The 2019 European paper on pediatric dialysis

Justine Bacchetta, MD, PhD
Reference Center for Rare Diseases of Calcium and Phosphate Metabolism
Reference Center for Rare Renal Diseases
Annual Dialysis Conference, Kansas City 2020

Rationale for the 3H study

- Hemodiafiltration (HDF)
- Combination of diffusive and convective solute transport
- Highly permeable membrane
- Clearance of middle-molecular-weight solutes
- Ultra-pure water => decreased low-grade endotoxemia
- Better intra-dialytic hemodynamic stability

- Adults undergoing HDF
- ESHOL, CONTRAST and FRENCHIE studies
- Survival benefit of HDF as compared to high-flux HD
- Critical dose-response relationship: magnitude of convection / survival

- Data in children before the 3H study
- Scarce, even though HDF has been used for 4 decades
- Small, single-center, retrospective analyses
- Likely
  - Improved nutrition and growth
  - Decreased inflammation
  - Regression of LVH
  - Improved anemia control

The 3H study: a multi-center prospective observational cohort study to compare HD and HDF over a 1-year follow-up

29 centres in 10 countries screened
28 centres included
190 children recruited

There are ~450 children on extra-corporeal dialysis in Europe

Participating centres

Trial design

Inclusion criteria:
- All children 5-20 years old undergoing HDF in pediatric dialysis centres
- Age-matched HD patients
- Dialysis frequency 2 times / week, 4 hours per session
- Prevalent HDF and HD patients must achieve a single pool Kt/V>1.2 in the month preceding recruitment

Exclusion criteria:
- Living donor kidney transplant planned within 6 months

Treatment strategies:
- High-flux HD or post-dilutional HDF

Assignment:
- Non-randomized

Follow-up:
- 12 months

Protocol:
- Standardized dialysis prescriptions, none for:
  - Target convection volume of 12-15L/m² (post-dilution)

Analysis plan:
- Per-protocol analysis (must receive >80% of all dialysis sessions as HD or HDF)
Main outcome = cIMT SD score
Validity checks +++

- cIMT data analysis by a blinded observer
- Re-analysis of US scans for n = 20 data pairs randomly selected and all identifier information and pairing removed
- Intra and extra-observer coefficient variation < 3.5%

Recruitment - flow chart

190 children recruited (26 centres, 10 countries)
13 excluded
177 entered study
106 HD
71 HDF
1 year follow-up
78 HD (74%)
55 HDF (77%)

Reasons for exclusion
- Age < 5 years n = 1
- Dialysis frequency < or > 3/wk n = 5
- Dialysis duration < 6hrs/session n = 2
- Pre-dilution HDF n = 2
- No ultra-pure water for HDF n = 2
- Transplanted on day of study n = 1

Loss to follow-up n = 44
- Transplanted n = 35 (80%)
- Moved centres n = 5
- Switched HDF to HD n = 4
- No deaths

Patients (1)

Table 1. Demographics of children at study entry (only includes those with 1-year follow-up)

<table>
<thead>
<tr>
<th>Number</th>
<th>HDP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Demographic
- Patient no. (N)
- Male: Female
- White: Black: Other
- Body mass index (SD)
- Other morbidities
- Diabetes
- Heart disease
- Hypertension
- Pulmonary
- Arthritis
- Immune system disorder
- Autonomic dysfunction
- Renal failure
- End-stage renal disease
- Previous diabetes
- Previous hypertension
- Previous heart disease
- Previous autoimmune disease
- Previous malignancy
- Previous other morbidities
- Previous hospitalisation
- Siblings with diabetes
- Siblings with hypertension
- Siblings with heart disease
- Transplant history
- Transplant success
- Transplant rejection

Patients (2)

Table 1. Demographics of children at study entry (only includes those with 1-year follow-up)

<table>
<thead>
<tr>
<th>Number</th>
<th>HDP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Demographic
- Patient no. (N)
- Male: Female
- White: Black: Other
- Body mass index (SD)
- Other morbidities
- Diabetes
- Heart disease
- Hypertension
- Pulmonary
- Arthritis
- Immune system disorder
- Autonomic dysfunction
- Renal failure
- End-stage renal disease
- Previous diabetes
- Previous hypertension
- Previous heart disease
- Previous autoimmune disease
- Previous malignancy
- Previous other morbidities
- Previous hospitalisation
- Siblings with diabetes
- Siblings with hypertension
- Siblings with heart disease
- Transplant history
- Transplant success
- Transplant rejection

HDF halts the progression of cIMT

Predictors of higher cIMT-SDS at 12 months
- HD group
- Higher IDWG% and UF rate
- Higher systolic BP
- Higher β2 microglobulin

cIMT SDS at baseline and 1-year

Incident vs Prevalent patients

HDF halts the progression of cIMT
Adjusted analysis for cIMT

- Adjustment for potential confounders performed using propensity score approach
- Factors that might influence HD or HDF choice based on clinical experience: age, gender, country, blood flow and water quality

HD patients had a greater increase in cIMT SDS of +0.47 (95%CI +0.07 to 0.87; p = 0.02) as compared to HDF.

MAP SDS at baseline and 1-year

At 12-months MAP > 2SD in HD 81% HD F 37%

Predictors of higher MAP at 12-months:
- Higher IDWG
- Higher beta 2 MIG
- Higher PTH

At 12-months: Delta MAP ± 2SD in HD vs HD (propensity score): -0.15 95%CI -1.13; p=0.01

PWV SDS at baseline and 1-year

Predictors of higher PWV-SDS at 12-months:
- Higher IDWG
- Higher systolic and diastolic BP SDS
- Lower hemoglobin
- Higher PTH

Change in Height SDS

15% on HD and 25% on HDF on rhGH therapy

No difference in height-SDS in GHR-hy HDF vs HD patients (p = 0.08).

There was an inverse association between final height-SDS and β2-microglobulin levels (beta = -0.07 per 10 mg/L higher level; 95%CI = -0.14 to 0; p = 0.05).

At 12-months: Delta Height HDF-hyD propensit score: 0.2 95%CI -0.33; p=0.03

Clearances by HDF

- B2-microglobulin
  - Prototype middle-molecule (11.8 kDa)
  - Early and sustained fall in HDF shown in many studies
  - Lower levels in HDF at baseline is seen only in prevalent HDF patients

Bone and mineral metabolism

No differences in:
- Type of phosphate binders or cinacalcet use
- Serum and dialysate calcium levels
- 25-hydroxy vitamin D levels

PTH is a middle molecule (mol wt - 9.5 kDa)

FGF23 and bone biomarkers: pending

FGF23 levels are ~30% lower on HDF
Reduced systemic inflammation in HDF

Lower hs-CRP levels even at baseline
Early effect of ultra-pure water and improved clearances of cytokines?

SWITCH study
HD → HDF keeping all other parameters constant, within a period of 3 months there was a significant reduction in hs-CRP

HDF is safe

No change in serum albumin level after 12-months on HDF

Patient related outcomes

Self-reporting on 6-monthly questionnaires

Correlations
- Ultrafiltration volume per session
- Hemoglobin

No correlations with
- 24-h ABPM / systolic or diastolic BP
- Residual renal function

PROMs - post-dialysis recovery time

Improved outcomes on HDF
SONG-HD - fatigue is a highly prioritized outcomes for dialysis patients

Discussion

Strengths
- Largest cohort study in paediatric dialysis
- Children do not have confounding CVD or diabetes and are mainly non-smokers
- Growth is a unique and sensitive outcome parameter

Limitations
- Non-randomised; cohort study within the IPHN Registry
- Blinding not possible
- Both incident and prevalent patients included
- Surrogate end-points only
- Partially Industry funded
- No health economic analysis
- Different countries with different global management of patients

Conclusion: HDF for all in-centre patients?

- We need a randomised trial..... but until this is done, HDF could be used based on
  - Safety
  - Biological plausibility
  - Data from adult RCTs
  - 3H study in children
- Early benefits of HDF - use even if short period on dialysis anticipated
- HDF is beneficial even in those with residual renal function
I have to say that I had hesitations when I had to choose THE 2019 paper...

Higher eGFR at Dialysis Initiation Is Not Associated with a Survival Benefit in Children

Eka Wondi,1,7 Günel,1,7 Johansen,1,7 Michael C. Chaloupka,1,7 Bradley A. Wondi,1,7
Charles R. McCullough,1,7 Raman Urdaneta,1,7 and Anna Kup1,7

Tone’s Up! Start Dialysis Later in Children
Nicholas O. Larkin1,7 and Jonathan C. Craig1

Clinical Research | www.jpr.org

Acknowledgements
Rukshana Shroff, GOSH, London
Bruno Ranchin, Lyon

And all of you for your attention!