RENAL REPLACEMENT THERAPY IN INBORN ERRORS OF METABOLISM

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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% (?)

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

**PATIENT**
- home
- peripheral hospital
- 3rd level hospital

**DIAGNOSIS**
- Mother: “sleeps too long”
- Hyperammonemia
- Metabolic defect

**TREATMENT**
- (May) Start Pharmacological Treatment
- Starts (continues) Pharmacological Treatment
- RESPONSE
- NO RESPONSE
- RE-FEEDING
- DIALYSIS
- OUTCOME ANALYSIS

Interactions:
- Metabolism expert
- Neonatologist
- Nephrologist
- Biochemistry Lab
0-4 HOURS MEDICAL TREATMENT IN NEONATAL HYPERAMMONEMIA

- **Non-responders** (dialysis)
- **Responders** (med. treatment alone)

Picca, 2002, unpublished
## AMMONIUM CLEARANCE AND FILTRATION FRACTION USING DIFFERENT DIALYSIS MODALITIES

<table>
<thead>
<tr>
<th>Patient (n)</th>
<th>Type of Dialysis</th>
<th>Qb (ml/min)</th>
<th>Qd (ml/min)</th>
<th>Ammonium Clearance (ml/min/kg)</th>
<th>Ammonium Filtration Fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CAVHD</td>
<td>10-20</td>
<td>8.3 (0.5 l/h)</td>
<td>0.87-0.97</td>
<td>12.5-14.3</td>
</tr>
<tr>
<td>3</td>
<td>CVVHD</td>
<td>20-40</td>
<td>33.3-83.3 (2-5 l/h)</td>
<td>2.65-6.80</td>
<td>53.0-58.0</td>
</tr>
<tr>
<td>2</td>
<td>HD</td>
<td>10-15</td>
<td>500</td>
<td>3.95-5.37</td>
<td>95.0-96.0</td>
</tr>
<tr>
<td>4</td>
<td>PD</td>
<td></td>
<td></td>
<td>0.48-2.7 (1.4±1.1, about 0.48 ml/min/kg)</td>
<td></td>
</tr>
</tbody>
</table>

Picca et al., 2001

Arbeiter et al., 2009
NH4\textsubscript{p} (percent of initial value)

TIME (hours)

CAVHD patients

CVVHD patients

HD patients

Picca et al. Ped Nephrol 2001
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Prognostic Indicators</th>
</tr>
</thead>
</table>
| McBryde       | 2006 | • $pNH_4$ at admission $<$ 180 $\mu$mol/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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of treatment</td>
<td></td>
</tr>
<tr>
<td>Birth BW (g)</td>
<td></td>
</tr>
<tr>
<td>Age at admission (hrs)</td>
<td></td>
</tr>
<tr>
<td>BW at admission (g)</td>
<td></td>
</tr>
<tr>
<td>BE at admission</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>pNH₄ pre-medical treatment (µmol/L)</td>
<td>0.056</td>
</tr>
<tr>
<td>pNH₄ pre-dialysis (µmol/L)</td>
<td>0.62</td>
</tr>
<tr>
<td>pNH₄ peak (µmol/L)</td>
<td>0.25</td>
</tr>
<tr>
<td>pNH₄ dialysis 50% decay time (hrs)</td>
<td></td>
</tr>
<tr>
<td>Dialysis duration (hrs)</td>
<td></td>
</tr>
<tr>
<td>Coma total duration (hrs)</td>
<td></td>
</tr>
<tr>
<td>Predialysis coma duration (hrs)</td>
<td>0.93</td>
</tr>
<tr>
<td>Predialysis coma duration (hrs)</td>
<td>0.075</td>
</tr>
<tr>
<td>CAVHD</td>
<td></td>
</tr>
<tr>
<td>CVVHD</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td></td>
</tr>
<tr>
<td>DP</td>
<td>0.08</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td></td>
</tr>
</tbody>
</table>

**n = 47**

Picca, unpublished, 2009
EFFICIENCY OF PERITONEAL VS. EXTRACORPOREAL DIALYSIS ON AMMONIUM DECAY

PD vs. CVVH, HD, CAVH
p: NS
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
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.
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)
### 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>BW (kg)</th>
<th>Age at treatment (days)</th>
<th>CECRT</th>
<th>Leucine plasma level</th>
<th>Leucine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>T (hr)</td>
<td>QS (ml/min)</td>
<td>QD (ml/min)</td>
</tr>
<tr>
<td>1</td>
<td>3.7</td>
<td>12</td>
<td>12</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2.9</td>
<td>11</td>
<td>11</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>22</td>
<td>12</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>3.2</td>
<td>16</td>
<td>13</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3.1</td>
<td>12</td>
<td>12</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3.2</td>
<td>13</td>
<td>11</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>2.4</td>
<td>12</td>
<td>8</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>3.6 ± 0.4</td>
<td>34 ± 3</td>
<td>72 ± 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 |
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
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

KEY POINTS OF OXALOSIS
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 1 primary hyperoxaluria.
Table 3 | Oxalate kinetics

<table>
<thead>
<tr>
<th>Patient</th>
<th>BSA (mean) (m²)</th>
<th>Oxalate_{Plasma} (mean) (µmol/l)</th>
<th>Diuresis (mean) (ml/day)</th>
<th>Mode of elimination</th>
<th>Clearance_{Oxalate} (mean) (l/week/1.73 m²)</th>
<th>Removal_{Oxalate} (mean) (mmol/week/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.56</td>
<td>51</td>
<td>1900</td>
<td>Urine</td>
<td>138</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CCPD</td>
<td>103</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Σ 241</td>
<td>Σ 10.1</td>
</tr>
<tr>
<td>B</td>
<td>0.80</td>
<td>117</td>
<td>0</td>
<td>HD</td>
<td>444</td>
<td>24.1</td>
</tr>
<tr>
<td>C</td>
<td>0.47</td>
<td>82</td>
<td>0</td>
<td>HD</td>
<td>158</td>
<td>12.4</td>
</tr>
<tr>
<td>D</td>
<td>0.54</td>
<td>132</td>
<td>0</td>
<td>HD</td>
<td>342</td>
<td>20.2</td>
</tr>
<tr>
<td>E</td>
<td>1.47</td>
<td>137</td>
<td>3140</td>
<td>Urine</td>
<td>95</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HD</td>
<td>164</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Σ 259</td>
<td>Σ 23.0</td>
</tr>
<tr>
<td>F</td>
<td>0.47</td>
<td>111</td>
<td>630</td>
<td>Urine</td>
<td>88</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CCPD</td>
<td>66</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HD</td>
<td>222</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Σ 376</td>
<td>Σ 19.6</td>
</tr>
</tbody>
</table>

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

\[ \chi^2 = 37.68 \]
\[ Y_0 = 194.5 \pm 8.99 \]
\[ A_1 = -311.9 \pm 60.6 \]
\[ T_1 = 6.77 \pm 1.53 \]
\[ R^2 = 0.988 \]

\[ \chi^2 = 57.1 \]
\[ Y_0 = 175.7 \pm 11.4 \]
\[ A_1 = -253.8 \pm 32 \]
\[ T_1 = 7.18 \pm 1.72 \]
\[ R^2 = 0.980 \]
Pt #1
INTERDIALYSIS pOXALATE INCREASE

\[ y = 13.9x + 10.9 \]
\[ p = 0.017 \]
\[ r = 0.982 \]

\[ y = 19.5x + 9.08 \]
\[ p < 0.0001 \]
\[ r = 0.999 \]
### Patient #1

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

Calculations adapted from Marangella, 1992 and Yamauchi, 2001
# PATIENT #2

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

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)
Pt #1

- Pre-kidney transplant
- Pre-liver transplant (post-HD)

Graph showing the change in pOxalate over time (µmol/l) with markers at different 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
ACKNOWLEDGEMENTS

**Bambino Gesù Children Hospital:**
- **Metabolic Unit:** Carlo Dionisi-Vici, MD; Andrea Bartuli, MD; Gaetano Sabetta, MD
- **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!)

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

**In Turin**
- 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>BW (kg)</th>
<th>Age at treatment (days)</th>
<th>T (hrs)</th>
<th>QS</th>
<th>QD (ml/min)</th>
<th>QF</th>
<th>initial (μM)</th>
<th>at 3h of CECRT (μM)</th>
<th>final (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>2.8</td>
<td>11</td>
<td>14</td>
<td>25</td>
<td>25</td>
<td>0.0</td>
<td>3147</td>
<td>1181*</td>
<td>482</td>
</tr>
<tr>
<td>9</td>
<td>2.7</td>
<td>9</td>
<td>3</td>
<td>25</td>
<td>25</td>
<td>0.0</td>
<td>3489</td>
<td>1388</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>2.7</td>
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<td>7</td>
<td>25</td>
<td>25</td>
<td>0.0</td>
<td>1680</td>
<td>844</td>
<td>513</td>
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<tr>
<td>10</td>
<td>3.1</td>
<td>9</td>
<td>10</td>
<td>25</td>
<td>25</td>
<td>0.0</td>
<td>2782</td>
<td>1464</td>
<td>631</td>
</tr>
</tbody>
</table>

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 3h30 of CECRT.

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>BW (kg)</th>
<th>Age at treatment (days)</th>
<th>T (hr)</th>
<th>QS</th>
<th>QD (ml/min)</th>
<th>QF</th>
<th>initial (μM)</th>
<th>final (μM)</th>
<th>mass removal (μmol/session)</th>
<th>Cl (ml/min)</th>
<th>Vd1 (% BWt)</th>
<th>Vd2 (% BWt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.7</td>
<td>12</td>
<td>12</td>
<td>20</td>
<td>0</td>
<td>2.0</td>
<td>2186</td>
<td>1131</td>
<td>2.0</td>
<td>1.7</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>2.9</td>
<td>11</td>
<td>11</td>
<td>20</td>
<td>16</td>
<td>1.0</td>
<td>3818</td>
<td>1275</td>
<td>6.6</td>
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<th>Qd (ml/min)</th>
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<th>At 3 hrs (μmol/l)</th>
<th>Final (μmol/l)</th>
<th>Mass removal (μmol)</th>
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Pt #2
INTERDIALYSIS pOXALATE INCREASE

\[ \chi^2 = 153.67 \]
\[ Y_0 = 189.9 \pm 16.7 \]
\[ A_1 = -262.8 \pm 58.27 \]
\[ T_1 = 6.75 \pm 2.51 \]

\[ R^2 = 0.949 \]
Pt #2
INTERDIALYSIS pOXALATE INCREASE

\[ y = 91.1x + 8.6 \]
\[ p = 0.048 \]

\[ r = 0.952 \]
ALL PATIENTS: NH₄ LEVELS AND COMA DURATION BEFORE ANY TREATMENT

peak pNH₄ (m mol/l)

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85

hours

[Graph showing peak NH₄ levels and coma duration]
DIALYZED PATIENTS: NH$_4$ LEVELS AND COMA DURATION BEFORE DIALYSIS

- **peak pNH$_4$ (m mol/l)**
- **hours**

- **good outcome**
- **bad outcome**

$n=14$