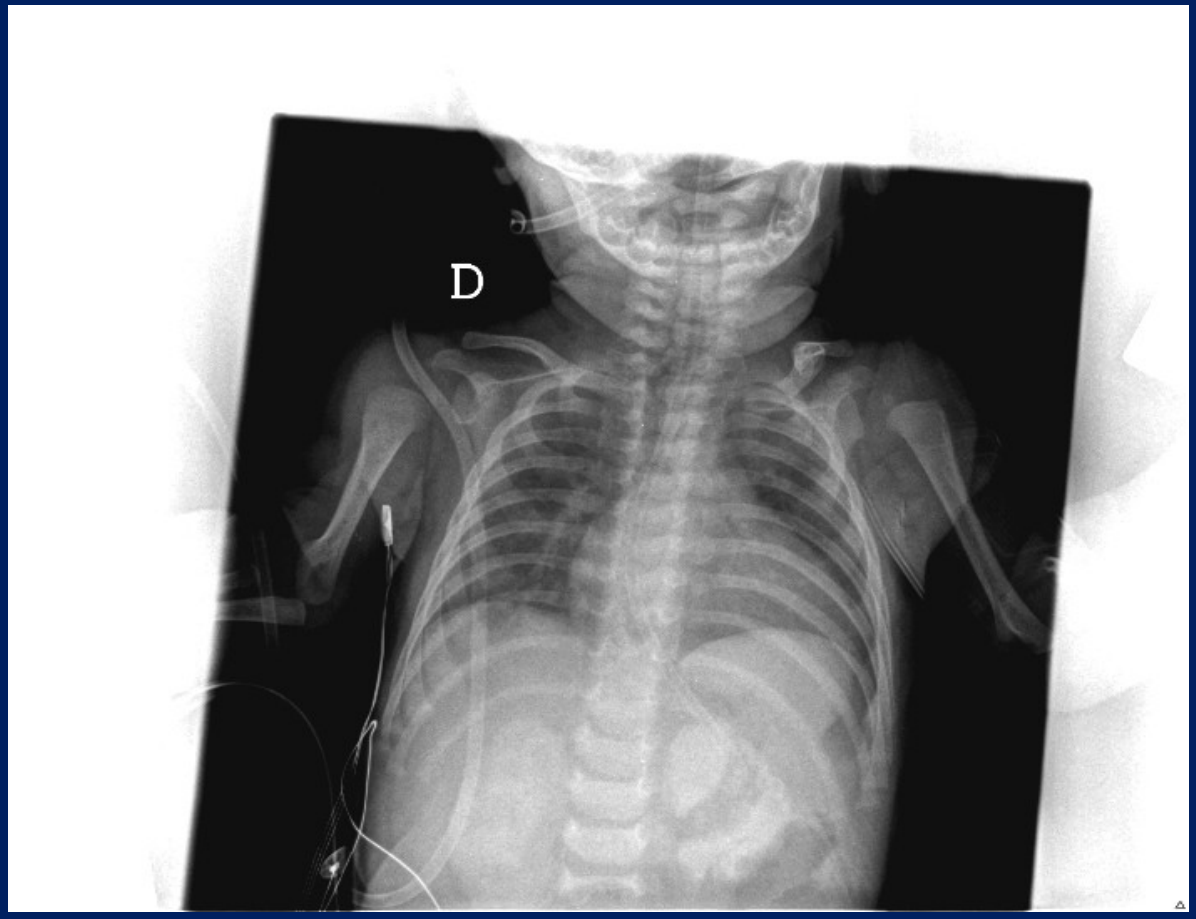
Calculations adapted from Marangella, 1992 and Yamauchi, 2001

PATIENT #2

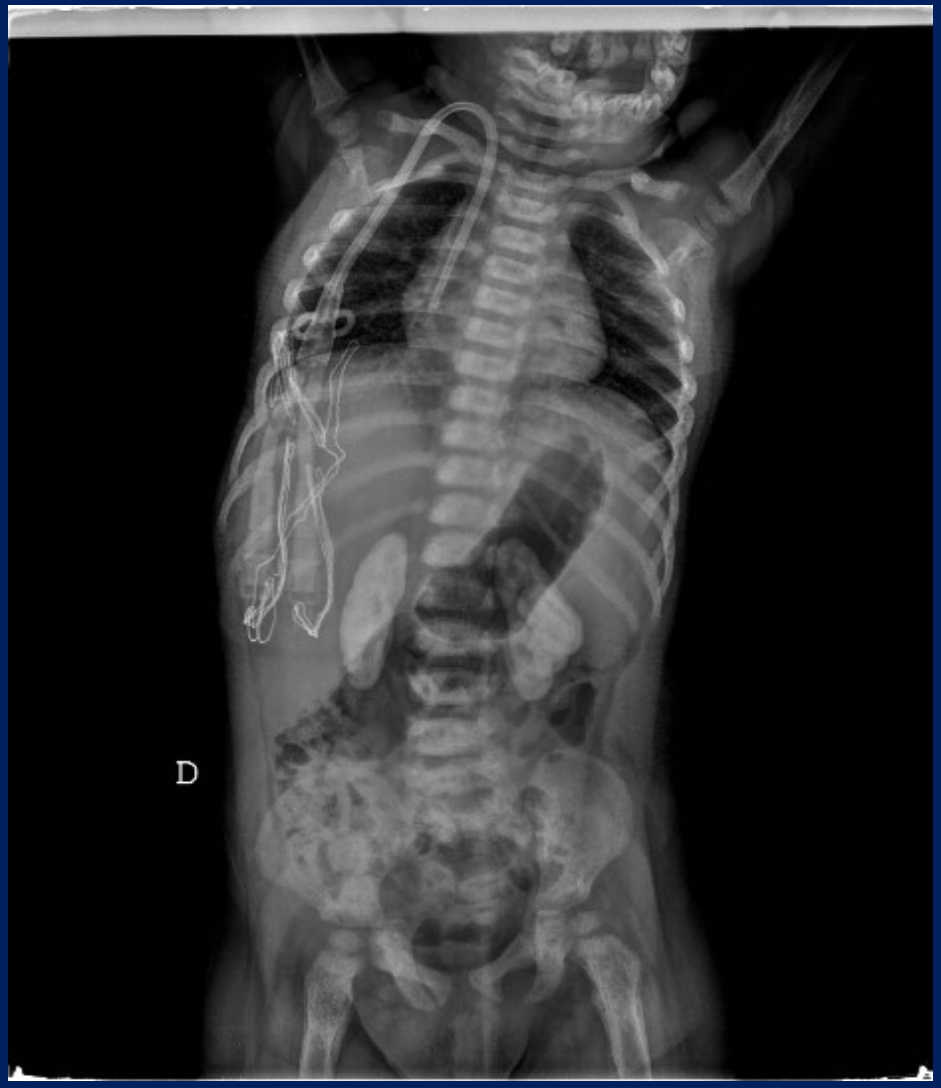
Patient age, body weight HD setting, blood flow	*Plasma Oxalate, µmol/l*	*Mass Removal, µmol*	*Generation Rate, µmol/l/h*	*Distribution Volume, L (% of BW)*	*Tissue Deposition, µmol/24h/kg*	*Oxalate clearance, l/week/1.73 m²*
6 months, 6.1 kg daily CVVHD, Qb 60 ml/min	PreHD: 238 PostHD: 74	425	-	-	-	82
11 months, 7.7 kg daily CVVHD, Qb 60 ml/min	PreHD: 178 PostHD: 41	463	9.12	2.81 (36.5)	20	130

Calculations adapted from Marangella, 1992 and Yamauchi, 2001

Pt #1

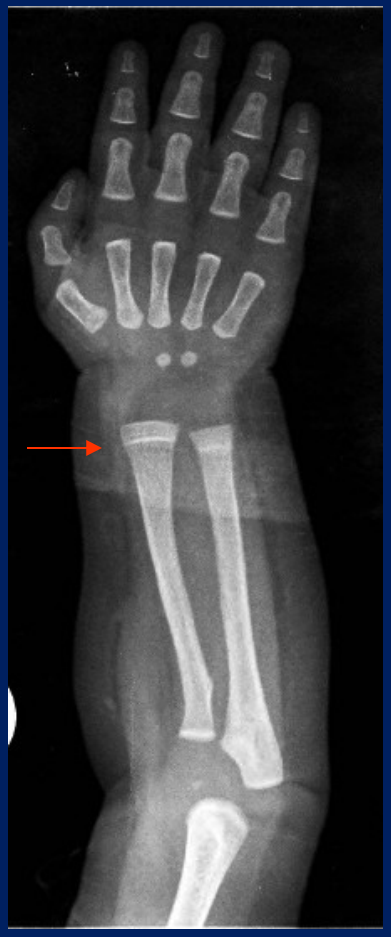


4.5 months

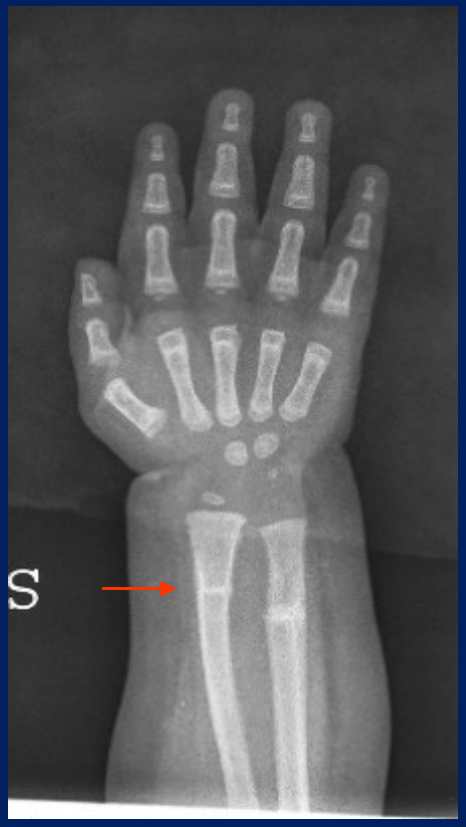


30 months

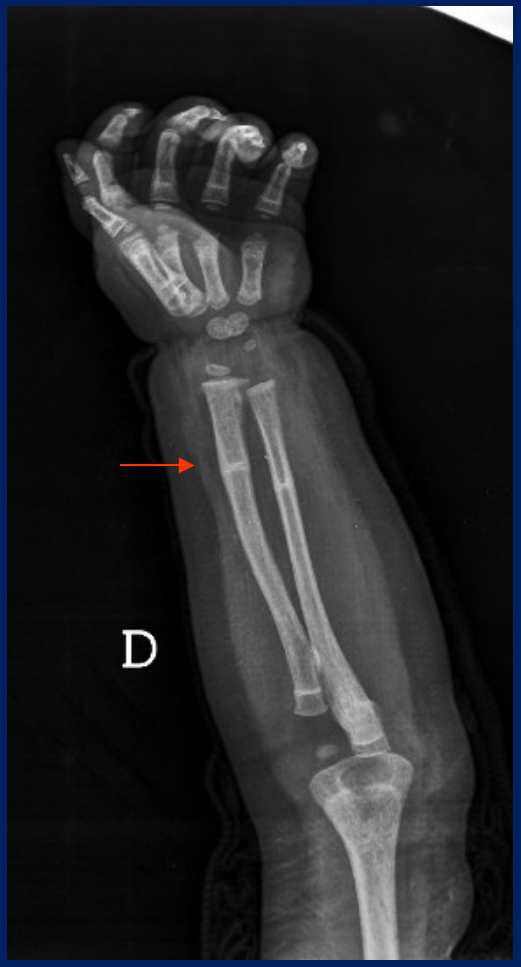
Pt #1. Migration of one single translucent band from growth cartilage to metaphysis (2)



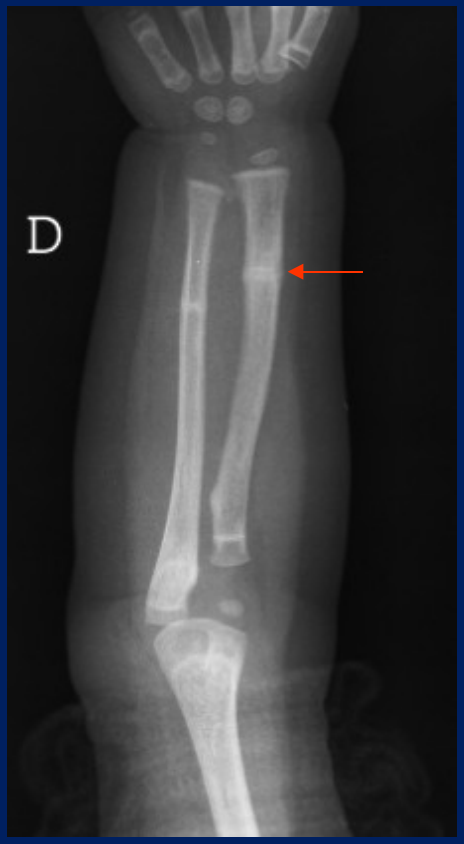
6 months



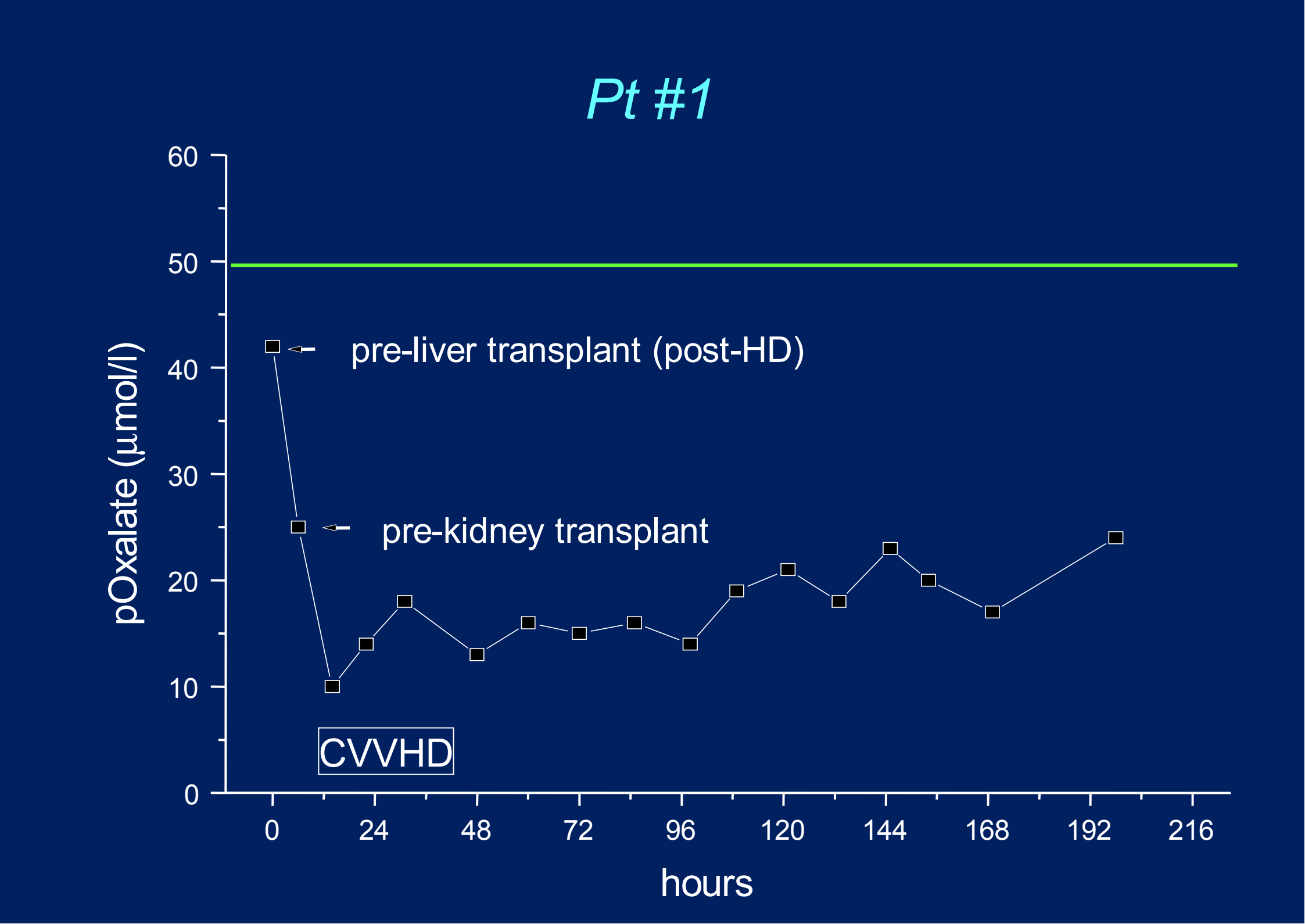
12 months



16 months



18 months


Pt #1
60
50
40
30
20
10
0
pOxalate (µmol/l)
pre-liver transplant (post-HD)
pre-kidney transplant
CVVHD
0
24
48
72
96
120
144
168
192
216
hours

CONCLUSIONS- RRT in OXALOSIS

- ***WHY:***
  - RRT may be needed under particular circumstances
- ***WHEN:***
  - As soon as oxalosis is discovered
- ***HOW TO PERFORM:***
  - Intensive dialysis regimens (daily extracorporeal and nocturnal PD) are recommended
  - High frequency is more important than high efficiency
- ***HOW TO GET INFORMATION:***
  - Oxalate kinetics provides evidence that oxalate generation rate is more severe in children than in adults

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- *Clinical Biochemistry Lab*: Cristiano Rizzo BSc, PhD; Anna Pastore BSc, PhD
- *NICU:* all doctors and nurses
- *Dialysis Unit*: Francesco Emma, MD, all doctors and nurses (thanks!)

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- *SINP* (Italian Society of Pediatric Nephrology)
- All doctors from Pediatric Nephrology and NICUs of Genova, Milan, Turin, Padua, Florence, Naples, Bari.

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- Michele Petrarulo and Martino Marangella, MD for Ox determination and precious advices
- Roberto Bonaudo, MD and Rosanna Coppo, MD for data about oxalosis pt #2

In USA

- Timothy E. Bunchman MD, for this opportunity. Thanks, Tim.

Table 2. *Leucine kinetic modeling validation performed with retrospectively acquired data from three neonates with acute phase maple syrup urine disease treated with CECRT*

			CECRT				Leucine plasma level		
Patient	BW (kg)	Age at treatment (days)	T (hrs)	QS	QD (ml/min)	QF	initial (μM)	at 3h of CECRT (μM)	final (μM)
8	2.8	11	14	25	25	0.0	3147	1181*	482
9	2.7	9	3	25	25	0.0	3489	1388	—
9	2.7	10	7	25	25	0.0	1680	844	513
10	3.1	9	10	25	25	0.0	2782	1464	631
Leucine blood concentration decrease from initial level in % (mean ± SEM)								77 ± 3	

Continuous veno-venous extracorporeal removal therapy (CECRT) characteristics and leucine plasma levels at several time points during CECRT. Patient nine underwent a second CECRT session due to filter clotting which occurred at time three hours after initiation of the first session.

T, CECRT duration; QS, blood flow; QD, dialysate flow; QF, filtration and fluid replacement flow (net ultrafiltration was nil).

* leucine level at 5h30 of CECRT.

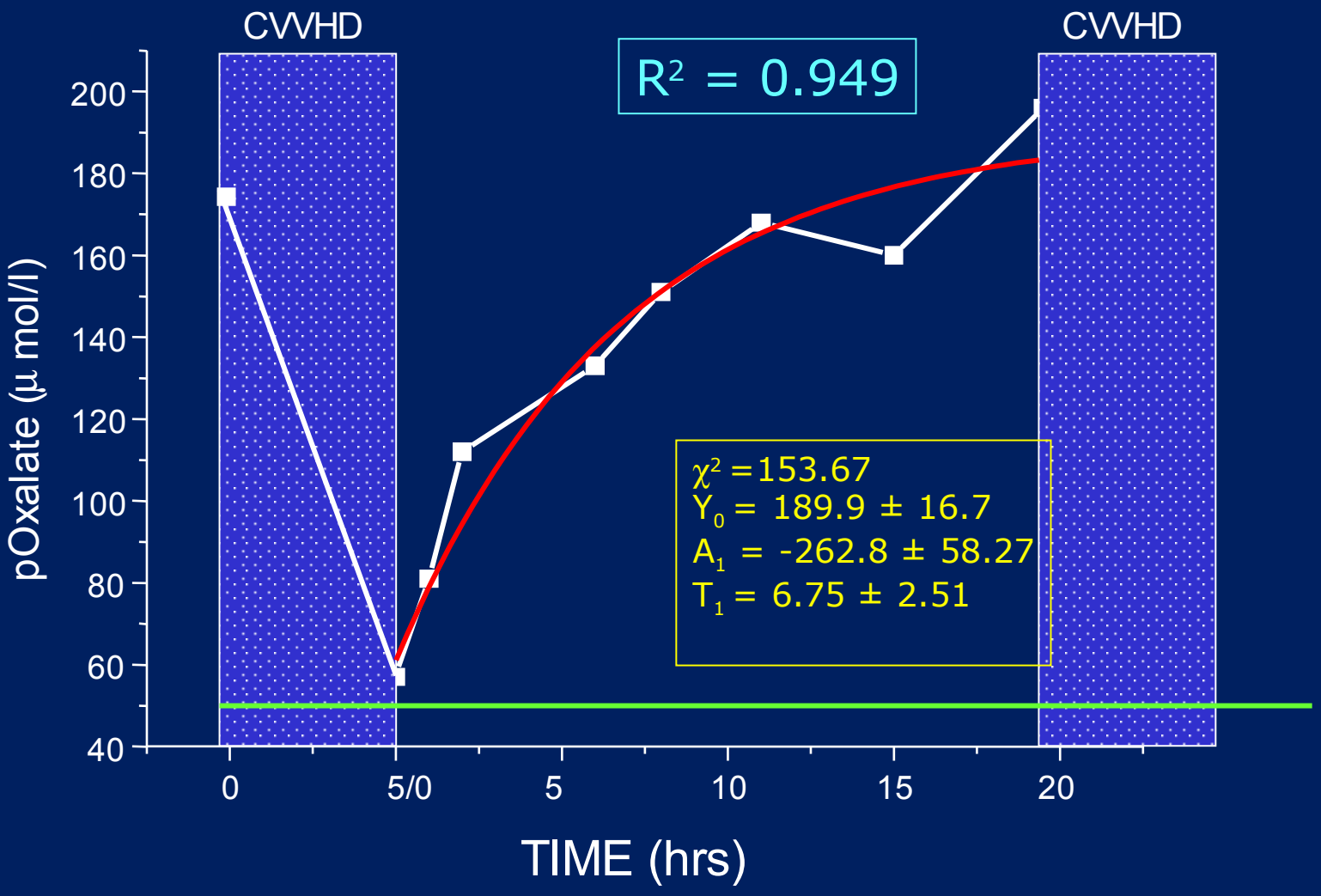
Jouvet, 2005

Table 1. *Kinetic modeling of leucine plasma concentration changes derived from data obtained from seven neonates with acute phase maple syrup urine disease treated with CECRT*

			CECRT				Leucine plasma level		Leucine			
Patient	BW (kg)	Age at treatment (days)	T (hr)	QS	QD (ml/min)	QF	initial (μM)	final (μM)	mass removal (mmol/session)	Cl (ml/min)	Vd1 (% BWt)	Vd2 (% BWt)
1	3.7	12	12	20	0	2.0	2186	1131	2.0	1.7	37	42
2	2.9	11	11	20	16	1.0	3818	1275	6.6	4.3	45	95
3	2.0	22	12	20	25	0.0	2536	488	3.5	3.9	42	89
4	3.2	16	13	30	0	7.4	3117	679	5.1	3.5	25	75
5	3.1	12	12	40	0	8.7	2226	305	4.0	4.1	29	68
6	3.2	13	11	40	0	9.5	3189	196	6.2	4.8	24	60
7	2.4	12	8	30	27	0.0	1629	496	2.3	2.8	36	76
Mean ± SEM										3.6 ± 0.4	34 ± 3	72 ± 7

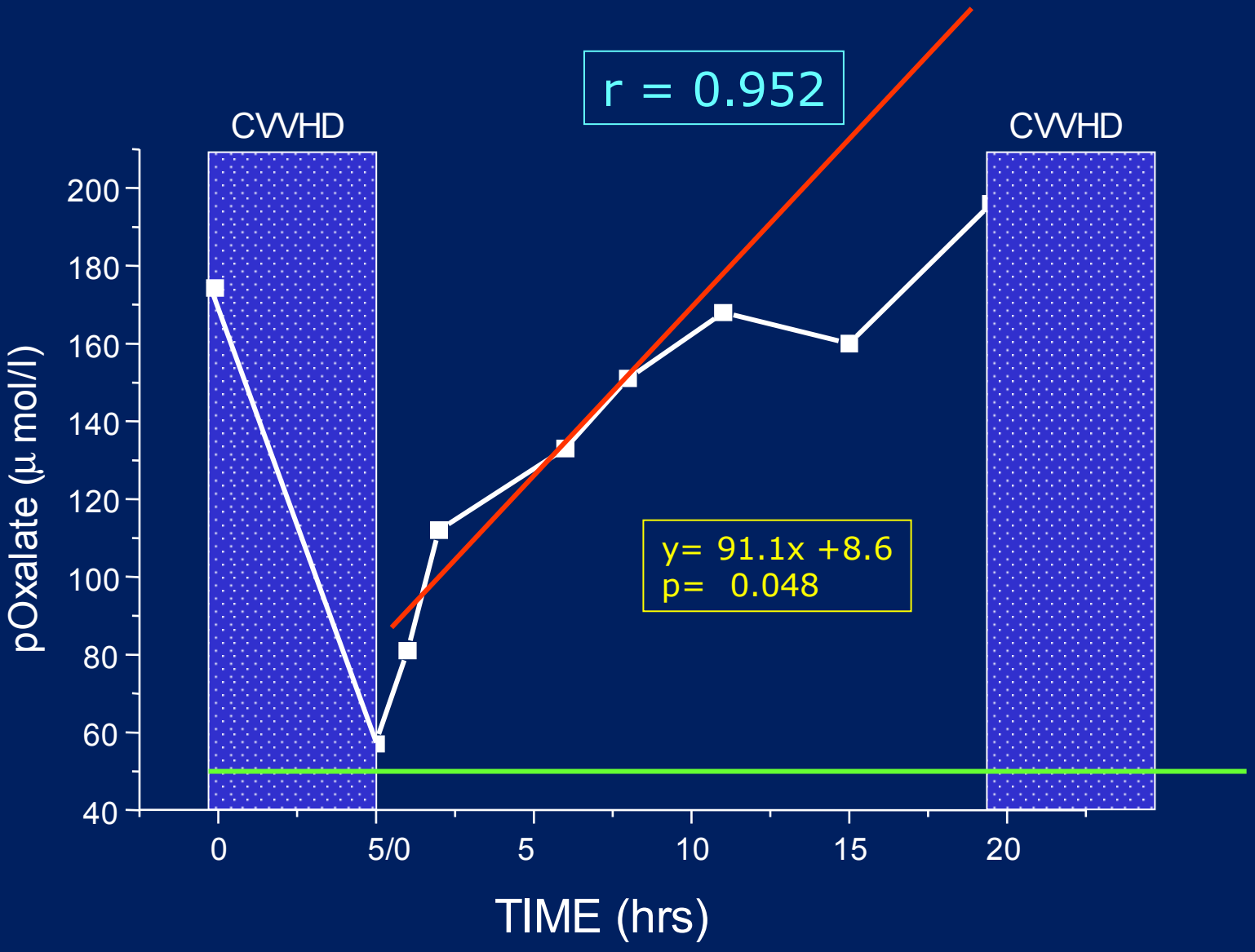
BW (kg)	Time (hrs)	Qb (ml/min)	Qd (ml/min)	Initial (μmol/l)	At 3 hrs (μmol/l)	Final (μmol/l)	Mass removal (μmol)	Cl Leu (ml/min)
3.6	14	34-40	50	1190	571	94	5.063	8.8

Pt #2
INTERDIALYSIS pOXALATE INCREASE

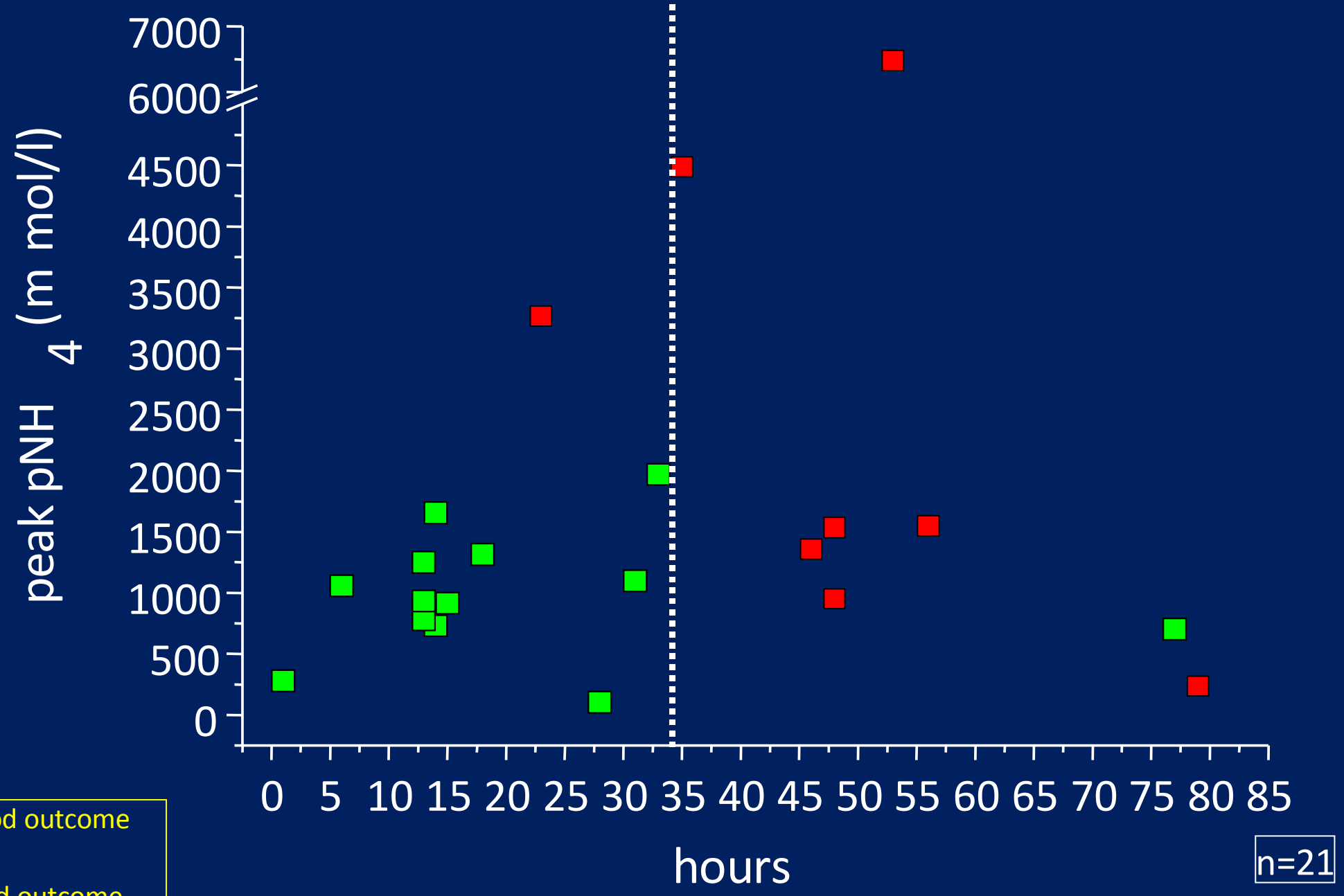


Pt #2

INTERDIALYSIS pOXALATE INCREASE



ALL PATIENTS: NH_4 LEVELS AND COMA DURATION BEFORE ANY TREATMENT



DIALYZED PATIENTS: NH_4 LEVELS AND COMA DURATION BEFORE DIALYSIS