At what eGFR should we start dialysis?

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No conflict of interest

This presentation is dedicated to all our patients and their families who come to our clinic with statements like:

- “Doctor, mum said I might need to start dialysis now. I am afraid and I don’t really want to…” (5 years old, CAKUT)
- “Doc, when will we start dialysis? I cannot wait any more! I am really fed up…” (13 years old, FSGS)
Background

Criteria to start dialysis

Aim when starting dialysis

Early vs. Late
Background

Criteria to start dialysis

1. **Uremic symptoms** (pericarditis, encephalopathy….)
2. **Abnormal biochemical findings** (severe hyperK+ and/or acidosis)
3. **Diuresis-resistant fluid overload** (pulmonary oedema)
4. **Failure to growth**

Aim when starting dialysis

1. Prolong life
2. Improve life
Poll Question (1) : A clinician should base their decision to initiate maintenance dialysis on a child on the presence of...

a) Biochemical abnormalities difficult to control by medications, diuresis-resistant fluid overload and growth, but not eGFR

b) Answer (a) including eGFR. The primary renal disease (PRD) should not affect our decision.

c) Answer (a) including PRD. The eGFR should not affect our decision.

d) Biochemical abnormalities difficult to control by medication, diuresis-resistant fluid overload, PRD, growth, HTN, eGFR, patient-related QoL and a shared decision making with parents/families.
When **should children be considered** to start dialysis?

5 → 10 → 15 ml/min/1.73m²

European Paediatric Peritoneal Dialysis Working G. Guidelines, Perit Dial Int 2001  < 10-15 mL/min/1.73m²
When **should children be considered** to start dialysis?

European Paediatric Peritoneal Dialysis Working G. Guidelines, Perit Dial Int 2001

RRT in children should be **considered** when the eGFR falls $< 14 \text{ mL/min/1.73m}^2$

RRT in children should be **recommended** when the eGFR falls $< 8 \text{ mL/min/1.73m}^2$

5 10 15 ml/min/1.73m$^2$
When should children be considered to start dialysis?

Canadian Society of Nephrology, 2014
- Start dialysis if < 6 mL/min/1.73m²

European Paediatric Peritoneal Dialysis Working Group Guidelines, Perit Dial Int 2001
- Close monitoring if < 10-15 mL/min/1.73m²

- RRT in children should be recommended when the eGFR further falls < 8 mL/min/1.73m²

Update KDOQI 2015: symptoms & signs
- RRT in children should be considered when the eGFR falls < 14 mL/min/1.73m²
When **should children be considered** to start dialysis?

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**RRT in children should be considered when the eGFR falls < 14 mL/min/1.73m²**

**Canadian Society of Nephrology, 2014**
- RRT in children should be **recommended** when the eGFR further falls < 8 mL/min/1.73m²

**Canadian Society of Nephrology, 2014**
- Start dialysis if < 6 mL/min/1.73m²

**NICE National Institute for Health and Care Excellence**
- 2018: 5-7 mL/min/1.73m² if no symptoms

**European Society for Paediatric Nephrology**
- Close monitoring if < 15 mL/min/1.73m²

**Update KDOQI 2015: symptoms & signs**
When **should children be considered** to start dialysis?

- **Canadian Society of Nephrology, 2014**: Close monitoring if below 15 mL/min/1.73m². Start dialysis if below 6 mL/min/1.73m².
- **European Paediatric Peritoneal Dialysis Working G. Guidelines, Perit Dial Int 2001**: RRT in children should be considered when the eGFR falls < 14 mL/min/1.73m².
- **RRT in children should be recommended when the eGFR further falls < 8 mL/min/1.73m²**.
- **Update KDOQI 2015**: KDIGO 2019: There is no specific eGFR for initiation of dialysis in the absence of symptoms and current data do NOT support pre-emptive dialysis initiation.

**KDIGO 2019**: 5-7 mL/min/1.73m² if no symptoms.
When are children currently starting dialysis?

1) ESPN/ERA-EDTA Registry for children, Preka et al, Nephrol Dial Transplant 2019

Median eGFR at start of RRT was 8.2 mL/min/1.73m² (IQR 6.2-10.7 mL/min/1.73m²)

2) US Renal Data System Registry in children, Okuda et al, AJKD 2019

Median eGFR at start of RRT was 7.8 mL/min/1.73m² [IQR 5.6-10.5 mL/min/1.73m²]

Winnicki et al, JASN 2019, Increase in children who start dialysis at higher eGFR > 10 → Median eGFR 12.8 (IQR 11.1-16.0)
Poll Question (2) : According to the only RCT in adults and the 3 largest paediatric registry observational studies, what is the main conclusion regards the optimal time to start maintenance dialysis?

a) “The earlier the better”

b) “The later the better”

c) There is no evidence supporting benefit from early initiation. However, decisions in children should be made on a case-by-case basis.

d) There is no evidence supporting benefit from early initiation. However, when eGFR is between 5 and 7 ml/min/1.73m2 dialysis should always be initiated.
Only one RCT in 2010, the “IDEAL study”

RCT between 2000-2008
828 adults
- 404 early-starters (eGFR 10-14ml/min/1.73m²)
- 424 late-starters (eGFR 5-7 ml/min/1.73m²)
- Median follow-up: 3.59 years
Cooper et al, IDEAL Study, NEJM 2010:

Primary outcome: Time-to-death
37.6% (152/404) early-starters (eGFR 10-14)
36.6% (155/424) late-starters (eGFR 5-7)
(HR with early initiation 1.04; 95% CI, 0.83-1.30, p=0.75)

Secondary outcome:
No significant difference of adverse events
(cardiovascular, infections, complications of dialysis)
Is there evidence to guide us in the timing of dialysis initiation in children?

1. Quality of Life (QoL)
2. Mortality
3. Morbidity
   - Infection & Inflammation
   - Growth
   - Anaemia
   - Metabolic disease
4. Economic considerations
Quality of Life (QoL)
Quality of Life (QoL)

1. Chronic dialysis in children is associated with **lower QoL scores than any other chronic condition apart from cancer**!
2. Depression
3. Loss of schooling, less well with schoolwork
4. Family breakdown, difficulties maintaining employment
5. Restricted lifestyle, worse adherence
6. Feeling of “being different”

Clementi et al, Psychosocial considerations and recommendations for care of pediatric patients on dialysis. Pediatr Nephrol 2019


• **9,963** incident dialysis patients
• Age: **1-17 years old**

• **5 groups (eGFR):**
  • <5 (late starters)  
  • 5-6.9  
  • 7-8.9  
  • 9-11.9  
  • > 12 (early starters)

![Graph showing hazard ratios for mortality across estimated glomerular filtration rates (eGFRs) at dialysis therapy initiation.](image)

Okuda et al, Am J Kidney Dis 2019

↑Mortality risk across ↑ eGFRs
US renal data system registry

Okuda et al, Am J Kidney Dis 2019

Figure 3. Hazard ratios for mortality across estimated glomerular filtration rates (eGFRs) at dialysis therapy initiation.

Figure 4. Hazard ratios for mortality in patients (A) younger than 6 years and (B) 6 years or older. Abbreviation: eGFR, estimated glomerular filtration rate.
US renal data system registry  

Winnicki et al, JASN 2019

- **15,170** incident dialysis patients
- **Age:** 1 - 18 years old

- **2 groups (eGFR):**
  - **≤ 10 ml/min/1.73m²** → late starters
  - **> 10 ml/min/1.73m²** → early starters

>36% Mortality risk across ↑ eGFRs

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**Table 2.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 1995–2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n=14,696)</td>
<td>1.36 (1.24 to 1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients initiated on HD (n=8794)</td>
<td>1.56 (1.39 to 1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients initiated on PD (n=5902)</td>
<td>1.07 (0.91 to 1.25)</td>
<td>0.44</td>
</tr>
<tr>
<td>Years 2006–2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n=6757)</td>
<td>1.34 (1.11 to 1.62)</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients initiated on HD (n=4151)</td>
<td>1.68 (1.33 to 2.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients initiated on PD (n=2606)</td>
<td>0.86 (0.62 to 1.20)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*A total of 474 persons missing from adjusted analysis due to missing covariate data.

*b A total of 217 persons missing from adjusted analysis due to missing covariate data.
• 2,963 incident dialysis patients
• Age: < 18 years old
• 2 groups (eGFR):
  - < 8 ml/min/1.73m² → late starters
  - ≥ 8 ml/min/1.73m² → early starters

Mortality risk: Late vs early initiation of dialysis:
- HR 1.00, 95% CI: 0.66-1.51
- aHR 0.82, 95% CI: 0.54-1.25

Likelihood to receive a Tx within 1, 2 & 5 years after initiating dialysis:
1- year: 0.93, 95% CI 0.81-1.08 (aHR 1.00, 95% CI 0.86-1.16)
2- years: 0.98, 95% CI 0.88-1.10 (aHR 1.03, 95% CI 0.92-1.15)
5- years: 0.97, 95% CI 0.89-1.07 (aHR 1.02, 95% CI 0.93-1.12)
Is there evidence to guide us in the timing of initiation of dialysis in children?

1. Quality of Life (QoL)
2. Mortality
3. Morbidity
   - Cardiovascular morbidity
   - Growth
   - Infection & Inflammation
   - Anaemia
   - Metabolic disease
4. Economic considerations
Cardiovascular morbidity (HTN, LVH)

- IDEAL study (adults): no difference in LVEF, LVM, LVAV

- Children:

<table>
<thead>
<tr>
<th></th>
<th>Early-starters (&gt; 10 ml/min/1.73m²)</th>
<th>Late-starters (&lt;7 ml/min/1.73m²)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI (g/m²)</td>
<td>53 ± 28</td>
<td>60 ± 28</td>
<td>NS</td>
</tr>
<tr>
<td>LVH</td>
<td>51%</td>
<td>64%</td>
<td>NS</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Frequency of hospitalizations (episodes/person-year)</td>
<td>1.8</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/l) (N=0-6)</td>
<td>3.64 ± 2.00</td>
<td>4.37 ± 3.28</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.5 ± 2.1</td>
<td>10.3 ± 1.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Preka et al NDT 2019
Growth (Height, BMI)

Mean Height SDS
- Early starters: -1.79 (95% CI: -1.88 to -1.71)
- Late starters: -1.76 (95% CI: -1.84 to -1.68)

11% underweight with eGFR < 6 vs. 5.3% with eGFR 9-12 ml/min/1.73m²

Mean BMI SDS at first observation according to eGFR at initiation of CPD

Schaefer et al, Sci Rep 2019
Further comorbidities:

1. **Infection & Inflammation** (IDEAL study, ESPN/ERA-EDTA registry data) – No difference

2. **Anaemia** [ESPN/ERA-EDTA Registry data showed slightly higher prevalence among late starters (aOR 1.14, 95%CI 0.99-1.32)]

3. **Metabolic disease** (ESPN/ERA-EDTA Registry data showed commoner hyperphosphatemia in early vs late starters (28% vs 24%)}
Further comorbidities:

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Economic considerations:

- **IDEAL study**: higher dialysis-related costs associated with early start but similar resources costs (managing adverse events)
- **No data in children**
Poll Question (3): After all conservative treatment efforts have been tried, there is some evidence that early initiation of dialysis in children might improve:

a) Hypertension  
b) Growth  
c) Metabolic Bone Disease  
d) Over-all-morbidity
Non eGFR-based approaches to determine timing of dialysis initiation

1. **Symptoms assessment** - smartphone-based mobile health apps

2. **Equations helping in estimating ESKD: Kidney Failure Risk Equation (KFRE) & CKD progression risk timelines**
   - Winnicki et al, JAMA Pediatr 2018
   - Furth et al, Am J Kidney Dis 2018

3. **Novel markers of kidney function linked to kidney deterioration**
   (uremic retention solutes, proximal tubular secretion molecules) and the **impact of RRF** in outcome.

4. **Increased emphasis on the importance of patient-provider-caregiver shared decision-making**

Indoxyl sulfate
P-crestyl sulfate
Hippurate etc
Conclusions

1. **IDEAL study in adults**: the only RCT → no clinical benefit of starting dialysis early
Conclusions

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**Paediatric studies:**

1. **US renal data registry studies**: incremental and linear association between eGFRs at dialysis initiation and mortality, such that higher eGFRs at dialysis therapy initiation were associated with higher risk for mortality (except in patients < 6 years old)
Conclusions

1. **IDEAL study in adults**: the only RCT → no clinical benefit of starting dialysis early

**Paediatric studies:**

1. **US renal data registry studies**: incremental and linear association between eGFRs at dialysis initiation and mortality, such that higher eGFRs at dialysis therapy initiation were associated with higher risk for mortality (except in patients < 6 years old)

2. **ESPNA/ERA-EDTA data registry**: Not any association between timing of dialysis initiation and mortality, access to transplantation or growth. The only difference observed was with HTN, which was more prevalent in late starters → special attention for prevention of CVD should be considered when opting for conservative treatment
Recommendations

1. Using eGFR as the primary guide for when to start dialysis is a strategy that should likely be abandoned.
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2. Dialysis-initiation decision-making should be done using a patient-centered approach in which symptom assessment and patient-level goal ascertainment is central.
Recommendations

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2. Dialysis-initiation decision-making should be done using a patient-centered approach in which symptom assessment and patient-level goal ascertainment is central.

3. A reasonable approach is to defer initiation of dialysis in asymptomatic individuals until the development of signs and symptoms consistent with uremic syndrome that may reasonably be expected to improve with dialysis treatment.
Recommendations

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3. A reasonable approach is to defer initiation of dialysis in asymptomatic individuals until the development of signs and symptoms consistent with uremic syndrome that may reasonably be expected to improve with dialysis treatment.

4. Deferred initiation does not, however means deferred preparation, and early discussions regarding medical and psychosocial preparation for the initiation of dialysis should not be delayed (placement of dialysis access, dialysis modality selection, advance care planning, assistance with home therapies).
Recommendations

1. Using eGFR as the primary guide for when to start dialysis is a strategy that should likely be abandoned.

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4. Deferred initiation does not, however means deferred preparation, and early discussions regarding medical and psychosocial preparation for the initiation of dialysis should not be delayed (placement of dialysis access, dialysis modality selection, advance care planning, assistance with home therapies).

5. Critical need for the Nephrology research community to pursue work to better understand and define the components of the uremic syndrome.
The optimal time for starting dialysis in children should be discussed case by case and is definitely NOT merely dependent on the level of eGFR/Creat level.

Thank you for your attention!

Happy to take questions/comments @ evgenia.preka@gmail.com
Extras (if needed for the discussion)
Limitations to acknowledge

Biases (survival, potential selection biases, lead-time biases…)

Nature of observational studies (although large)

Residual confounding factors (RRF? doses of GH? Feeding management?)

Change in methods for Screat calculation:
  • before 2005 Jaffe method
  • 2005-2009 transition period for most centers
  • after 2009 Schwartz formula
• **1,603** incident dialysis patients
• **Age: 3 months - 16 years old**

25% late referrals (LR > 3 months)
Median follow-up: 4.8 (2.9-7.6) years

No difference in **mortality** (HR 1.30; 95%CI, 0.7-2.3; p=0.40)

**Transplantation (Tx) up to 1 year:**
- 61% ER vs. 21% LR
- No difference in Tx after the 1st year
### What is the optimal time/eGFR to start dialysis in children?

<table>
<thead>
<tr>
<th>Study design</th>
<th>Okuda et al, AJKD 03/2019</th>
<th>Preka et al, NDT 04/2019 in press</th>
</tr>
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<tbody>
<tr>
<td>Setting &amp; Participants</td>
<td>Retrospective cohort; USRDS Registry</td>
<td>Retrospective cohort; ESPN/ERA-EDTA Registry</td>
</tr>
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<td>9,963 incident dialysis patients; aged 1-17 years old</td>
<td>2,963 incident dialysis patients; Aged &lt; 18 years old</td>
<td></td>
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<tr>
<td>Primary outcome</td>
<td>1. Time-to all-cause death</td>
<td>1. Patient’s survival 2. Access to Transplantation</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Predictors of dialysis initiation (early vs. late)</td>
<td>1. Growth 2. Cardiovascular risk factors</td>
</tr>
<tr>
<td>Groups divided (according to eGFR at start of dialysis)</td>
<td>5 groups: &lt;5, 5-6.9, 7-8.9, 9-11.9, &gt;12</td>
<td>2 groups: &lt; 8 ml/min/1.73m² → late starters 2. ≥ 8 ml/min/1.73m² → early starters</td>
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↑Mortality risk across ↑eGFRs

Patients with HTN should be carefully considered.
NAPRTCS Data: Overall survival according to age at which chronic PD was initiated for treatment of ESRD