CKB-MBD therapy beyond vitamin D: when and how to use calcimimetics and bisphosphonates in pediatric ESRD

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Annual Dialysis CONFERENCE

presented by the Karl Nolph, MD, Division of Nephrology

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Disclosures

- **Consultancy and speaker**
- Kyowa Kirin
- Alnylam
- Dicerna
- Amgen
- Pfizer
- Alexion
- Bayer
- Lilly
- Vifor

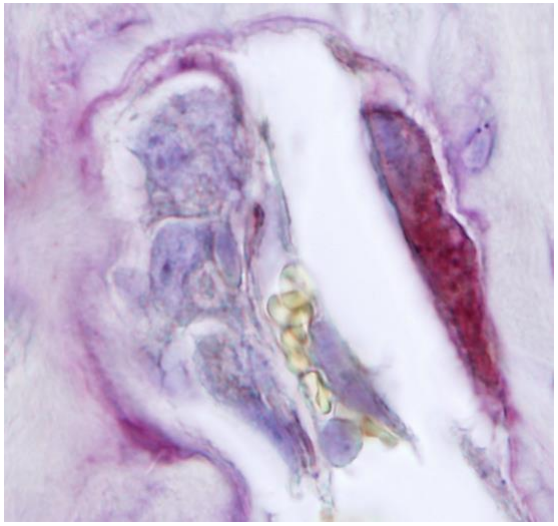
- **Research grants**
- Kyowa Kirin
- Amgen
- Horizon
- Novartis
- Crinex

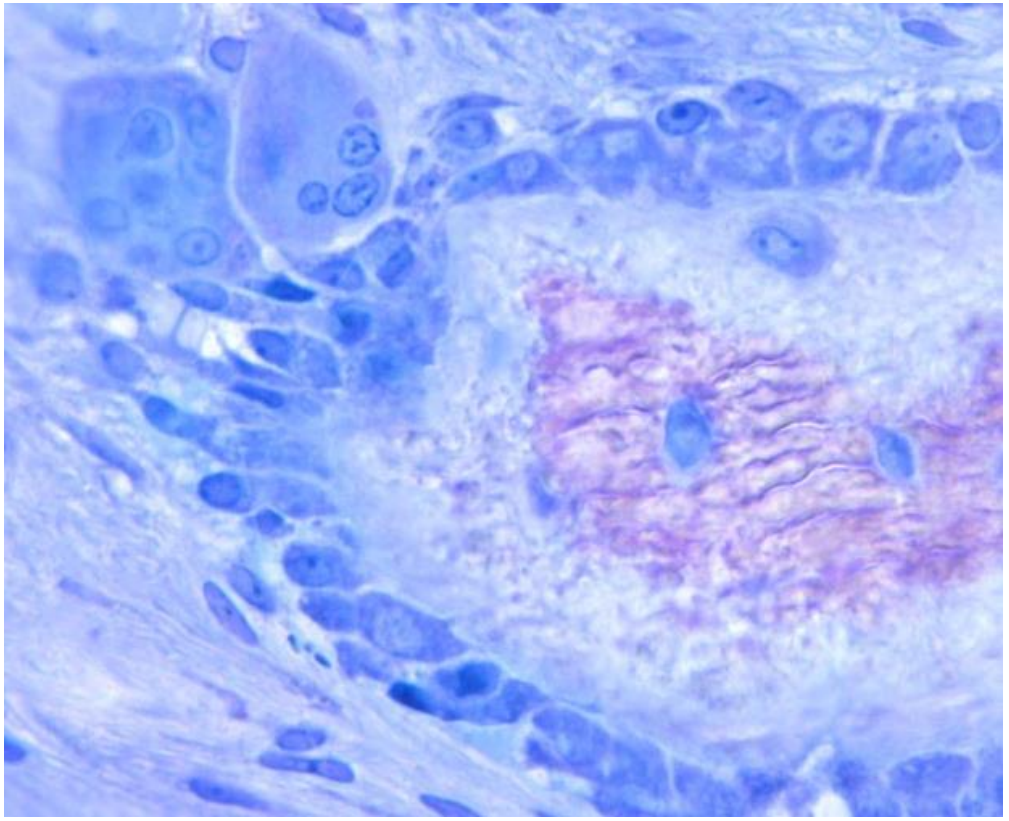
- **Travel grants**
- Kyowa Kirin

Outline of the talk

- Brief introduction to pediatric CKD-MBD
- Global management of pediatric CKD-MBD
- Calcimimetics: rationale to use them, and practical points
- Bisphosphonates : rationale to use them, and practical points
- Conclusion

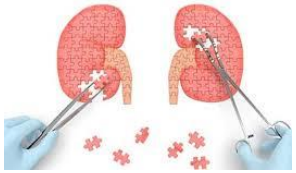
Brief introduction to pediatric CKD-MBD

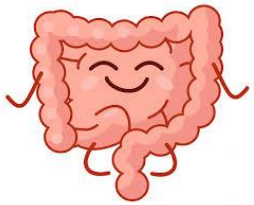




Calcium and phosphate metabolism: a deregulation in CKD

1-25 vitamin D





Phosphate Calcium

FGF23 / Klotho

PTH

⇒ Consequences on bone and vessels

⇒ Bone and mineral disorders

⇒ CKD-MBD

Stimulating effect / Inhibiting effect

Adapted from Bacchetta, Metabolism 2020

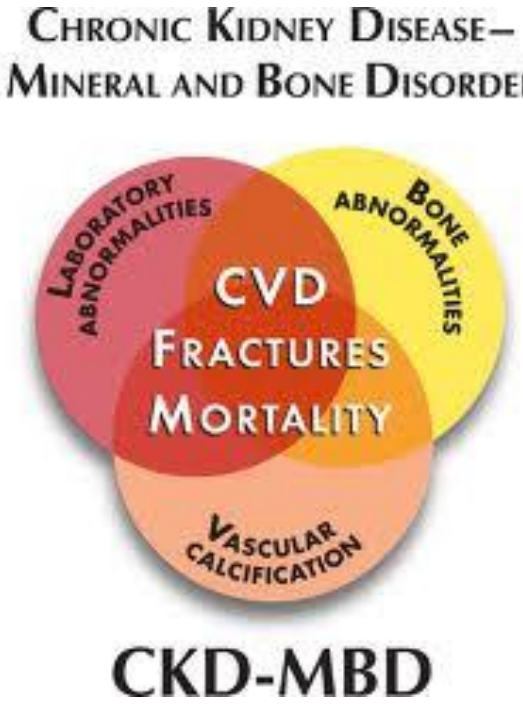
CKD-MBD as a multi-systemic disease

Hypocalcemia
Hyperphosphatemia

HyperPTH
Decreased 1-25 D

Prurit
Skin necrosis

Keratitis
Corneal calcifications



Renal osteodystrophy

Growth retardation
GH resistance

Proximal myopathy

Vascular calcifications

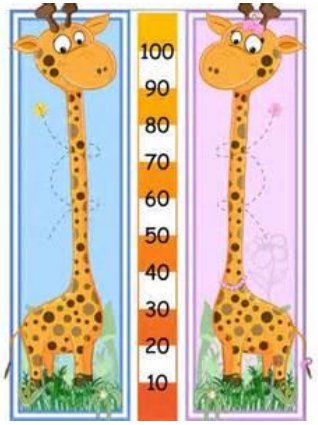
GFR < 60 mL/min per 1.73 m^2

How to evaluate CKD-MBD in pediatric CKD in daily practice?

- **Growth / nutrition**

European guidelines

NDT 2020

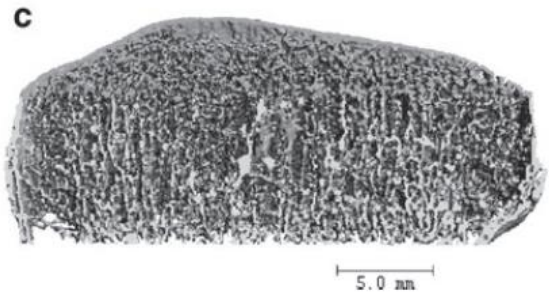


- **Biomarkers**
  - Calcium, phosphate
  - PTH, 25OH-D
  - ALP

- **Bone imaging**
  - Wrist X-ray for skeletal age
  - Targeted X-ray in case of clinical symptoms
  - No interest for DXA

- **Cardio-vascular evaluation**
  - BP, Ambulatory BP monitoring
  - Cardiac US

- **Research tools**
  - FGF23, sclerostin, other bone biomarkers
  - Bone MRI, pQCT, HR-pQCT, US…
  - Bone biopsy
  - Carotid IMT, PWV



Clinical consequences of pediatric renal osteodystrophy

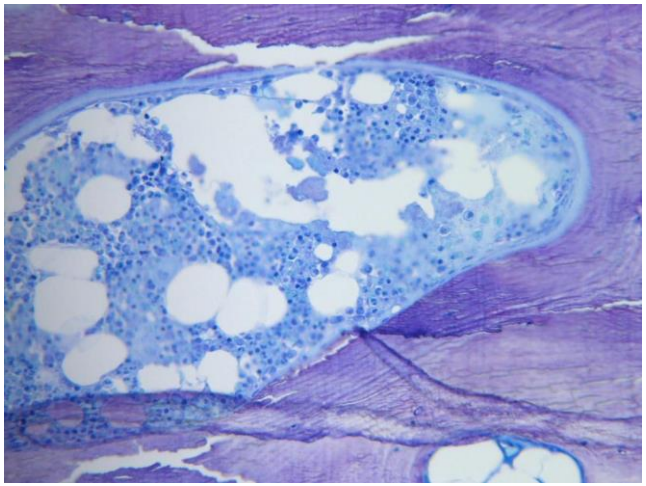
Adynamic bone
« *Low PTH state* »

Mainly due to vitamin D analogs and calcium salts

Growth retardation +++

Calcifications +++

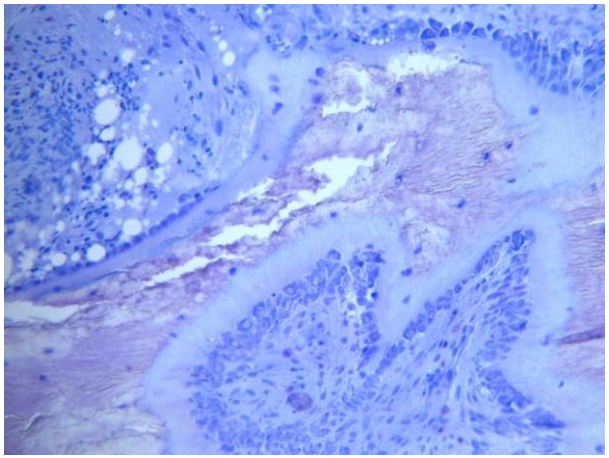
Fractures +++



Osteitis fibrosa
« *High PTH state* »

Growth retardation +

Calcifications +++



Salusky and Kuizon, 2004

Two main challenges for pediatric nephrologists… in the field of CKD-MBD

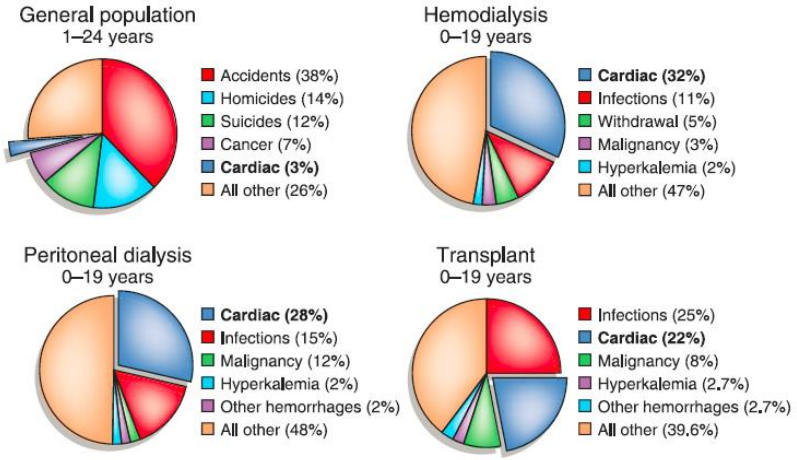
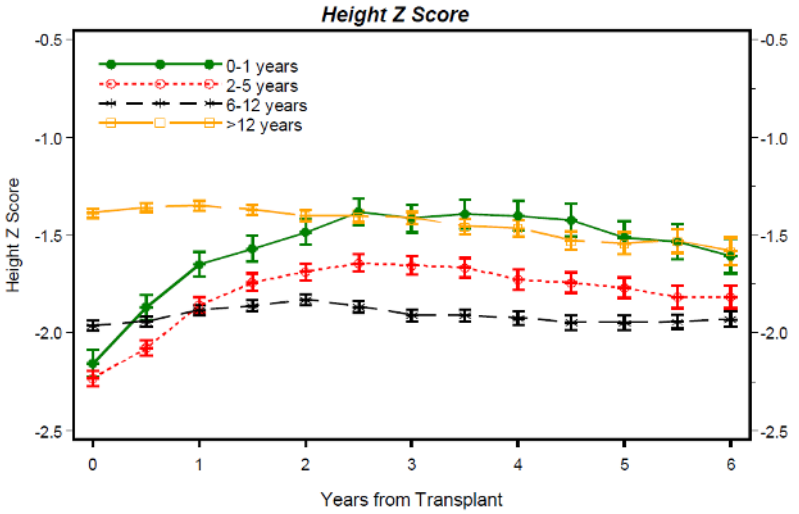


Figure 1. Leading causes of death in general pediatric population and in children on renal replacement therapy. Data are presented as percentages. Data for dialysis and transplant patients are from the USRDS (2011).[2] Data for general pediatric population are from Mathews *et al.* (2011).[1]

Cardiovascular disease



Growth retardation and fracture risk

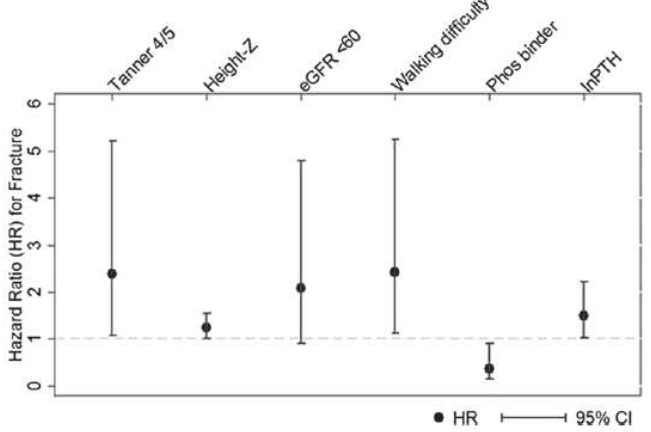
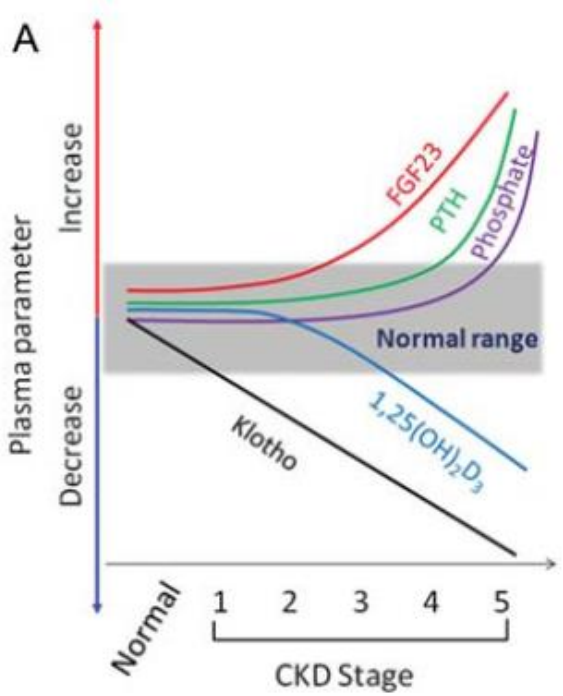
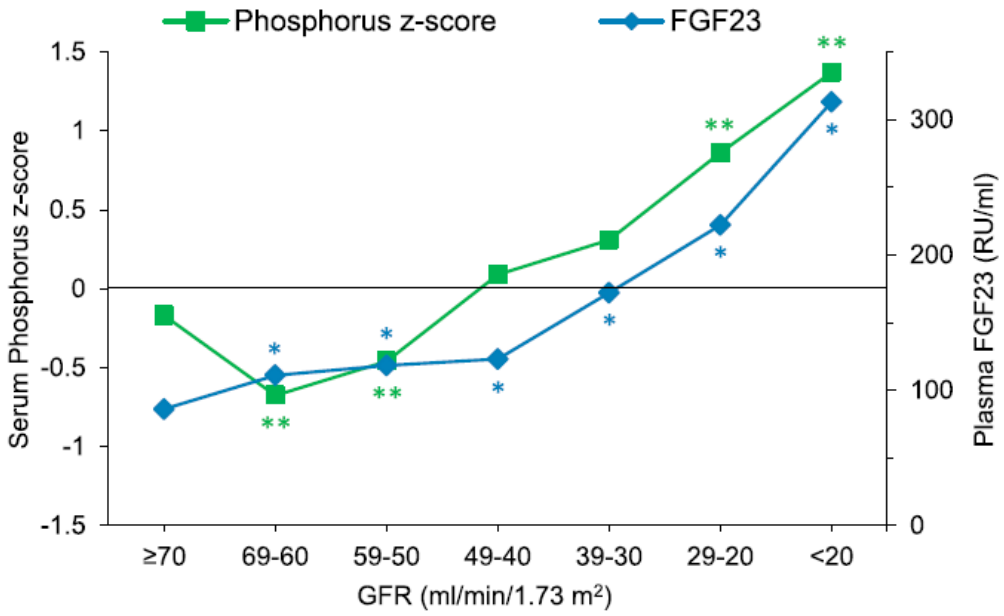


Figure 1. Final multivariable Cox regression model: correlates of incident fracture. [a]HR for males ≥15 years versus females ≥15 years=(3.94*0.67)=2.6. [b]PTH natural log transformed.

Mitsnefes, JASN 2012; NAPRTCS 2010; Denburg JASN 2015

Changes of biomarkers with declining renal function





Portale, clin J Am Soc Nephrol 2014

Chang HU, NDT 2012
Pavik, NDT 2012

High PTH levels are associated with…

- Longitudinal growth (>500 pg/mL)
- Vascular calcifications
- Anemia
- Left ventricular hypertrophy
- Cardiovascular disease
- Mortality

- Data from the IPPN registry
  - More than 1800 children
  - 87 centers
  - 31 countries

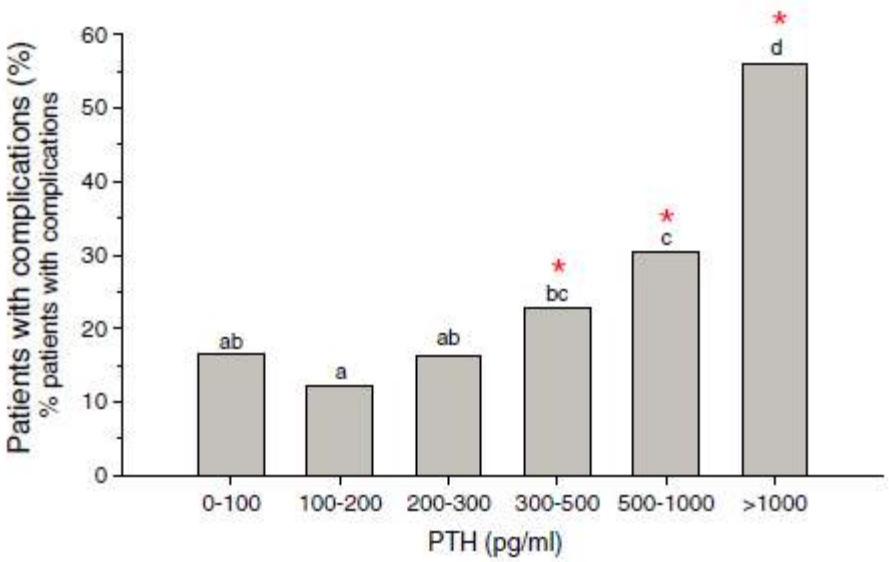
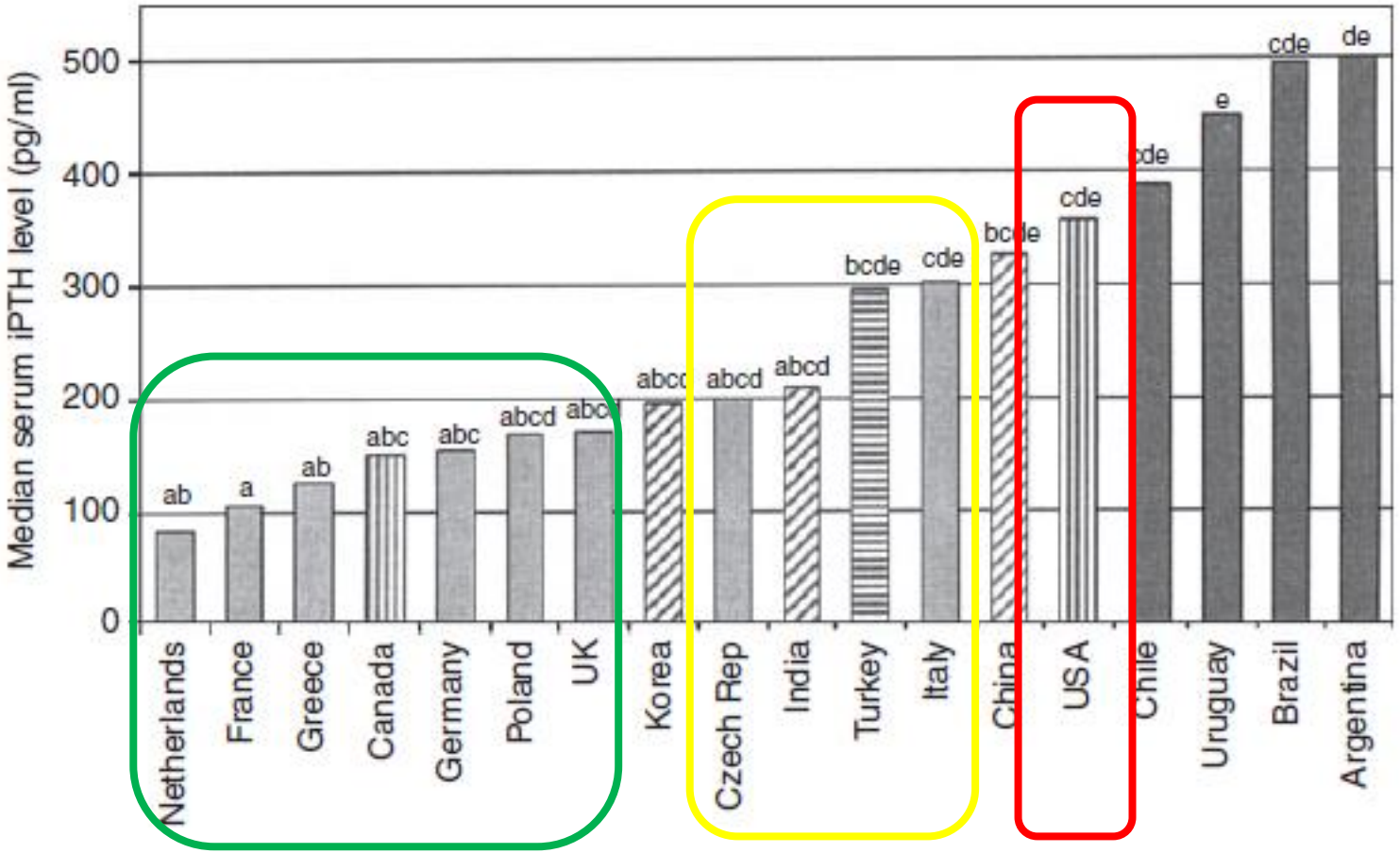


Fig. 3 Percentage of patients with alterations of bone and mineral metabolism (bone pain, limb deformities, extraosseous calcifications, radiological osteomalacia and/or osteopenia) stratified by time-averaged mean parathyroid hormone (PTH) levels. Groups sharing same letters do not differ significantly; (Fig. adapted from 39; used with permission)

Haffner Pediatr Nephrol 2013

PTH levels depend on geography!



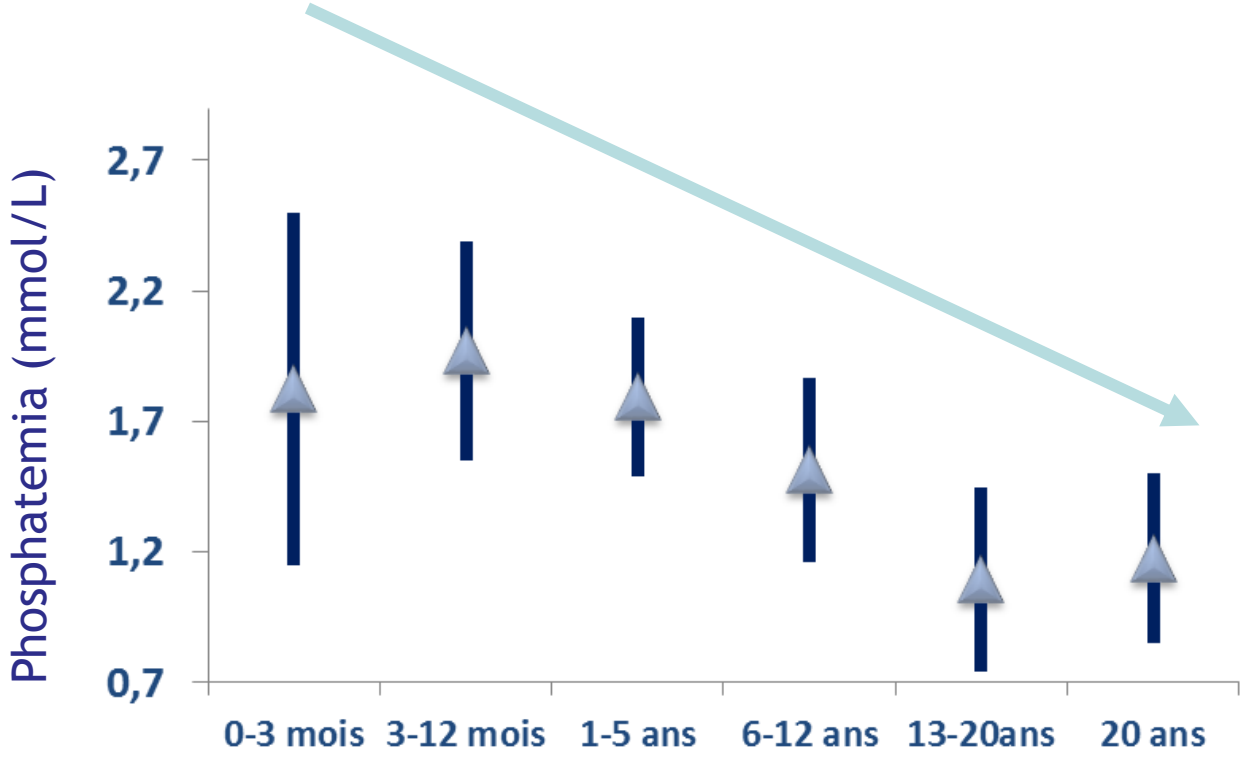
Borzych, Kidney International 2010

PTH levels: different guidelines… different targets…

- **K-DOQI 2005**
  - PTH 3-5 times above the upper normal limit : **200-300** pg/mL
- **European guidelines 2006**
  - European Pediatric Dialysis Working Group
  - Keep PTH levels within 2-3 times the upper normal limit: **120-180** pg/mL
- **K-DIGO 2017**
  - PTH 2-9 times above the upper normal limit : **120-540** pg/mL
- **Limited clinical evidence**
- Data from IPNN in PD: optimal range 1.7-3 times above the upper normal limit: **100-200** pg/mL

Haffner Pediatr Nephrol 2013

Simple biomarkers: reference values for phosphate must be adapted to age +++

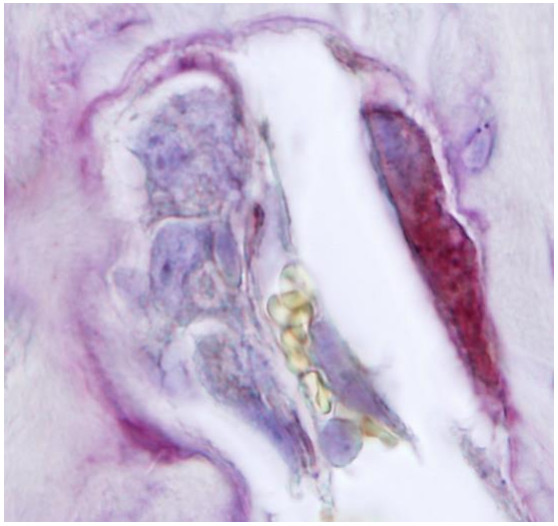


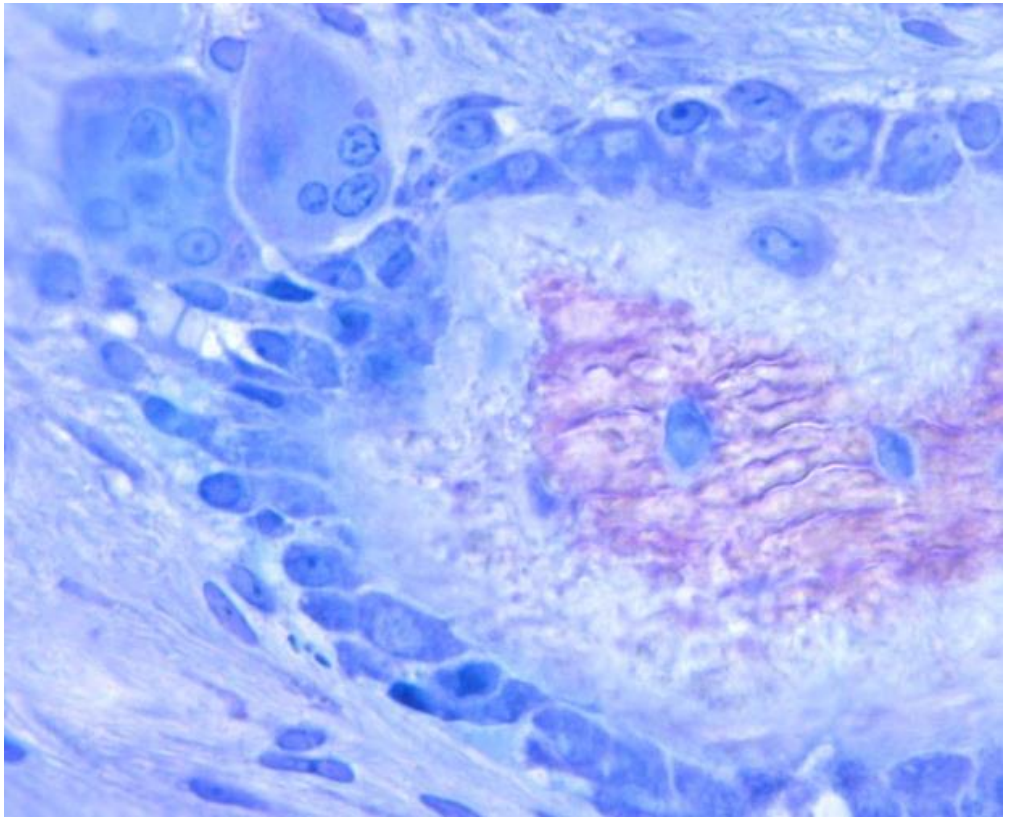
⇒ **Z-score of phosphate depending on age ++++**

⇒ **Same for nutritional intakes for Ca and Phosphate**

Ardeshirpour Pediatr Endocrinol Rev 2007

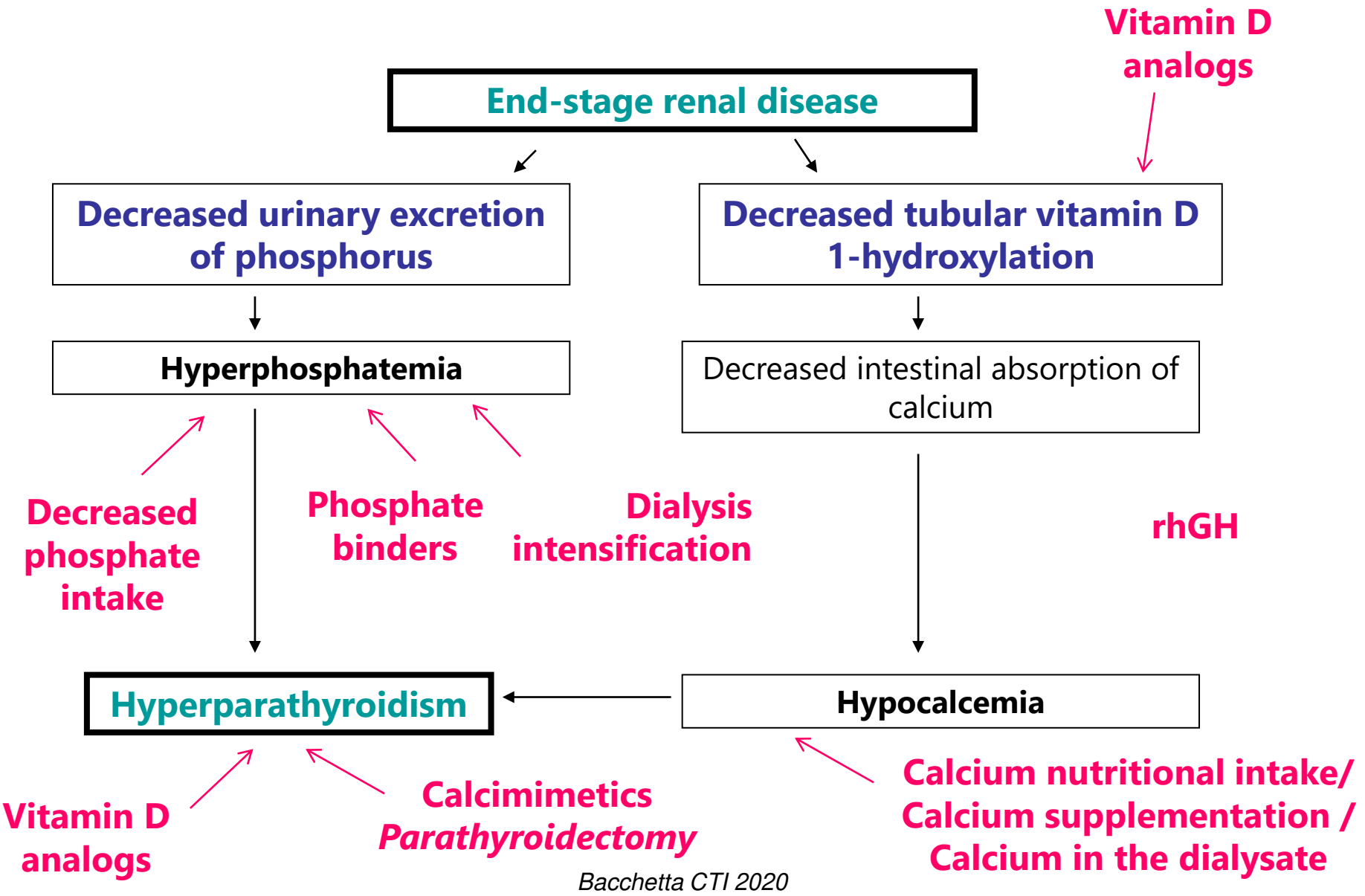
Global management of pediatric CKD-MBD





The cornerstones of CKD-MBD management in 2021

25 OH vitamin D supplementation
Target 75-120 nmol/L

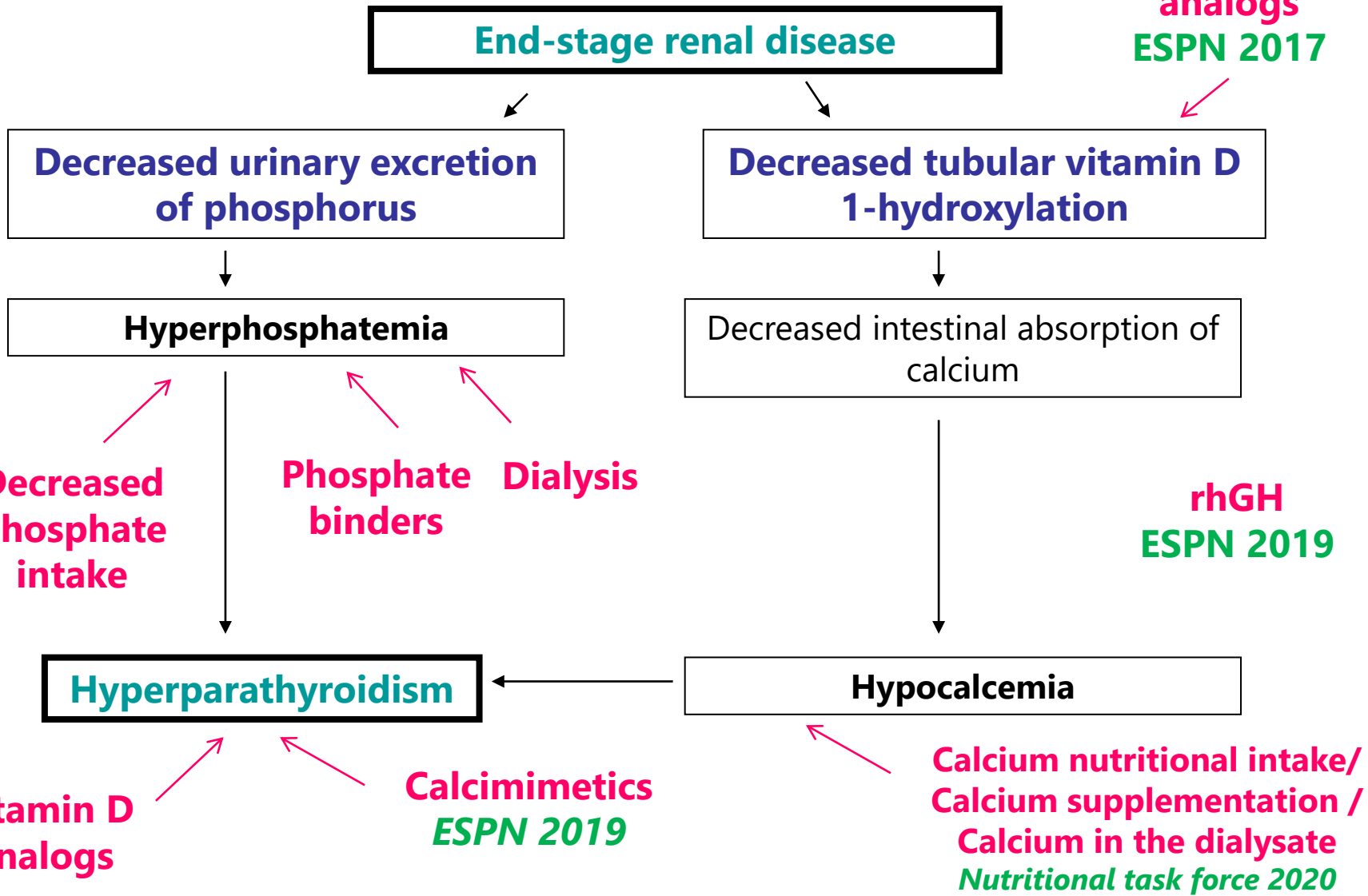


Bacchetta CTI 2020

25 OH vitamin D supplementation ESPN 2017

International guidelines

Ped Neph 2006 / Nutrition KDOQI 2008/ KDIGO 2017



It is crucial to assess nutritional calcium and phosphate intake in pediatric CKD-MBD: enough calcium and not too much phosphate…

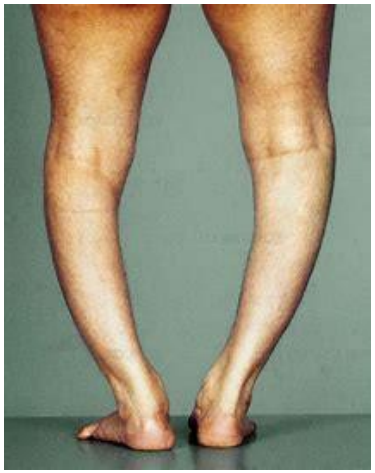
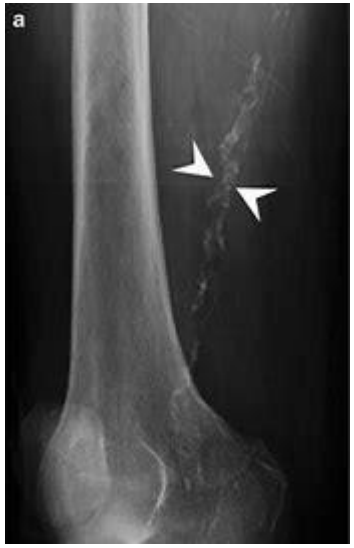


Table 7 Summary of SDI (suggested dietary intake) for calcium and phosphate in children with CKD2-5D

Age (years)	SDI calcium (mg)	SDI phosphate (mg)
0–<4 months	220	120
4–<12 months	330–540	275–420
1–3 years	450–700	250–500
4–10 years	700–1000	440–800
11–17 years	900–1300	640–1250

For children with poor growth, reference to the SDI for height age may be appropriate. This is the age that corresponds to their height when plotted at the 50th centile on a growth chart



Not enough calcium: increased risk of rickets

Too much phosphate: increased risk of vascular calcifications

Mc Alister et al Pediatr Nephrol 2020, Bacchetta et al Calcif Tissue Int 2020

Pros and cons of vitamin D analogs

- **Pros**
  - Cheap
  - Easily available
  - Well-known drug

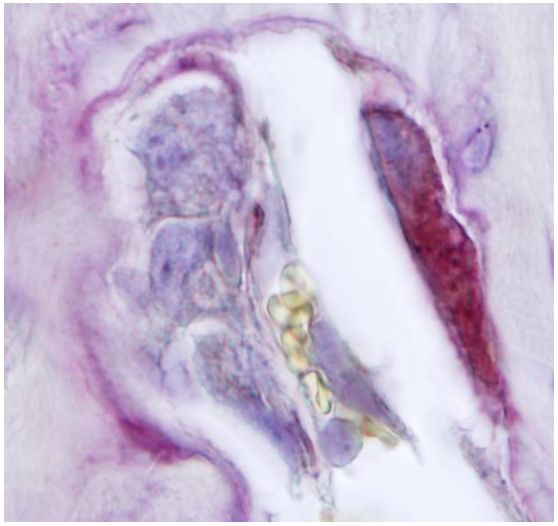
- **Cons**
  - Increases calcium levels
  - But also phosphate levels
  - Can promote vascular calcifications
  - Can promote low bone turnover
  - May affect growth in CKD children
  - Increases FGF23 levels

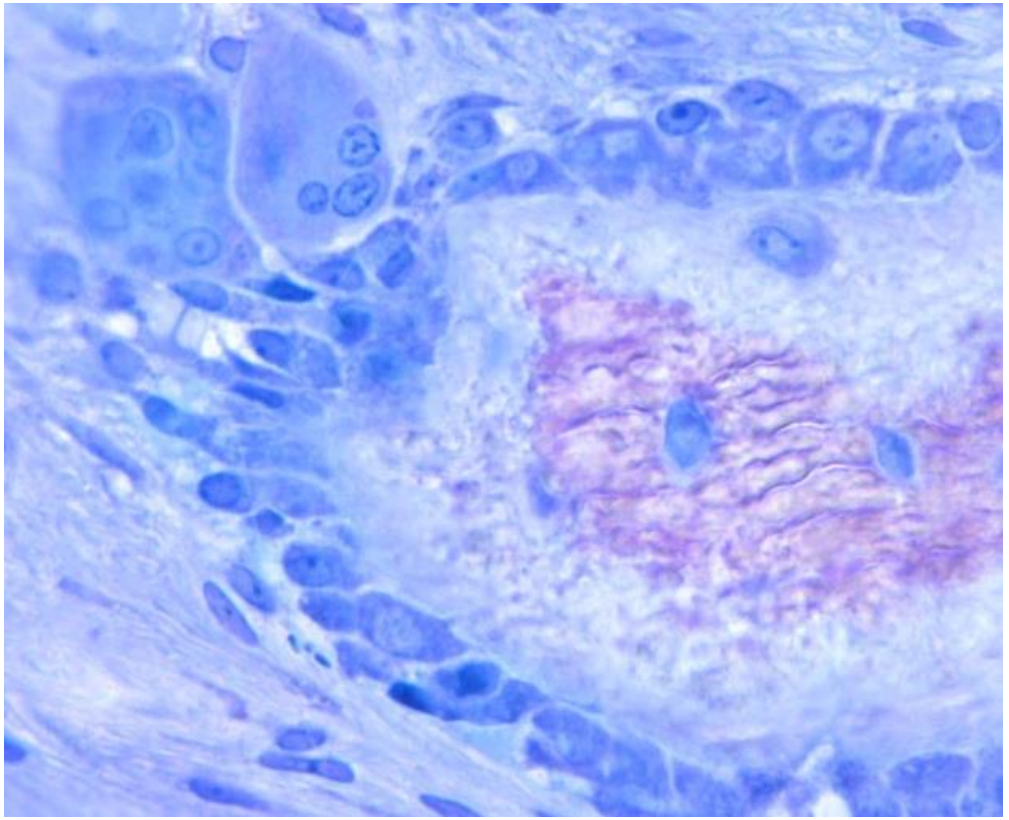
Recommendation: We suggest starting vitamin D analogues in the lowest dose to achieve target PTH concentrations and maintain normocalcaemia. Subsequent titration of vitamin D therapy may be performed based on trends in serum calcium, phosphate and PTH levels.

GRADE
Strength of recommendation: 2
Level of evidence: D

Shroff, NDT 2017

Calcimimetics: rationale to use them, and practical points





Nephrol Dial Transplant (2019) 1–18
doi: 10.1093/ndt/gfz159

ndt
Nephrology Dialysis Transplantation

Cinacalcet use in paediatric dialysis: a position statement from the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders Working Group of the ERA-EDTA

Justine Bacchetta[1,2,3,4], Claus Peter Schmitt[5], Gema Ariceta[6], Sevcan A. Bakkaloglu[7], Jaap Groothoff[8], Mandy Wan[9], Marc Vervloet [10], Rukshana Shroff[9,*] and Dieter Haffner[11,12,*] on behalf of the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders and Dialysis Working Group of the ERA-EDTA**

The 2019 European consensus paper on the use of cinacalcet in children above 3 years undergoing hemodialysis: only if calcium is above 2.40 mmol/L (9.6 mg/dL)

In a child >3 years of age	Requirements before initiating cinacalcet therapy	Titration phase	Maintenance phase
Clinical parameters	Optimization of conventional management of CKD-MBD	Evaluation of potential side effects at every visit	Evaluation of potential side effects at every visit
		Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects	Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects
	Evaluation of calcium intake from diet, medications and dialysate	Evaluation of calcium intake from diet, medications and dialysate	Evaluation of calcium intake from diet, medications and dialysate
	Calculation of QTc interval	Realization of an ECG in case of hypocalcaemia	Realization of an ECG in case of hypocalcaemia; if ECG performed for another reason and increased QTc interval, cinacalcet withdrawal
	Evaluation of comorbidities of interest (seizures, cardiac arrhythmia, liver disease)		
	Explanation to parents		
Biological parameters	Calcium level ≥2.40 mmol/L	Weekly evaluation of calcium and phosphate levels	At least monthly evaluation of calcium and phosphate levels, target range for calcium within the normal range for age and in any case >2.2 mmol/L
		Cinacalcet withdrawal if calcium levels <2 mmol/L	Cinacalcet withdrawal if calcium levels <2 mmol/L and decrease/withdrawal if calcium levels between 2 and 2.2 mmol/L
	Persistent and secondary SHPT, no PTH threshold level clearly identified	Weekly evaluation of PTH levels, 12–24 h after cinacalcet administration	At least monthly evaluation of PTH levels, 12–24 h after cinacalcet administration, target range 100–200 pg/mL
		Cinacalcet withdrawal if PTH levels <100 pg/mL	Cinacalcet withdrawal if PTH levels <100 pg/mL
Therapeutic parameters	Verification of concomitant therapies that can interfere with cinacalcet	Starting dose of ≤0.2 mg/kg/day, increments by 0.2 mg/kg/day to a maximum of 2.5 mg/kg/day. Dose titration intervals should be at least 4 weeks	

Bacchetta et al, NDT 2019

Background to this position statement

- **Knowledge of cinacalcet in CKD**
  - Mainly comes from adult trials, and mainly the EVOLVE trial
  - Children
    - 2 RCTs
    - 9 uncontrolled or observational studies
    - Case reports

- **Approval**
  - Not approved in pediatric CKD by FDA
  - Approved by EMA in 2017

Factors to consider before starting cinacalcet

1	We recommend that serum calcium, phosphate, PTH and 25OH vitamin D levels are regularly monitored, and treatment decisions based on trends in these levels, are considered together.	Grade B / moderate recommend ation
2	We recommend that albumin corrected calcium levels are used. Ionised calcium levels are a more accurate measure of free (bioavailable) calcium, and should be used where available.	Grade C / weak recommend ation
3	We recommend that serum calcium and phosphate levels are kept within the age-appropriate normal range. Calcium intake from diet, medications and dialysate should be taken into account when evaluating calcium and phosphate levels.	Grade B / moderate recommend ation

Main messages

⇒ **To evaluate calcium levels BUT also calcium intake coming from all the different sources**

⇒ **To base decisions on trends**

Which patients may benefit from cinacalcet therapy and what are the contra-indications for its use?

4	We suggest that cinacalcet is used in children above 3 years of age on dialysis who have persistent and severe hyperparathyroidism in the presence of high or high-normal calcium levels, despite optimized conventional management, including active vitamin D.	Grade B / moderate
5	There is no clear threshold level of PTH above which cinacalcet therapy should be started.	Ungraded
6	Do not start cinacalcet in patients with albumin corrected calcium levels below 2.40 mmol/L.	Grade X / strong
7	Do not start cinacalcet in patients with prolonged QT interval.	Grade X / strong
8	We recommend that cinacalcet is used with caution in patients with history of seizures, cardiac arrhythmia, significant liver disease, or poor adherence to medications.	Grade X / moderate
9	We suggest that drugs that prolong the QTc interval or interact with cinacalcet are used with caution; the relative benefit of the drug or withholding cinacalcet must be considered on an individual patient basis.	Grade X / moderate

Main messages

⇒ **Be cautious with calcium levels within the lower normal range**

⇒ **Try to optimise conventional management first**

⇒ **Know the contra-indications**

Concomitant drugs that are contra-indicated with cinacalcet

Table 6. Concomitant drugs that are contra-indicated with cinacalcet

Mechanism	Example of drug that is contra-indicated in association with cinacalcet
Potential to increase QTc	Ondansetron
	Albuterol
	Salbutamol
Inhibitors of CYP3A4	Grapefruit juice
	Erythromycin
	Clarithromycin
	Ketoconazole
	Itraconazole
Inhibitors of CYP2D6	Flecanide
	Propafenone
	Metoprolol
	Desiprimine
	Nortroptyline
	Clomipramine

This list is not exhaustive: before prescribing cinacalcet or new therapies to patients already receiving cinacalcet, physicians in charge of the patients are responsible for checking the potential interferences and contra-indications.

What is the treatment schedule?

10	We recommend a starting dose of cinacalcet of ≤ 0.2 mg/kg/day based on dry weight rounded to the nearest whole dose unit.	Grade B / moderate
11	The cinacalcet dose may be increased in increments of 0.2 mg/kg per day to a maximum daily dose of 2.5 mg/kg (not exceeding 180 mg) based on PTH levels provided that albumin corrected calcium serum levels remain above 2.2 mmol/l. Dose titration intervals should be at least 4 weeks.	Grade B / moderate
12	Cinacalcet can be given orally or by nasogastric/gastric tube, once daily.	Ungraded
13	We suggest that the minimal effective cinacalcet dose is used to maintain PTH levels in the desired PTH target range, taking into account its effects on calcium and phosphate concentrations.	Grade B / moderate
14	We suggest to decrease cinacalcet dose when PTH levels are in the lower target range between 100 and 150 pg/mL, low for the individual patient or declining too rapidly, and to discontinue cinacalcet when PTH concentrations are below the target range.	Grade B / moderate
15	**We recommend that serum calcium levels are maintained within the normal range for age, by titrating conventional therapy including nutritional calcium intake, calcium-based phosphate binders, vitamin D analogs, and dialysate calcium, and by titrating cinacalcet dose**	Grade B / moderate
16	We suggest decreasing or withdrawing cinacalcet when albumin corrected serum calcium levels fall below 2.2 mmol/L.	Grade X / moderate

Main messages

⇒ **Find the minimal effective dose to maintain PTH within the desired PTH target range**

⇒ **Adapt doses depending on PTH but also on calcium levels**

How should a child on cinacalcet therapy be monitored?

17	We suggest that serum calcium levels are monitored within one week of starting cinacalcet therapy, weekly during the titration phase, and at least monthly when maintenance dose has been established in a stable patient.	Grade C / moderate
18	We suggest that PTH serum levels are checked on a monthly basis.	Grade B / moderate
19	**We recommend that children and their caregivers are informed of symptoms of hypocalcemia**, the importance of adherence to taking all medications regularly as well as instructions regarding serum calcium monitoring, and caution about other medications which may prolong QTc interval or interact with cinacalcet.	Grade X / moderate
20	**We recommend that cinacalcet is withhold when albumin corrected serum calcium levels are below 2.0 mmol/L** and/or ionized calcium levels are below 1.0 mmol/L. Cinacalcet may be restarted in a lower dose when serum calcium levels return to the higher end of the normal range.	Grade X / moderate
21	**Withdraw cinacalcet in case of symptomatic hypocalcemia** including paraesthesia, myalgia, cramps, tetany and convulsions, long QT interval or severe side effects.	Grade X / strong

Main messages

⇒ **Monitor calcium levels regularly**

⇒ **Inform patients and parents of the risk of hypocalcemia (and when to think of it…)**

How should patients with persistent severe SHPT despite conventional therapy and cinacalcet be treated?

22	We suggest that parathyroidectomy is considered in case of severe and persistent SHPT despite optimized cinacalcet and conventional therapy including active vitamin D.	Grade C / weak

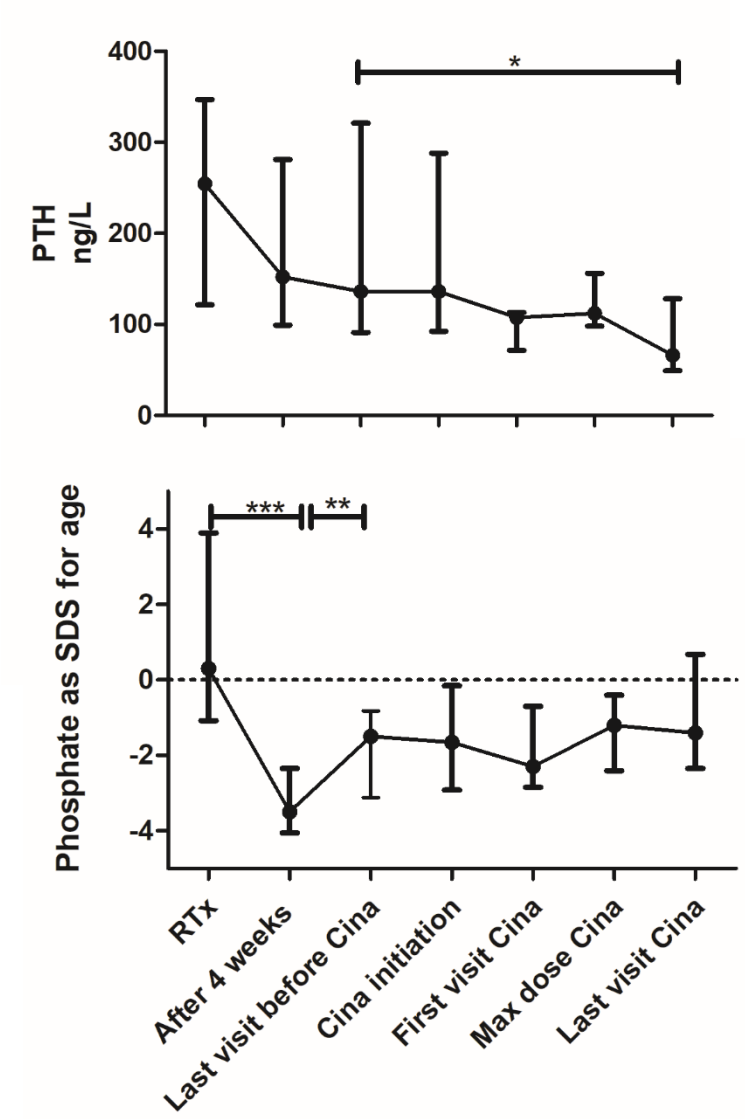
Questions that remain open (1)

- **Suggested research topics**
  - Real-world data => international registry on cinacalcet
  - Combination of moderate vit D analogs and earlier start of cinacalcet?
  - Effects of cinacalcet on a growing bone
  - Effects of cinacalcet pre-Tx on the outcomes post-Tx

Questions that remain open (2)

- **Other pediatric populations that may benefit from cinacalcet therapy**
  - Pre-dialysis patients with tubulopathies???
  - Post-transplant SHPT?
  - Interest in the youngest children?

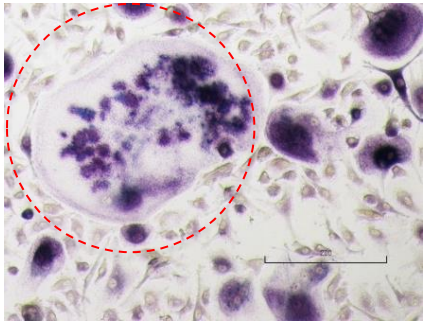
- **CERTAIN registry**
  - 20 pediatric patients having received cinacalcet after Tx



Bernardor, and the CERTAIN consortium, Pediatr Nephrol 2020

Perspectives: low D analogs and low calcimetics?

Osteoclastic differentiation



6 Healthy adult donors

19 CKD pediatric patients

M-CSF
RANKL

KP2326
1.25-OH vitD

D0 D3 D6-D7

DIFFERENTIATION
TRAP staining

qRT-PCR ANALYSIS *hVDR* and *hCaSR*

WESTERN BLOT
Proteins → ERK/P-ERK
KP2326 10^{-6}M

Trough osteoclast differentiation

Concentrations KP2326	Concentrations 1.25-OH vitD
10^{-9}M	0.1 nM
10^{-8}M	0.5 nM
10^{-7}M	1 nM
10^{-6}M	2.5 nM
10^{-5}M	5 nM

Bernardor JBMR 2020

Osteoclast-mediated resorption

Healthy adult donors

M-CSF
RANKL

KP2326
10^{-9}M
10^{-6}M

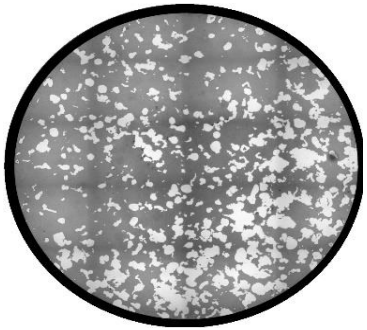
Monocyte

Ostéoclast

D0 D3 D4 D6-D7

M-CSF
RANKL

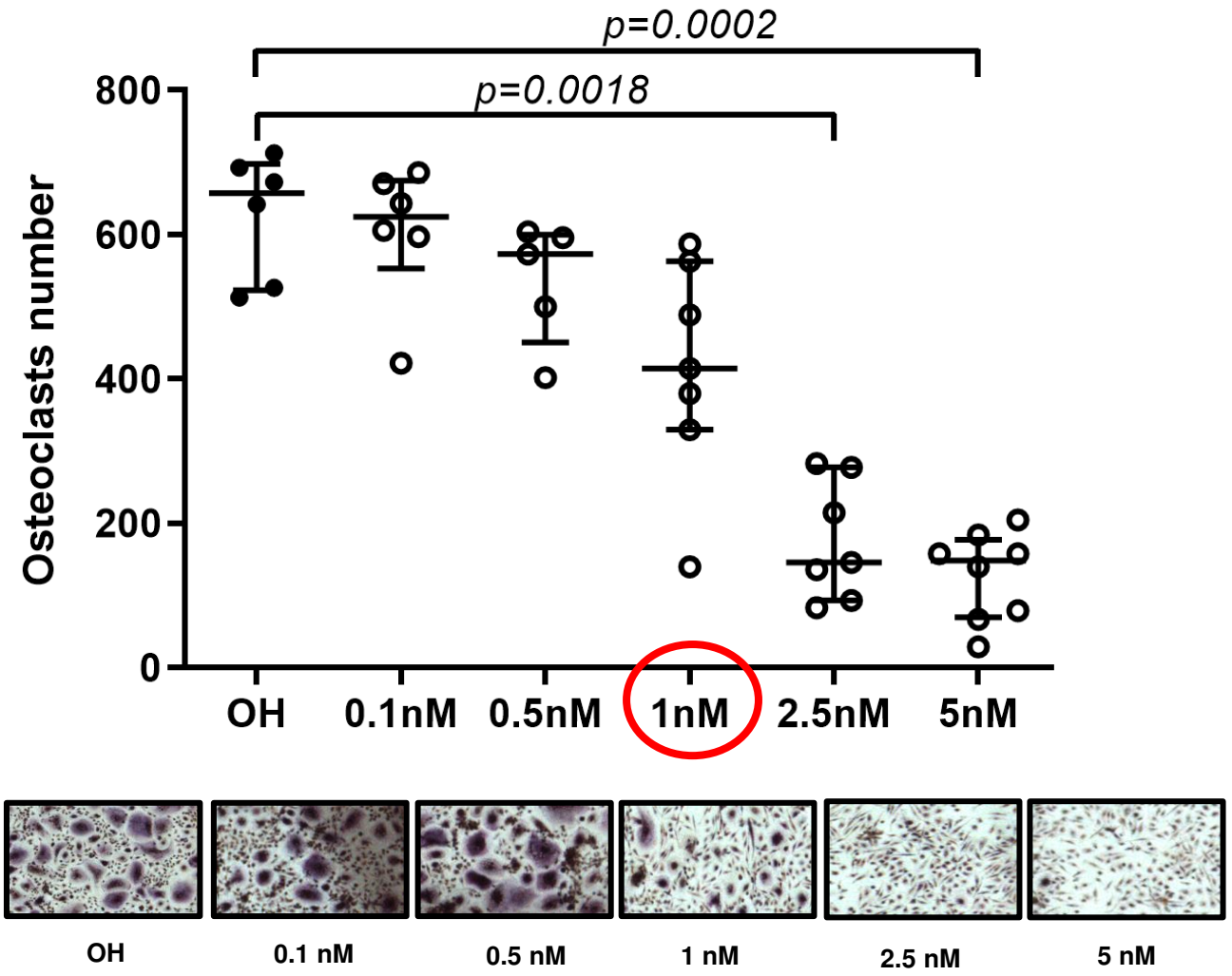
RESORPTION



Silver nitrate staining

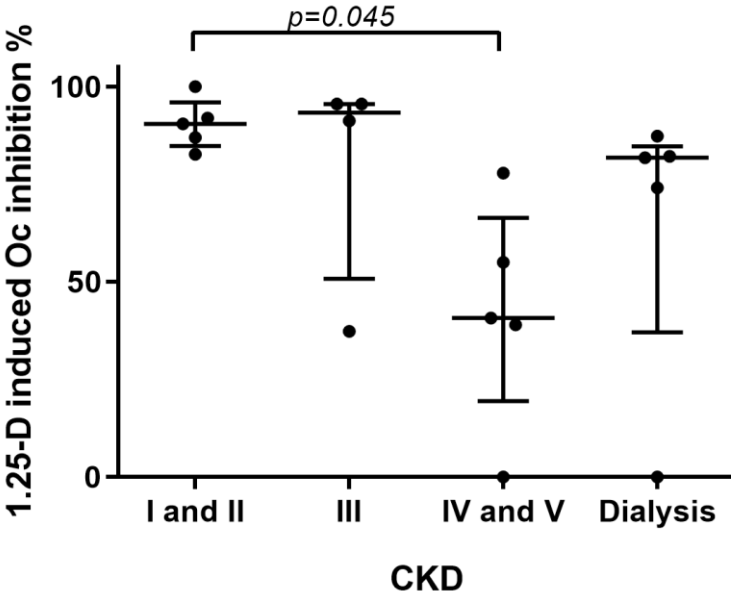
Bernardor JBMR 2020

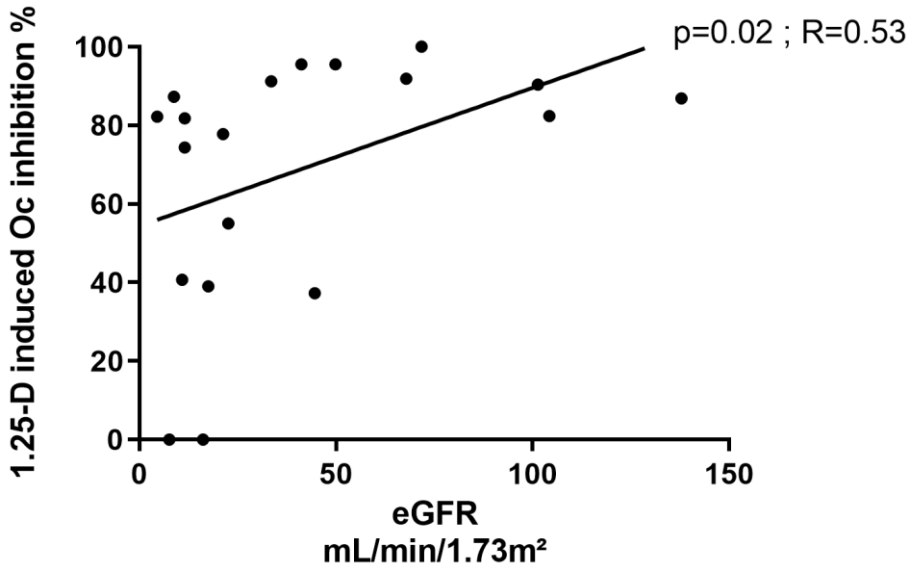
1.25-D inhibits osteoclast differentiation in healthy controls in a dose-dependent manner

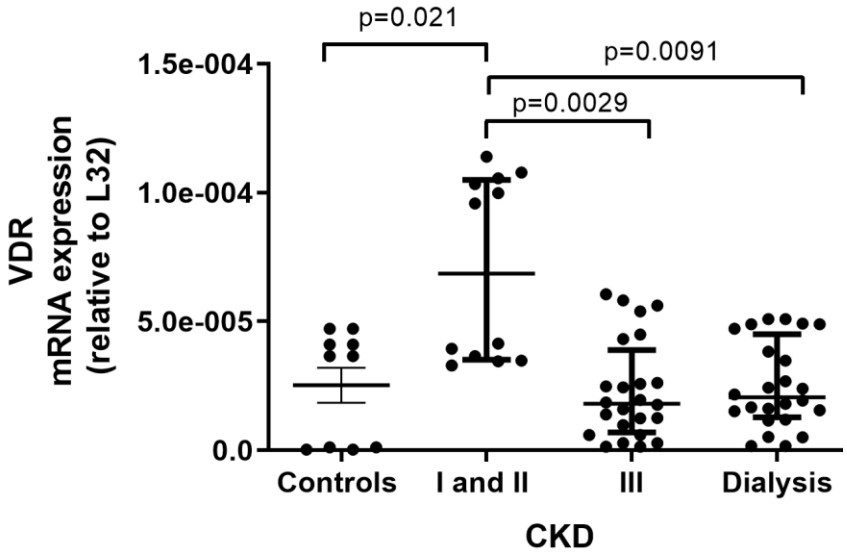


Bernardor JBMR 2020

In CKD children, there is a progressive resistance to 1.25-D effects on osteoclastic differentiation when renal function worsens

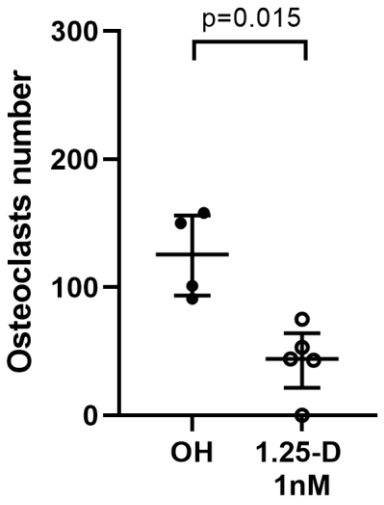


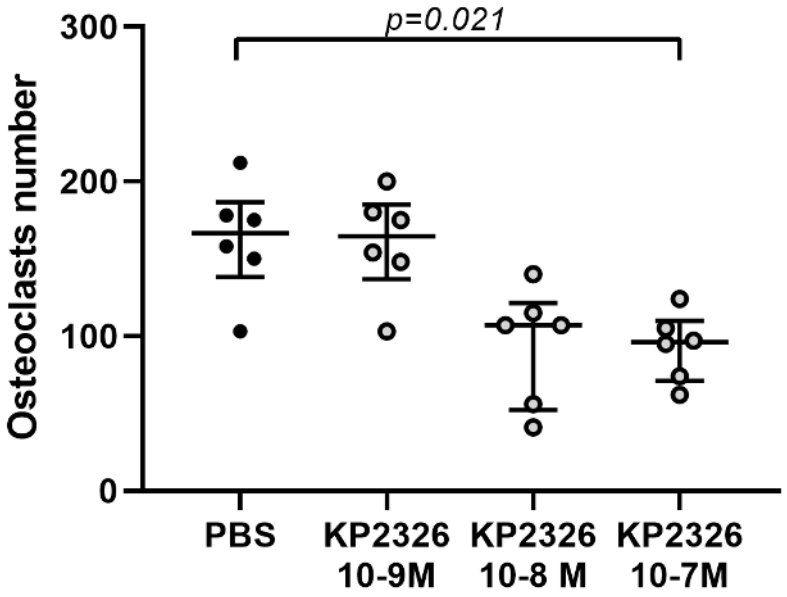


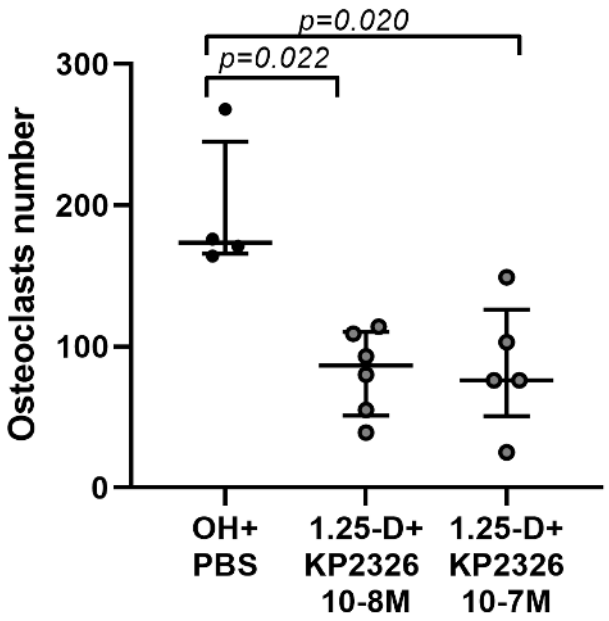


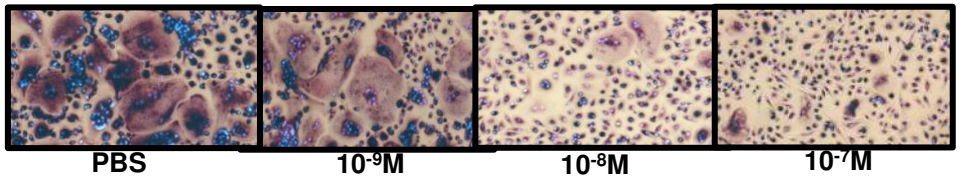
Bernardor JBMR 2020

In healthy controls, KP2326 inhibits osteoclastic differentiation





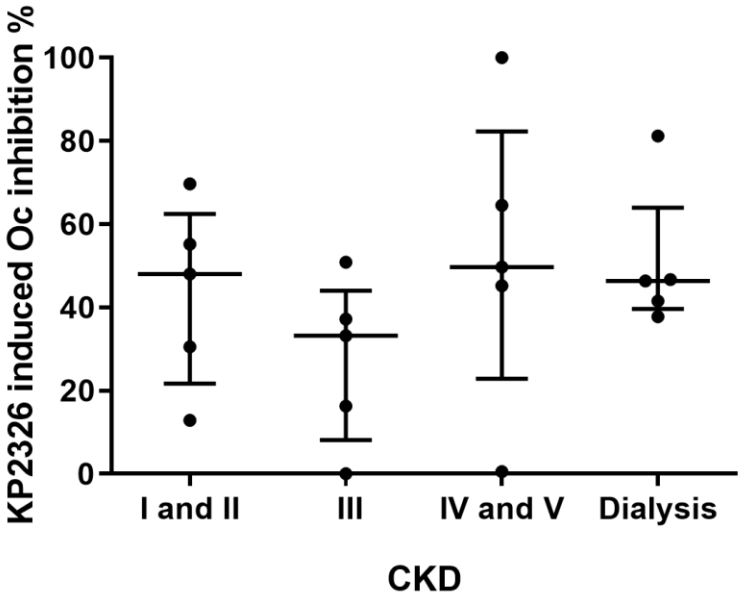


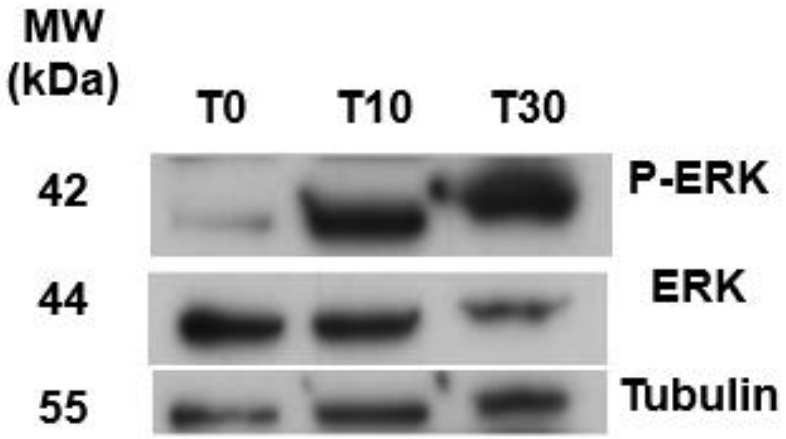


KP2326 concentrations

Bernardor JBMR 2020

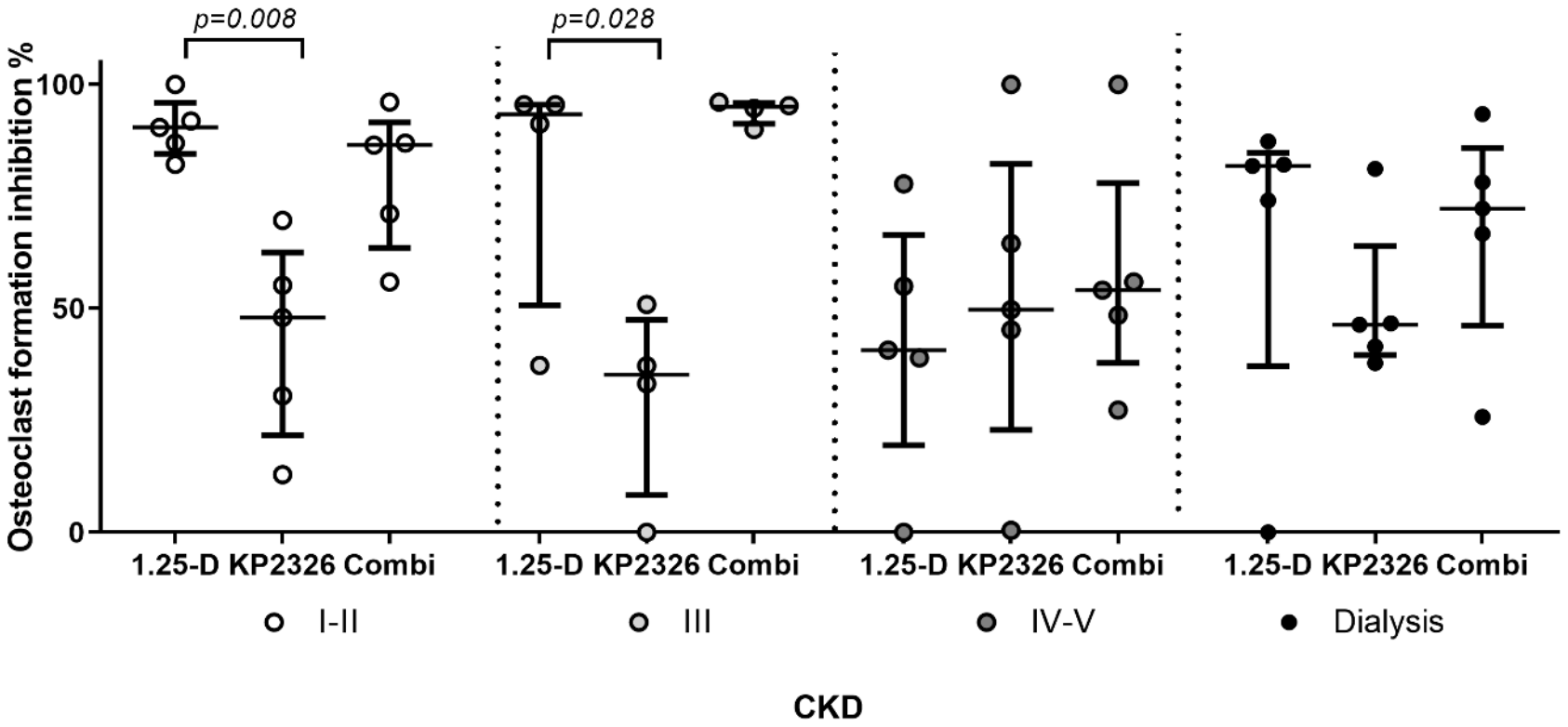
In CKD children, KP2326 inhibits osteoclast differentiation,however to a lesser extent than 1.25-D, with no effect of the degree of renal impairement, through Erk signaling





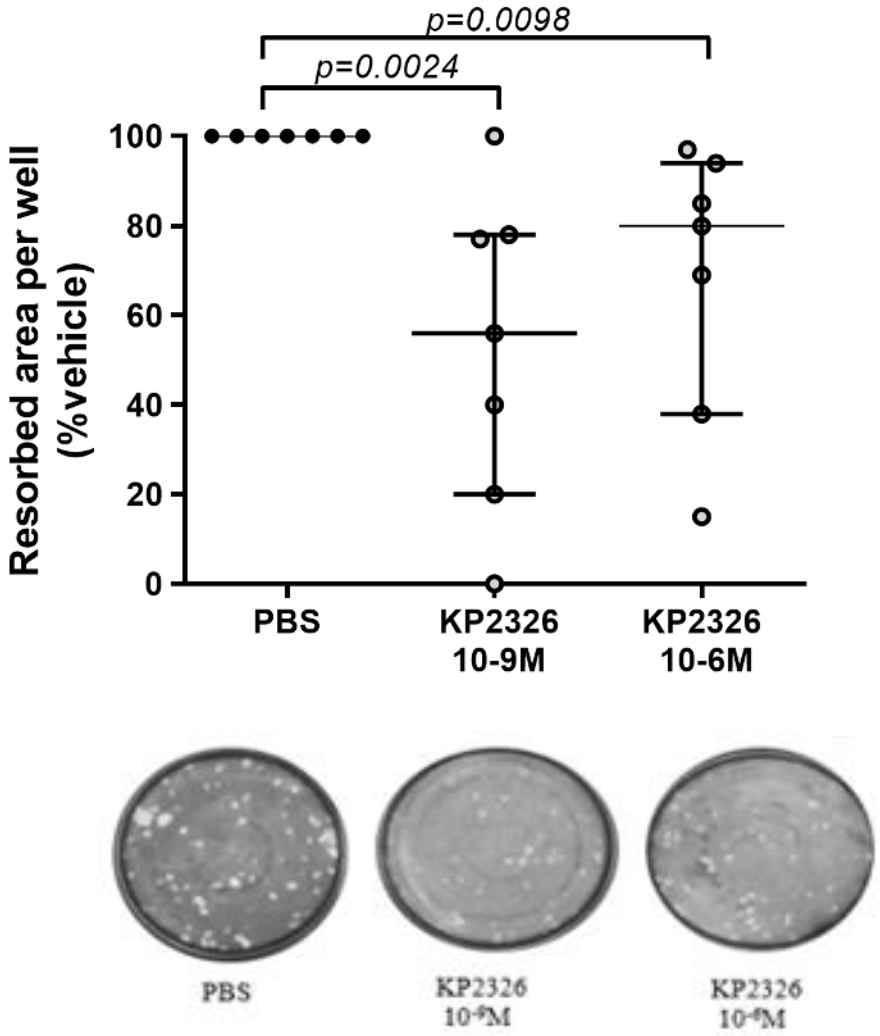
Bernardor JBMR 2020

In CKD children, the combination of 1.25-D and KP2326 inhibits osteoclastic differentation, without synergistic effect



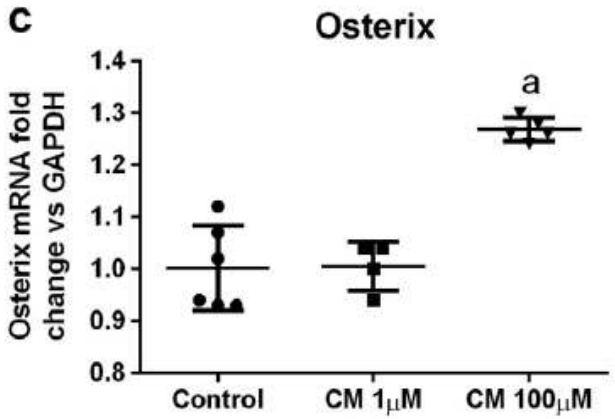
Bernardor JBMR 2020

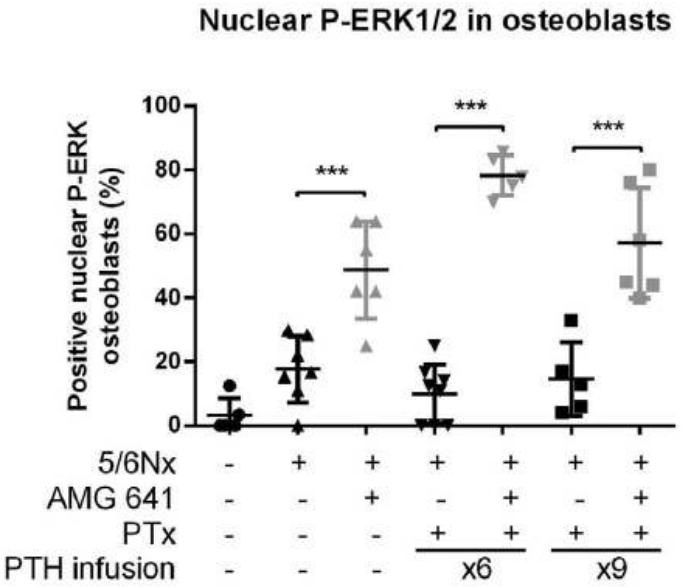
In healthy controls, KP2326 inhibits bone resorption

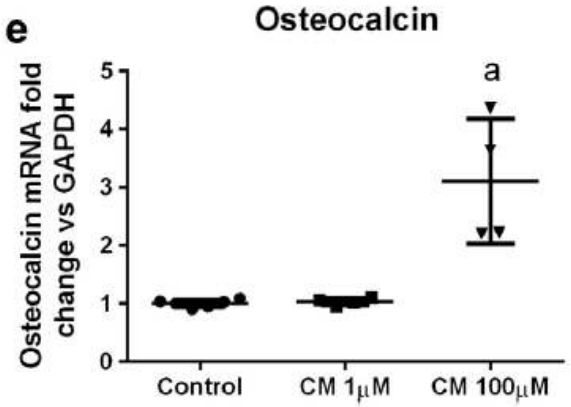


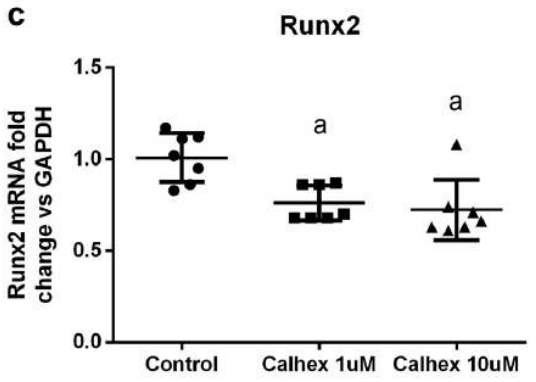
Bernardor JBMR 2020

Calcimimetics promote osteogenic differentiation and mineralization in human MSCs in vitro => pro-anabolic effect









Inverse results with calcilytic agents

Diaz-Tocados Kidney Int, 2019

Perspectives: low D analogs and low calcimimetics?

- **Experimental evidence both in osteoblasts and in osteoclasts**

- **Direct anabolic effects of calcimimetics on osteoblasts**
  - Promotion of differentiation and mineralization in human mesenchymal stem cells
  - Increased osteoblast number and bone formation in normal and uremic rats

- **Direct effects of calcimimetics on osteoclasts**
  - Moderate inhibition of osteoclastic differentiation (in a lesser extent than 1-25-D)
  - Inhibition of bone resorption activity

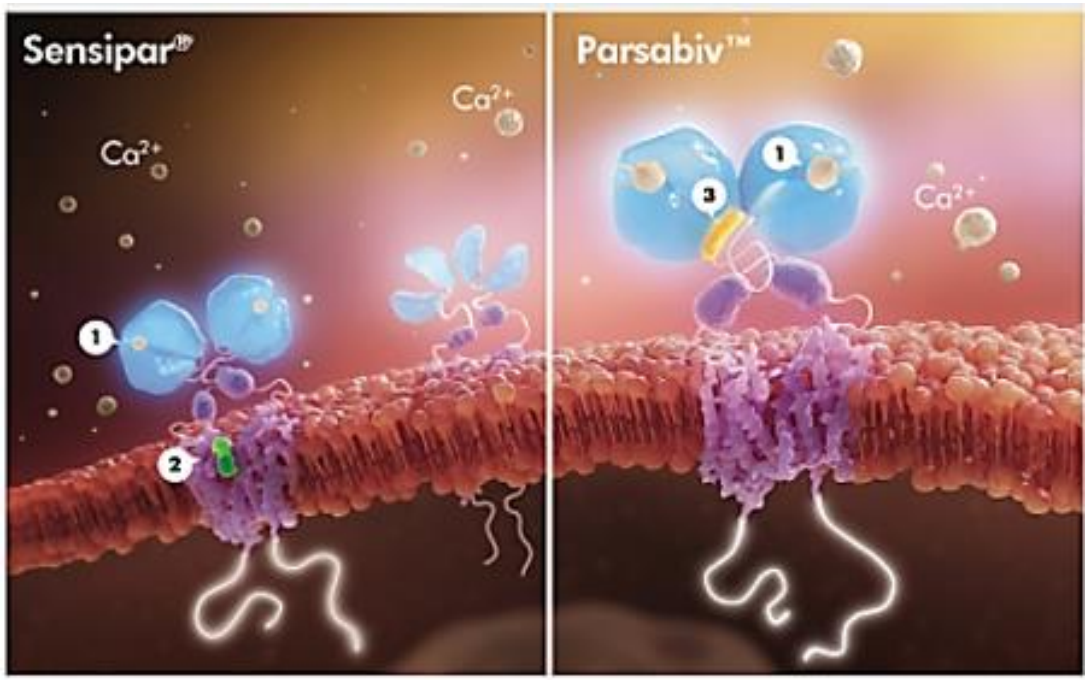
- **No synergistic effect when co-treating human PBMCs/OCs with both 1.25-D and KP2326**
  - **The use of decreased doses of 1.25-D with low-doses of calcimimetics could control SHPT**
  - **Without substantially affecting osteoclastogenesis**
  - **And therefore decreasing the risk of adynamic osteodystrophy?**

Obviously we need more experimental and clinical data to support this hypothesis

Bernardor JBMR 2020; Diaz-Tocados Kidney Int, 2019

Next steps to improve compliance?

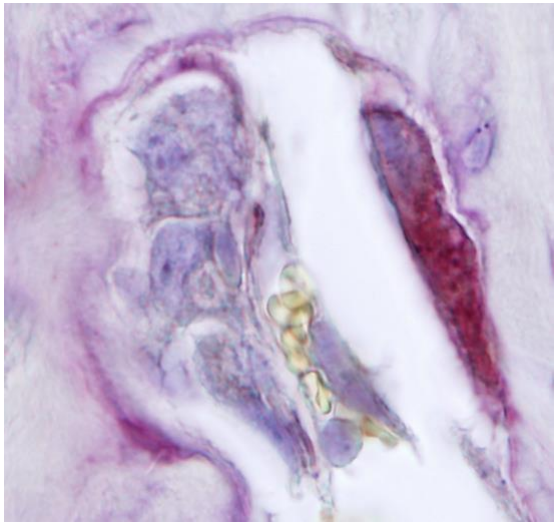
- **Ongoing pediatric clinical trials with etelcalcetide**
  - Iv calcimimetic
  - Should be given at the end of the HD session, thrice weekly
  - Not exactly the same mechanism of action than cinacalcet

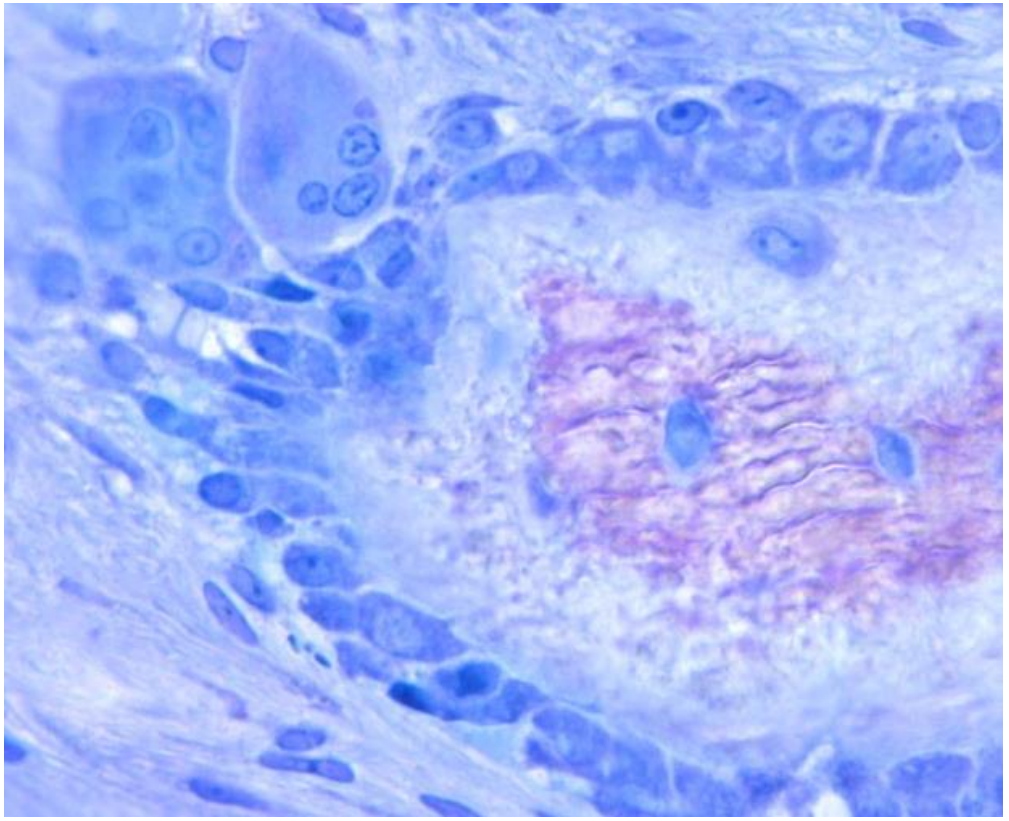


Cinacalcet Etelcalcetide

Amgen® Images

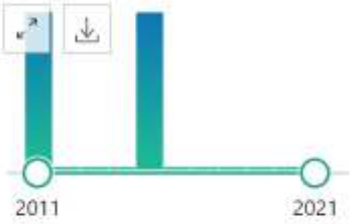
Bisphosphonates: rationale to use them, and practical points





PubMed: 113 papers in adults, 321 in dialysis, 2 in CKD children!

RESULTS BY YEAR



TEXT AVAILABILITY

- [ ] Abstract
- [ ] Free full text
- [ ] Full text

ARTICLE ATTRIBUTE

- [ ] Associated data

ARTICLE TYPE

1 Cite Share

Revisiting KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference.

Ketteler M, Elder GJ, Evenepoel P, Ix JH, Jamal SA, Lafage-Proust MH, Shroff R, Thadhani RI, Tonelli MA, Kasiske BL, Wheeler DC, Leonard MB.

Kidney Int. 2015 Mar;87(3):502-28. doi: 10.1038/ki.2014.425. Epub 2015 Feb 4.

PMID: 25651364 Free article.

KDIGO convened a Controversies Conference in October 2013 to review the **CKD**-MBD literature published since the 2009 guideline. Specifically, the objective of this conference was to determine whether sufficient new data had emerged to support a reassessment of the **CKD** ...

2 Cite Share

Can bisphosphonates play a role in the treatment of children with chronic kidney disease?

Haffner D, Fischer DC.

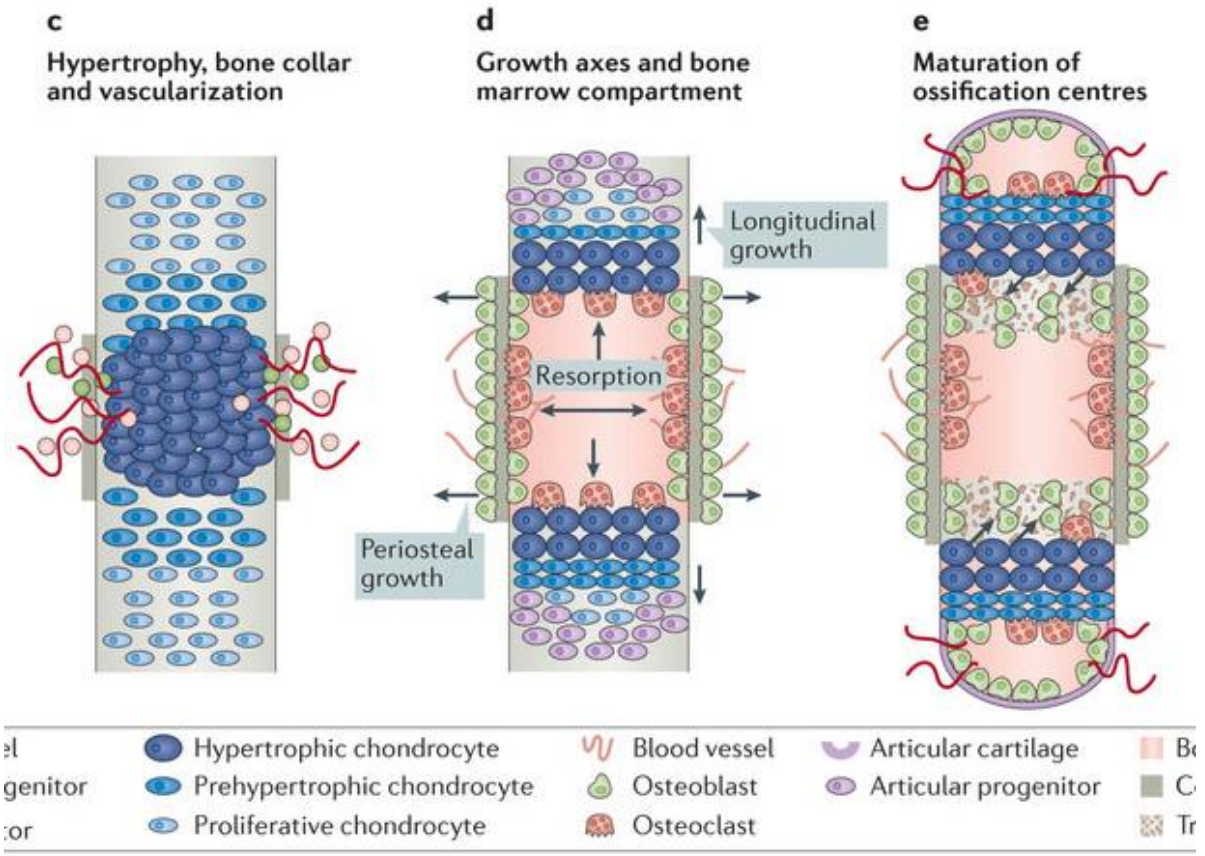
Pediatr Nephrol. 2011 Dec;26(12):2111-9. doi: 10.1007/s00467-010-1739-z. Epub 2011 Jan 27.

PMID: 21267600 Review.

In **pediatric CKD** patients the efficacy and safety of these drugs have not yet been addressed adequately and thus no evidence-based recommendations regarding the optimal type of **bisphosphonate**, dosage, or duration of therapy are available. ...Thus, the widespr ...

How do bisphosphonates work?

- **Pyrophosphate agonist**
- **Inhibition of osteoclastic activity** through the inhibition of the farnesyl-pyrophosphate synthase enzyme
- **Inhibition of bone resorption**
- **Subtle effects are also seen in osteoblasts**: of utmost importance when evaluating BP in children, because of endochondral ossification that may affect longitudinal growth



Haffner, Pediatr Nephrol 2011

Can biphosphonates play a role in the treatment of CKD children?

Table 1 Potential indications for the use of bisphosphonates in pediatric chronic kidney disease (CKD) patients

Indication
Osteoporosis due to glucocorticoid treatment before or after renal transplantation
Hypercalcemia due to severe secondary hyperparathyroidism
Vascular calcifications
Calcific uremic arteriolopathy (calciphylaxis)

Table 2 Clinical trials and case reports on bisphosphonate therapy in children with osteoporosis after renal transplantation or on glucocorticoid treatment due to glomerular/rheumatological diseases

Reference	Agent	*n*	Median age/ time since Tx	Diagnosis	Outcome	Results
[13]	Oral alendronate 5 mg/day	30	15 years/ 12 months	Osteoporosis after RTX	LS aBMD	Increase in BMD ($p<0.001$)
[59]	Oral alendronate 1–2 mg/kg/week	22	14 years/ 12 months	Osteoporosis after RTX rheumatology patients	LS aBMD	BMD increased in the study group but not in controls ($p=0.013$)
[44]	IV pamidronate 0.5 mg/kg, 3 days	3	14 years/ 1–2 times	Hypercalcemia/ osteopenia after RTX or on PD	S-calcium, LS aBMD	Resolution of hypercalcemia ($n=2$), stable BMD ($n=2$)
[57]	IV pamidronate 1 mg/kg/2 months	34	Not reported/ 36 months	Osteoporosis after RTX and rheumatology patients	LS aBMD	BMD increased in the study group compared with controls ($p=0.0057$)
[58]	Oral pamidronate 125 mg/day	44	9 years/ 3 months	Glomerulonephritis	LS aBMD	Decrease in BMD in control group ($p=0.0017$), but not in the study group

Tx=treatment; RTX=renal transplantation; LS=lumbar spine; aBMD=areal bone mineral density; PD=peritoneal dialysis

Haffner, Pediatr Nephrol 2011

What about denosumab?

- No data on Pubmed (at least in children with CKD)
- Experience in dialysis adults in Lyon
  - N= xxx

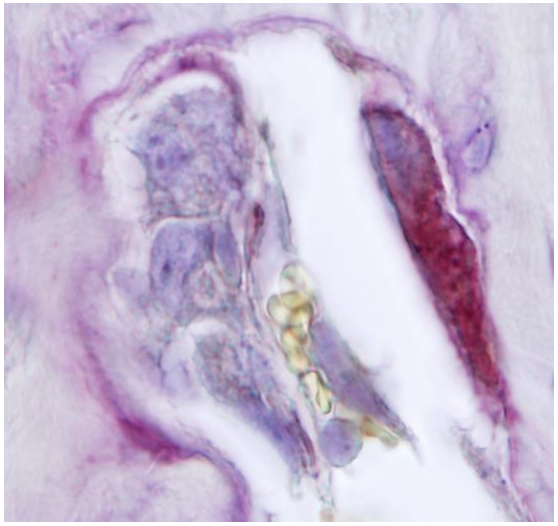
xxx

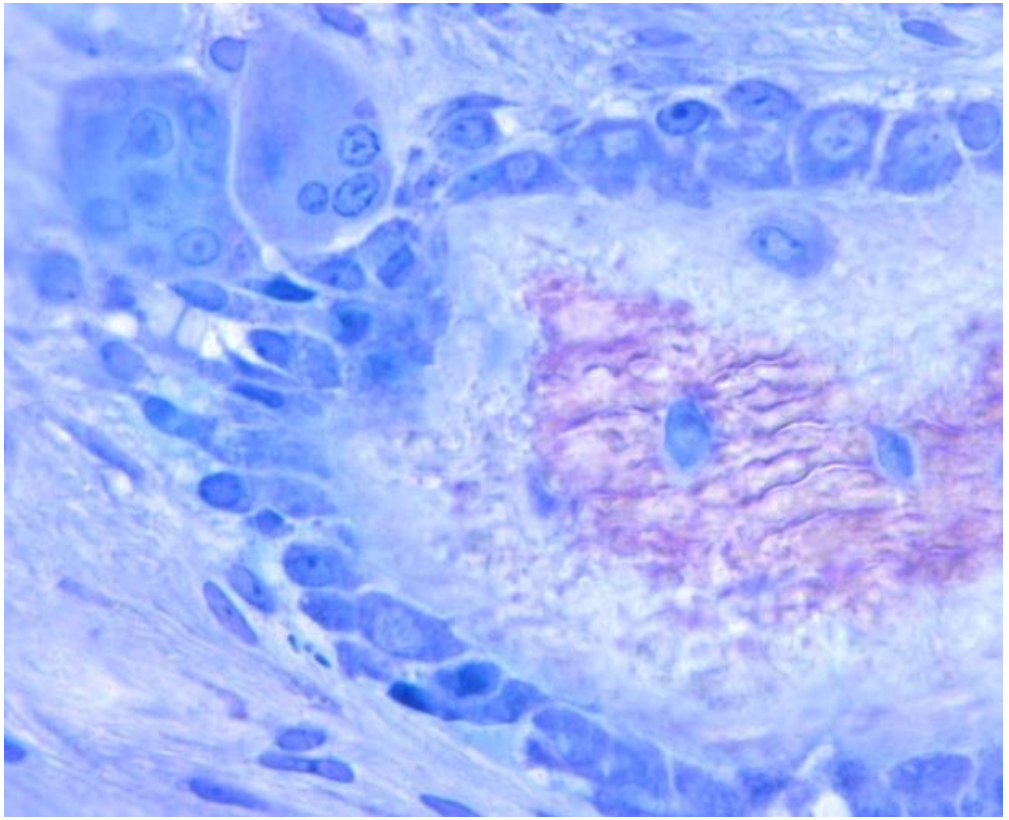
What about recombinant PTH therapy in patients with low turnover?

- No data on Pubmed
- Experience in dialysis adults in Lyon
  - N= xxx

xxx

Conclusion





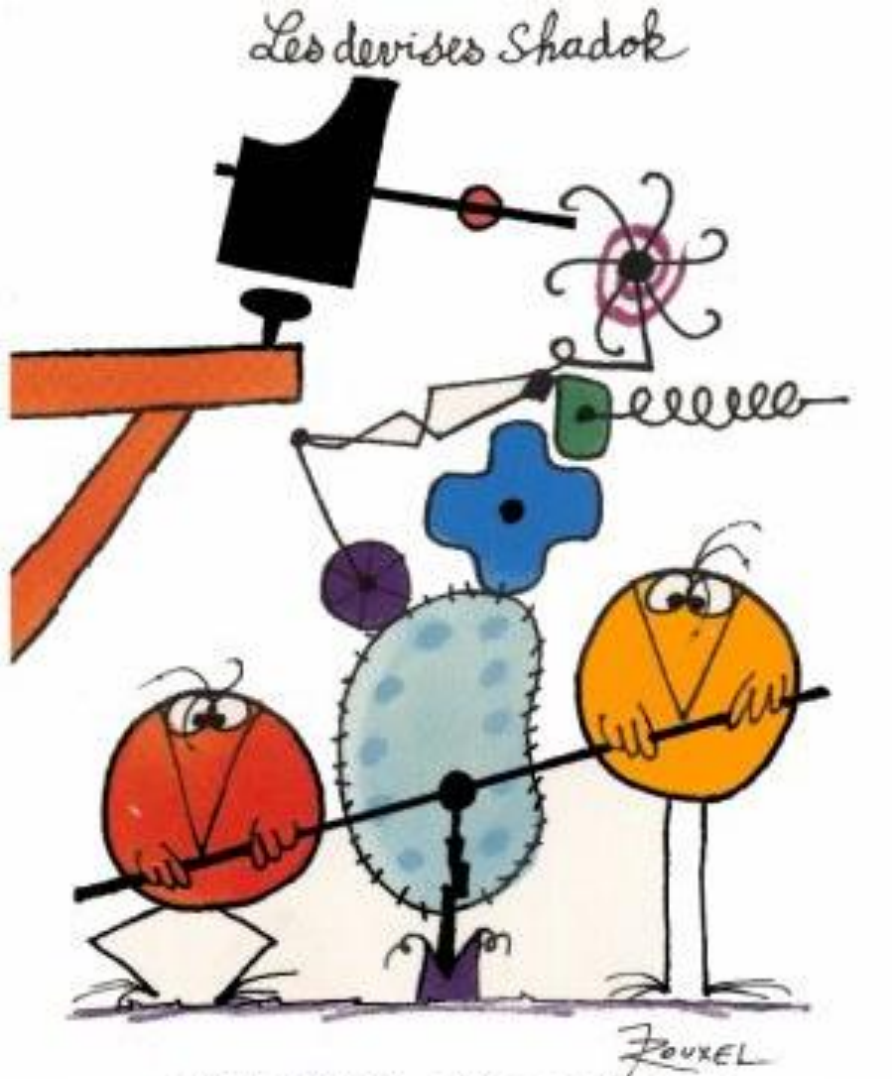
In this patient should you prescribe cinacalcet?

14-year old boy HDF 3 x 4 h/week CAKUT	M-2	M-1	M0
Calcium (mmol/L)	2.29	2.26	2.17
Phosphorus (mmol/L)	1.56	1.67	1.96
25 OH (nmol/L)			43
PTH (15-65 pg/mL)	500	688	830
Cholecalciferol	80 000 UI/3 months	80 000 UI/3 months	80 000 UI/3 months
Alfacalcidol	0.5 µg	0.75 µg	1 µg
Calcium Carb	500 mg x 3	500 mg x 3	500 mg x 3
Sevelamer Carb	1600 mg x 3	1600 mg x 3	1600 mg x 3

No…

14-year old boy HDF 3 x 4 h/week CAKUT	M-2	M-1	M0
Calcium (mmol/L)	2.29	2.26	2.17
Phosphorus (mmol/L)	1.56	1.67	1.96
25 OH (nmol/L)			43
PTH (15-65 pg/mL)	200	300	450
Cholecalciferol	80 000 UI/3 months	80 000 UI/3 months	80 000 UI/3 months
Alfacalcidol	0.5 µg	0.75 µg	1 µg
Calcium Carb	500 mg x 3	500 mg x 3	500 mg x 3
Sevelamer Carb	1600 mg x 3	1600 mg x 3	1600 mg x 3

You may give native D supplementation + send back the child to the dietician for phosphate intake + increase sevelamer…
Hypocalcemia is a “no-go” for cinacalcet



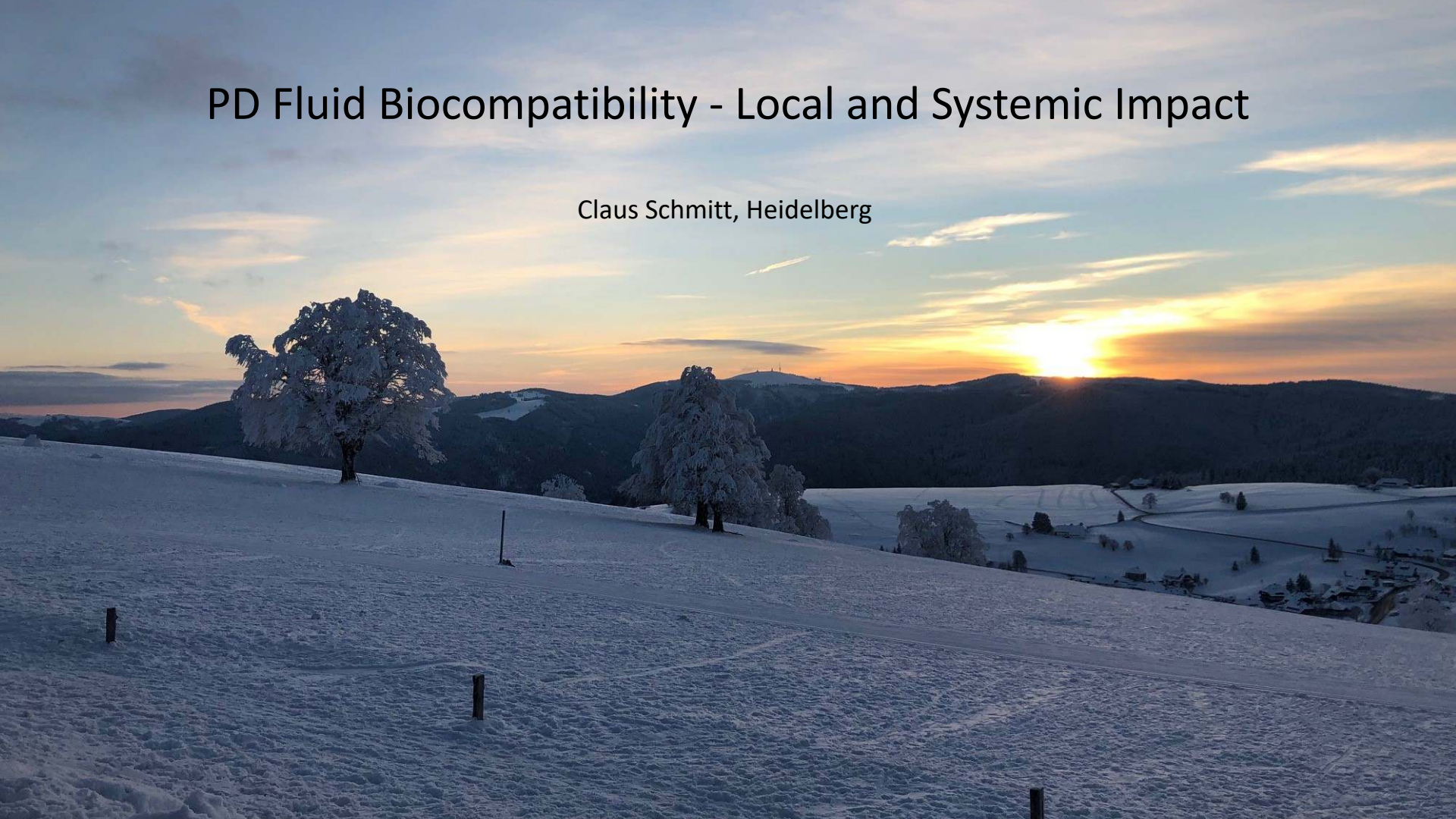
Why thinking simple when you can think complicated?

To avoid uncontrolled PTH levels in pediatric ESRD, keep phosphate under control and do not forget calcium intake!

Justine.bacchetta@chu-lyon.fr

PD Fluid Biocompatibility - Local and Systemic Impact

Claus Schmitt, Heidelberg



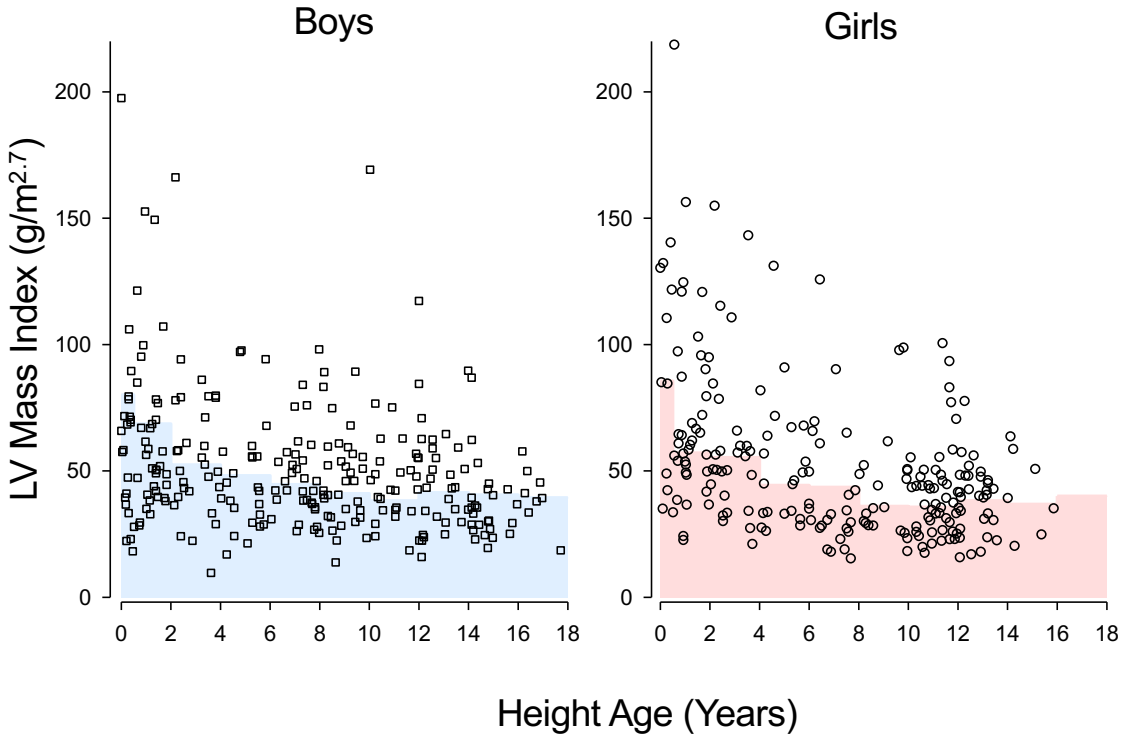
Biocompatibility

Refers to the ability of a biomaterial to

1. **perform its desired function** with respect to a medical therapy
2. **without eliciting any undesirable local or systemic effects** in the recipient or beneficiary of that therapy,
3. but **generating the most appropriate beneficial cellular or tissue response** in that specific situation, and **optimising the clinically relevant performance** of that therapy.

Williams, DF. On the mechanisms of biocompatibility. Biomaterials 2008

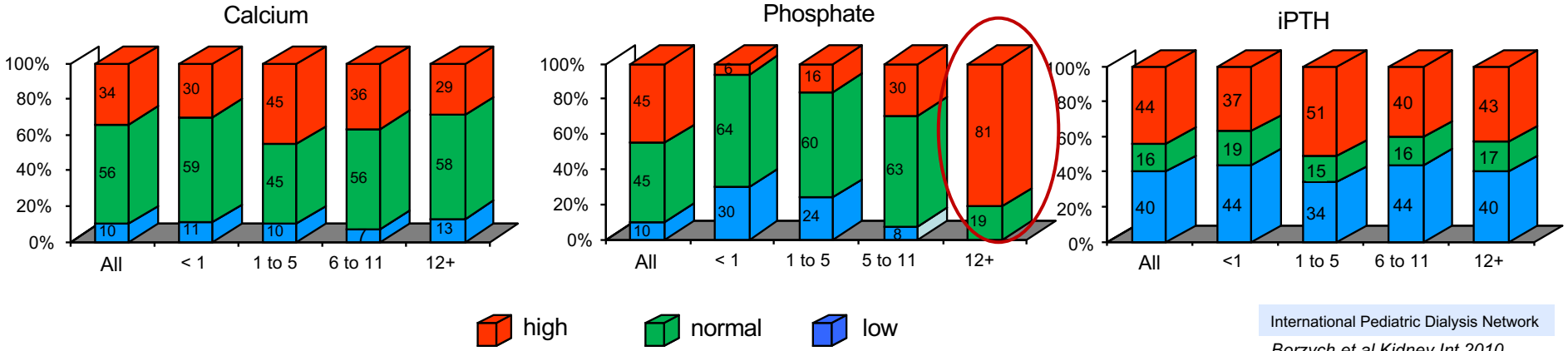
Increased Left Ventricular Mass - a surrogate marker of inadequate blood pressure-, salt- and water control in PD



Coloured area = within normal range

International Pediatric Dialysis Network

CKD MBD in PD

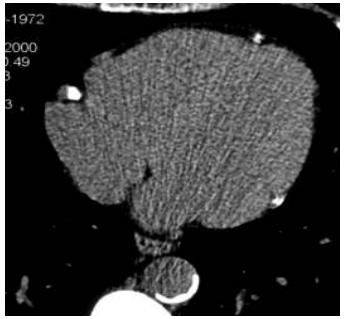


International Pediatric Dialysis Network

Borzych et al Kidney Int 2010

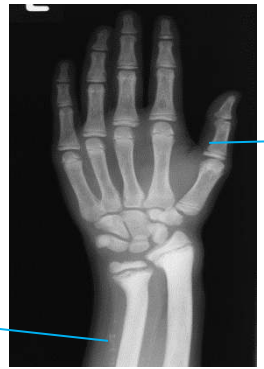
Accelerated Vasculopathy in Children with Chronic Renal Failure (CKD)

28 years
Juvenile onset of ESRD



ECG-gated CT

16 years
ESRD since 4 years



- Unrelated underlying disease (CAKUT)
- No life-style related CVD
- No aging related alterations

=> *Specific CKD/PD related CVD*

Biocompatibility

Refers to the ability of a biomaterial to

1. perform its desired function with respect to a medical therapy
2. without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy,
3. but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy.

Williams, DF. On the mechanisms of biocompatibility. Biomaterials 2008

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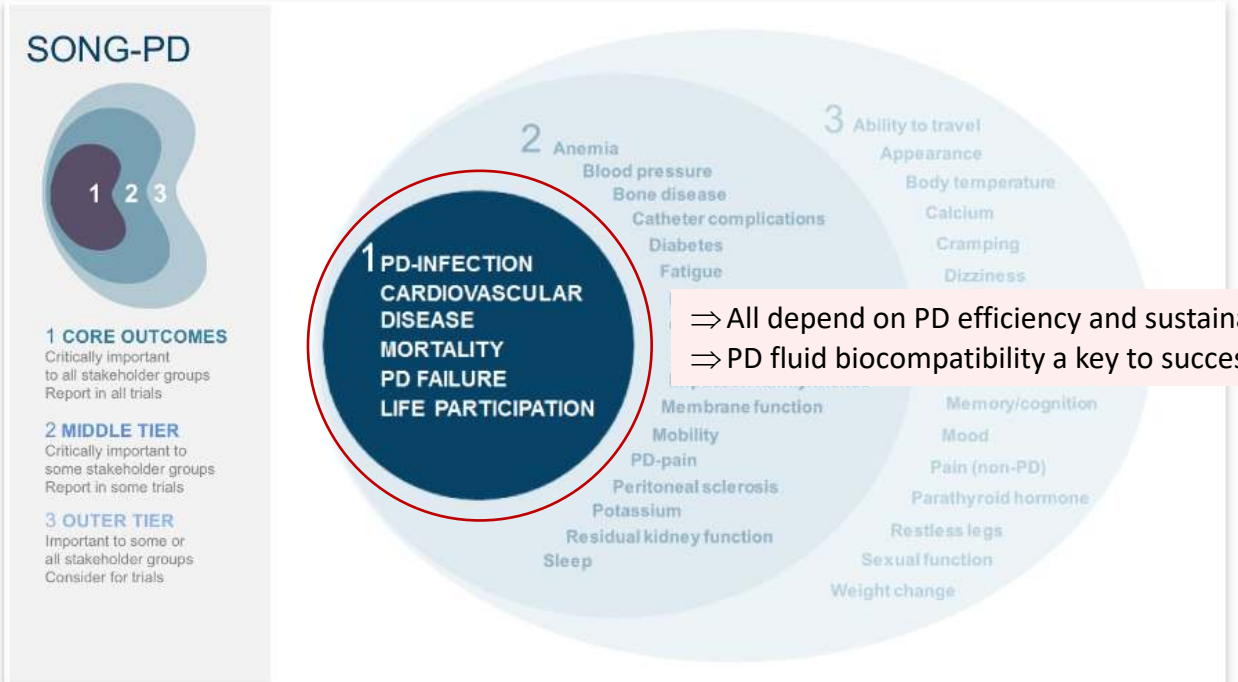


⇒ All depend on PD efficiency and sustainability
⇒ PD fluid biocompatibility a key to success

Stakeholders:
- Patients/caregivers
- Health care professionals

Free water-soluble low molecular weight molecules

Molecule	Molecular Weight	Group
2-Heptenal (µg/L)	112	RCC
2-Hexenal (µg/L)	98	RCC
2-Nonenal (µg/L)	140	RCC
2-Octenal (µg/L)	126	RCC
4-Decenal (µg/L)	154	RCC
4-HO-decenal (µg/L)	170	RCC
4-HO-hexenal (µg/L)	114	RCC
4-HO-nonenal (µg/L)	156	RCC
4-HO-octenal (µg/L)	142	RCC
4-Pyridone-3-carboxamide-1-β-D-ribonucleoside (µg/L)	272	Nicotinamide
8-Hydroxy-2'-deoxyguanosine (µg/L)	283	Purine
α-Keto-δ-guanidinovaleric acid (µg/L)	173	Guanidine
Anthranilic acid (µg/L)	137	
Argininic acid (µg/L)	175	Guanidine
Asymmetric dimethylarginine (µg/L)[a]	202	Guanidine
Cysteine (µg/L)	121	Aminoacid
Decanal (µg/L)	156	RCC
Dimethylamine (mg/L)	45	Amine
Ethylamine (µg/L)	45	Amine
Guanidine (µg/L)	59	Guanidine
Guanidinoacetic acid (µg/L)	117	Guanidine
Guanidino succinic acid (mg/L)	175	Guanidine
Heptanal (µg/L)	114	RCC
Hexanal (µg/L)	100	RCC
Hypoxanthine (mg/L)	136	Purine
Malondialdehyde (µg/L)	72	RCC
Methylguanidine (µg/L)	73	Guanidine
Monomethylamine (µg/L)	31	Amine
Neopterin (µg/L)	253	Purine
Nicotinamide (µg/L)	122	Nicotinamide
N-methyl-2-pyridone-5-carboxamide (mg/L)	152	Nicotinamide
N-methyl-4-pyridone-3-carboxamide (µg/L)	152	Nicotinamide
Nonanal (µg/L)	142	RCC
Noradrenalin (µg/L)	382	Catecholamine
Oxalate (mg/L)	90	
Phenylacetic acid (mg/L)	136	
Symmetric dimethylarginine (µg/L)	202	Guanidine
Trimethylamine (µg/L)	59	Amine
Trimethylamine-N-oxide (mg/L)	75	Amine
Uric acid (mg/L)	168	Purine

Middle molecules

Molecule	Molecular Weight	Group
α1-Acid glycoprotein (g/L)	43,000	Protein
α1-Microglobulin (mg/L)	33,000	Protein
β-Trace protein (mg/L)	26,000	Protein
β2-Microglobulin (mg/L)	11,818	Protein
Adiponectin (mg/L)	30,000	Protein
Angiogenin (µg/L)	14,400	Protein
Calcitonin (ng/L)	3450	Protein
Complement factor D (mg/L)	23,750	Protein
Cystatin C (mg/L)	13,300	Protein
Fibroblast growth factor-23 (ng/L)	32,000	Protein
Glutathion, oxidized (mg/L)	613	Tripeptide
IGF-1 (µg/L)	7650	Protein
IL-6 (ng/L)	24,500	Cytokine
IL-8 (ng/L)	8000	Cytokine
IL-10 (ng/L)	18,000	Cytokine
Leptin (µg/L)	16,000	Protein
Myoglobin (µg/L)	17,000	Protein
Osteocalcin (µg/L)	5800	Protein
PTH (ng/L)	9500	Protein
Prolactin (µg/L)	22,000	Protein
Resistin (µg/L)	12,500	Cytokine
Retinol binding protein (mg/L)	21,200	Protein
Soluble intracellular adhesion molecule-1 (µg/L)	4270	Protein
TNF-α (ng/L)	26,000	Cytokine
Vascular endothelial growth factor (ng/L)	34,250	Protein

Protein-bound molecules

Molecule	Molecular Weight	Group
3-Carboxy-4-methyl-5-propyl-2-furan-propanoic acid (mg/L)	240	
Acrolein, total (mg/L)	56	RCC
Acrolein, free (µg/L)	56	RCC
Carboxymethyllysine (mg/L)	204	AGE
Dihydroxyphenylalanine (mg/L)	197	Catecholamine
Hippuric acid, total (mg/L)	179	Hippurate
Hippuric acid, free (mg/L)	179	Hippurate
Homocysteine (mg/L)	135	Aminoacid
Indican (mg/L)	295	Indole
Indole-3-acetic acid, total (mg/L)	175	Indole
Indole-3-acetic acid, free (mg/L)	175	Indole
Indoxyl sulfate, total (mg/L)	212	Indole
Indoxyl sulfate, free (mg/L)	213	Indole
Indoxyl-β-D-glucoronide (mg/L)	408	Indole
Kynurenic acid (µg/L)	189	Indole
p-Cresylsulfate, total (mg/L)	31	Phenol
p-Cresylsulfate, free (mg/L)	31	Phenol
Pentosidine (µg/L)	342	AGE
Phenol (mg/L)	94	Phenol
Putrescine (µg/L)	88	Polyamine
Spermidine (µg/L)	145	Polyamine
Spermine (µg/L)	202	Polyamine
Thiocyanate (mg/L)	58	

Duranton F et al, J Am Soc Nephrol. 2012

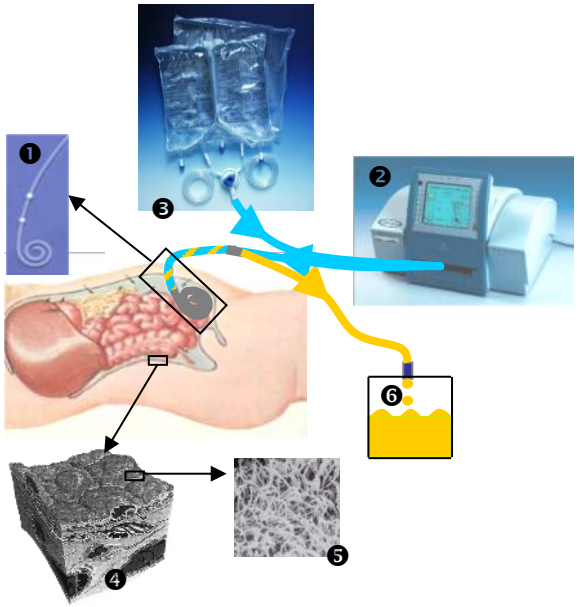
Peritoneal dialysis vs. healthy kidneys:

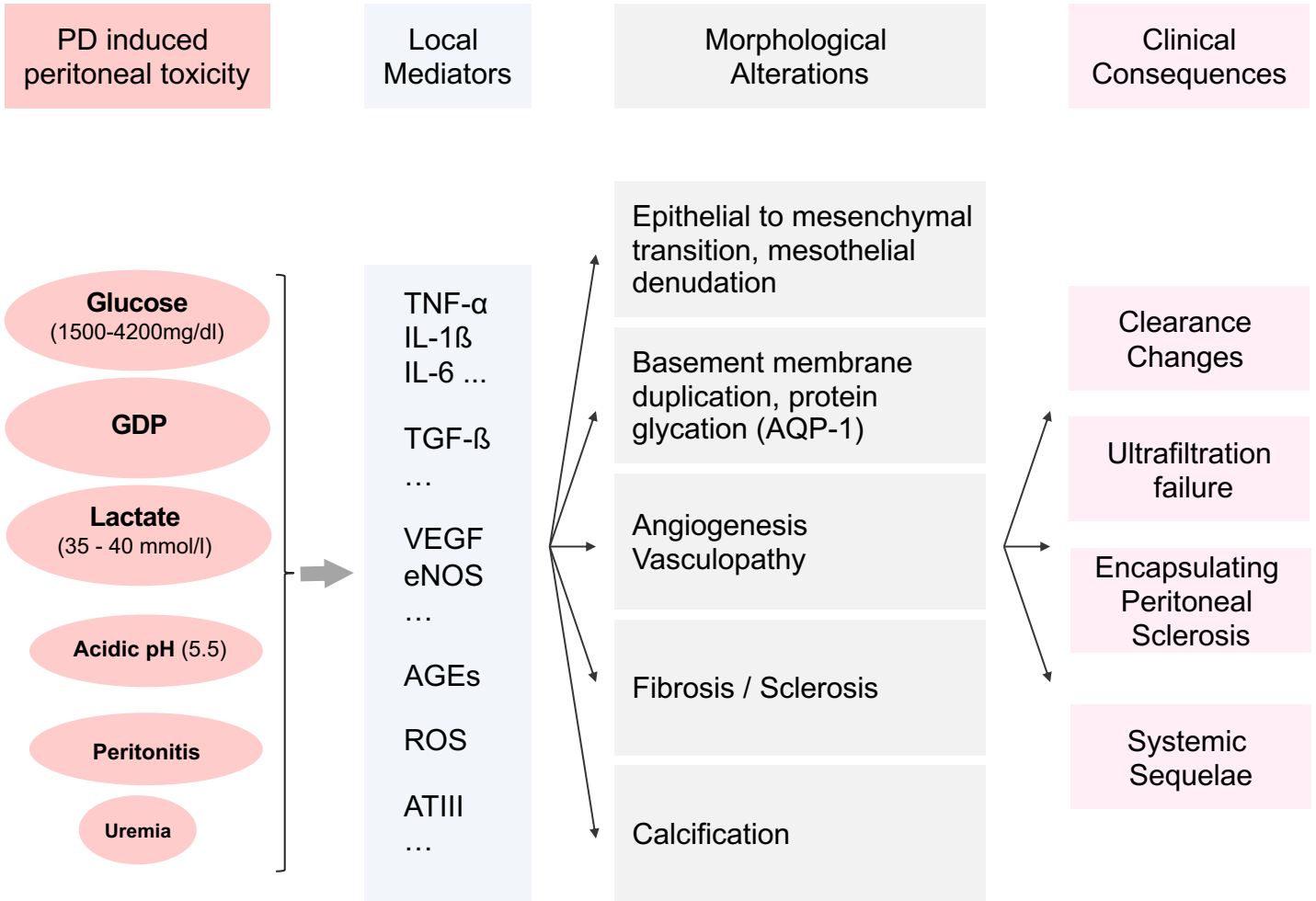
- 10-15% removal of small solutes/toxins
- less removal of middle molecules
- no removal of protein bound toxins
- some protein loss (incl. albumin, bound toxins)

- Rather simple technique but the devil is in the details

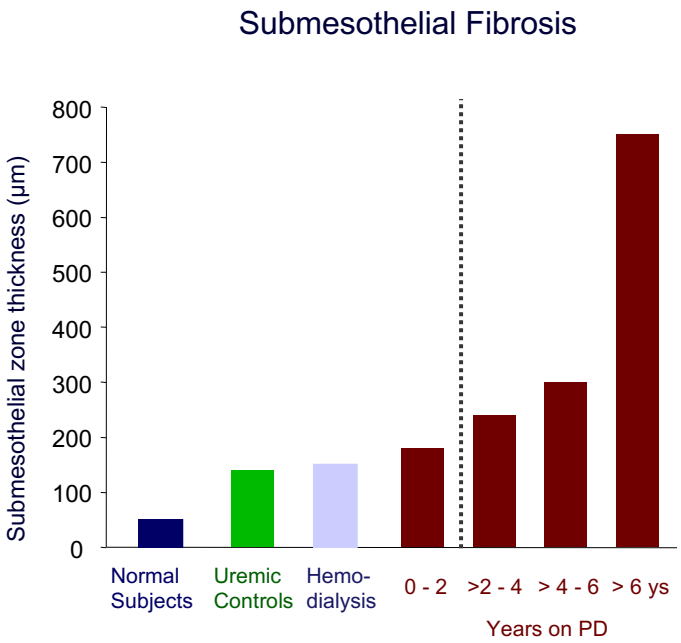
PD fluid components	CAPD
Sodium (mmol/l)	134
Chloride (mmol/l)	102,5
Calcium (mmol/l)	1.25/1.75
Magnesium (mmol/l)	0.5
Glucose (%)	1,5/2.3/4.25
Osmolarity (mosmol/l)	356-509
Lactate (mmol/l)	35
pH	5.5
Formaldehyde (µmol/l)	5.4 ± 0.4
3,4 DGE (µmol/l)	16.2 ± 0.8

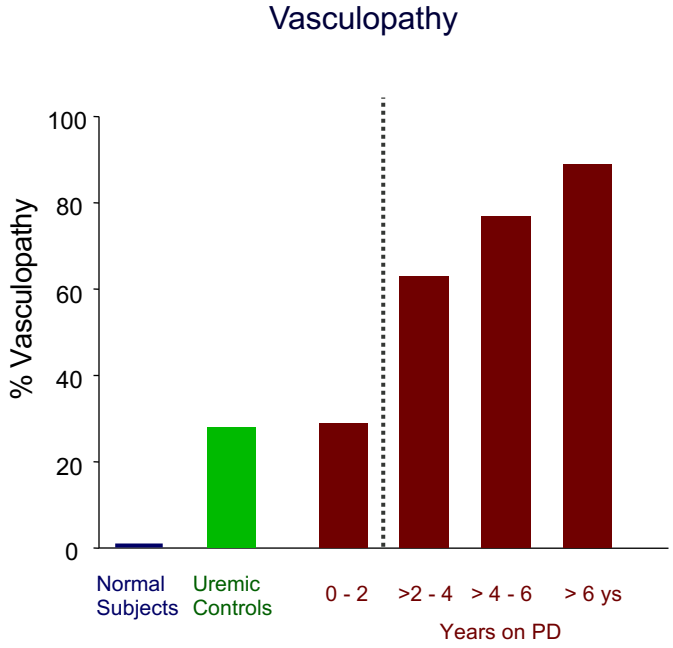
= 1500 - 4250 mg/dl




PD induced peritoneal toxicity
Local Mediators
Morphological Alterations
Clinical Consequences
Glucose (1500-4200mg/dl)
GDP
Lactate (35 - 40 mmol/l)
Acidic pH (5.5)
Peritonitis
Uremia
TNF-α
IL-1ß
IL-6 ...
TGF-ß
…
VEGF
eNOS
…
AGEs
ROS
ATIII
…
Epithelial to mesenchymal transition, mesothelial denudation
Basement membrane duplication, protein glycation (AQP-1)
Angiogenesis Vasculopathy
Fibrosis / Sclerosis
Calcification
Clearance Changes
Ultrafiltration failure
Encapsulating Peritoneal Sclerosis
Systemic Sequelae

PD membrane transformation with conventional, acidic PD fluids with high glucose degradation product content





Williams et al, JASN 2002

Biocompatibility

Refers to the ability of a biomaterial to

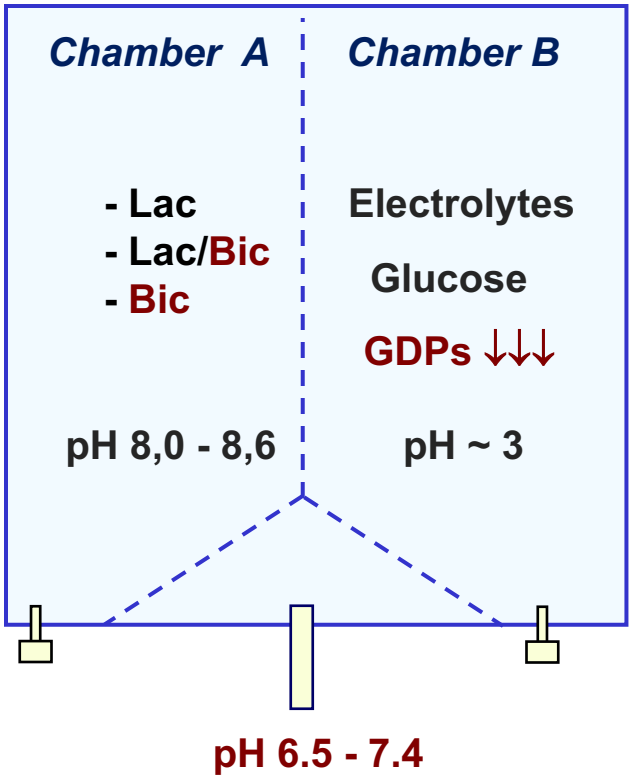
1. perform its desired function with respect to a medical therapy
2. without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy,
3. but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy.

Williams, DF. On the mech *atibility*

PD membrane deterioration

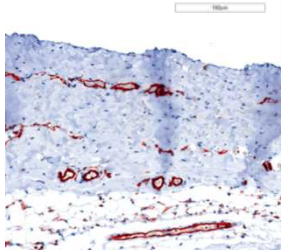
e.g. systemic inflammation (independent of peritonitis)

Neutral pH PD fluids, with low glucose degradation product content

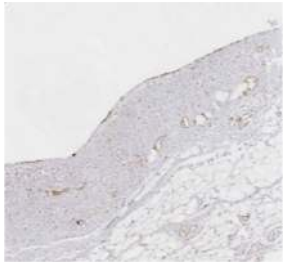


Transformation of the PD membrane with low GDP PD

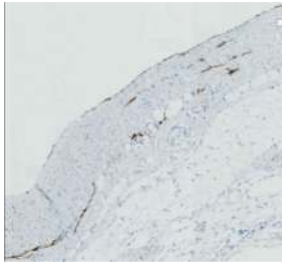
Vessels (CD31)



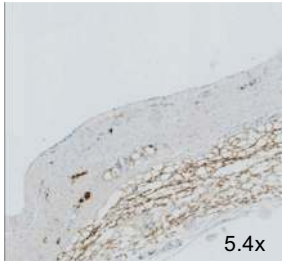
Vessels (AQP1)



Lymphatics (Podoplanin)

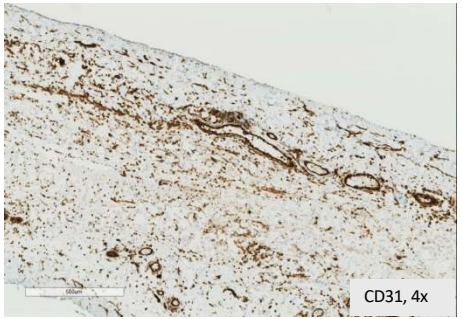


Nerves (S 100)

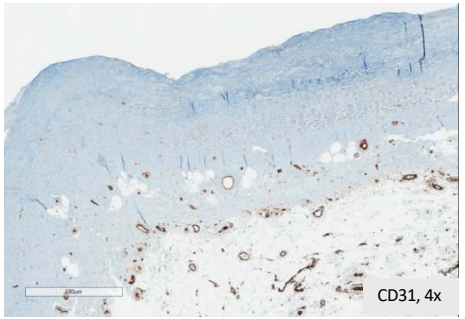


Schaefer B et al. Sci Rep. 2016

PD 2 years (BicaVera®)



9.1 years of PD (Physioneal®)

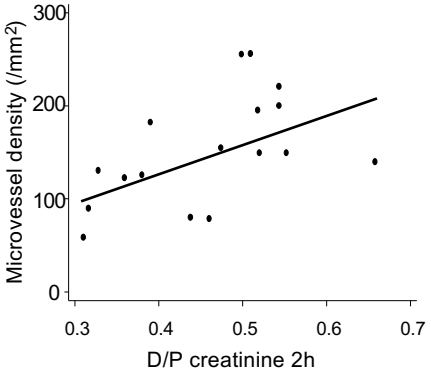


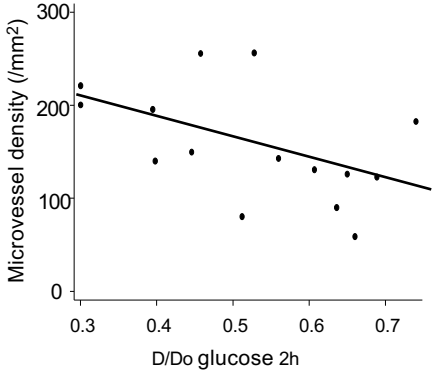
Severe, early peritoneal membrane transformation with low GDP PD

	CKD5 n=90	PD <6 Mo n=13	PD 6-12 Mo n=19	PD 12-24 Mo n=21	PD 24-48 Mo n=16	PD ≥48 Mo n=13	p
PD duration (months)	0	**4.0 (2.3, 4.8)**	9.0 (7.3, 10.0)	15.7 (12.8, 19.0)	33.0 (27.3, 36.2)	72.3 (63.0, 85.2)	<0.001
Glucose exposure (g/m²/day)	63 (27, 102)	105 (88, 131)	116 (85, 186)	100 (86, 123)	117 (57, 153)	131 (118, 154)	0.011
Mesothel coverage (0-6)	4 (3, 6)	2 (0, 6)	2 (0, 3)	1 (0, 3)	0, (0, 2.5)	0 (0, 2)	<0.001
Submesothelial thickness (µm)	268 (208, 380)	330 (304, 482)	424 (358, 525)	300 (237, 420)	373 (258, 511)	826 (328, 950)	<0.001
Microvessel density (/mm²)	124 (78, 174)	179 (132, 274)	236 (125, 368)	161 (97, 385)	181 (112, 269)	169 (89, 237)	0.002
Submesothelial microvessels / mm	29 (20, 47)	57 (32, 138)	106 (69, 172)	58 (30, 96)	59 (26, 90)	70 (38 185)	<0.001
Lymphatic vessel density (/mm²)	28.1 (18.9, 49.6)	23.3 (16.2, 35.4)	32.9 (10.8, 46.3)	28.5 (21.8, 45.9)	39.5 (14.7, 55.0)	25.1 (16.5, 44.5)	0.9
Diffuse podoplanin staining	0%	15%	21%	21%	31%	36%	0.002
Blood vessel density (/mm²)	**85.6 (46.7, 147.9)**	**180.0 (142.8, 251.0)**	166.0 (73.7, 311.8)	120 (64.4, 286.4)	175.7 (96.0, 269.5)	131 (47.7, 202.8)	<0.001
Endothelial surface area (µm²/µm³)	7.3 (4.1, 10.3)	10.0 (9.4, 15.4)	12.3 (7.7, 19.1)	9.0 (5.3, 17.3)	10.2 (7.8, 13.2)	9.0 (4.4, 11.3)	0.004
L/V ratio	0.5 (0.4, 0.6)	0.4 (0.4, 0.5)	0.4 (0.3, 0.4)	0.4 (0.3, 0.5)	0.3 (0.2, 0.5)	0.4 (0.2, 0.6)	0.008

Schaefer B et al KI 2018

Peritoneal vessel density predicts transport function





MVLR Analysis *2 hours D/P creatinine*

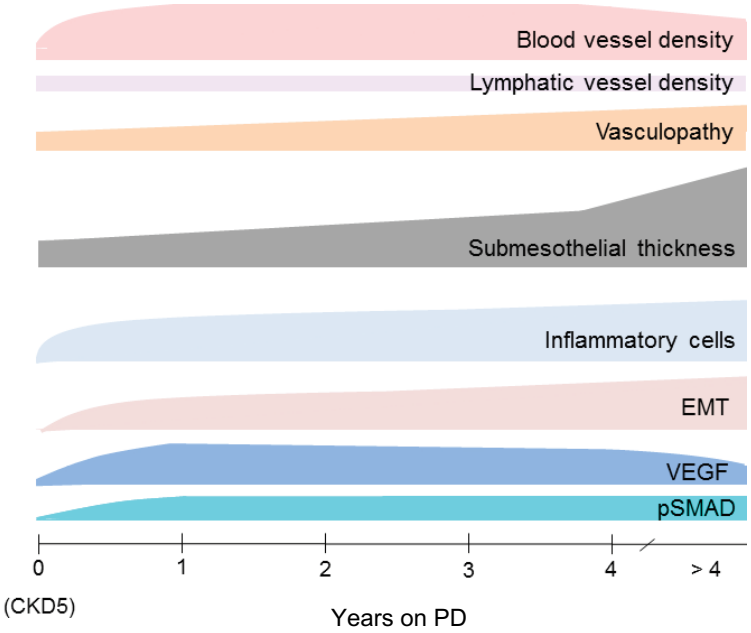
	Coeff.	lower CI95%	upper CI95%	p-value
Age (years)	0.007	-0.002	0.015	0.115
Dialytic glucose exposure (g/m²/day)	0.002	-0.000	0.003	0.059
Microvessel density (/mm²)	0.166	0.069	0.264	**0.004**
Submesothelial thickness (µm)	-0.000	-0.001	0.000	0.111

MVLR Analysis *2 hours D/D_0 glucose*

	Coeff.	lower CI95%	upper CI95%	p-value
Age (years)	-0.011	-0.027	0.005	0.142
Dialytic glucose exposure (g/m²/day)	-0.002	-0.005	0.001	0.147
Microvessel density (/mm²)	-0.203	-0.404	-0.003	**0.047**
Submesothelial thickness (µm)	0.001	-0.000	0.001	0.089

Schaefer B et al KI, 2018

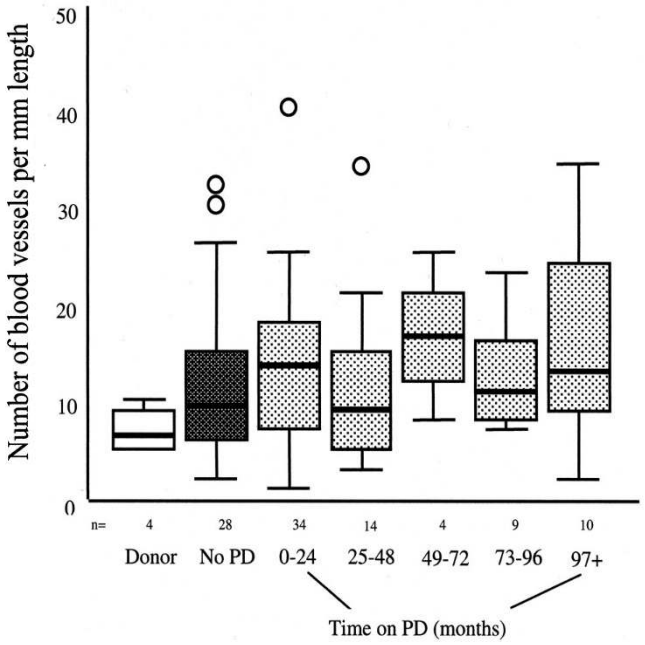
Peritoneal Transformation with Low GDP Fluids

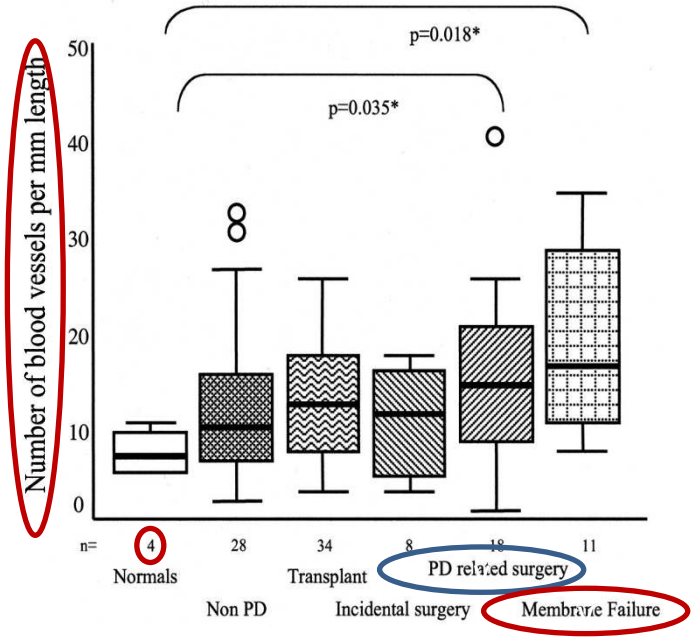


=> Driving force: high dialysate glucose concentrations (increasing with PD vintage)

Bartosova M & Schmitt CP, Front in Physiol 2019
Schaefer B et al, Kidney Int 2018

Less angiogenesis with conventional, acidic high GDP PD fluids





Williams et al, JASN 2002

Kidney International
Volume 94, Issue 2, August 2018, Pages 246-248

Commentary

Is the peritoneal dialysis biocompatibility hypothesis dead?

Peter G. Blake [1]

Where does this leave clinical practitioners of PD? If they have not been persuaded to use biocompatible fluids by now, the evidence from the Schaefer study will strengthen this view. If they have already been using the solutions, it has been a *leap of faith*, unsupported by high-level clinical evidence

Cochrane Database of Systematic Reviews

Biocompatible dialysis fluids for peritoneal dialysis

Cochrane Systematic Review - Intervention | Version published: 26 October 2018 see what's new

https://doi.org/10.1002/14651858.CD007554.pub3

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Htay Htay | David W Johnson | Kathryn J Wiggins | Sunil V Badve | Jonathan C Craig | Giovanni FM Strippol

Authors' conclusions

This updated review strengthens evidence that neutral pH, low GDP PD solution improves RRF and urine volume preservation with high certainty. These effects may be related to increased peritoneal solute transport and reduced peritoneal ultrafiltration,

42 studies, 3262 patients

=> **Neutral pH, low GDP PD solution improves RRF and urine volume preservation (high certainty)** (progressively greater preservation with increasing PD duration!)

=> These effects may be related to increased solute transport and reduced UF (low certainty)

=> Icodextrin increased UF ultrafiltration and mitigated uncontrolled fluid overload (moderate certainty).

=> **Effects on peritonitis, technique survival and patient survival remain uncertain**

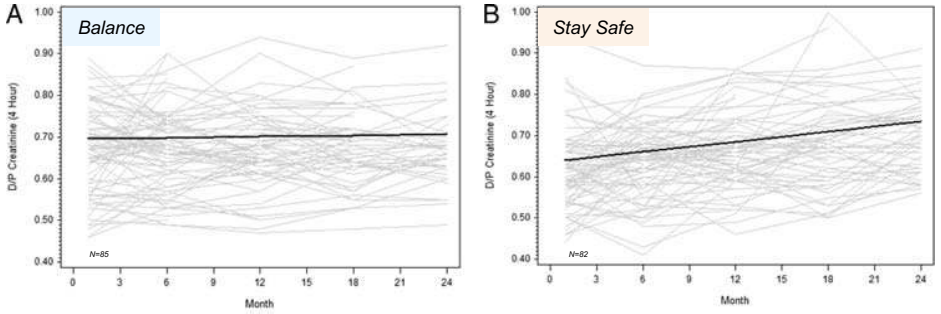
Faster solute transport and less UF with low GDP fluids during the first year of PD

Parameter	1 months		3 months		6 months		9 months		12 months	
Incident pts	Balance ($n = 85$)	Stay.safe ($n = 82$)	Balance ($n = 85$)	Stay.safe ($n = 80$)	Balance ($n = 76$)	Stay.safe ($n = 75$)	Balance ($n = 68$)	Stay.safe ($n = 68$)	Balance ($n = 62$)	Stay.safe ($n = 66$)
Weekly CpUr (L/week/1.73 m^2)	N/A	N/A								
n			85	78	75	74	68	68	62	65
Median			52	56	54	56	55*	58	56	59
[min, max]			[19, 70]	[6, 86]	[23, 71]	[13, 92]	[35, 90]	[20, 106]	[1, 71]	[1, 93]
Weekly CpCr (L/week/1.73 m^2)	N/A	N/A								
n			84	78	75	74	68	70	62	66
Median			40	39	41	43	39	43	43	44
[min, max]			[11, 54]	[2, 67]	[11, 58]	[12, 71]	[20, 74]	[17, 79]	[21, 63]	[20, 77]
UF (mL/day)	N/A	N/A								
n			85	79	75	74	68	70	62	66
Median			700*	1090	850*	1015	913*	1233	955	1150
[min, max]			[−700, 3500]	[−400, 2800]	[−1040, 1966]	[−1716, 4040]	[−1082, 2300]	[−1000, 2900]	[−600, 2700]	[−400, 3000]
D:P Cr 4 h			N/A	N/A			N/A	N/A		
n	83	82			75	73			60	66
Mean ± SD	0.67 ± 0.10*	0.62 ± 0.10			0.67 ± 0.10*	0.64 ± 0.09			0.67 ± 0.10	0.67 ± 0.09
D/D0 glucose 4 h			N/A	N/A			N/A	N/A		
n	83	82			75	73			59	66
Mean ± SD	0.39 ± 0.08*	0.43 ± 0.08			0.40 ± 0.08*	0.43 ± 0.07			0.40 ± 0.08	0.40 ± 0.08
4 h UF during PET (mL)			N/A	N/A			N/A	N/A		
n	83	82			75	73			60	66
Median	300*	354			300*	400			260*	400
[min, max]	[−200, 900]	[−100, 1085]			[−110, 900]	[−100, 1010]			[−200, 750]	[−80, 650]

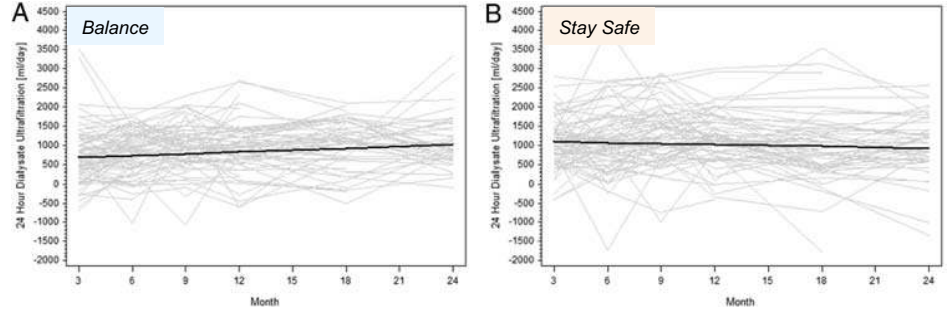
Johnson D et al, NDT 2012

BalANZ Trial: stable PD membrane function and less peritonitis with low GDP PD fluid

D/P Creatinine 4h *P<0.001*

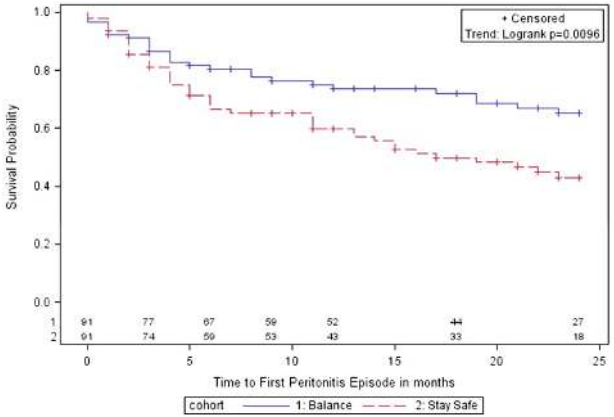


Ultrafiltration (ml/day) *P<0.01*



Johnson D et al, NDT 2012

Time to first peritonitis



0.30 versus 0.49 episodes per year (p=0.01)

Johnson DW et al, JASN 2012

Peritoneal Dialysis International, Vol. 32, pp. 497–506
doi: 10.3747/pdi.2012.00052

THE EFFECTS OF BIOCOMPATIBLE COMPARED WITH STANDARD PERITONEAL DIALYSIS SOLUTIONS ON PERITONITIS MICROBIOLOGY, TREATMENT, AND OUTCOMES: THE *BAL*ANZ TRIAL

The *bal*ANZ Trial Writing Committee: David W. Johnson,[1,2] Fiona G. Brown,[3] Margaret Clarke,[4] Neil Boudville,[5] Tony J. Elias,[6] Marjorie W.Y. Foo,[7] Bernard Jones,[8] Hemant Kulkarni,[9] Robyn Langham,[10,11] Dwarakanathan Ranganathan,[2,12] John Schollum,[13] Michael G. Suranyi,[14] Seng H. Tan,[15,16,17] and David Voss[18] on behalf of the *bal*ANZ Trial Investigators

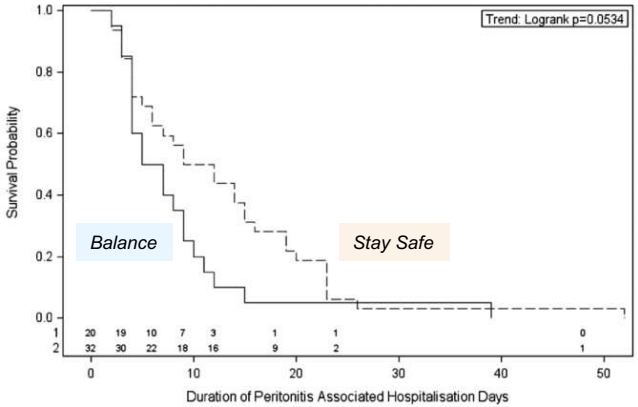
Peritonitis episodes / patient–year:

Balance: 0.30 (95% CI: 0.22 to 0.41)

Stay safe: 0.49 (95% CI: 0.39 to 0.62)

=> Incidence rate ratio: 0.61 (95% CI: 0.41 to 0.90; p = 0.01)

Duration of associated hospitalizations:



Clin J Am Soc Nephrol. 2018 Oct 8; 13(10): 1526–1533.
Published online 2018 Aug 31. doi: 10.2215/CJN.02380218
PMCID: PMC6218832
PMID: 30171050

Biocompatible Solutions and Long-Term Changes in Peritoneal Solute Transport

Emma H. Elphick,[1] Lucy Teece,[1] James A. Chess,[2] Jun-Young Do,[3] Yong-Lim Kim,[4] H. Bahl Lee,[5] Sara N. Davison,[6] Nicholas Topley,[7] Simon J. Davies,[1] and Mark Lambie[1]

Impact of peritonitis on peritoneal solute transport:

Patients on standard solutions (n=169):
D/Pcrea: + 0.020 (95% CI 0.01 to 0.03) per peritonitis episode

Patients on biocompatible solutions (n=29):
no change in D/Pcrea (−0.014; 95% CI, −0.03 to <0.01 per episode).

frontiers in Physiology

ORIGINAL RESEARCH
published: 02 April 2019
doi: 10.3389/fphys.2019.00356

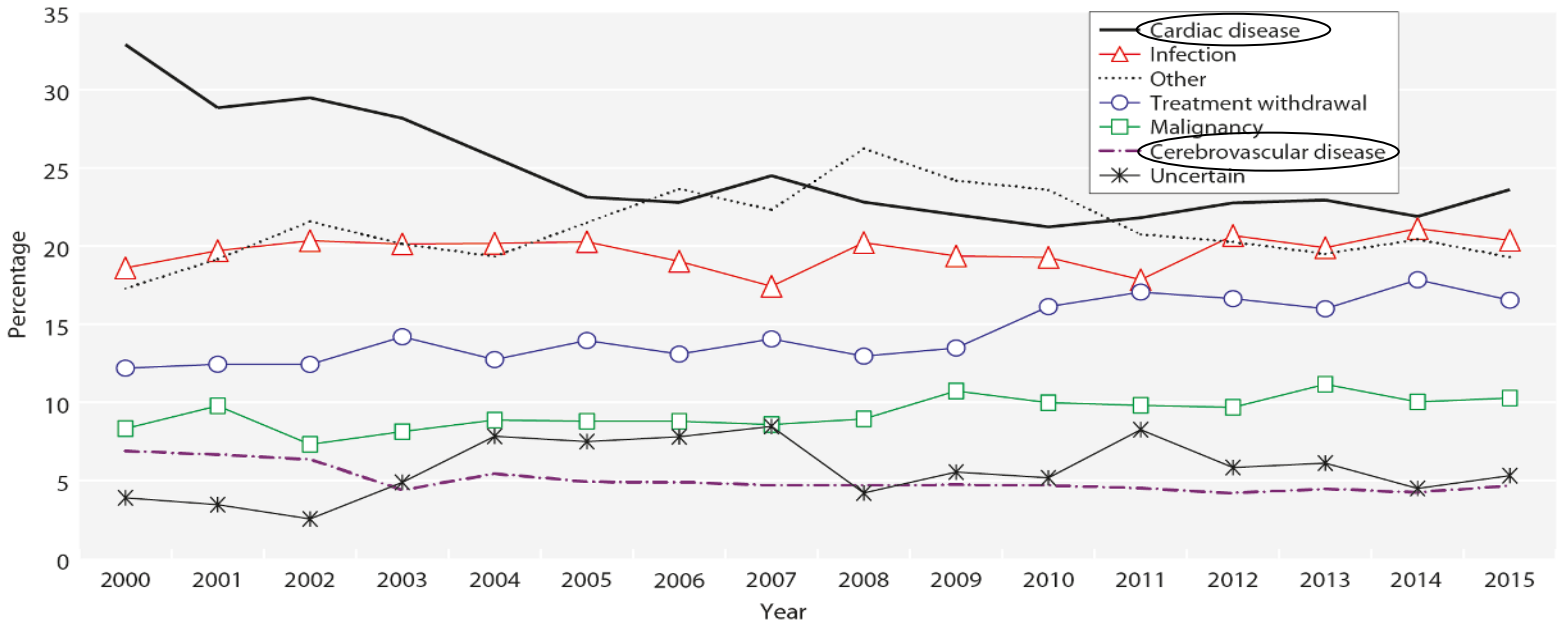
Peritoneal Dialysis Vintage and Glucose Exposure but Not Peritonitis Episodes Drive Peritoneal Membrane Transformation During the First Years of PD

Maria Bartosova[1†], Betti Schaefer[1†], Karel Vondrak[2], Peter Sallay[3], Christina Taylan[4], Rimante Cerkauskiene[5], Maria Dzierzega[6], Gordana Milosevski-Lomic[7], Rainer Büscher[8], Ariane Zaloszyc[9], Philipp Romero[10], Felix Lasitschka[11], Bradley A. Warady[12], Franz Schaefer[1], Akos Ujszaszi[13] and Claus Peter Schmitt[1]*

MATCHED

	No peritonitis (n=24)	peritonitis (n=24)	p-value
Age (years)	4.0 (1.8, 9.4)	3.3 (1.5, 10.1)	0.71
Female (%)	46%	58%	0.39
Body surface area (/m²)	0.6 (0.4, 1.2)	0.6 (0.5, 1.0)	0.88
PD duration (months)	11.3 (8.5, 21.4)	12.0 (8.5, 22.4)	0.66
Glucose exposure (mg/day/bsa)	97 (89, 132)	100 (85, 108)	0.64
Absent mesothel layer	46%	38%	0.53
Mesothelial cell coverage (0-6)	0.5 (0.0, 3.5)	1.0 (0.0, 3.0)	0.91
Submesothelial thickness (um)	304 (200, 358)	413 (250, 500)	0.24
Microvessel density (/mm²)	200 (107, 325)	170 (97, 318)	0.82
Microvessel number / mm	59 (32, 75)	82 (30, 116)	0.21
Lymphatic vessel density (/mm²)	39 (23, 56)	33 (22, 46)	0.41
Blood cap. vessel density (/mm²)	176 (71, 238)	139 (66, 362)	0.72
Total endothelial surface area (um²/um³)	10.0 (7.7, 19.0)	10.2 (5.9, 16.4)	0.82
Lym. endothelial surface area (um²/um³)	3.4 (1.8, 5.7)	2.6 (1.3, 4.4)	0.30
Blood cap. endothelial surface area (um²/um³)	8.0 (4.1, 12.8)	6.7 (3.3, 15.7)	0.89
L/V ratio	0.4 (0.2, 0.5)	0.4 (0.3, 0.5)	0.28
ASMA score (0-3)	1 (0, 1)	1 (0, 2)	0.55
CD45 score (0-3)	1 (1, 1.5)	1 (0, 2)	0.89
CD68 score (0-3)	1 (0, 1.5)	2 (1, 2)	0.11
Fibrine (% positive patients)	25%	25%	1.00
Epithelial–Mesenchymal Transition (% pos. Pat.)	46%	42%	0.77
EMT (cells/mm2)	49 (20, 198)	21 (8, 65)	0.34
Diffuse staining (% positive patients)	33%	23%	0.42
VEGF-A (% submesothelial area)	32 (19, 63)	35 (20, 51)	0.50
pSMAD2/3 (% submesothelial area)	18.1 (6.2, 29.1)	20.3 (7.3, 26.7)	0.65

UK Renal Registry: Cause of death in prevalent RRT patients by cohort year (2000–2015)



UK Renal Registry 20th Annual Report

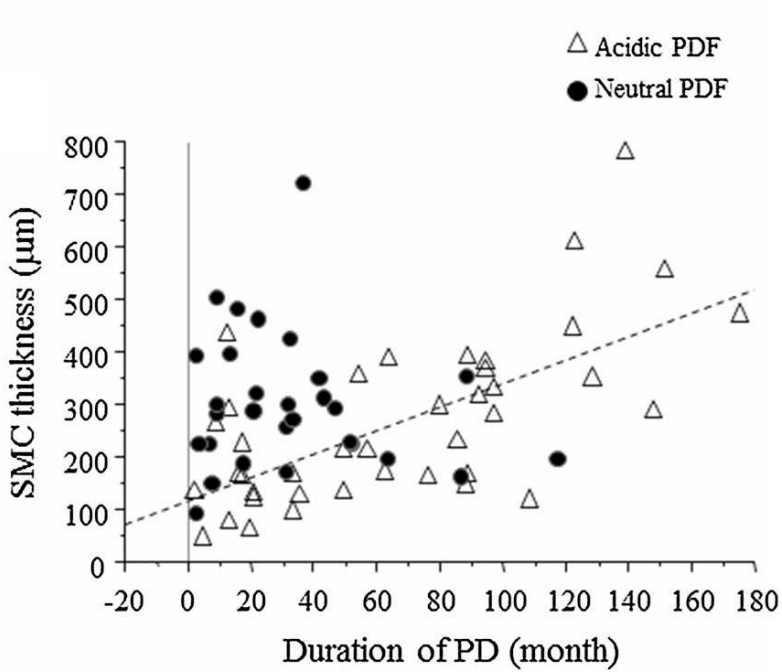
J Artif Organs (2015) 18:243–250
DOI 10.1007/s10047-015-0822-4

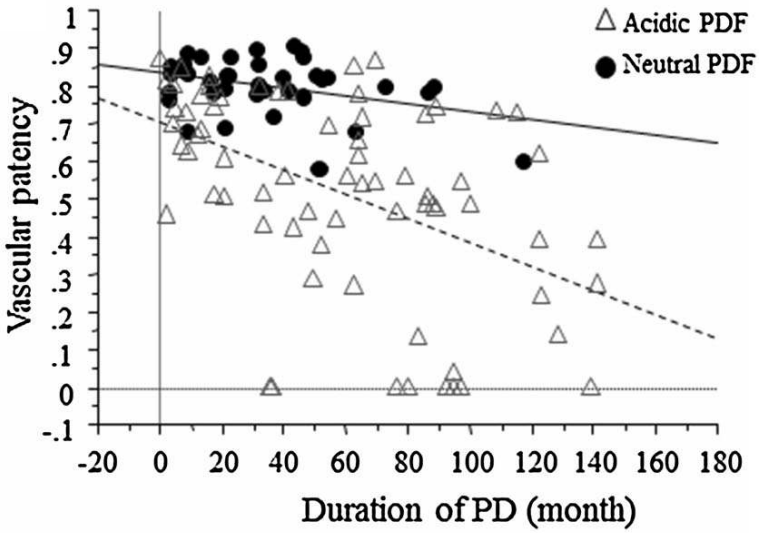
ORIGINAL ARTICLE

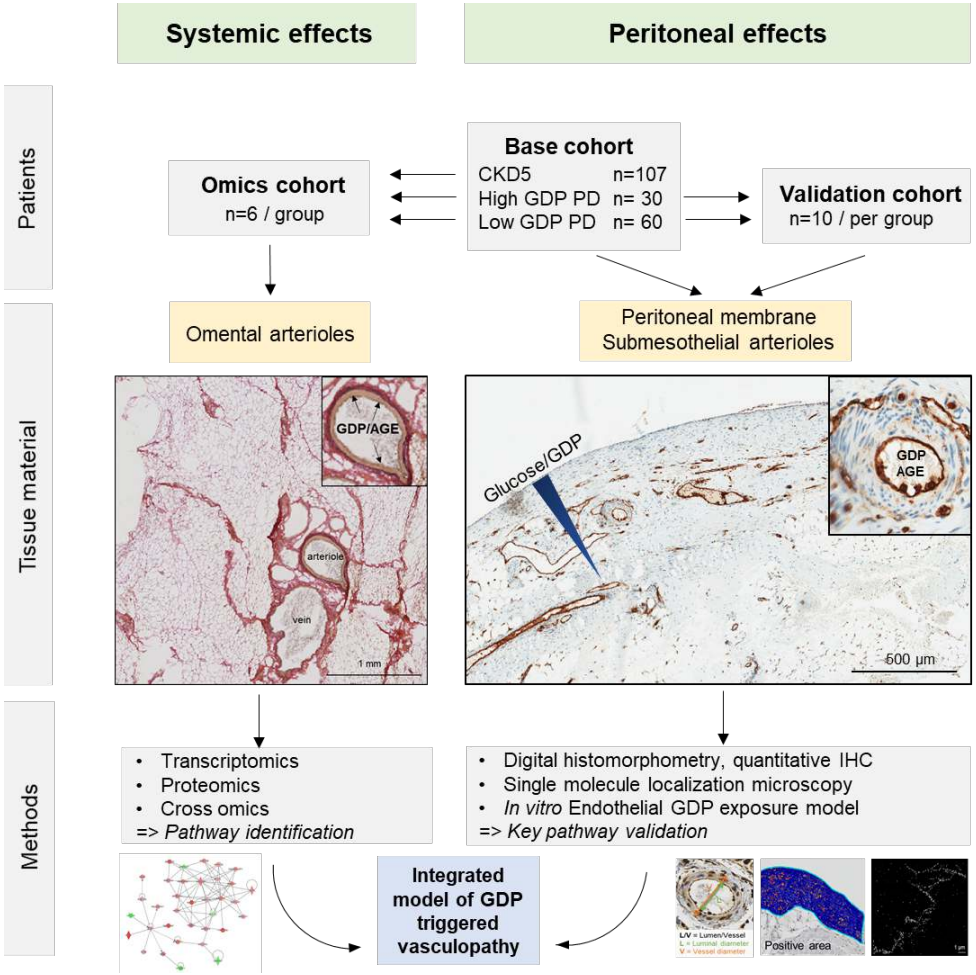
Artificial Kidney / Dialysis

Morphological characteristics in peritoneum in patients with neutral peritoneal dialysis solution

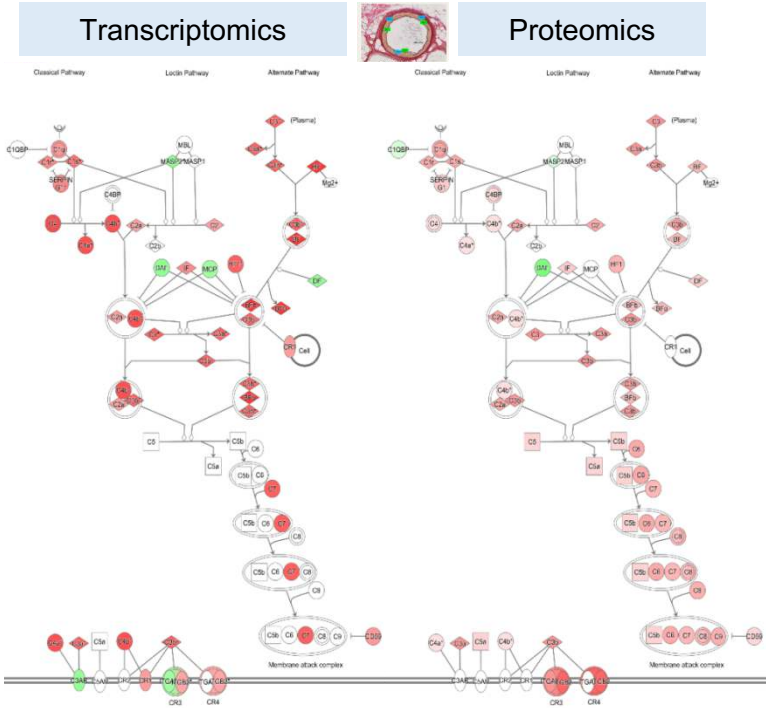
Chieko Hamada · Kazuho Honda · Kunio Kawanishi · Hirotaka Nakamoto · Yasuhiko Ito · Tsutomu Sakurada · Yudo Tanno · Toru Mizumasa · Masanobu Miyazaki · Misaki Moriishi · Masaaki Nakayama

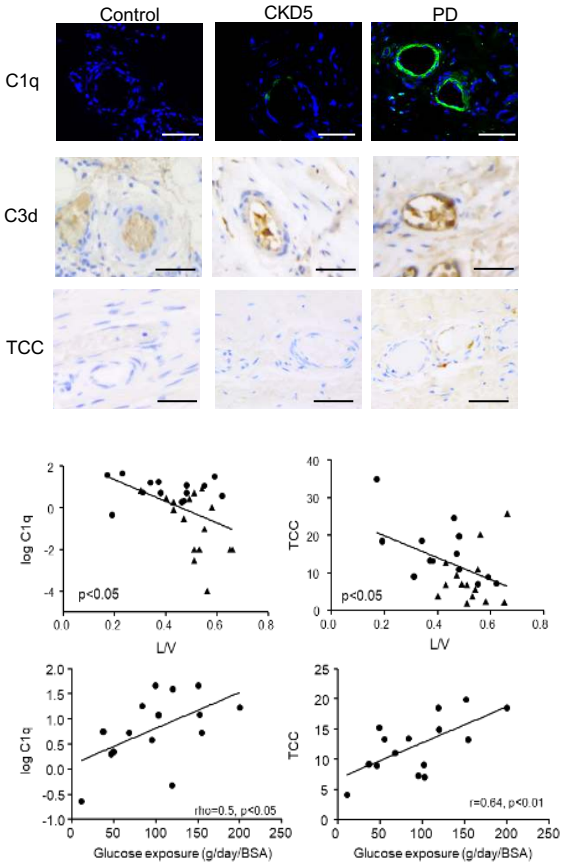





Systemic effects
Peritoneal effects
Patients
Tissue material
Methods
Base cohort
CKD5 n=107
High GDP PD n= 30
Low GDP PD n= 60
Omics cohort
n=6 / group
Validation cohort
n=10 / per group
Omental arterioles
Peritoneal membrane
Submesothelial arterioles
GDP/AGE
arteriole
vein
1 mm
Glucose/GDP
GDP
AGE
500 µm
• Transcriptomics
• Proteomics
• Cross omics
=> Pathway identification
• Digital histomorphometry, quantitative IHC
• Single molecule localization microscopy
• In vitro Endothelial GDP exposure model
=> Key pathway validation
Integrated model of GDP triggered vasculopathy
L/V = Lumen/Vessel
L = Luminal diameter
V = Vessel diameter
Positive area

Low GDP PD fluids and vascular damage: arteriolar complement activation

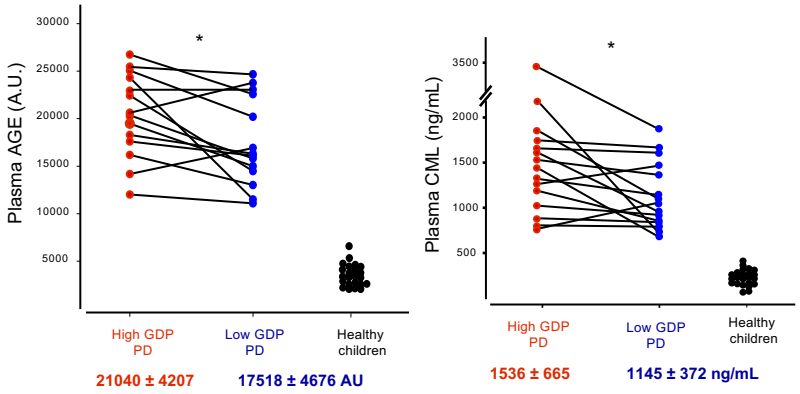




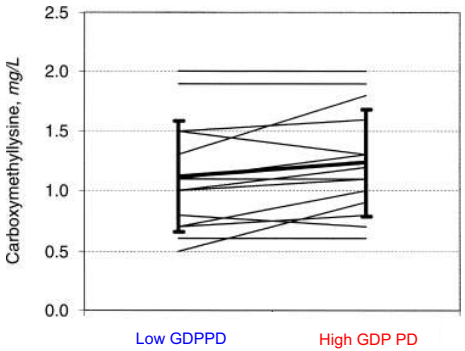
Bartosova M et al. JASN , 2018

Reduced plasma and tissue AGE concentrations with low GDP PD

Blood AGE concentrations

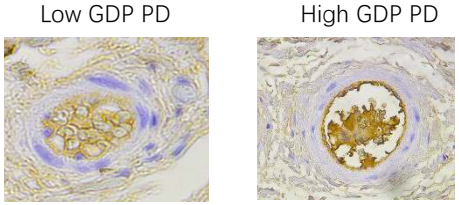


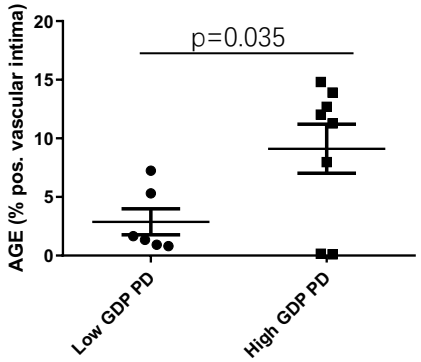
Schmitt CP et al, NDT 2007



Zeier et al. Kidney Int 2003

Omental arteriolar AGE deposition





Arteriolar Pathways Significantly Upregulated with Low and High GDP Fluids (IPA)

Low GDP-PD

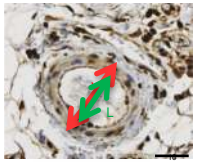
Disease / Function	p-value	z-score	# genes
Cell survival	1.56E-03	3.501	35
Cell viability	1.15E-03	3.437	34
Migration of cells	3.31E-07	2.953	57
Cell movement	7.00E-09	2.817	66
Chemotaxis	3.67E-04	2.478	18
Organization of actin cytoskeleton	2.15E-05	1.982	14
Recruitment of leukocytes	2.53E-03	1.722	11
Quantity of actin filaments	1.03E-03	1	5
Migration of phagocytes	3.55E-05	0.951	13
Angiogenesis	5.53E-05	0.807	29

High GDP-PD

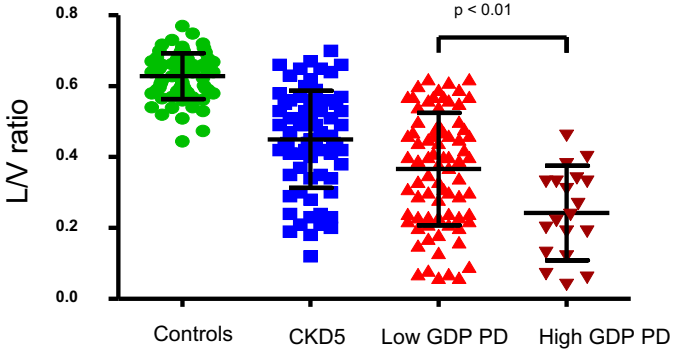
Diseases / Functions	p-value	z-score	# genes
Organismal death	1.27E-07	7.381	65
Apoptosis	1.50E-09	1.386	74
Cell death of epithelial cells	2.38E-03	1.33	15
Adhesion of endothelial cells	1.35E-03	1.223	7
Cellular infiltration	3.45E-04	1.129	16
Proliferation of smooth muscle cells	2.19E-03	0.639	10

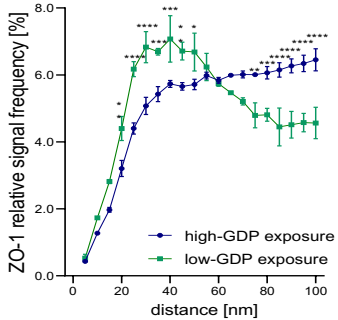
BH corrected

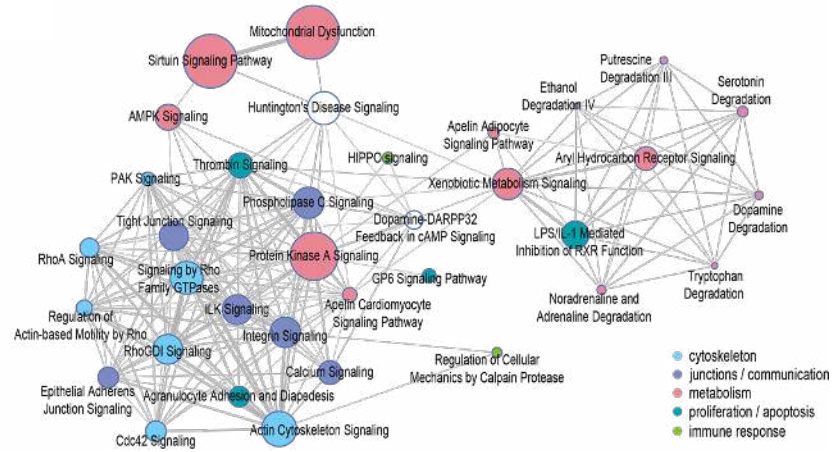
High GDP PD: More endothelial damage and lumen obliteration

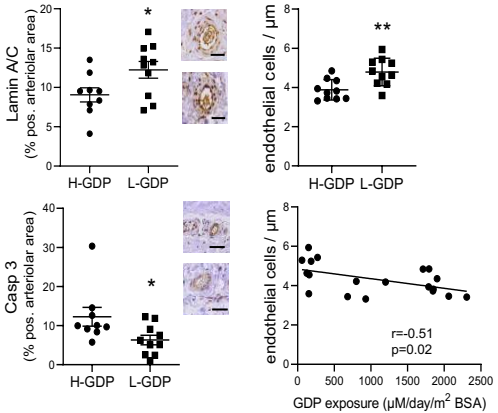


L/V: Lumen/Vessel Ratio
L: Luminal diameter
V: Vessel diameter





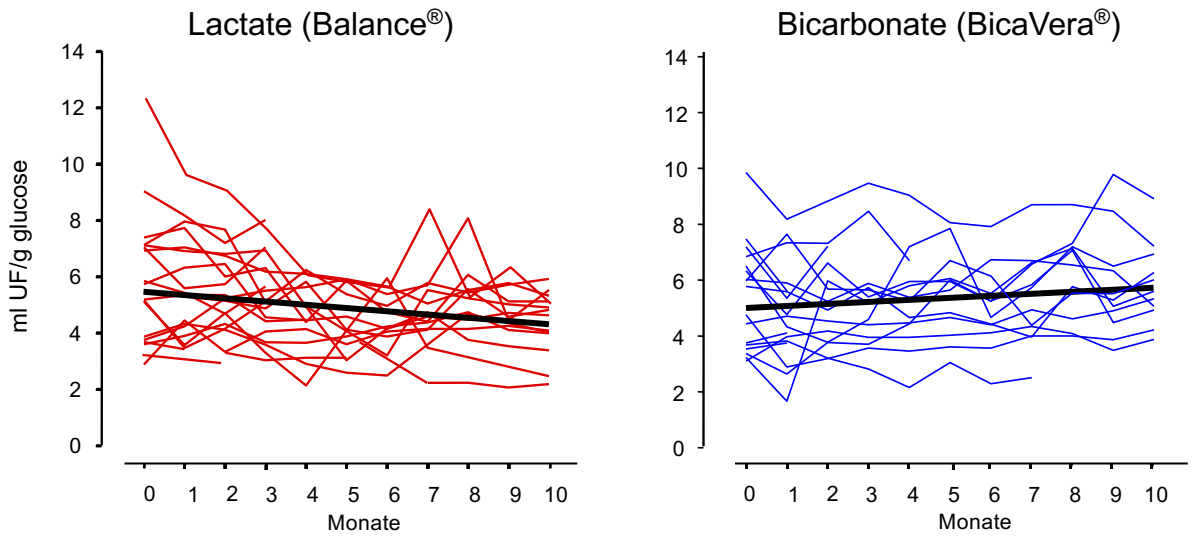




Enriched vasculopathy associated canonical pathways (n=223)
on transcriptomics and/or proteomics level in omental arterioles

Bartosova M et al. Circ Res rev.

PD **Puffer** and ultrafiltration capacity (Biokid Trial)



Different UF capacity over time ($p<0.01$ for slopes)

PD fluid type predicts intraindividual UF change ($p<0.01$)

Initial UF and changes in UF independent of time on PD and initial glucose exposure

Schmitt CP et al. CJASN, 2013

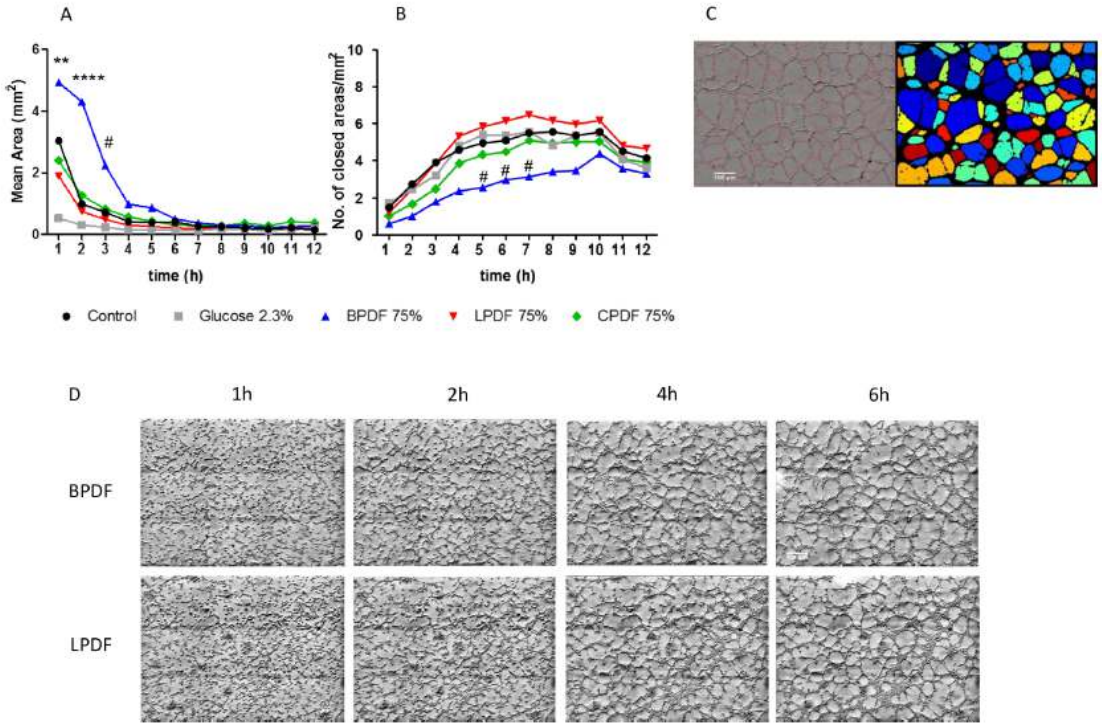


Fig 1. Tube formation assay. Angiogenic capacity analyzed by tube formation of human endothelial cells treated with different PD fluids. Automated analysis performed with CellProfiler Software showing (A) mean area and number of closed areas by endothelial cell branches (B) and (C) illustrative example of methodology (left image: red lines mark endothelial cells and their branches; right image: areas framed by endothelial cells are shown in different colors). Representative examples of the tubular network formed with BPDF and LPDF from 4 independent experiments performed in triplicates are given in (D). *p<0.05; **p<0.01; ***p<0.0001 for BPDF vs. all other; #p<0.05 BPDF vs. LPDF.

https://doi.org/10.1371/journal.pone.0189903.g001

Angiopoietein 1/2 related effects

American Journal of Kidney Diseases
Volume 75, Issue 6, June 2020, Pages 830-846

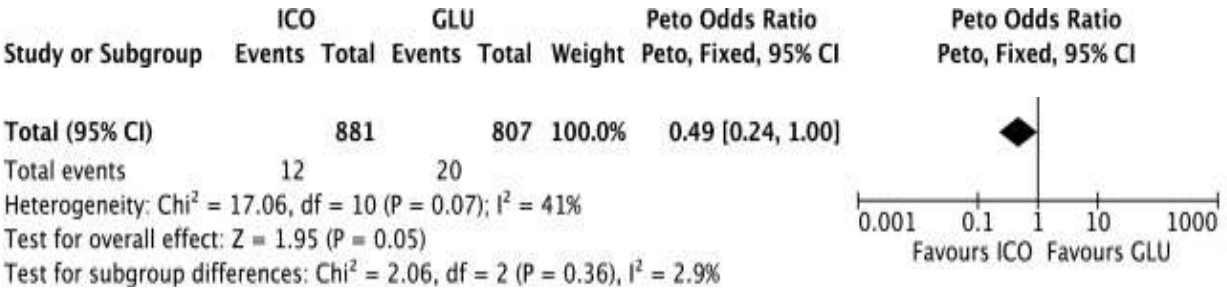
Original Investigation

Icodextrin Versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis: An Enriched Systematic Review and Meta-analysis of Randomized Controlled Trials

Käthe Goossen [1], Monika Becker [1], Mark R. Marshall [2,3,4], Stefanie Bühn [1], Jessica Breuing [1], Catherine A. Firanek [5], Simone Hess [1], Hisanori Nariai [6], James A. Sloand [5], Qiang Yao [7], Tae Ik Chang [8], JinBor Chen [9], Ramón Paniagua [10], Yuji Takatori [11], Jun Wada [12], Dawid Pieper [1]

19 RCTs, 1693 participants

- Ultrafiltration improved with icodextrin (208.92 [95% CI, 99.69-318.14] mL/24 h; high certainty of evidence)
- Fewer episodes of fluid overload (RR, 0.43 [95% CI, 0.24-0.78]; high certainty)
- Icodextrin probably decreased mortality risk compared to glucose-only PD (OR, 0.49 [95% CI, 0.24-1.00]; moderate certainty).



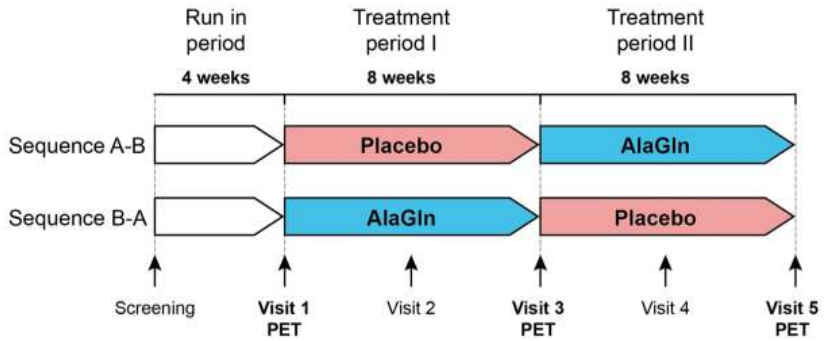
Perit Dial Int. 2021 Feb 10;896860820982218. doi: 10.1177/0896860820982218.
Online ahead of print.

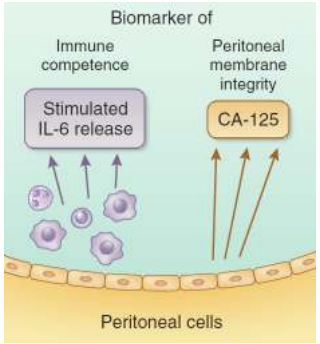
ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention

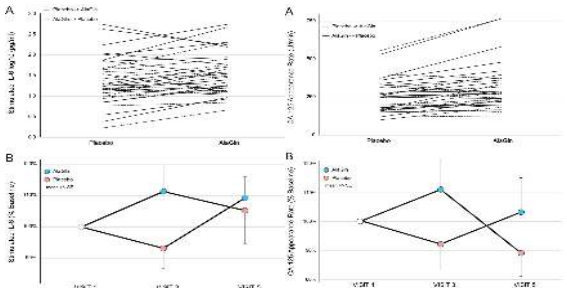
Johann Morelle [1], Joanna Stachowska-Pietka [2], Carl Öberg [3], Liliana Gadola [4], Vincenzo La Milia [5], Zanzhe Yu [6], Mark Lambie [7], Rajnish Mehrotra [8], Javier de Arteaga [9], Simon Davies [7]

Guideline 2b: Clinical implications and mitigation of fast solute transfer: A faster PSTR is associated with lower survival on PD. (GRADE 1A) This risk is in part due to the lower ultrafiltration (UF) and increased net fluid reabsorption that occurs when the PSTR is above the average value. The resulting lower net UF can be avoided by shortening glucose-based exchanges, using a polyglucose solution (icodextrin), and/or prescribing higher glucose concentrations. (GRADE 1A) Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload. (GRADE 1A)

AlaGln supplemented pH neutral, low GDP PD Fluid: PD Protec





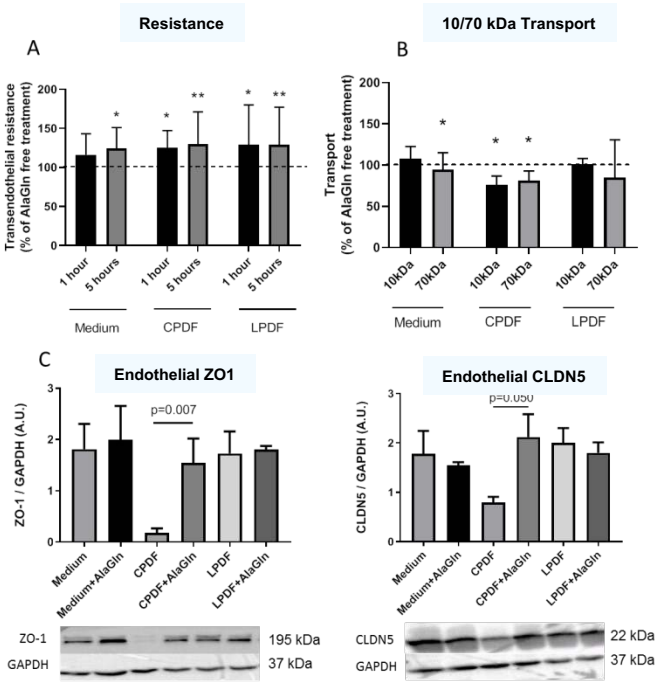


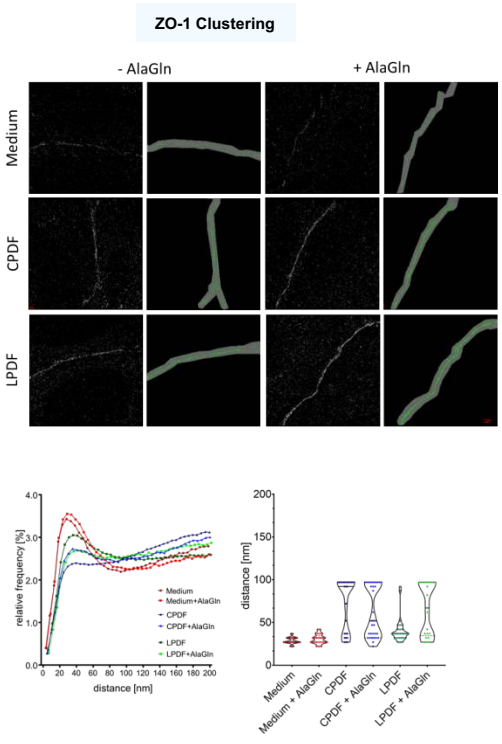
The RCT suggests:

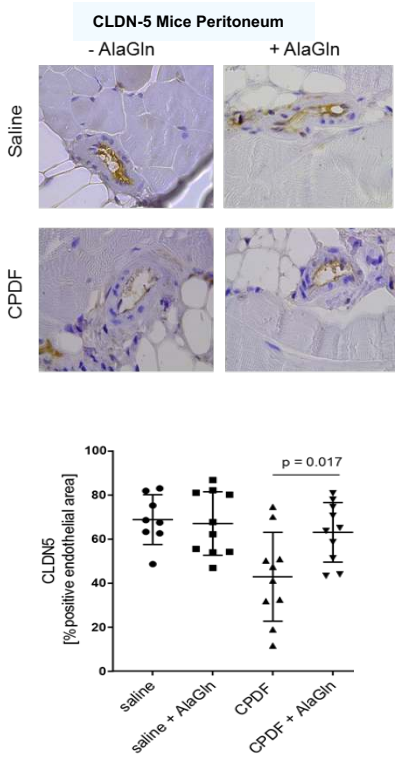
- Improved peritoneal membrane integrity (Ca125)
- Improved local immune competence (IL-6 release)
- Increased semipermeability of the PD membrane
  (less protein losses, higher D/P_{4h} potassium, phopshate and uric acid)
- Good tolerance, no safety signals
  Serum HbA1c 0.15% increased, uric acid and IL-8 reduced

Vychytil et al., Kidney Int 2018

Addition of AlaGln to PDF increases endothelial resistance, junction abundance and clustering, and reduces 10 and 70 kDa protein transport in experimental models of PD







Bartosova M et al., Biomolecules. 2020

AlaGln and Biocompatibility

Refers to the ability of a biomaterial to

1. perform its desired function with respect to a medical therapy
2. without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy,
3. but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy.

Williams, DF. On the mechanisms of biocompatibility. Biomaterials 2008

Risk profiling in PD

Registries:

- **United Kingdom Renal Registry**
  31 adult and 13 pediatric renal centers
- **Australia & New Zealand Dialysis & Transplant Registry**
  3282 PD patients in Australia / New Zealand
- **The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)**
  12000 patients (comorbidities, CV events, practice patterns)
- **Int Ped. PD and HD Registry**
  4000 pediatric PD and 1000 HD patients
- **Baxter**

Associated partners:

- **Fresenius Medical Care**
- **ERA/EDTA**

Tissue Biobanks

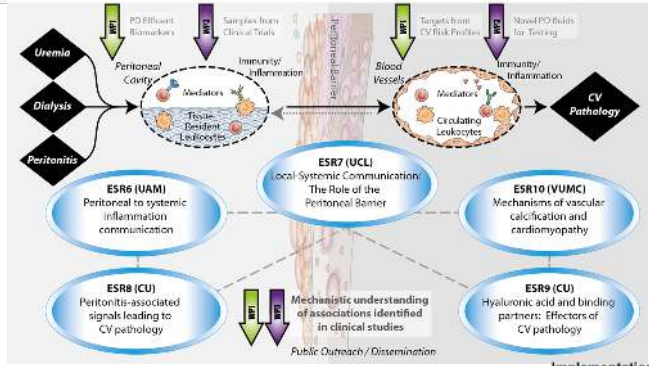
1. **International Pediatric PD Biobank**
2. **The Spanish NEFRONA study**
3. **Wales Kidney Research Tissue Bank**
4. **Louvain Tissue and Fluid Biobank**

Fluid / DNA Biobanks

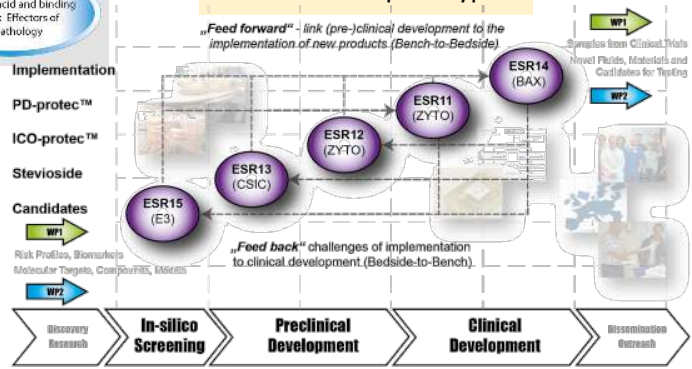
1. **Wales Kidney Research Tissue Bank**
2. **The PD CRAFT study**
3. **The Vienna PD BASE Biobank**
4. **Clinical trial samples**

IMPROVE-PD
New frontiers in Peritoneal Dialysis

Mechanisms of PD associated (CV) disease



Novel PD fluid prototypes



Where are we with PD fluid local and systemic biocompatibility?

Truly biocompatible PD fluids according to the definition are high hanging fruits
But:

- Neutral pH, low GDP fluids better preserve the peritoneal membrane in the long term, and better preserve residual renal function (and possibly CV health?)
- With neutral pH, low GDP fluids glucose still induces severe alterations: We need to entirely replace glucose by an inert osmotic compound
- Bicarbonate fluids should be superior in case of lactic acidosis (metabolic disorders, sepsis ...)
  Better preservation of UF than with low GDP lactate fluid? (1 pediatric RCT)
- Icodextrin solution improves UF and possibly survival
- Locally / systemically active supplements to PD fluids are a promising approach
- Large consortia and networks reach out for the high hanging fruits, you are welcome to join!

Thank you for you attention and cooperation!

HEIDELBERG
UNIVERSITY
HOSPITAL

Eszter Levai, Conghui Zhang, *Hanna Jenei*,
Maria Bartosova, Claus P. Schmitt, *Betti Schaefer*,
Sotirios G. Zarogiannis, Ivan Damgov, Iva Marinovic

Funding

- Improve PD – Horizon 2020, MC-ITN
- European Nephrology Dialysis Institute (ENDI)
- Alexander von Humboldt-Foundation
- German Research Foundation, SFB 1118/2
- German Research Foundation (Postdoc funding)
- Industrial support (Fresenius)

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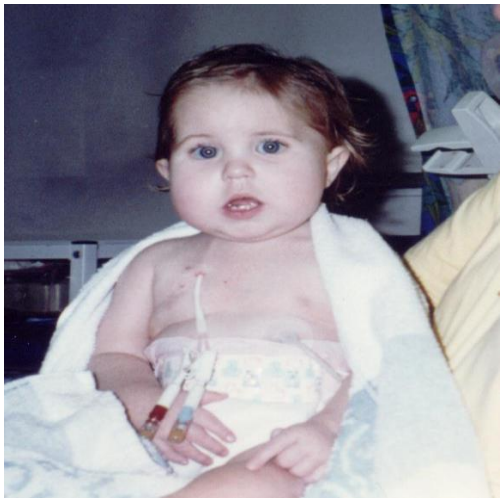
Claus Schmitt	clauspeter.schmitt@med.uni-heidelberg.de

The right access for the right patient at the right time

Rukshana Shroff

NHS
Great Ormond Street Hospital for Children
NHS Foundation Trust



Outline

– central venous lines (CVLs) vs arteriovenous fistulae (AVFs) vs arteriovenous grafts (AVGs) Pros and cons

Principle:

Vascular access preservation

Guidelines for pediatric vascular access

Nephrol Dial Transplant (2019) 1–20
doi: 10.1093/ndt/gfz011

ndt
Nephrology Dialysis Transplantation

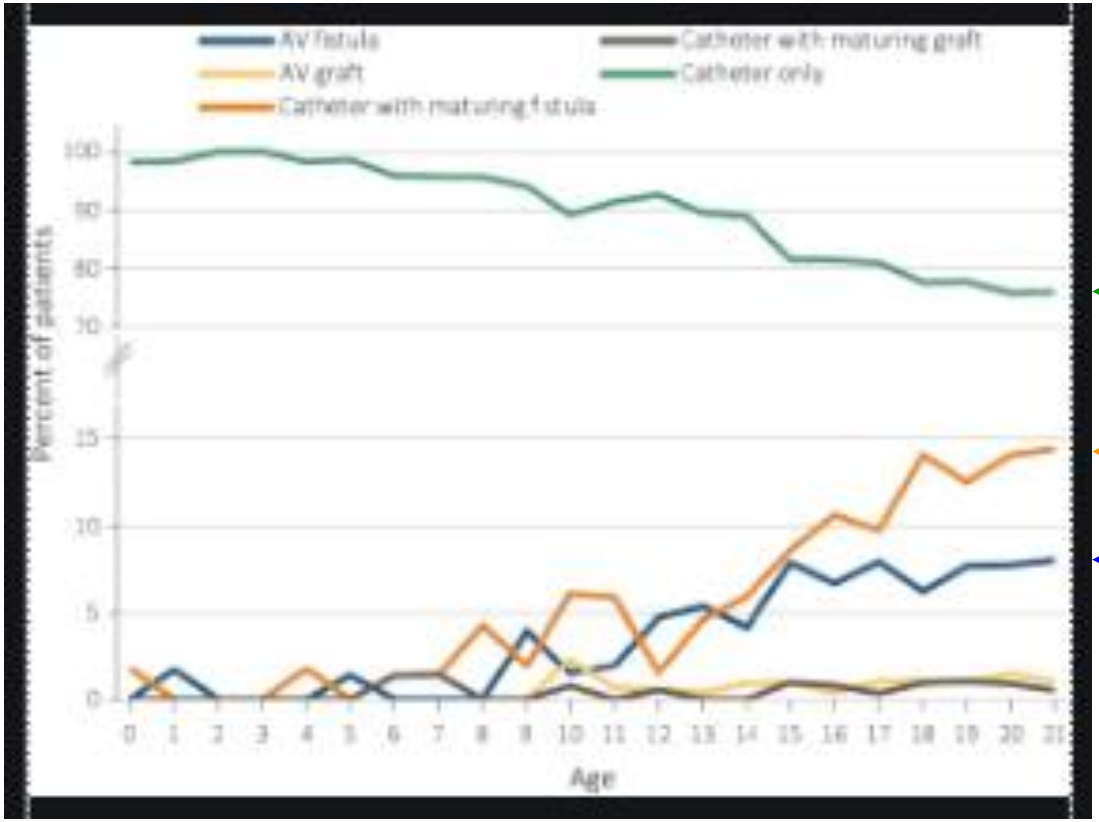
Vascular access in children requiring maintenance haemodialysis: a consensus document by the European Society for Paediatric Nephrology Dialysis Working Group

Rukshana Shroff[1], Francis Calder[1], Sevcan Bakkaloğlu[2], Evi V. Nagler[3], Sam Stuart[1], Lynsey Stronach[1], Claus P. Schmitt[4], Karl H. Heckert[4], Pierre Bourquelot[5], Ann-Marie Wagner[1], Fabio Paglialonga[6], Sandip Mitra[7] and Constantinos J. Stefanidis[8] on behalf of the European Society for Paediatric Nephrology Dialysis Working Group

european society for paediatric nephrology

International Pediatric Fistula First initiative – a call to action

AJKD 2008



CVLs

AVGs

AVFs

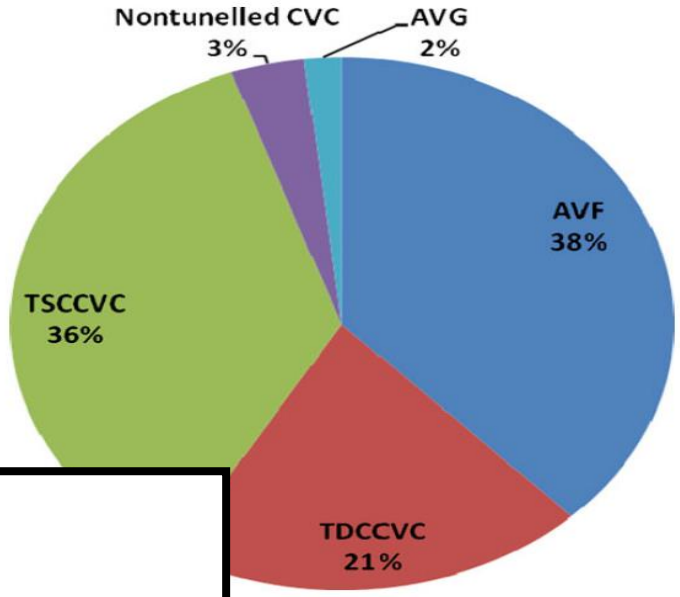
NAPRTCS

Pediatr Nephrol (2012) 27:999–1004
DOI 10.1007/s00467-011-2079-3

ORIGINAL ARTICLE

Vascular access: choice and complications in European paediatric haemodialysis units

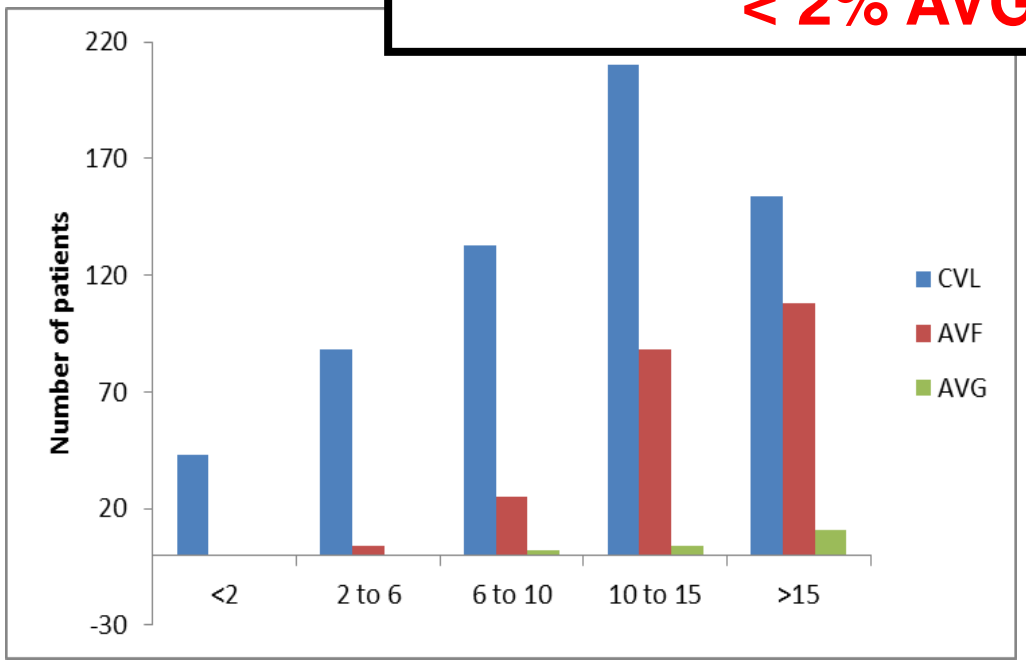
Wesley N. Hayes · Alan R. Watson · Nichola Callaghan · Elizabeth Wright · Constantinos J. Stefanidis · On behalf of the European Pediatric Dialysis Working Group



cular access. *AVF* arteriovenous fistula, *AVG* C central venous catheter, *TSC CVC* tunneled *CVC* tunnelled double-cuff CVC

In Europe
~ 60% CVCs
~ 38% AVFs
< 2% AVGs

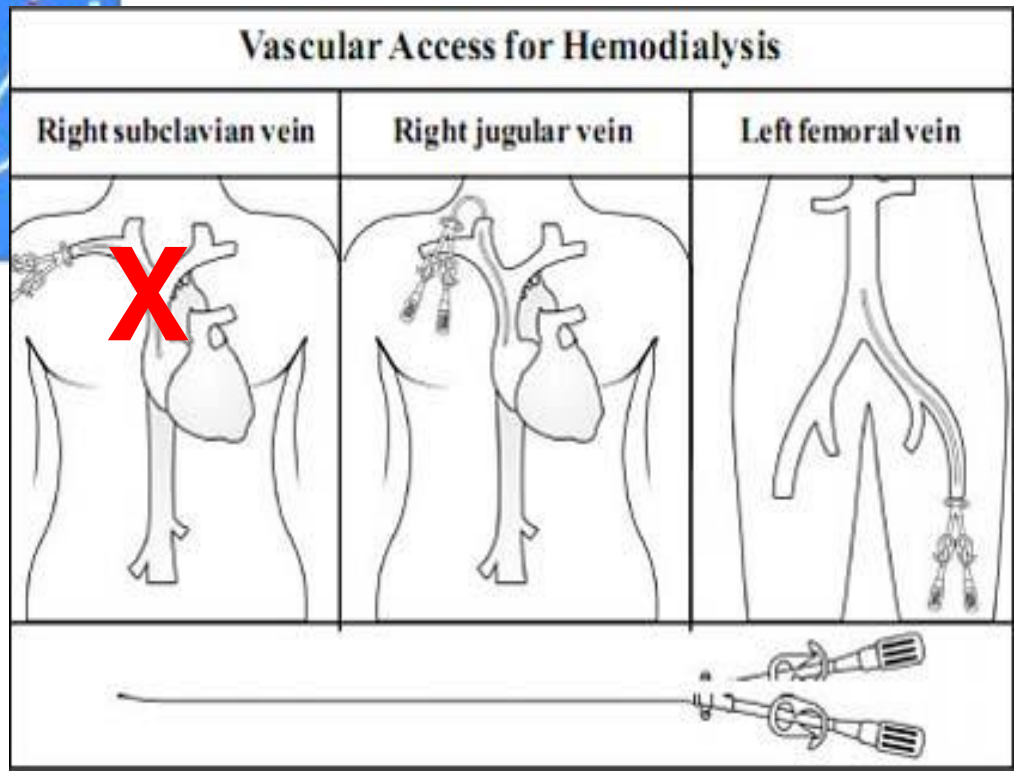
International Pedi



552 chronic HD/HDF patients
- 55 pediatric dialysis units in 27 countries
- 5 year data

Borzych-Duzalka et al; AJKD 2019

Central venous lines (CVLs)

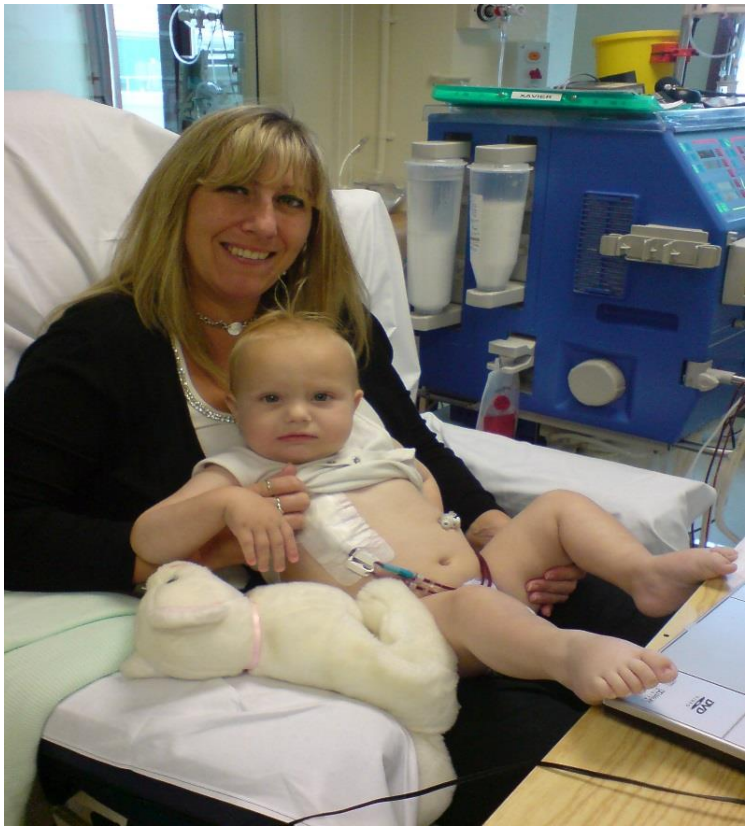


Avoid subclavian line placement – high risk of subclavian stenosis

CVLs – the risks

Increased risk with CVL of:

- Infection
- Poor dialysis adequacy
- Hospitalisations
- Thrombosis
- Death



Type of vascular access and survival among incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study.
J Am Soc Nephrol 2005; 16:1449-1455

Pediatr Nephrol (2013) 28:321–326
DOI 10.1007/s00467-012-2318-2

ORIGINAL ARTICLE

A comparison of arteriovenous fistulas and central venous lines for long-term chronic haemodialysis

Alison Ma · Rukshana Shroff · Daljit Hothi · Marina Munoz Lopez · Faidra Veligratli · Francis Calder · Lesley Rees

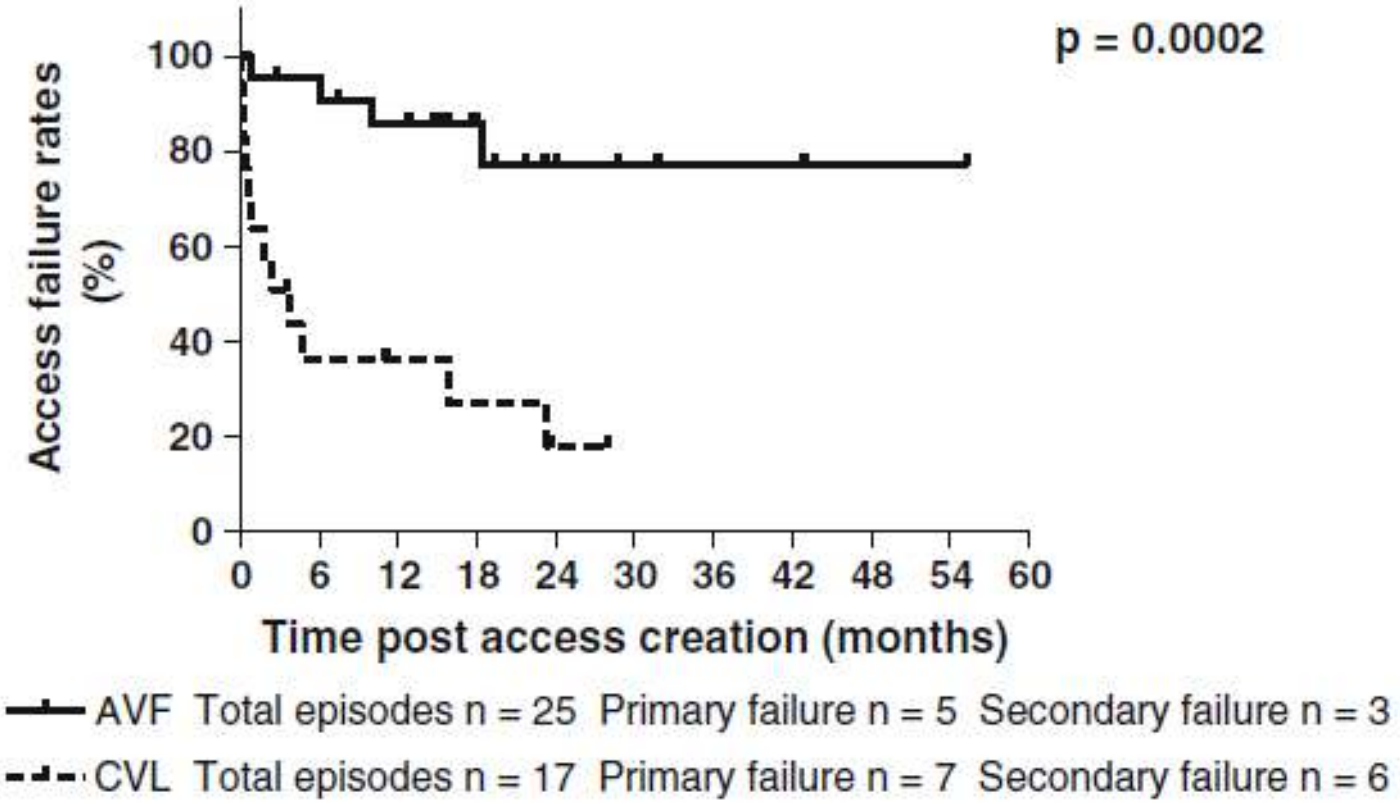


Fig. 1 Kaplan–Meier analysis of access survival in children on chronic haemodialysis (arteriovenous fistulas (AVF) versus central venous lines (CVL))

Clinical Course Associated with Vascular Access Type in a National Cohort of Adolescents Who Receive Hemodialysis: Findings from the Clinical Performance Measures and US Renal Data System Projects

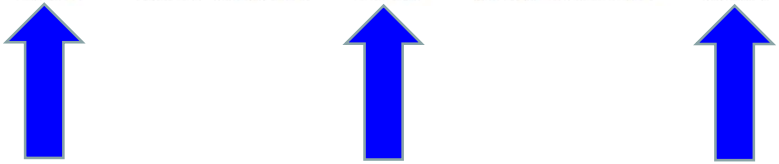
Clin J Am Soc Nephrol 1: 987–992, 2006.

Jeffrey J. Fadrowski,* Wenke Hwang,† Diane L. Frankenfield,‡ Barbara A. Fivush,* Alicia M. Neu,* and Susan L. Furth*§

Characteristic	Total Population (n = 418)	Stratified Population	
		Catheter (n = 175)	Permanent Access (n = 243)
Mean age (yr [SD])	15.6 (1.6)	15.4 (1.6)	15.7 (1.5)

Table 3. RR (catheter *versus* permanent access) of dialysis outcomes in adolescent patients who received hemodialysis[a]

Parameter	Hospitalization, All-Cause		Hospitalization, Infection-Related		Access Complication	
	RR[b]	95% CI	RR	95% CI	RR	95% CI
Vascular catheter *versus* permanent access	1.84[d]	1.38 to 2.44	4.74[d]	2.02 to 11.14	2.72[d]	2.00 to 3.69

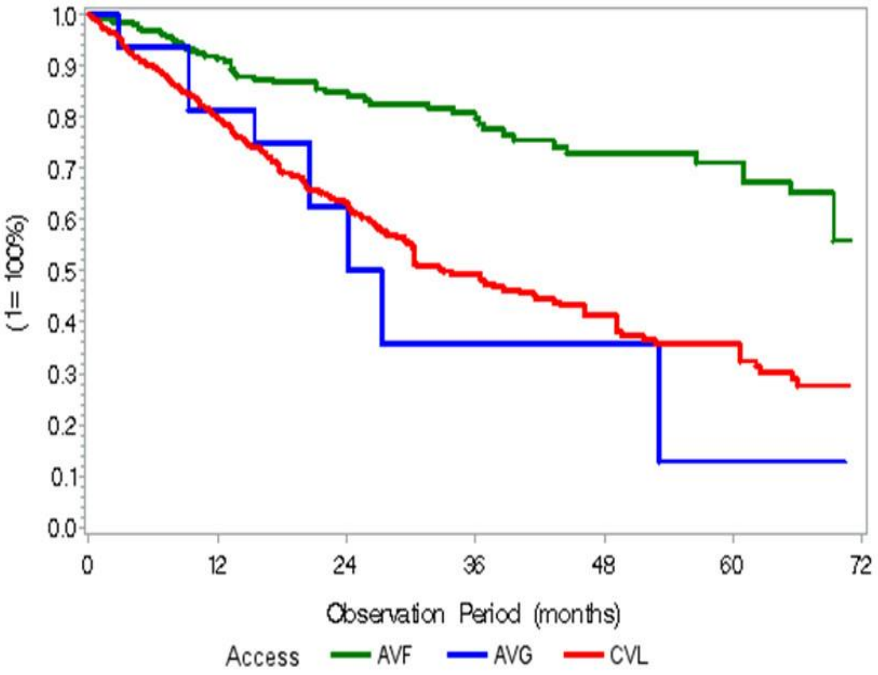


Access patency rates

International Pediatric Hemodialysis Network (n = 870)

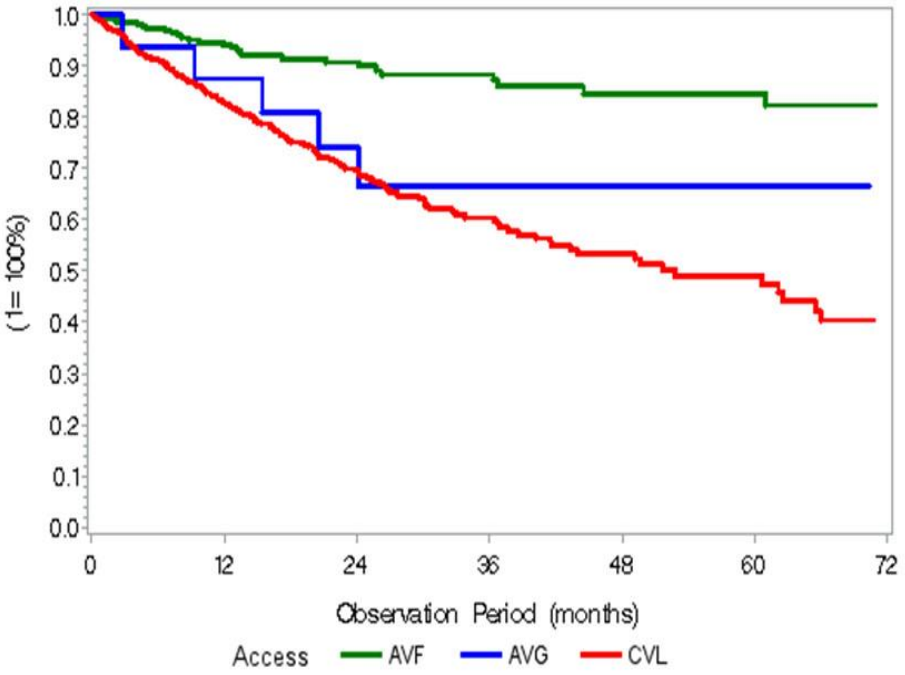
Primary patency

P<0.001 AVF vs. others



Event free survival probability until first intervention or surgical revision

Secondary patency



Event free survival probability until access exchange (to CVL, AVF or AVG)

Borzych-Duazalka D et al, Am J Kidney Dis 2019

Access survival – CVLs < AVG < AVFs

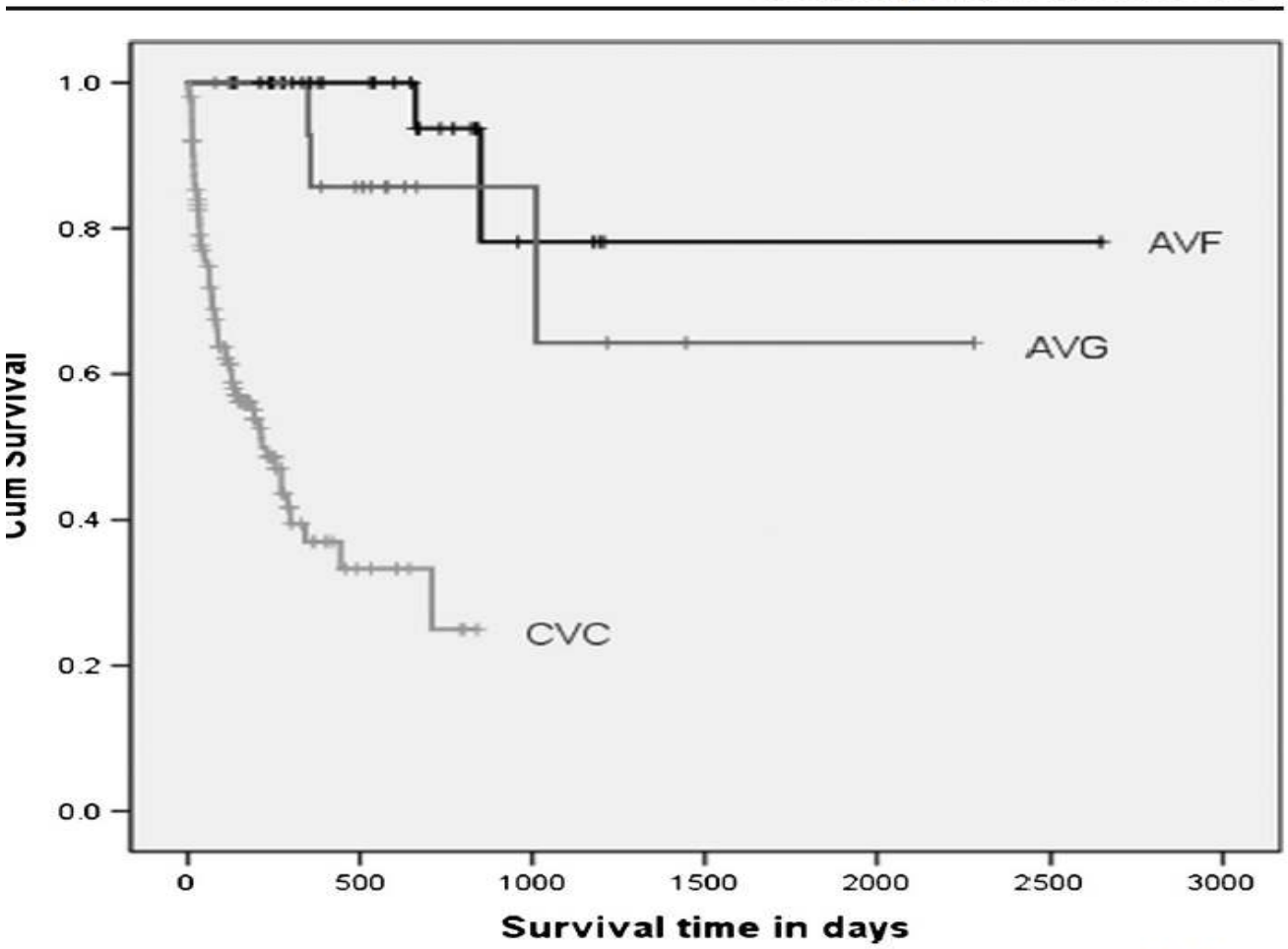
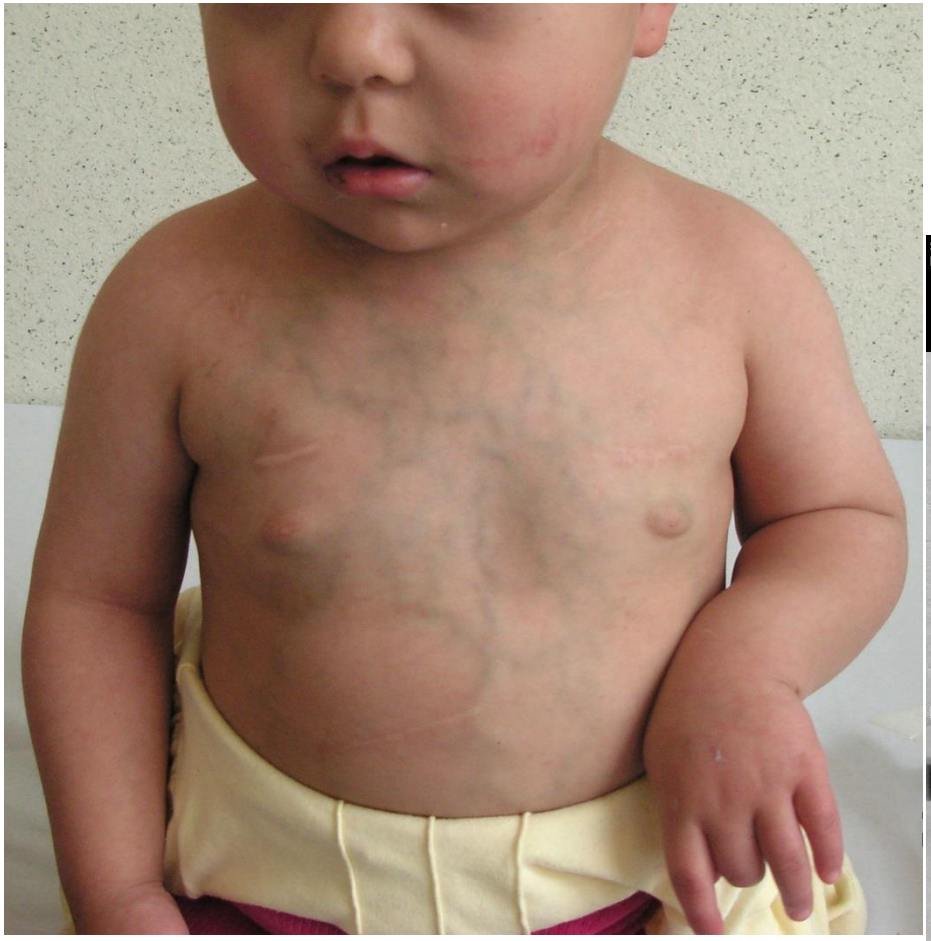
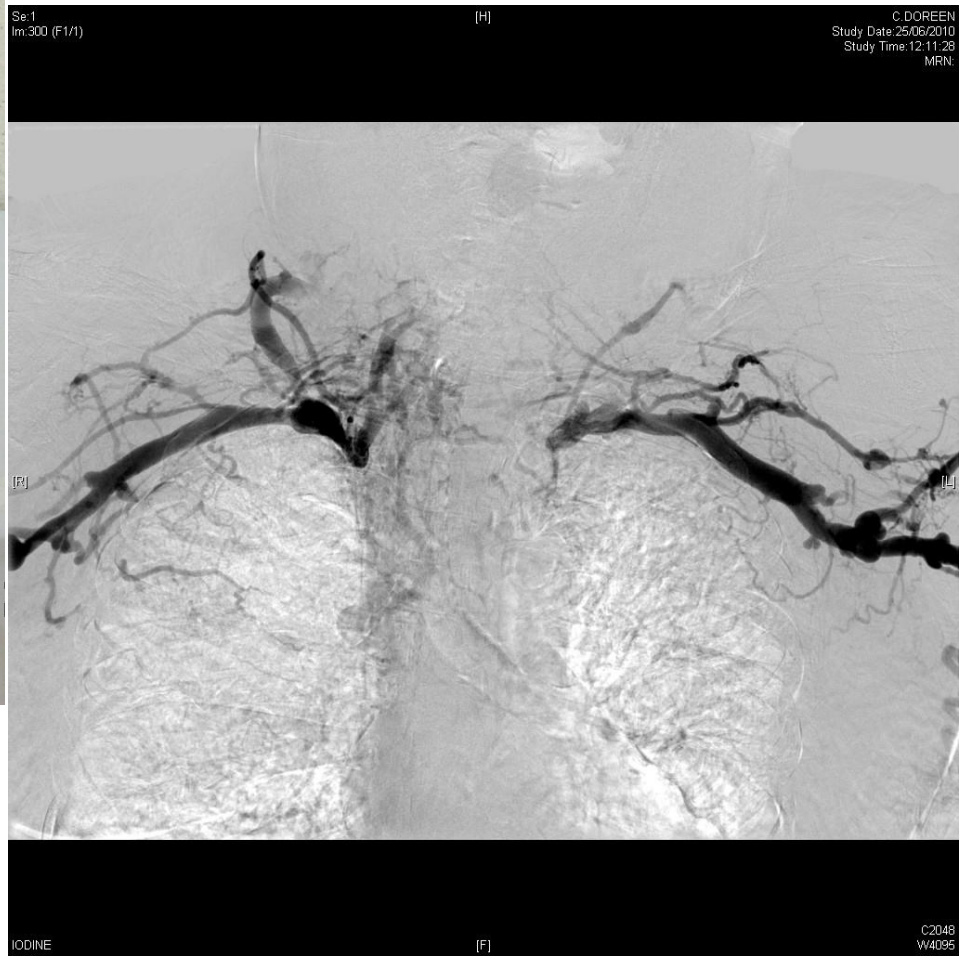


Fig. 2 Cumulative (*Cum*) Survival of arteriovenous fistula (AVF) vs. arteriovenous graft (AVG) and central venous catheter (*CVC*). $p<0.001$

Central Veins





Pros and cons of CVLs

Pros	Cons
Easily placed	Infection rates high
Can be used immediately	Failure rates and replacement rates high
Painless to the patient	Blood flow rates are variable, leading to potentially poor clearance
Requires little planning prior to placement	Permanent damage to central venous system (stenosis/ thrombosis) may occur
Easily removed if used as "transitional" access for future PD or transplant patients	Damage to central vessels can prohibit future AVF/AVG placement in ipsilateral extremity
No vascular steal	Possible Arrhythmia
Decreased risk of high-output cardiac failure	

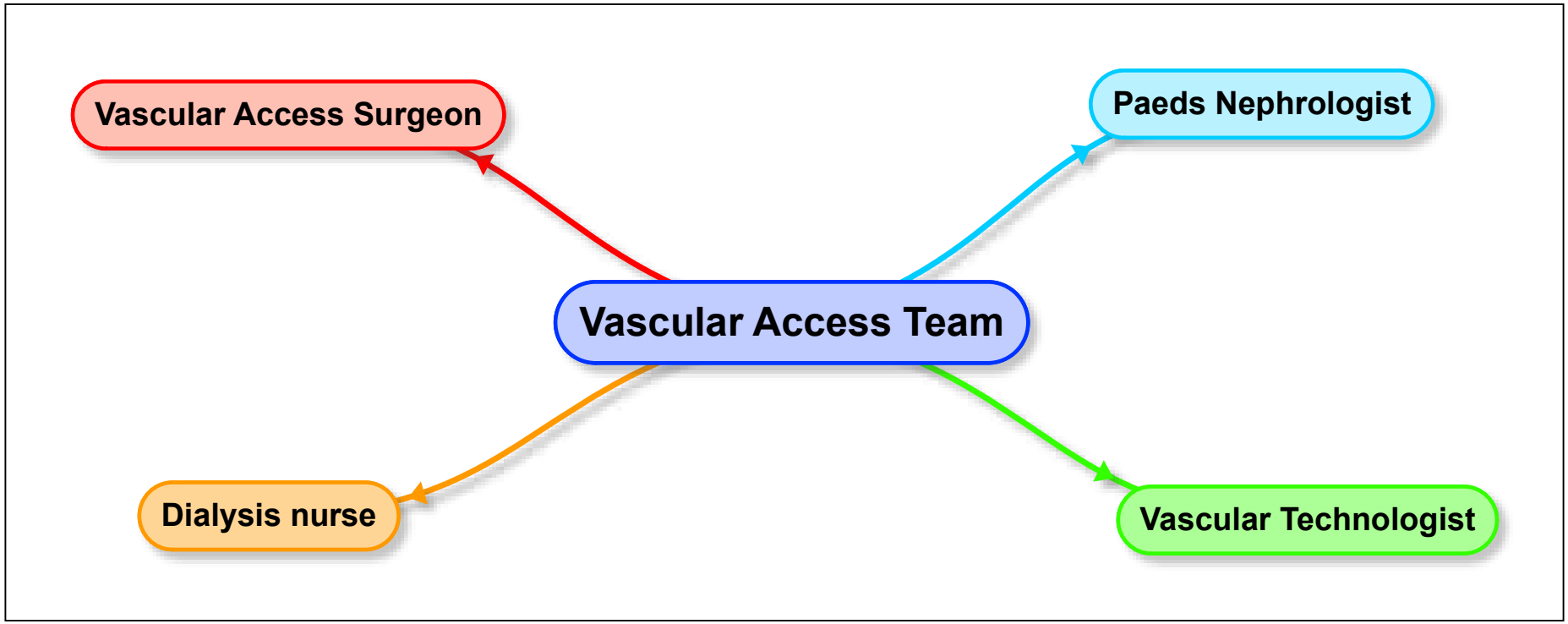
Pediatr Nephrol (2009) 24:1121–1128
DOI 10.1007/s00467-008-0812-3

EDUCATIONAL REVIEW

Hemodialysis vascular access options in pediatrics: considerations for patients and practitioners

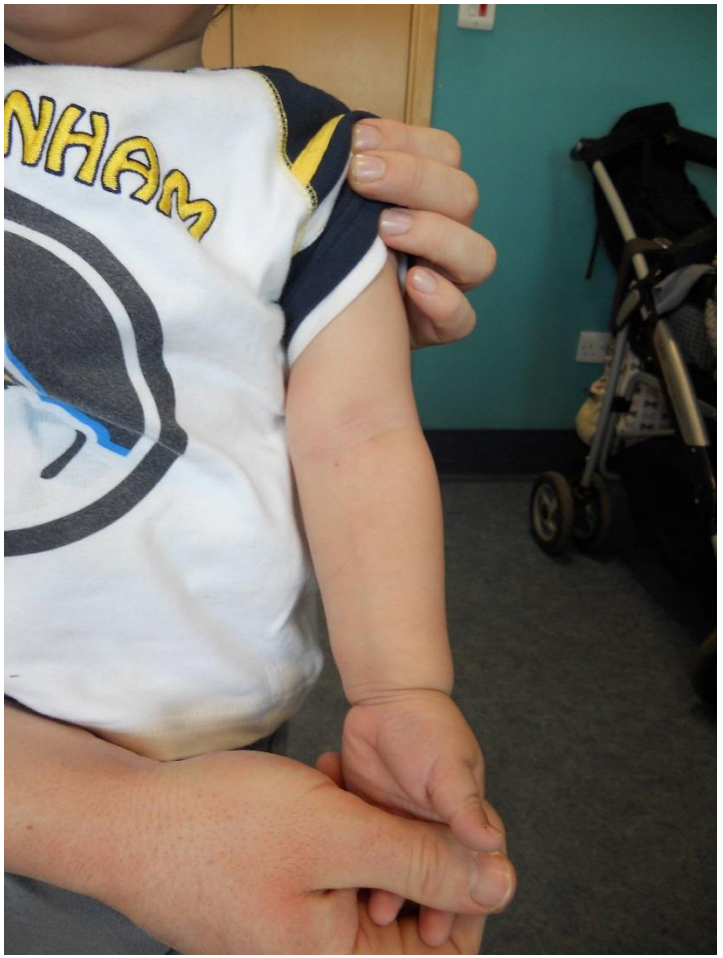
Deepa H. Chand · Rudolph P. Valentini · Elaine S. Kamil

‘One – Stop’ Vascular Access Clinic



Vascular Access Strategy

- See the patient early
- Vein preservation
- Non-dominant before dominant
- Distal before proximal
- Native before Graft
- Avoid CVLs

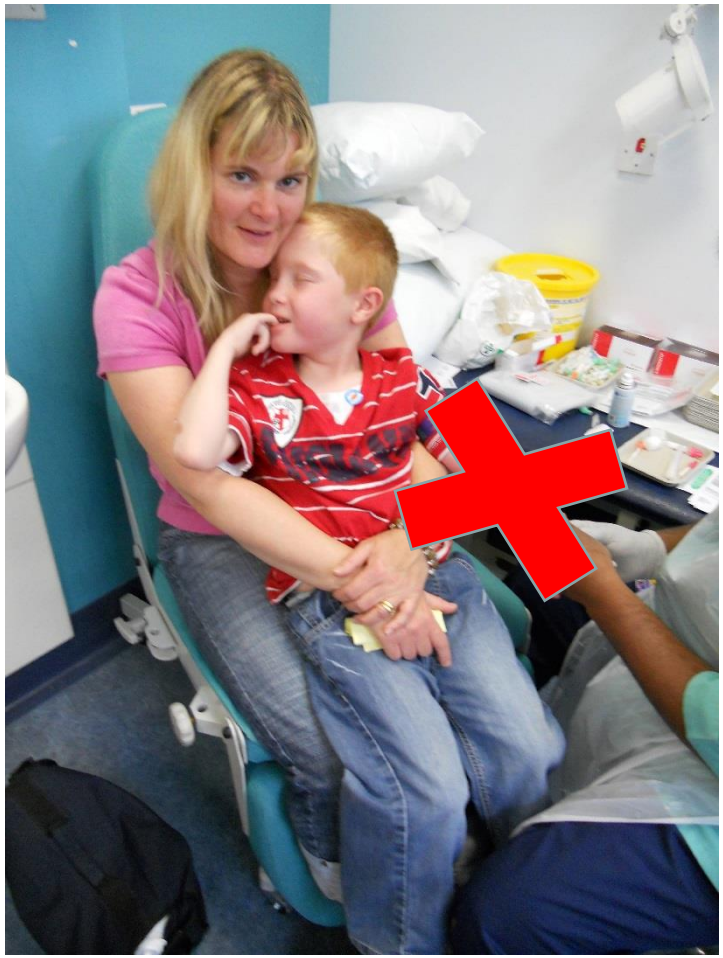


See the patient early

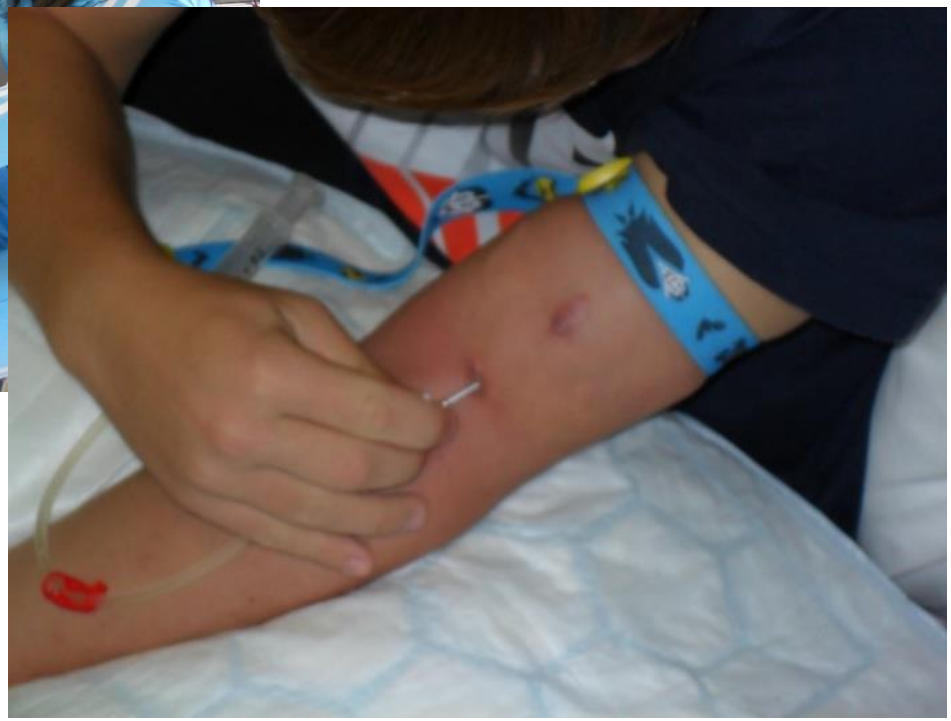
- eGFR < 30ml/min
  - No age / weight limit

Aim:

- Discuss dialysis types and access options
- Vein preservation
- Psychological preparation



Non-dominant limb



Venous Assessment - clinical

- **Peripheral veins**
  - Size
  - Dilation
  - Continuity
  - Length
  - Straightness
  - Depth

Assess with / without tourniquet

- **Central veins**

Venous Assessment - ultrasound

Ultrasonic Angiology Department

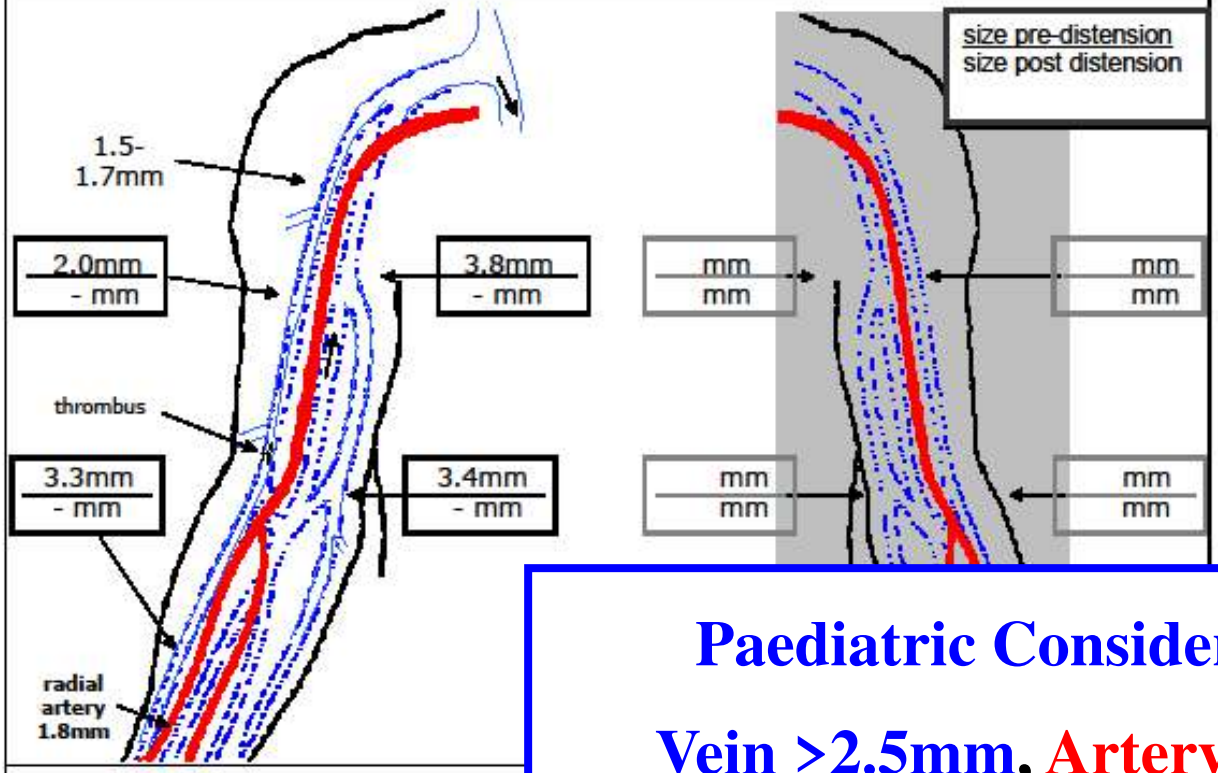
Patient Name:
Hospital Number: DOB:
Address:

Hospital: GOSH
Consultant:

Ultrasonic Angiology Department
2nd Floor, Borough Wing,
Guy's Hospital, London SE1 9RT
Tel/Fax: 0207 188 6778/6771
Head of Dept: Dr. TS Padayachee

V5

RENAL ONE STOP CLINIC Scan Date: 02.06.2015



Conclusion:

RIGHT ARM

Paediatric Considerations

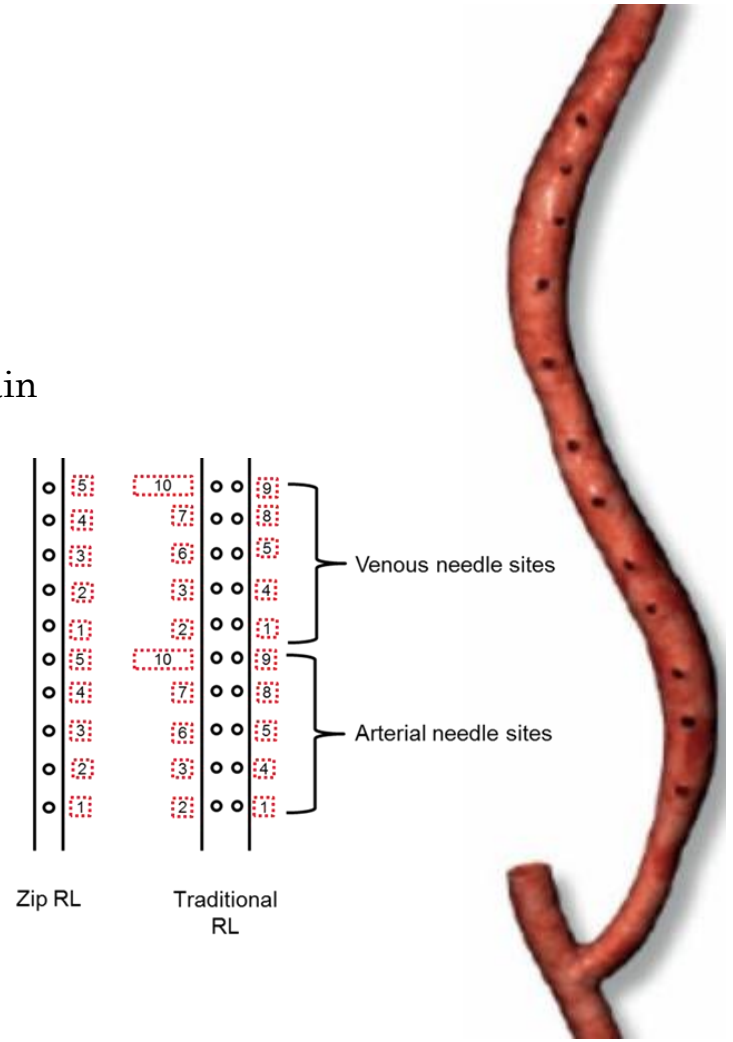
Vein >2.5mm, Artery >1.5mm

Looking after your AVF - Cannulation Technique

- Preservation of function
- Patient/Parental Confidence
- Prevention:
  - Aneurysm
  - Infiltration - “Blow”
  - Stenosis
  - Haemorrhage
  - Thrombosis
  - Reduced Infection

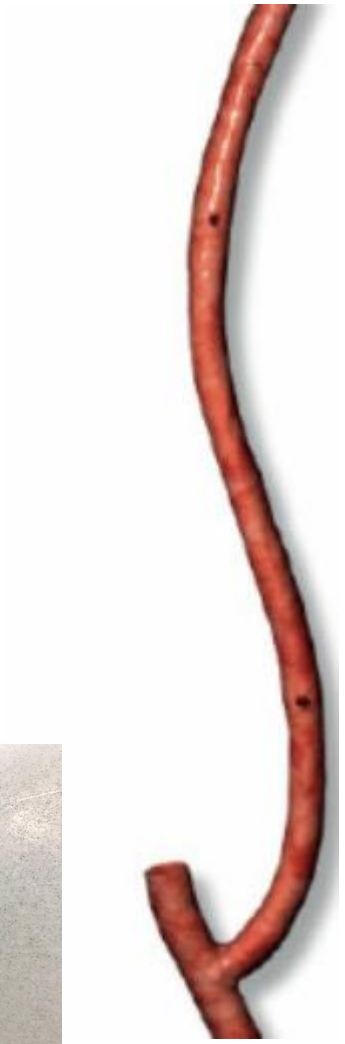
Ladder Technique

- Technique:
  - Over at least 8cm segment
  - Each site 0.5-1cm above previous
  - Sharp needles
  - Zip / Central
  - Traditional / Side to side
  - Move up the vein
  - Once reach the top, move to the bottom again
- Benefits:
  - Decreased risk of aneurysm formation
  - Less risk of stenosis
  - Lower infection risk
- Disadvantage
  - Harder needle insertion
  - Increased risk of infiltration
  - Requires patient and staff confidence
  - Still requires planning



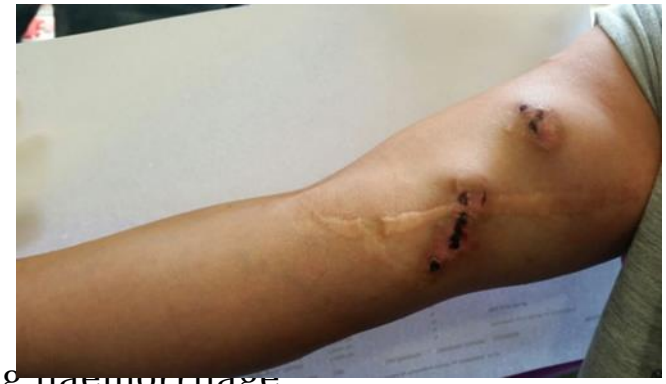
Buttonhole

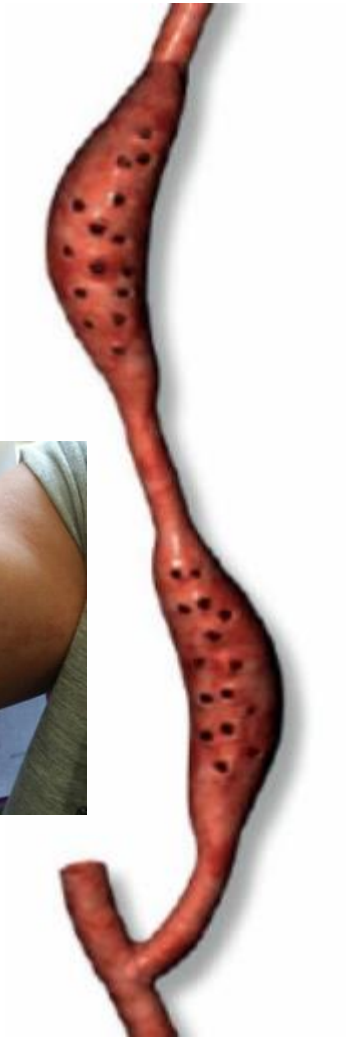
- Technique:
  - Same hole in the skin, same place in the vein
  - Picking scabs
  - Start with sharp needles
  - Same person needling to establish a track
  - Blunt needles once track has been established
  - 3 – 4 buttonholes
- Benefits:
  - Less pain with needle insertion
  - Reduced bleeding time post needle removal
  - Less missed cannulations
  - Reduced infiltrations
  - Decreased risk of aneurysm formation
  - Promotes self cannulation
- Disadvantage
  - Scab picking!
  - Increased infection risk
  - Easy to mistake for area puncture



Area Puncture

- Technique:
  - Single cannulation site in one small area
  - Both cannulation sites on the same segment but do not meet
  - Sharp needles
- Benefits:
  - Patient choice – needle phobia
  - Small AVF – space
  - Reduced infiltrations
- Disadvantage
  - Aneurysms
  - Bleeding
  - Stenosis
  - Increased risk of life-threatening haemorrhage
  - Body image

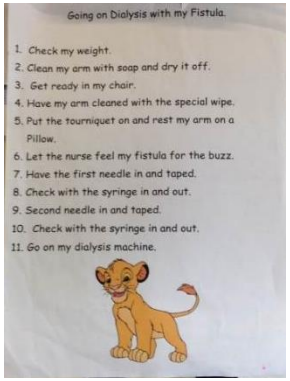




Why Encourage Self Cannulation?

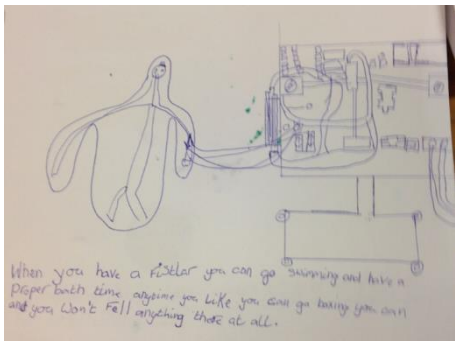
- Feeling of Control
- Less painful
- Reduce the feeling of fear and anxiety
- Longevity of the AVF
- Independence
- Home Haemodialysis

Psychological Preparation



- Play therapy
- Coping techniques
- Time
- Adhering to coping strategies/routine
- Experience – cannulation technique
- Trust

th



First cannulation

Pediatr Nephrol
DOI 10.1007/s00467-016-3382-9

ORIGINAL ARTICLE

Timing of first arteriovenous fistula cannulation in children on hemodialysis

Veronika Almási-Sperling[1] · Matthias Galiano[2] · Werner Lang[1] · Ulrich Rother[1] ·
Published online: 25 April 2016 ınne Regus[1]

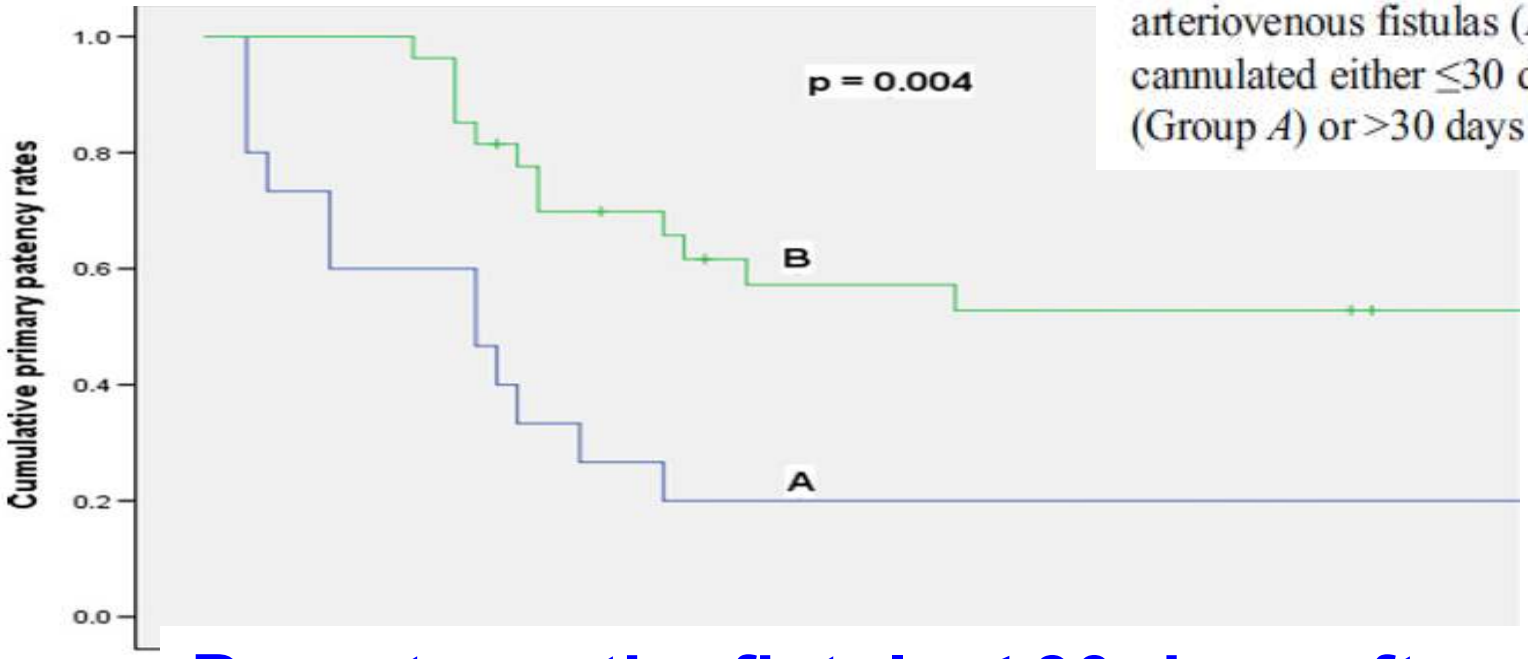


Fig. 2 Comparison of primary patency (PP) rates for arteriovenous fistulas (AVFs) cannulated either ≤30 days (Group *A*) or >30 days (Group *B*)

Do not use the fistula ≤ 30 days after it's creation; wait until 45 days

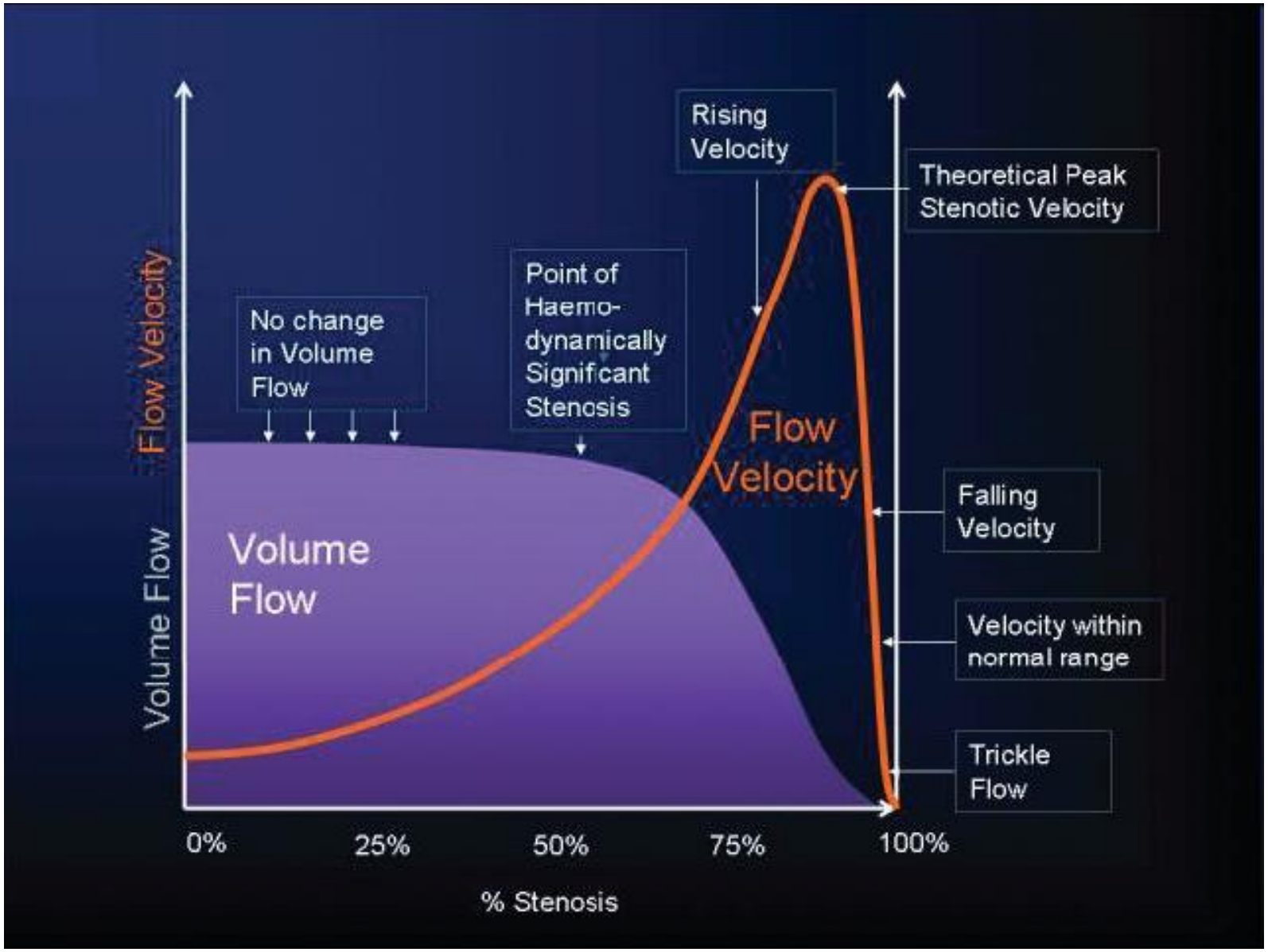
Looking after your AVF - Surveillance

- **Adequacy of dialysis**
- **Blood flow rate**
- **Clinical problems**
- **Diagnostic imaging / Dialysis parameters**
- **Examination**

Suggest 3-6 monthly surveillance

- ESPN guidelines; 2019
- ERBP guidelines; 2019

Surveillance – AVF stenosis



Surveillance – risk parameters

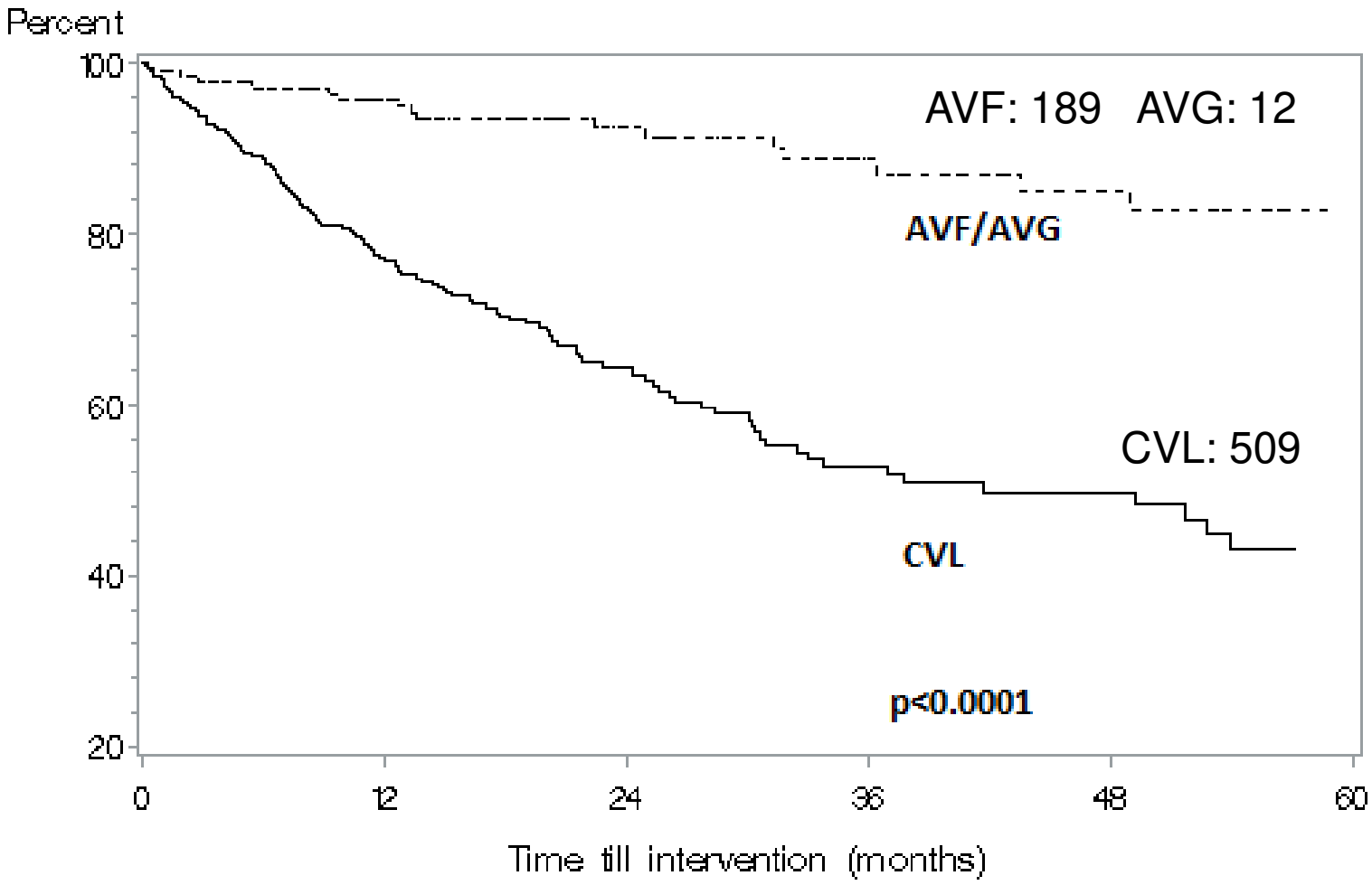
- 25% decrease in baseline volume flow

- Reduced blood flow:

<400ml/min AVF

<600ml/min AVG

Access survival – IPHN data



Borzych-Duzalka et al; AJKD 2019

Predictors of patency for AVF and AVG

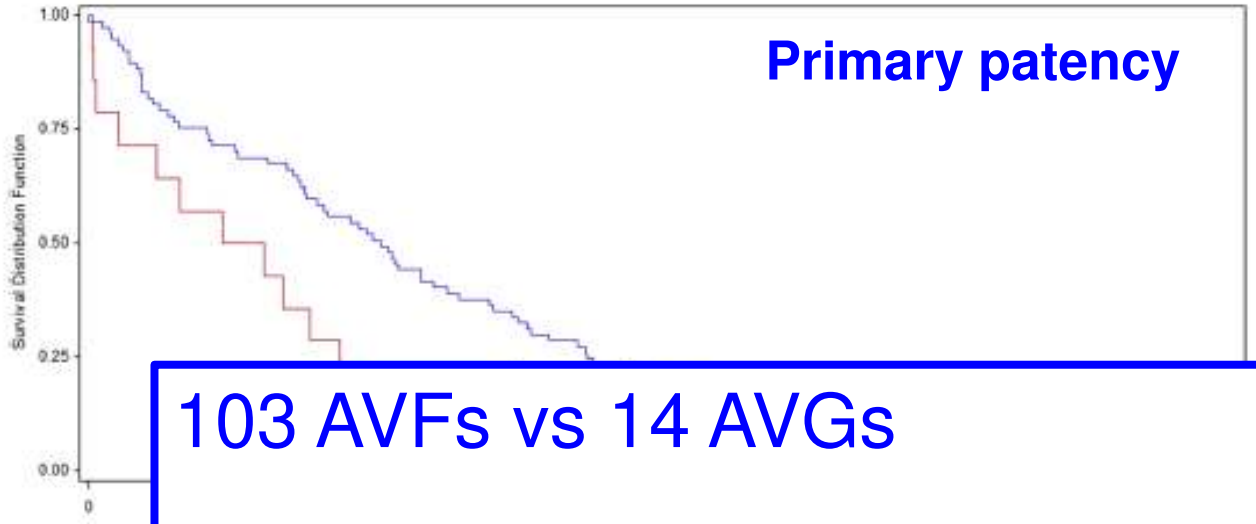


Fig. 1 Primary p
arteriovenous fis
in children on c

103 AVFs vs 14 AVGs

- AVF superior to AVGs
- Intervention-free survival was the only predictor of secondary patency

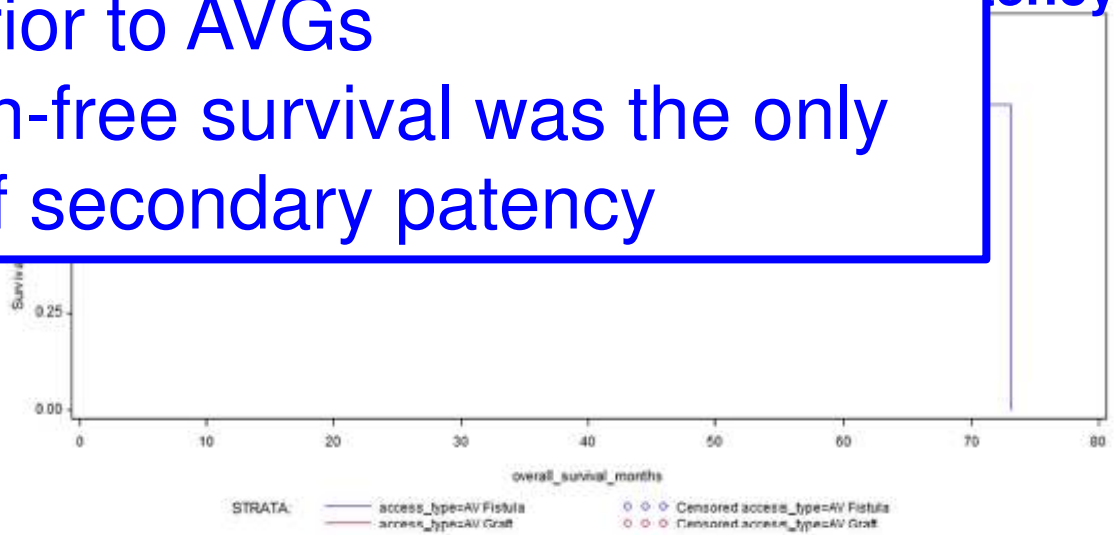
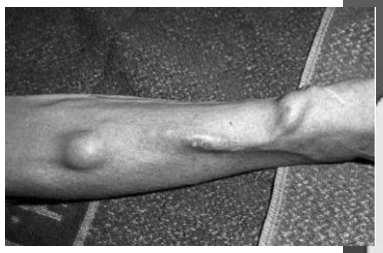


Fig. 2 Secondary patency. Kaplan-Meier analysis of secondary patency for arteriovenous fistulae (AVF) (blue) and arteriovenous graft (AVG) (red) in children on chronic hemodialysis. When censored for those permanent vascular access (PVA) that were functional at the end of study (circles), AVF ($N = 88$) demonstrated superior secondary patency rates than AVG ($N = 13$) ($p = 0.0227$, Wilcoxon rank test). Secondary patency outcome is defined in months

Onder et al;
Ped Nephrol 2019

Causes of AVF loss



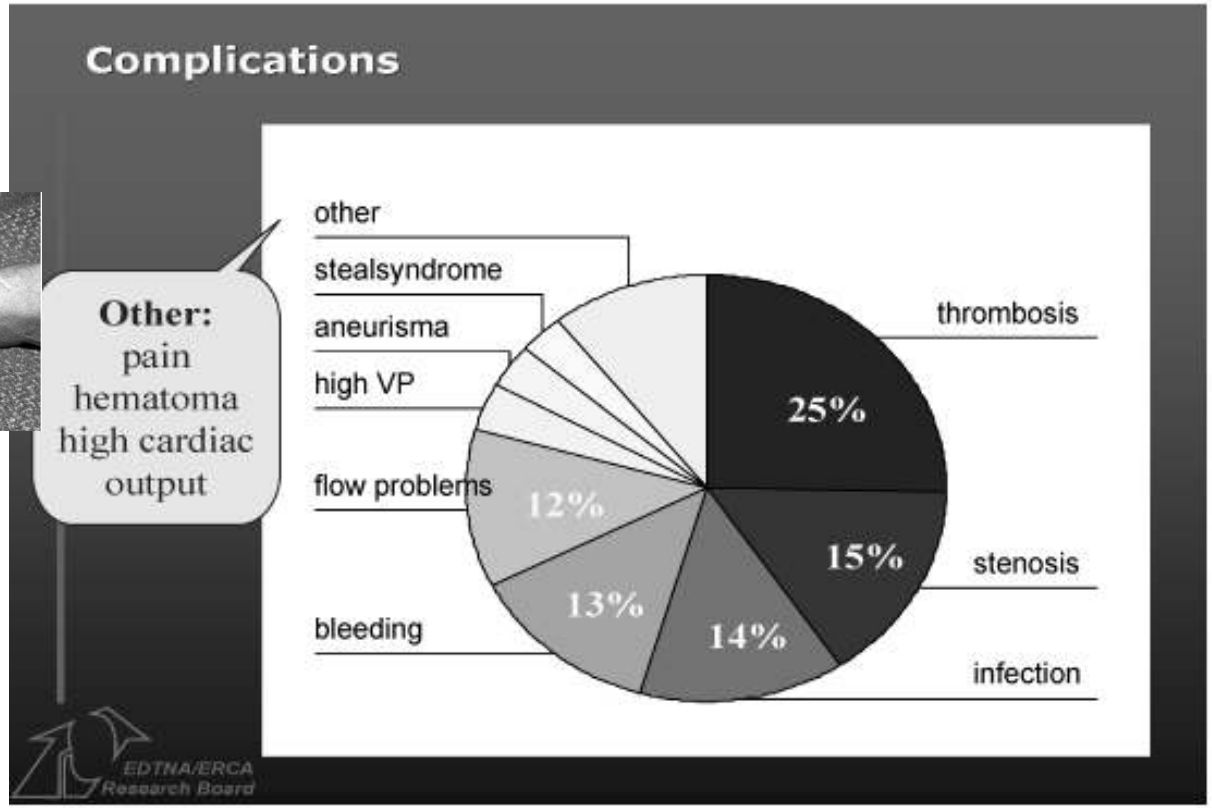
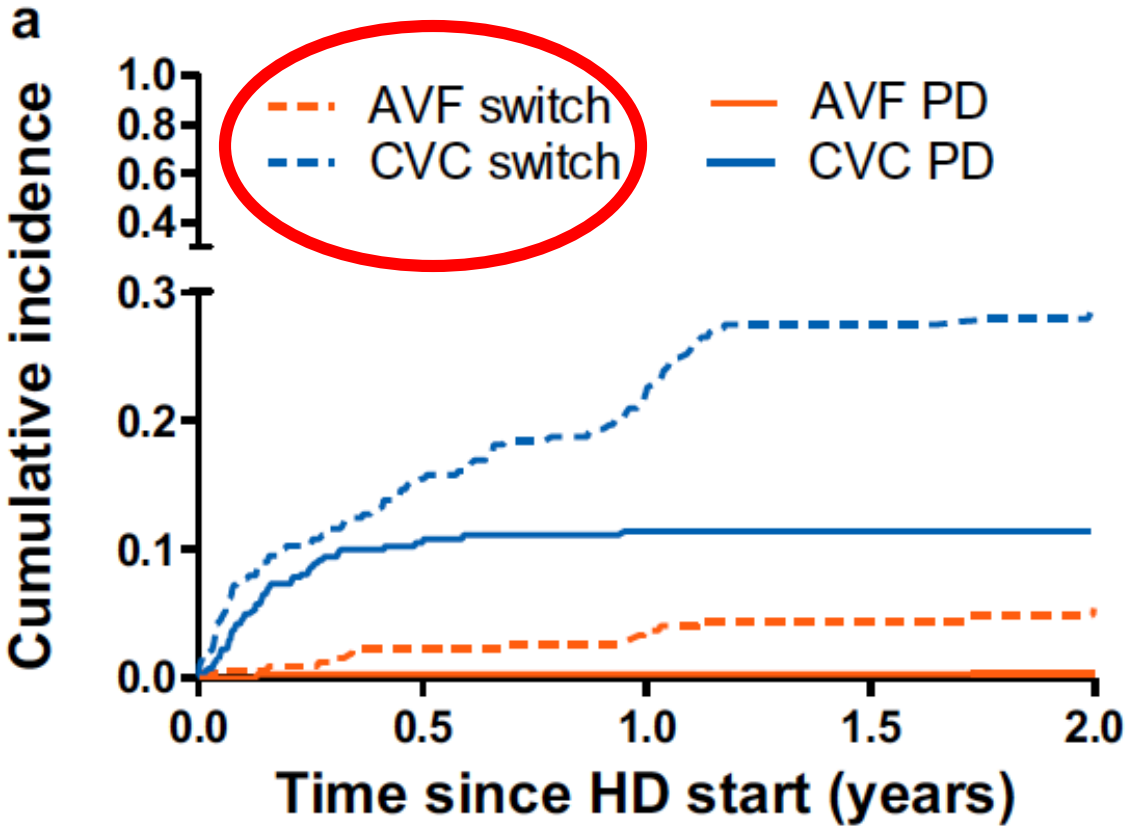


Figure 3: Overview of VA complications in a European population


Upper arrow indicates the radial artery. Stenosis found between the two lower arrows.

McCann M., Einarsdottir H., Van Waeleghem J.P., Murphy F., Sedgewick J. (2009).Vascular access management II: AVF/AVG cannulation techniques and complications. *Journal of Renal Care* **35**(2), 90–98.

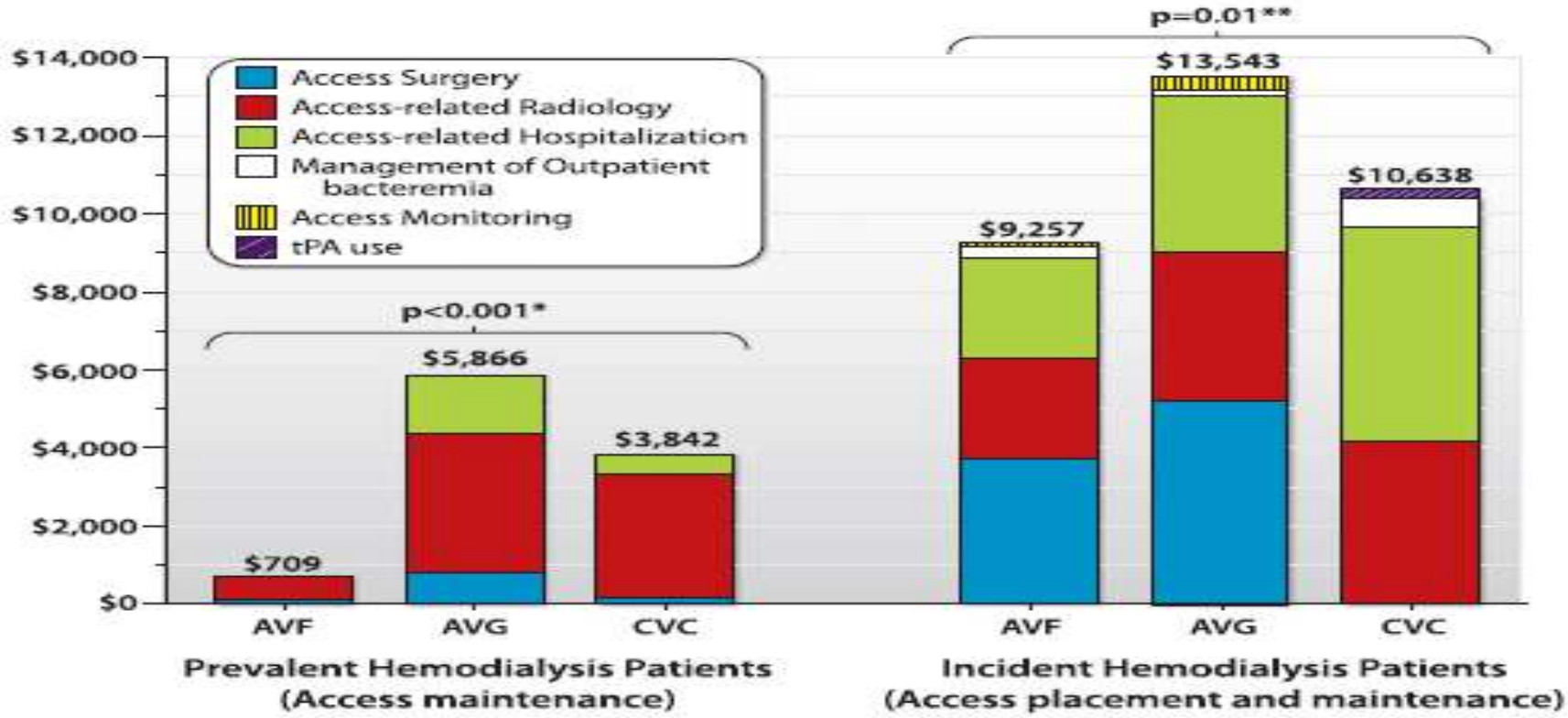
Vascular access changes



Patients who started with an AVF were 91% less likely to switch to a second VA as compared to those who started with a CVC
(adjusted hazard ratio (aHR), 0.09; 95% CI, 0.05–0.16)

ESPN/ERA-EDTA Registry; Ped Nephrol 2019

$$$$$?



All costs reported in 2009 Canadian dollars (1 CAD = 0.82 USD)
Abbreviations: tPA=tissue Plasminogen Activator, AVF=Arteriovenous Fistula, AVG=Arteriovenous graft, CVC=Central Venous Catheter
* Comparison of costs using Kruskal-Wallis test
** Comparison of log transformed costs using one-way ANOVA

Controversies and Concerns in Hemodialysis
Series Editor: Marcello Tonelli

What's Next After *Fistula First*: Is an Arteriovenous Graft or Central Venous Catheter Preferable When an Arteriovenous Fistula Is Not Possible?

Matthew T. James,*† Braden J. Manns,*†‡ Brenda R. Hemmelgarn,*† and Pietro Ravani*† for the Alberta Kidney Disease Network

Seminars in Dialysis—Vol 22, No 5
2009 pp. 539–544

Pros and cons for vascular access types

AVFs

Pros

- Allows for high blood flow rates
  => efficient dialysis delivery
- Superior access patency rates
- Best long-term survival
- Lowest hospitalization rates
- Higher Hb, lower EPO requirement
- Patients can bathe and swim without restrictions

Cons

- Not possible in small(er) children
- Needs time to mature
- Needling pain
- cosmetic features
- (high output cardiac failure)
- (steal syndrome)

CVLs

Pros

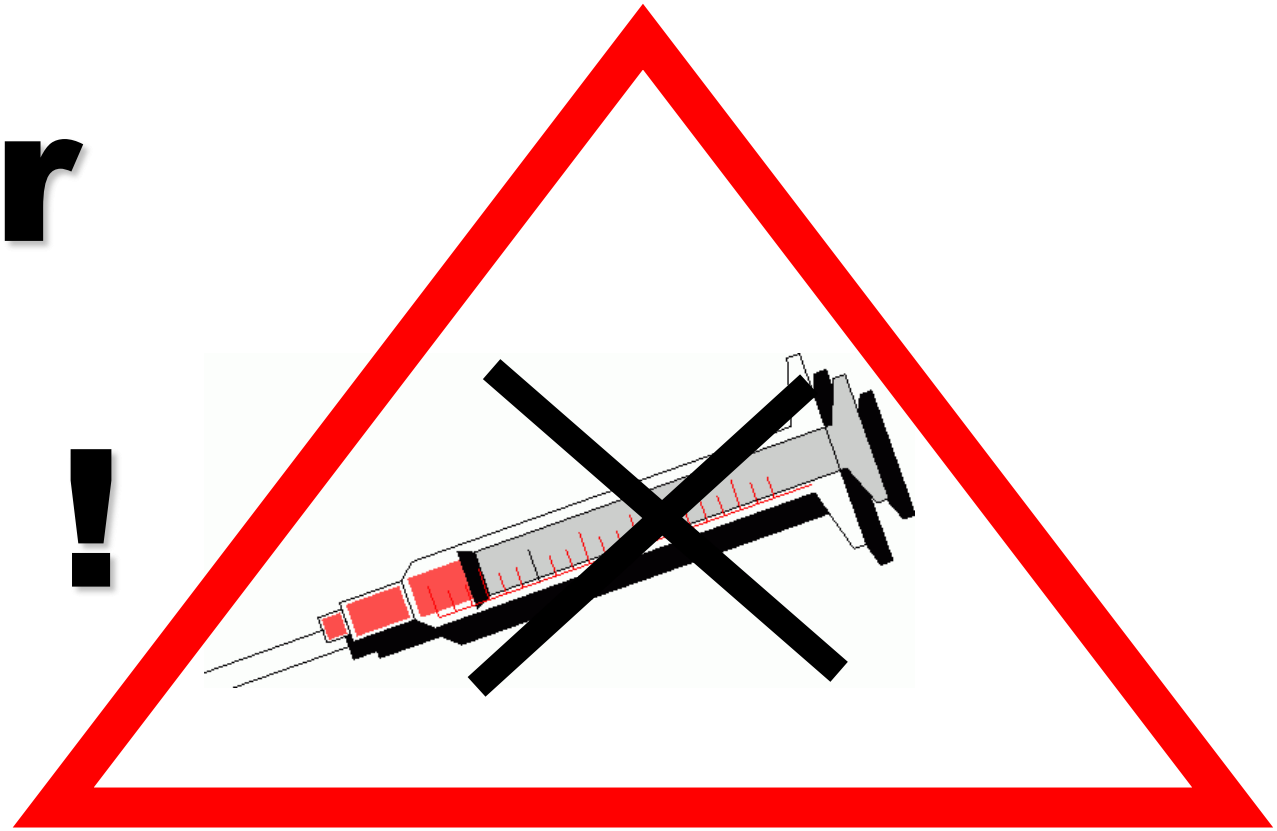
- Immediate access
- Needle-free dialysis

Cons

- High infection rate
- Inadequate blood flow (malposition, fibrin sheath formation)
- Restriction of the child‘s activities (swimming)
- Higher hospitalisation rates
- More likely to require access revision
- Central venous thrombosis or stenosis

Save Your Veins

Your Life !



No to Needling

Guidelines for paediatric vascular access

Nephrol Dial Transplant (2019) 1–20
doi: 10.1093/ndt/gfz011

ndt
Nephrology Dialysis Transplantation

Vascular access in children requiring maintenance haemodialysis: a consensus document by the European Society for Paediatric Nephrology Dialysis Working Group

Rukshana Shroff[1], Francis Calder[1], Sevcan Bakkaloğlu[2], Evi V. Nagler[3], Sam Stuart[1], Lynsey Stronach[1], Claus P. Schmitt[4], Karl H. Heckert[4], Pierre Bourquelot[5], Ann-Marie Wagner[1], Fabio Paglialonga[6], Sandip Mitra[7] and Constantinos J. Stefanidis[8] on behalf of the European Society for Paediatric Nephrology Dialysis Working Group

european society for paediatric nephrology

Table 4. Summary of recommendations

	Category	Recommendation	GRADE
1.	Planning vascular access	1.1 Educate children with CKD and their carers about venous preservation, irrespective of the choice of future renal replacement therapy, and starting from their early contact with the nephrology services.	Ungraded
		1.2 Educate children with CKD Stage 4 (eGFR <30 mL/min/1.73 m^2 by Schwartz formula), those with rapidly declining kidney function, or those who need to start maintenance dialysis imminently, about kidney failure and options for its treatment, including kidney transplantation, peritoneal dialysis, HD in the home or in-centre, and conservative treatment, where appropriate.	Ungraded
		1.3 We suggest referring children with CKD Stage 4 who are being prepared for future HD to a dedicated vascular access team.	2D
2.	Optimal vascular access in children	2.1 We suggest that children requiring chronic HD start with a functioning AVF where appropriate.	2C
		2.2 Reserve cuffed CVLs for very small children depending on vessel size and surgical expertise, those requiring urgent or unplanned HD, patient preference and where a short period on HD is anticipated before transplantation.	Ungraded
		2.3 There is insufficient evidence to provide recommendations on AVGs in children.	Ungraded
3.	Preoperative evaluation for AVF formation	3.1 We suggest performing a structured history, physical examination and duplex ultrasound of upper limb arteries and veins to plan AVF creation.	2C
		3.2 We suggest performing appropriate imaging of central veins by venography, CT angiography or non-contrast MRI in children in whom central venous stenosis is suspected, such as those with previous CVLs.	2D
		3.3 Avoid AVF creation in the ipsilateral arm of a central venous stenosis.	Ungraded
4.	Site of AVF placement	4.1 Place an AVF in the non-dominant arm where possible.	Ungraded
		4.2 We suggest placing an AVF distally in the arm.	2D
5.	Timing of creation of vascular access	5.1 We suggest creating an AVF at least 3 months before its anticipated use.	2D
6.	Assessment of AVF maturation	6.1 We suggest assessing maturation 4–6 weeks after AVF formation by clinical examination and duplex ultrasound in order to plan the timing of AVF cannulation.	2D
7.	AVF cannulation	7.1 We suggest cannulating an AVF when it has matured adequately.	2D
		7.2 Use an aseptic technique for AVF cannulation.	Ungraded
		7.3 We suggest using either rope ladder or button hole technique for AVF cannulation.	2C
8.	AVF surveillance	8.1 We suggest that a structured physical examination of AVFs is routinely performed by dialysis nurses and medical staff.	2D
		8.2 We suggest that duplex ultrasound off dialysis or haemodilution technique on dialysis of volume flow is performed 3–6 times monthly for routine surveillance of AVFs.	2D
		8.3 We suggest an urgent referral to a vascular access surgeon if AVF complications are detected on clinical or ultrasound examination.	Ungraded
9.	Prevention of AVF and CVL thrombosis	9.1 We suggest that anti-platelet agents such as aspirin, ticlopidine or clopidogrel, given in the first few months after AVF creation, reduces AVF thrombosis	2D
		9.2 We suggest that t-PA is used as a catheter locking solution to prevent catheter thrombosis.	2B
		9.3 We suggest using t-PA as a thrombolytic agent for CVL thrombosis	2D

Thank you!