Welcome to

ERKNet/ESPN Educational Webinars on
Pediatric Nephrology & Rare Kidney Diseases

WEBINAR

08/11/22

Challenges in kidney transplantation in infants

Speaker: Burkhard Tönshoff, Heidelberg, Germany

Moderator: Elena Levtchenko, Leuven, Belgium

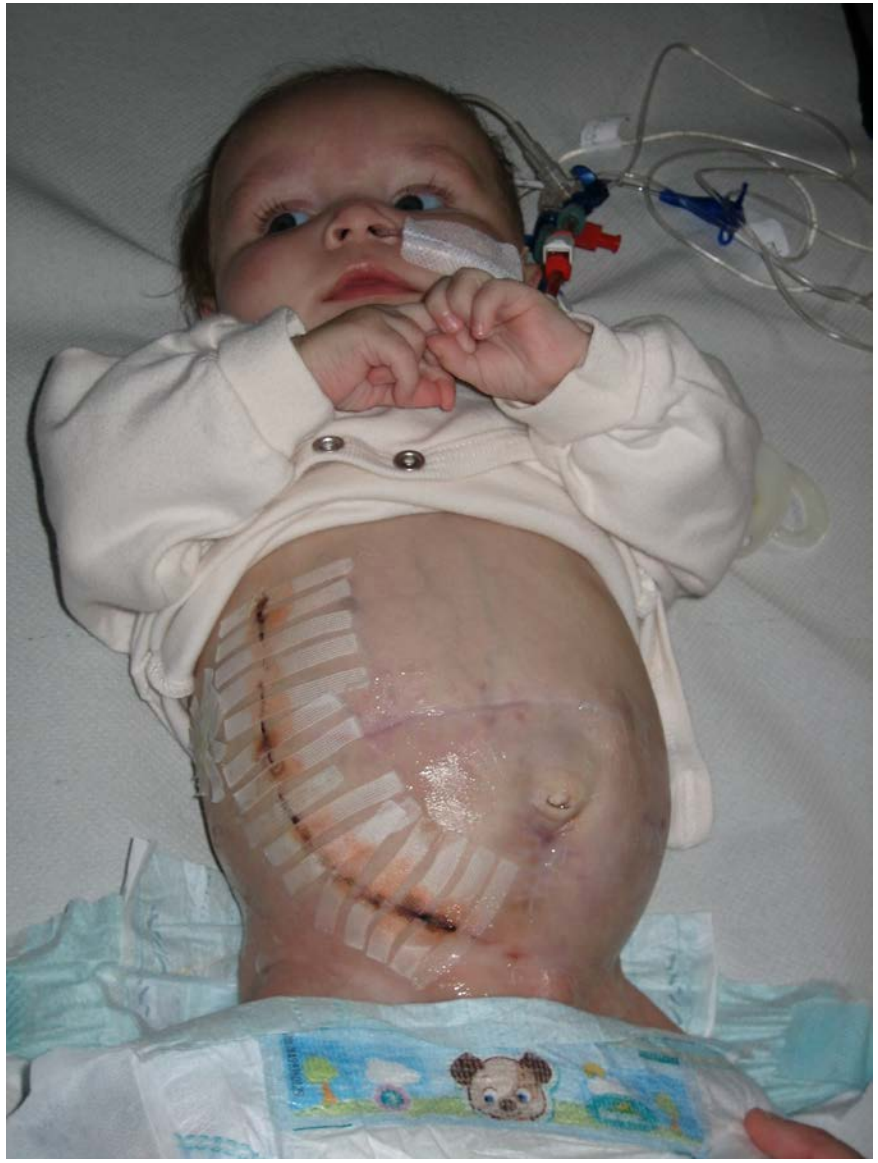
ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

ERTAIN
Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

Overview

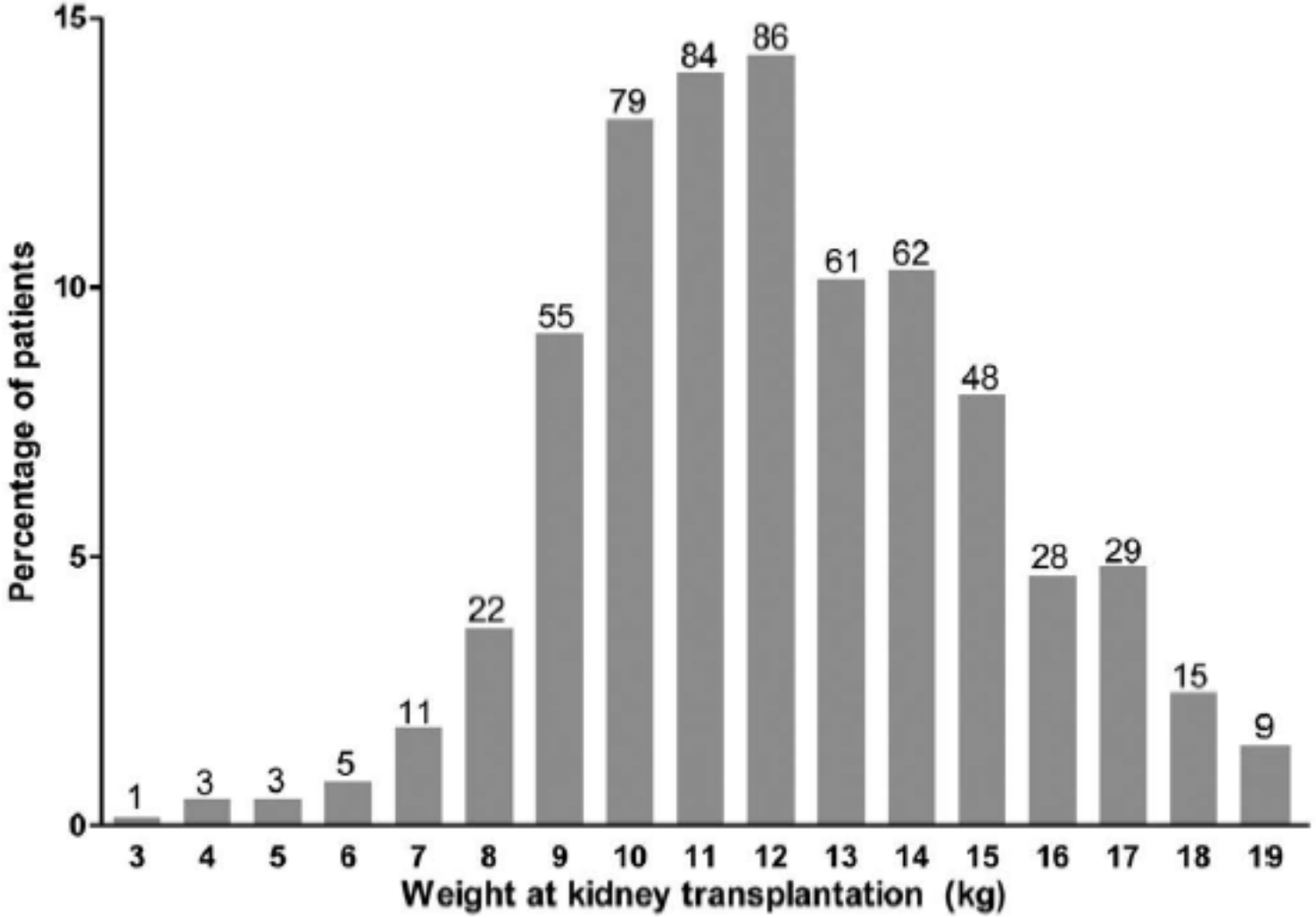
1. Overall outcome
2. Donor selection
3. Transplant surgery
4. Prevention of thrombosis
5. Fluid management
6. Immunosuppressive therapy
7. Microchimerism
8. Infectious prophylaxis
9. Specific outcome



Primary renal diseases in infants < 2 years of age requiring kidney transplantation
(2 – 5 % of paediatric KTx recipients)

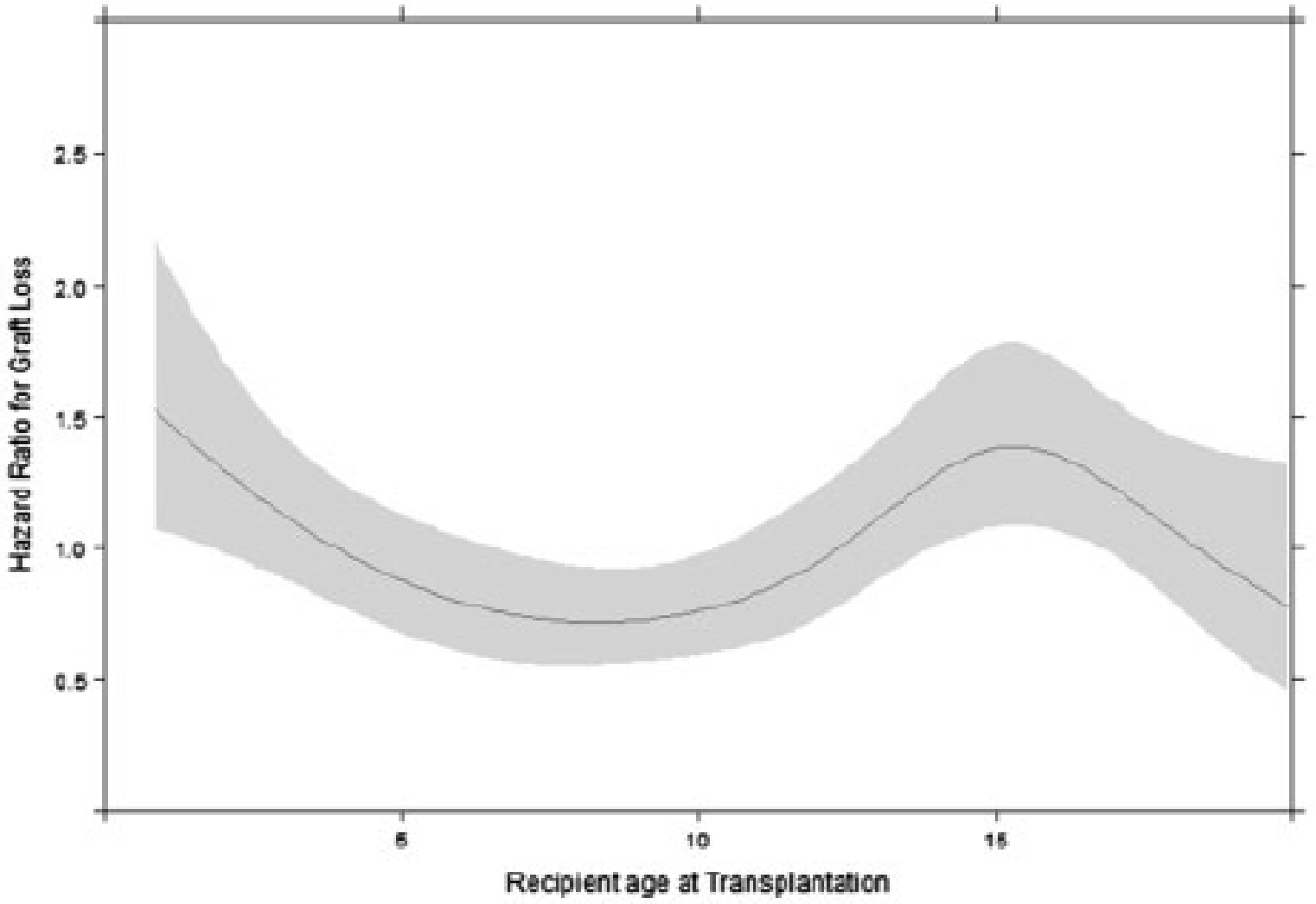
- Congenital anomalies of the kidney and urinary tract (CAKUT)
- Congenital nephrotic syndrome
- Neonatal cortical necrosis due to thrombosis
- ARPKD

Distribution of body weight at kidney transplantation in small children



Boehm M et al, Transplantation 2022

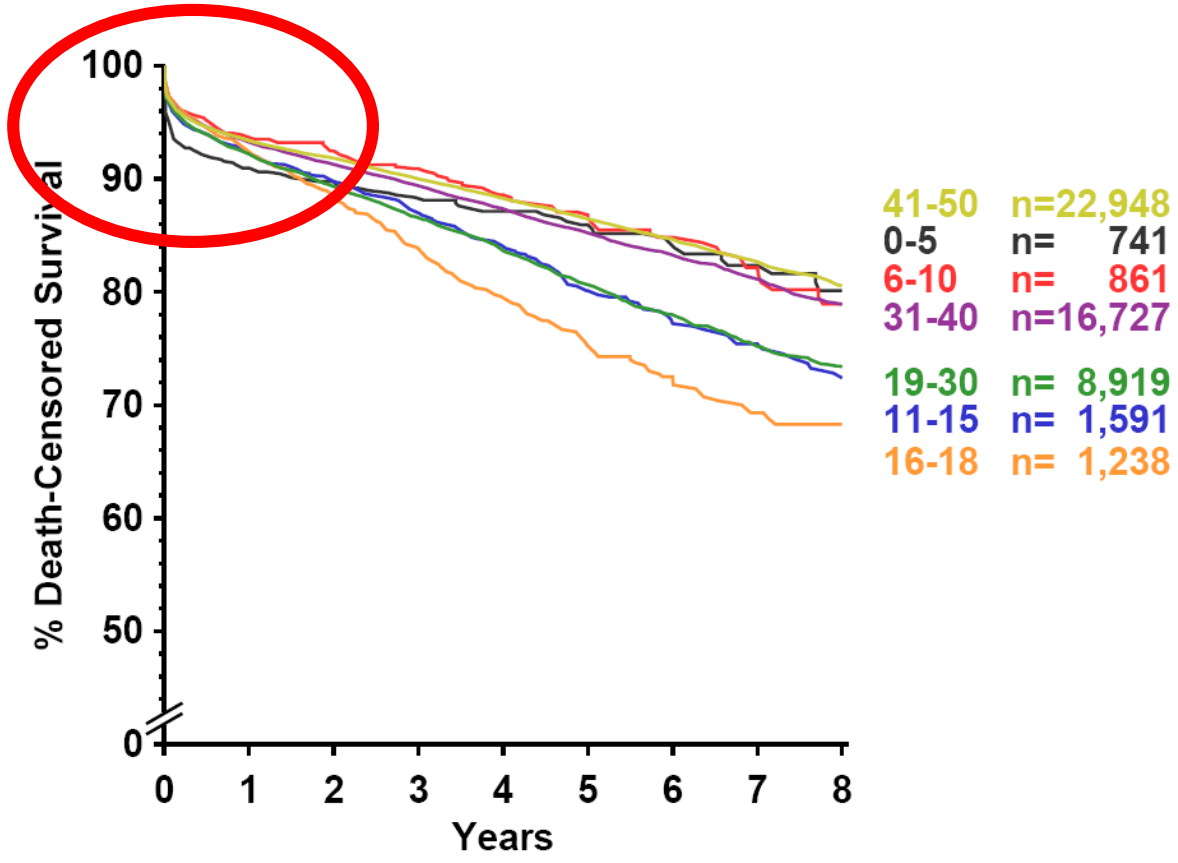
Association of recipient age at transplantation with hazard of graft loss*

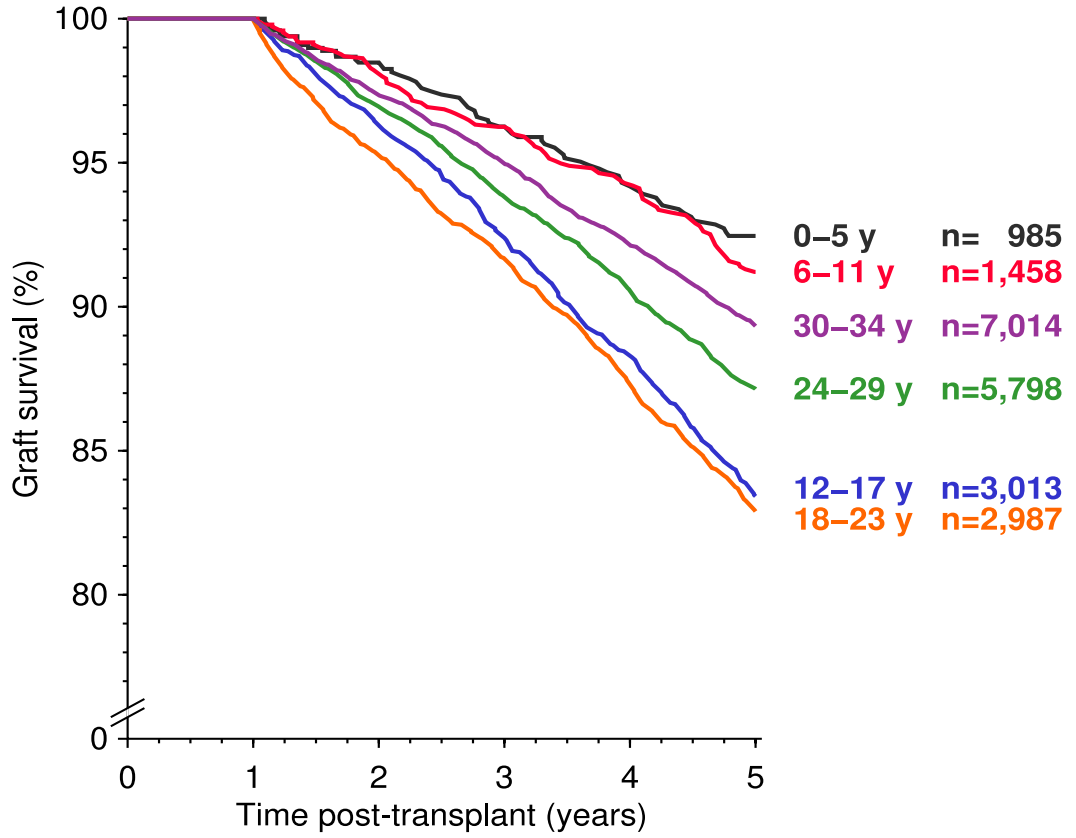


*adjusted for donor age, PRD with a high risk of disease recurrence, sex, pre-emptive transplantation, calendar year of transplantation and transplant source

Chesnaye NC et al, Nephrol Dial Transplant 2017

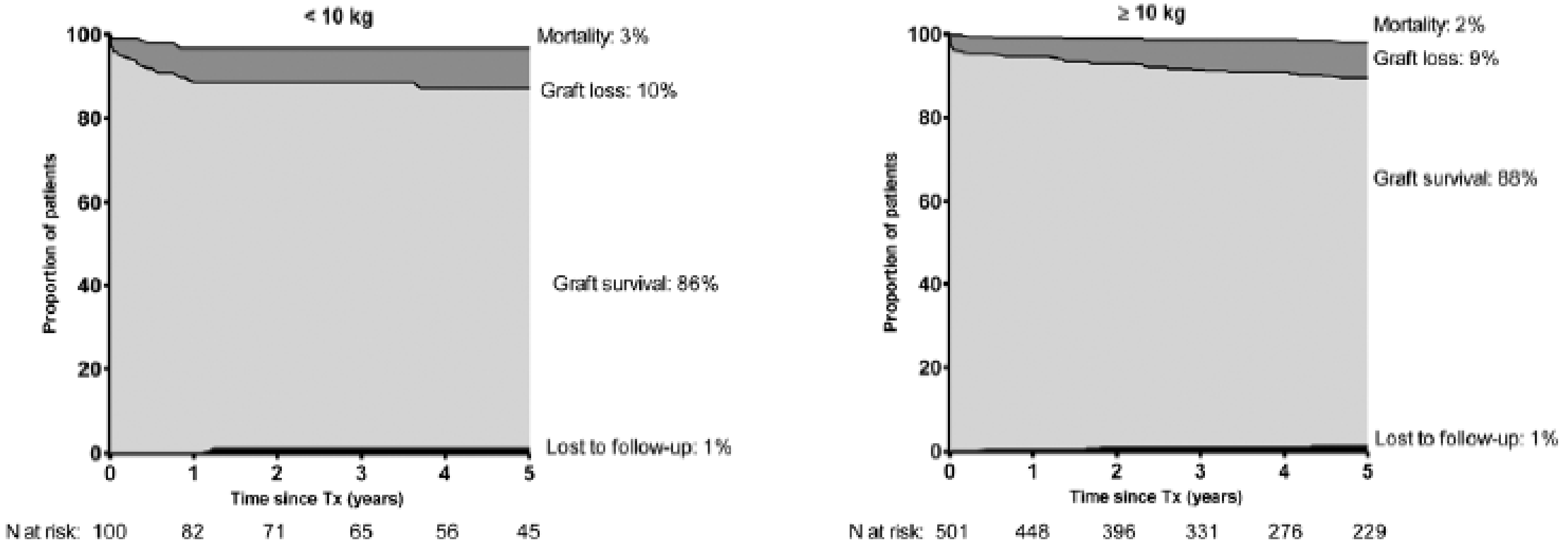
Association of recipient age with graft survival in deceased donor-kidney transplant recipients





Collaborative Transplant Study Heidelberg

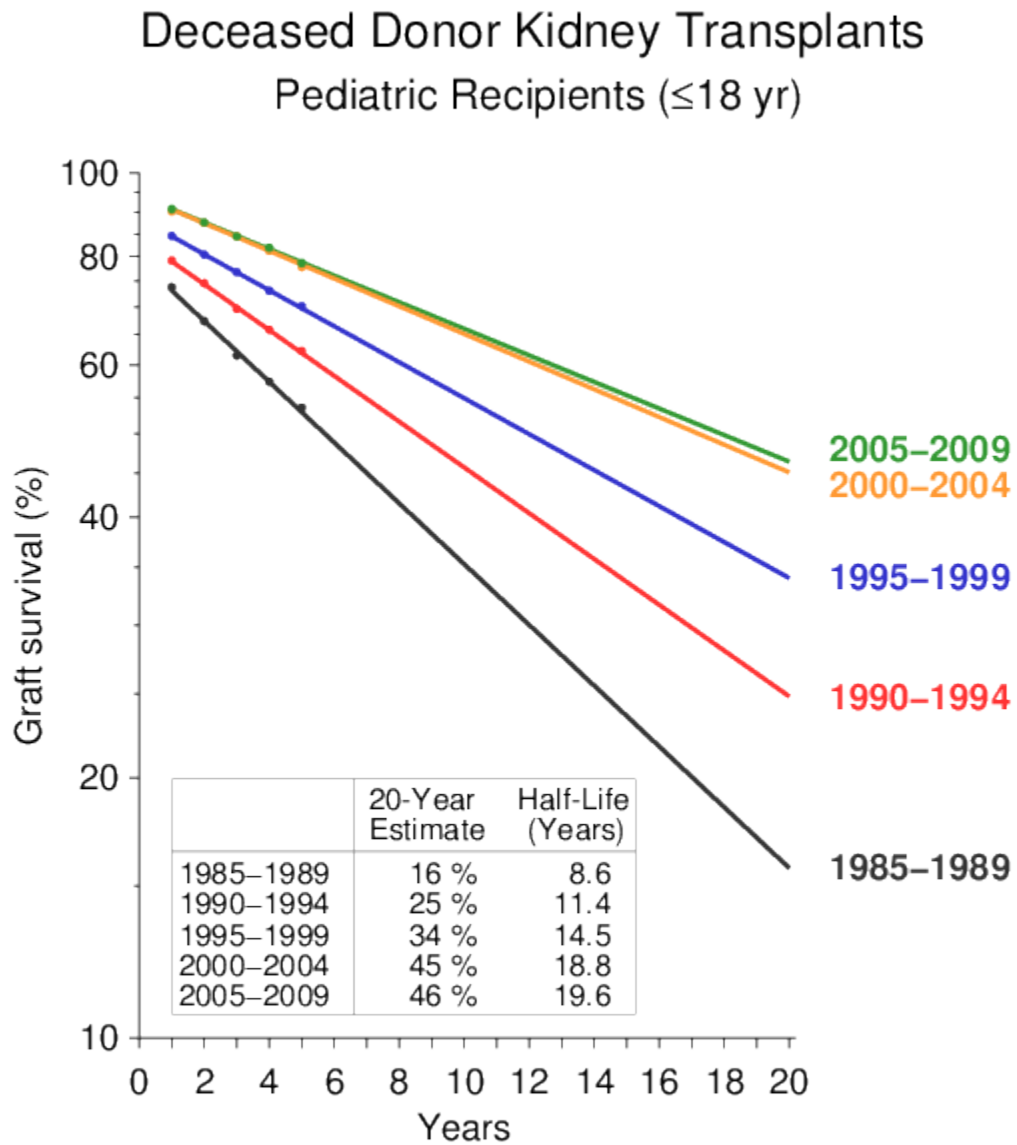
Cumulative incidence curves for 5-year graft survival, stratified by weight at transplantation



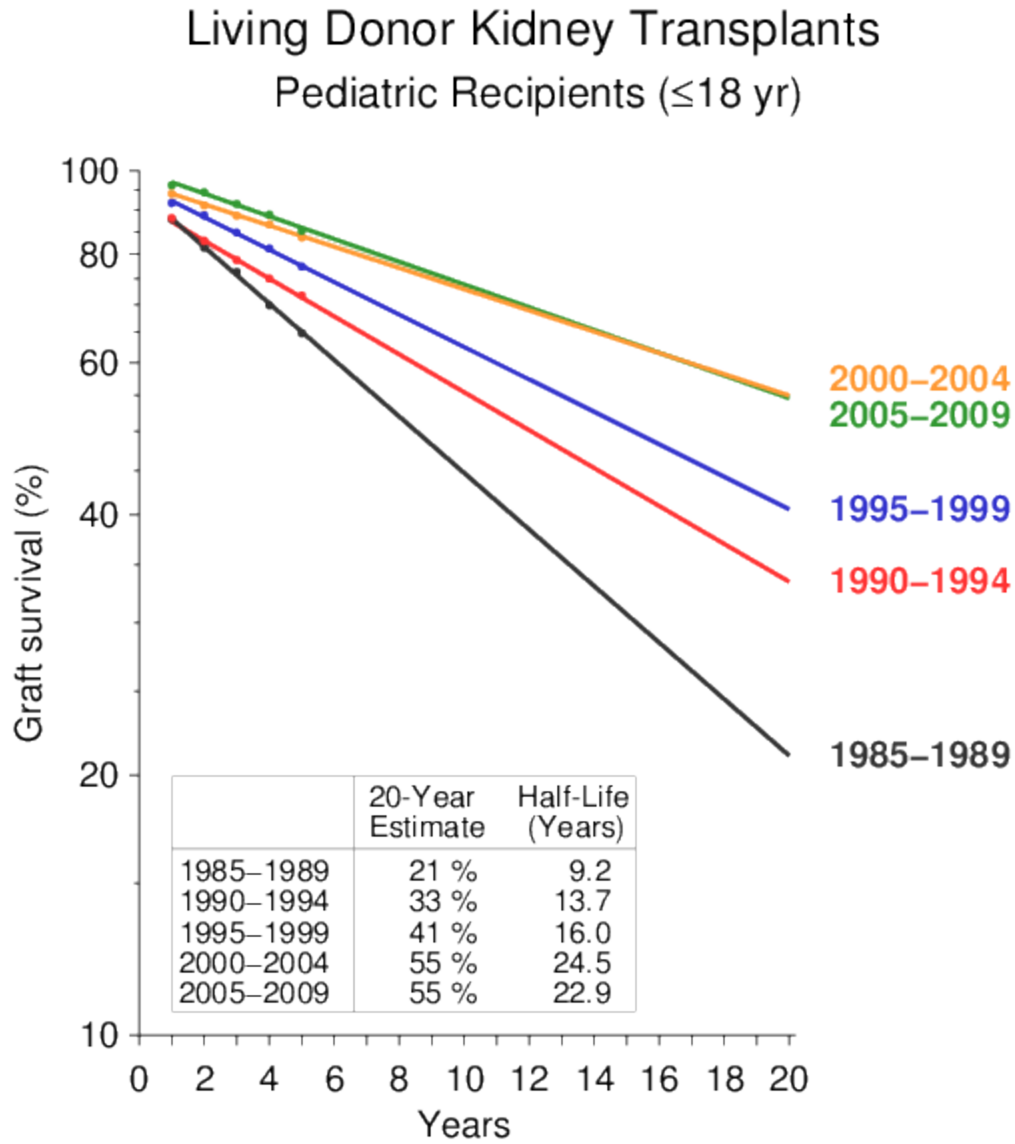
Graft failure risk at different times of follow-up

	HR (95% CI)—unadjusted	HR (95% CI)—adjusted[a]	HR (95% CI)—adjusted[b] N = 334
3 mo	1.40 (0.50-3.91)	1.95 (0.50-7.60)	[c]
1 y	2.49 (1.14-5.46)	3.84 (1.24-11.84)	[c]
5 y	1.80 (0.92-3.50)	1.71(0.68-4.28)	1.01 (0.28-3.66)

Boehm M et al, Transplantation 2022



Collaborative Transplant Study Heidelberg



Collaborative Transplant Study Heidelberg

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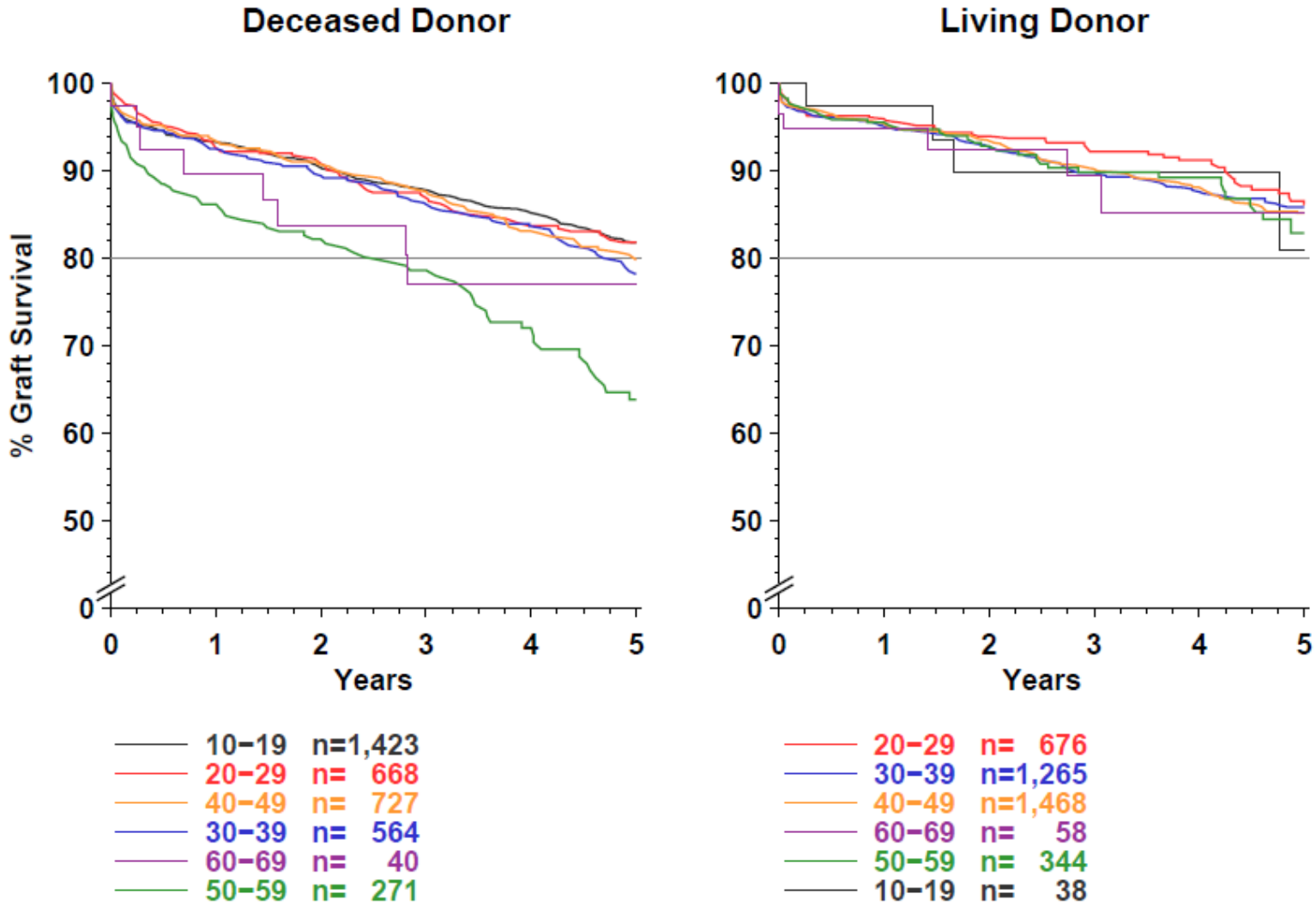
Question 1:
Which donors are preferable for kidney transplantation in infants?

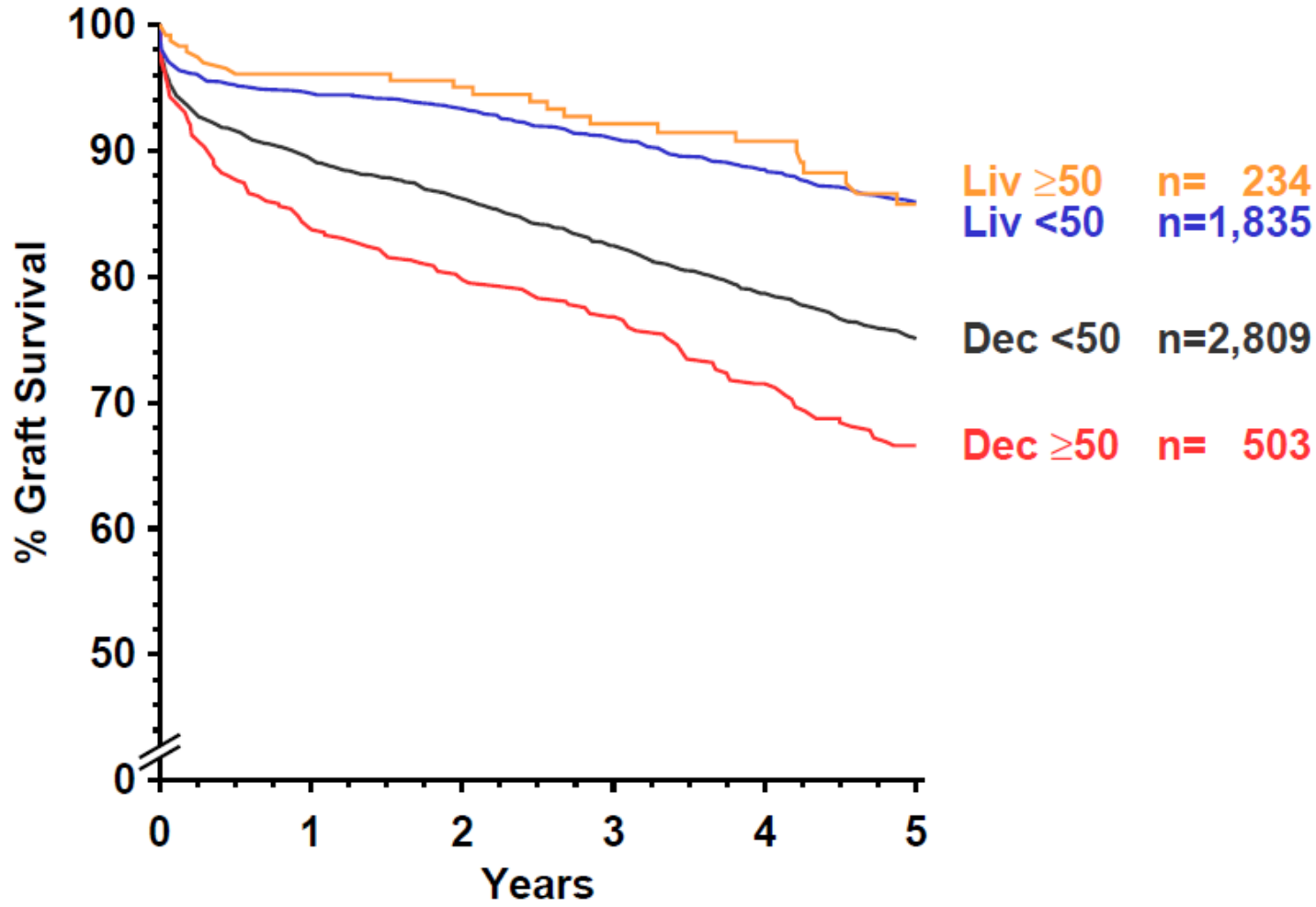
1. Donations from older living donors are not suitable for KTx in infants.
2. For young recipients, the allocation of deceased donors over the age of 5 years should be prioritized.
3. For young recipients, the allocation of deceased donors under the age of 5 years (small for small) should be prioritized.
4. Donations from older deceased donors are suitable for KTx in infants.

Pediatric Kidney TX 2000-2010 − Donor Age



Donor Relationship and Donor Age

Kidney Transplants 1990-2010, Europe
Recipient 0-18 yr



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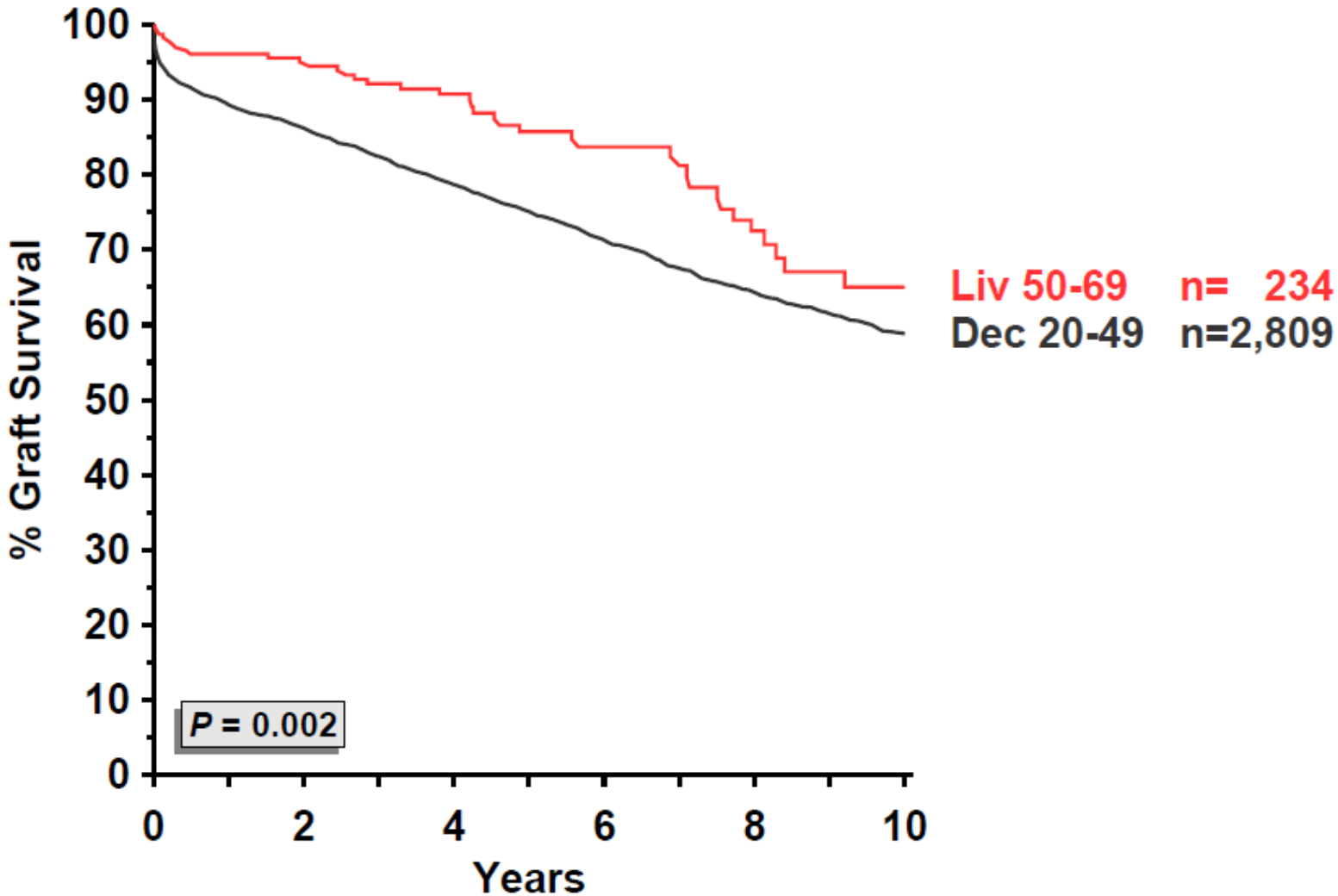
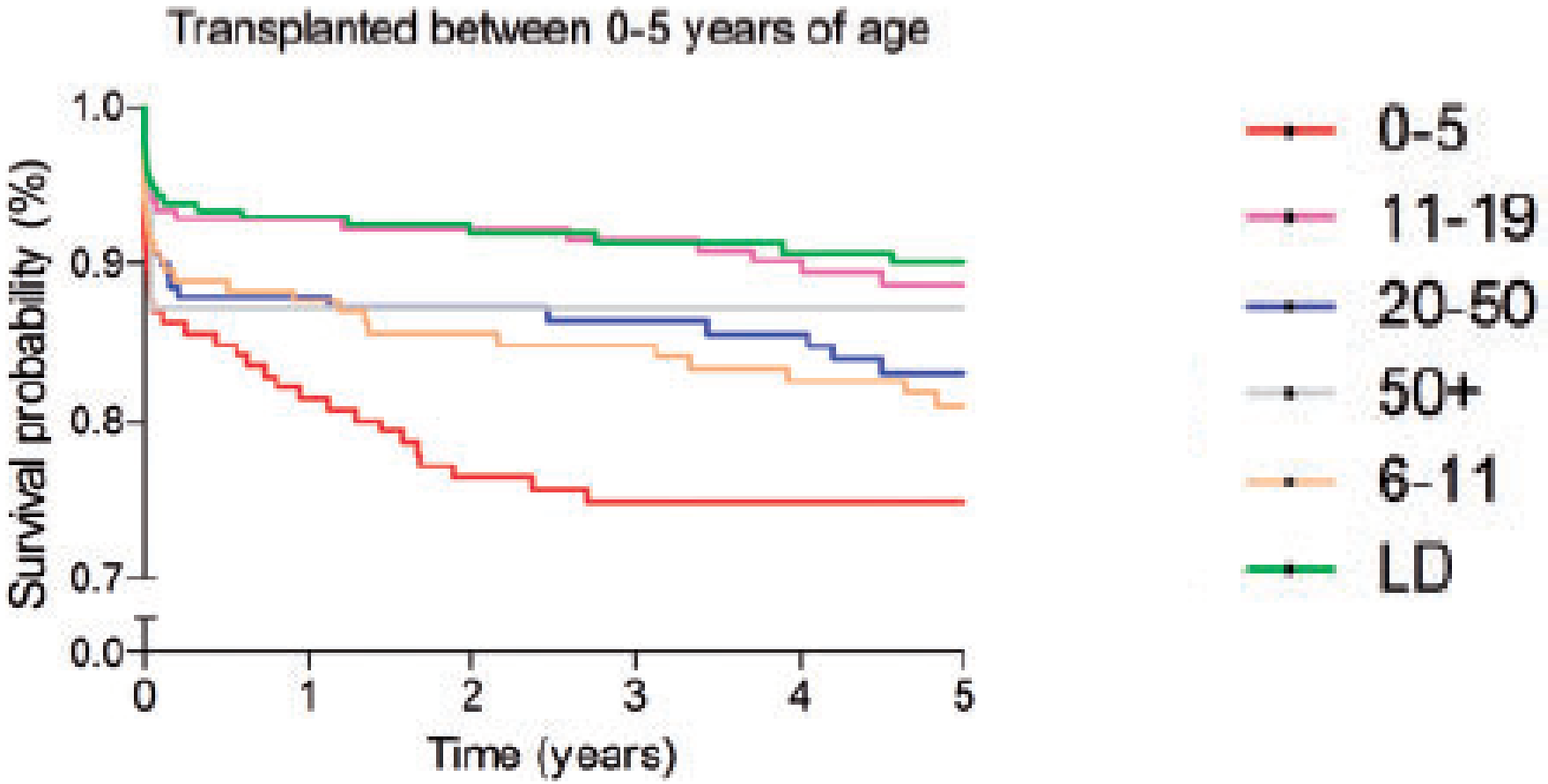
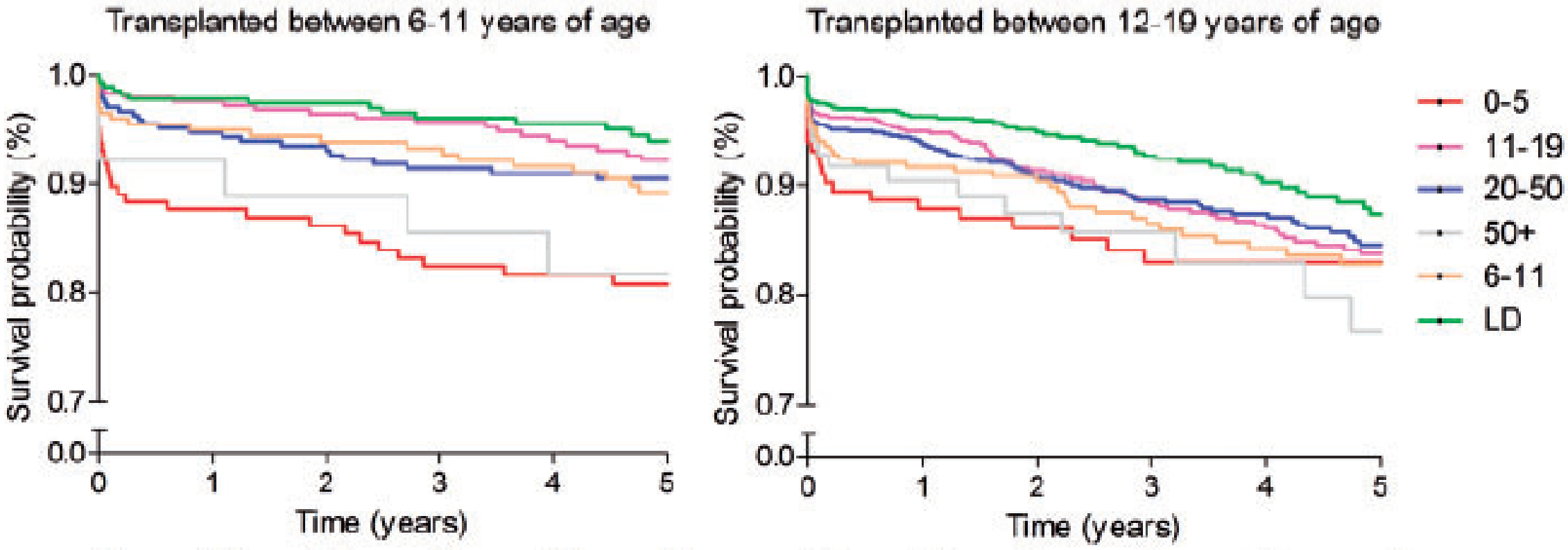


Kaplan–Meier survival curves for 5-year graft survival, stratified by deceased donor and recipient age groups and donor source



Chesnaye NC et al, Nephrol Dial Transplant 2017

Kaplan–Meier survival curves for 5-year graft survival, stratified by deceased donor and recipient age groups and donor source



Chesnaye NC et al, Nephrol Dial Transplant 2017

Conclusions

- Donations from older living donors provide excellent graft outcomes in all paediatric recipients.
- For young recipients, the allocation of deceased donors over the age of 5 years should be prioritized.

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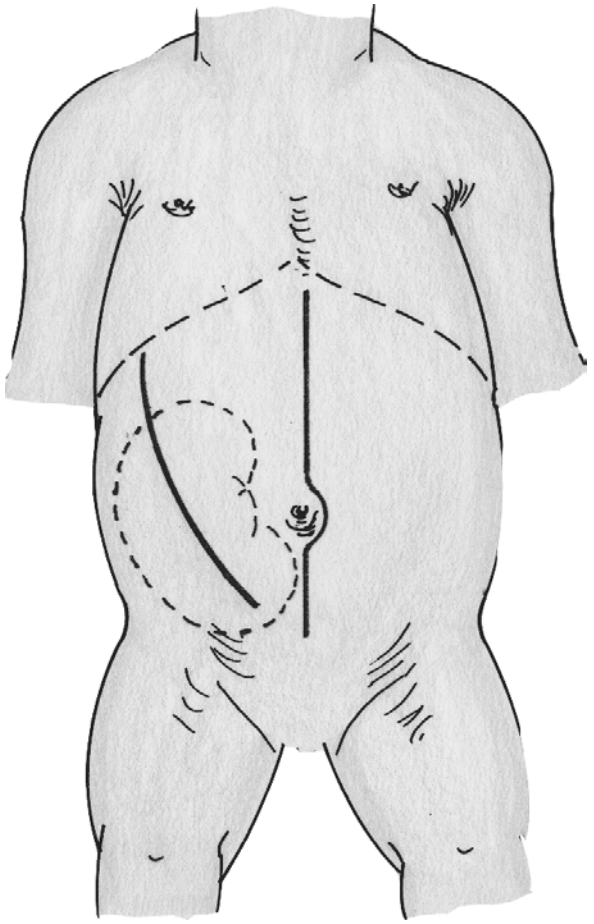
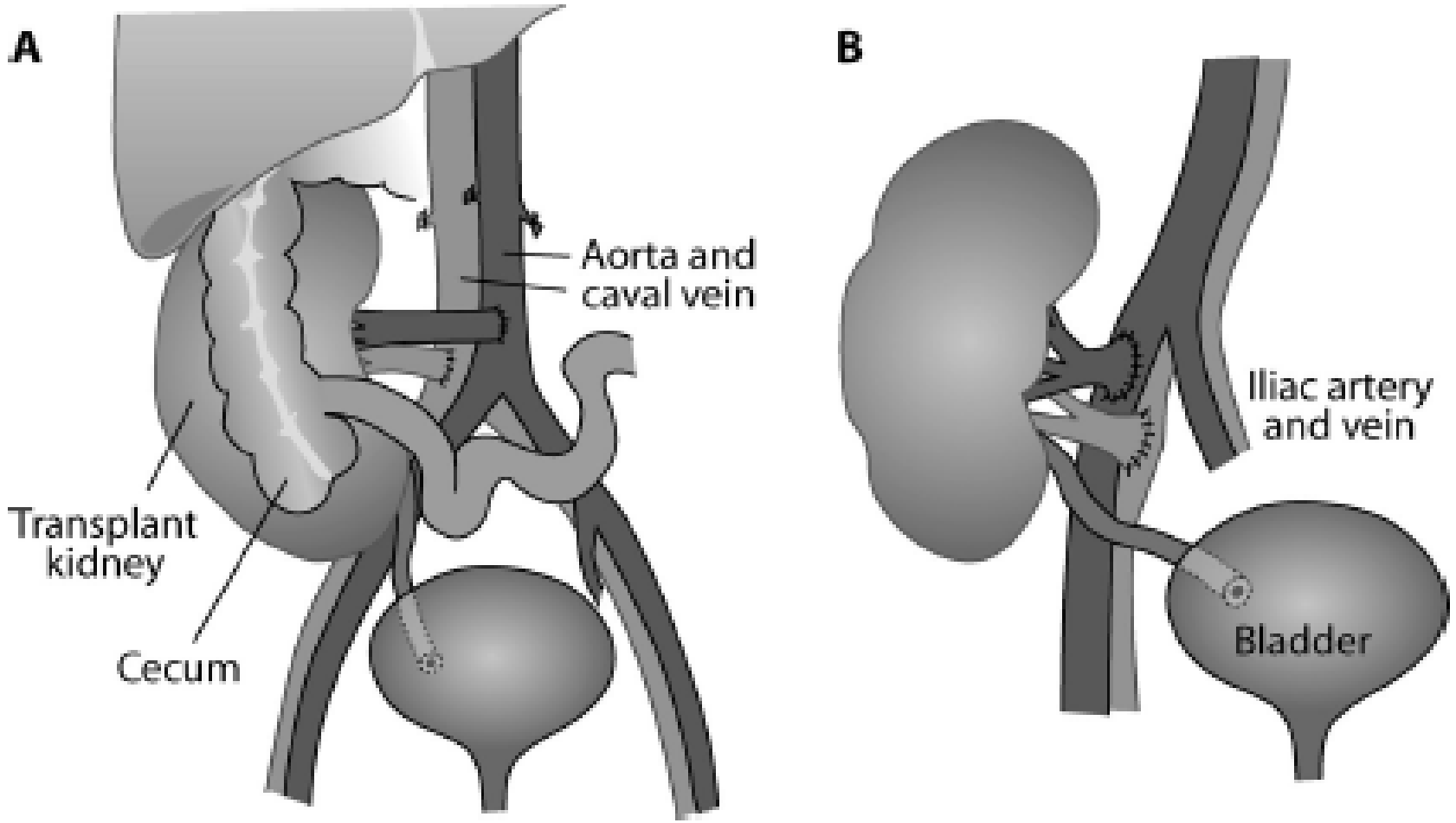
Large kidney —> Small recipient

- Typical situation in living donation and adult deceased donors
- Extraperitoneal approach preferable
- Simultaneous ipsilateral nephrectomy easy
- Minimal recipient body weight 8 -10 kg (?)
- Right side preferred independently of left or right transplant kidney





Jalanko H et al, Pediatr Nephrol 2016

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Causes of Graft Failure in Pediatric Renal Transplant Recipients - NAPRTCS

	Index Graft Failures		Subsequent Graft Failures		All Graft Failures	
	N	%	N	%	N	%
Total patients with graft failure	2427	100.0	320	100.0	2747	100.0
Cause of Graft Failure						
Death with functioning graft	226	9.3	23	7.2	249	9.1
Primary non-function	60	2.5	2	0.6	62	2.3
Vascular thrombosis	243	10.0	38	11.9	281	10.2
Other technical	29	1.2	4	1.3	33	1.2
Hyper-acute rejection	14	0.6	4	1.3	18	0.7
Accelerated acute rejection	33	1.4	8	2.5	41	1.5
Acute rejection	318	13.1	42	13.1	360	13.1
Chronic rejection	847	34.9	118	36.9	965	35.1
Recurrence of original kidney disease	156	6.4	31	9.7	187	6.8

UNIVERSITÄTS-
KINDERSPITAL
ZÜRICH

Current practice of antithrombotic prophylaxis in paediatric kidney transplantation

Results of an international survey on behalf of the ESPN

european
society for
paediatric
nephrology

Kathrin Buder, Matthias Zirngibl, Sascha Bapistella, Silvio Nadalin, Burkhard Tönshoff, Marcus Weitz,
Members of the «Transplantation Working Group» of the ESPN

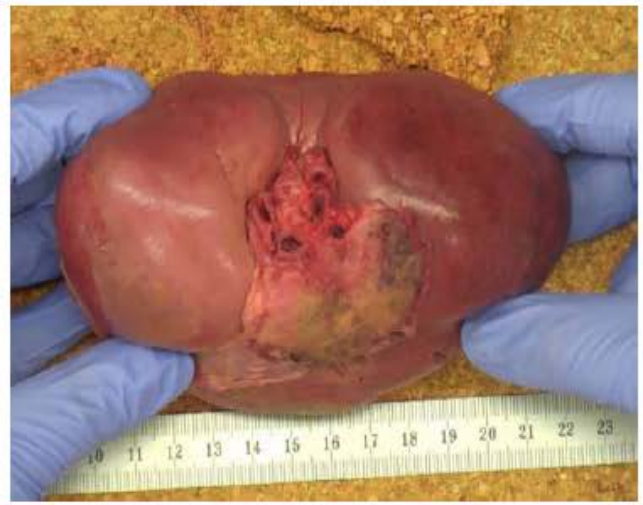
44th CERTAIN Workshop, December 4, 2020

Das Spital der Eleonorenstiftung

Renal graft thrombosis

Incidence:

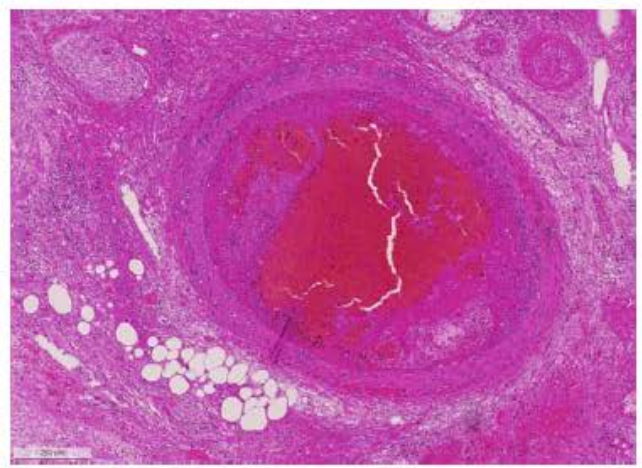
Adults:	0-6%
Children and adolescents:	0-13%



Major reason for graft loss:

~ 35% of first year graft losses

~ 18% of all graft losses



Keller AK et al. (2012) J Transplant 2012:793461.
Smith JM et al. (2006) Am J Transplant 6:585-588.

Pre-transplant thrombophilia screening

94% screened for thrombophilic risk factors:

- 55% in all recipients
- 39% in selected recipients

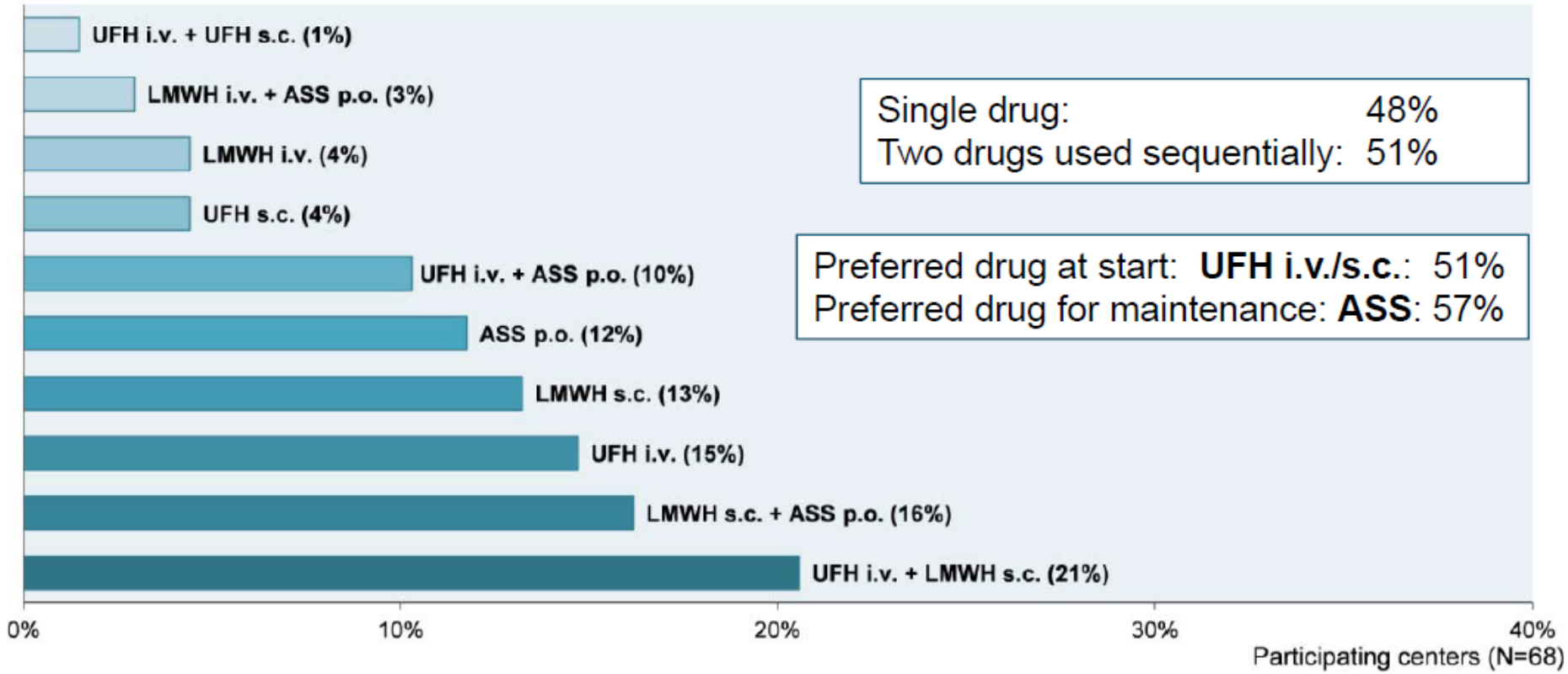
Main reasons for screening in selected recipients:

- 97% in case of positive family history for thromboembolic events
- 97% in case of previous thromboembolic events

Thrombophilia screening parameters

Parameters	n	% of total (N=74)
Quick, INR, PTT, fibrinogen, thrombin time	74	100
Platelet count	73	99
Protein C	63	85
Protein S	62	84
Antithrombin	61	82
Factor V Leiden mutation	58	78
Antiphospholipid antibodies	51	69
Lupus anticoagulant	49	66
Factor VIII	47	64
Homocysteine level	45	61
Prothrombin mutation	40	54
Methylentetrahydrofolate reductase polymorphism mutation	38	51
Lipoprotein (a)	25	34
Other parameters (specified by responders)	5	7

Strategies of antithrombotic prophylaxis



Antithrombotic prophylaxis in Heidelberg

- Standard risk: 100 E heparin/kg/day as continuous infusion i.v. for 7 (-14) days.
- In case of unfavorable vascular conditions (donor age <10 years or recipient weight <15 kg, multi-vessel supply of the graft, unfavorable anastomotic conditions, anamnestic tendency to thrombosis, thrombophilia): Heparin 200 - 400 E/kg/day (depending on bleeding risk, consult surgeon).
- Consider low-dose aspirin (1-2 mg/kg b.w.) 3 weeks posttransplant for renal artery stenosis or small-lumen pole vessels.
- After approximately 7 days, switch to enoxaparin sodium (Clexane®) s.c. in prophylactic dosage (0.5 to 1 mg/kg/d in 1 dose s.c.). Anti Xa level monitoring at prophylactic dosing is not routinely required (target anti-Xa level 4 h after administration: 0.2 - 0.4 E/ml).
- In patients with severely impaired renal function (creatinine clearance <30ml/min per 1.73 m^2): 50% of the dose).

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Fluid management in children <20 kg receiving an adult kidney: The Heidelberg protocol

- KTx recipients <20 kg in particular require a high volume intake.
- During preparation 10-20 ml/kg/h balanced crystalloids, Sterofundin ISO® (NaCl 0.9% only for critical potassium levels >/= 5 mmol/l) and albumin 5% (10-20 ml/kg).
- Target central venous pressure central venous pressure (CVP) in this phase: 7-10 mm Hg.
- During the creation of the vascular anastomoses (approx. 30 min) and BEFORE opening the aortic clamp: Generous crystalloid volume administration (see above) to a target CVP of >10 mm Hg, hematocrit 25-30%
- Aimed mean arterial blood pressure (MAP) in this phase: >80 mm Hg; catecholamines usually required.
- Theodrenalin-Cafedrin (Akrinor®), for prolonged hypotension norepinephrine/suprarenin (0.1 ug/kg b.w./min as starting dose).

Fluid management in children < 20 kg receiving an adult kidney

- After opening the anastomosis, there is a risk of a sharp drop in blood pressure and CVP in young children, due to redistribution of blood volume into the transplanted adult kidney.
- In this phase, maintaining hemodynamics with above mentioned values is especially critical (warm ischemia!, do not tolerate blood pressure drops).
- Up to 2 hours after declamping, drops in CVP of up to 50% can be expected (redistribution, ischemia mediators)!
- Fluid requirement (Sterofundin ISO®) 4-6 ml/kg/h, then adjusted to diuresis. In case of primary KTX function, high fluid requirement up to 70% of body weight, approx. 2500 mL/m² per day.
- CVP in the first 24 h 7-10 mm Hg (>10 cm H_2O), MAP >80 mm Hg,
  systolic blood pressure values of 100-120 mmHg are allowed in this early phase.
- After 48 h usually "physiological" antidiuresis due to hemodynamic adaptation of the adult kidney to the child’s cardiac output).

RENAL PERFUSION IN INFANT RECIPIENTS OF ADULT-SIZED KIDNEYS IS A CRITICAL RISK FACTOR.

Salvatierra, Oscar; Sarwal, Minnie

Transplantation. 70(3):412-413, August 15, 2000.

Optimizing infant intravascular volume by nasogastric or gastrostomy tube feeding of at least 2500 ml/m²/day for at least 6 months.

TABLE 1. Mean Schwartz glomerular filtration rates in infant recipients of adult-sized kidneys[a]

	6 mo.	1 yr
Protocol (n=14)	109±7*	102±10**
Nonprotocol (n=16)	70±3*	66±3**

[a] *, $P=0.001$; **, $P=0.004$.

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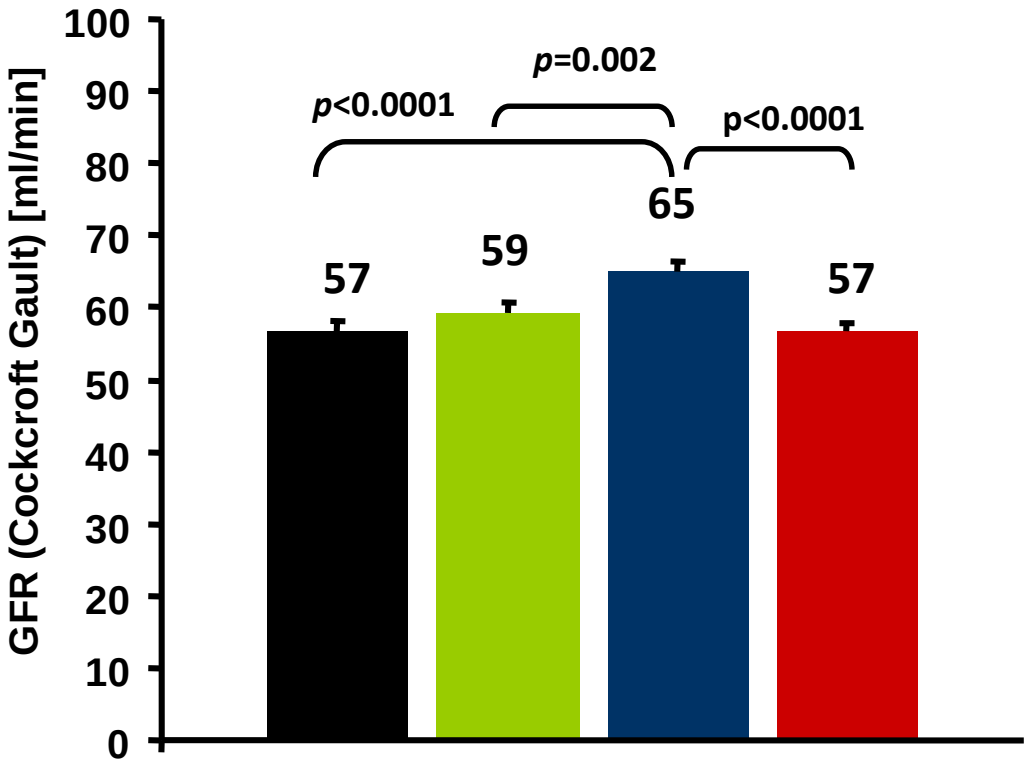
Question 2:

Which statement regarding immunosuppressive therapy in pediatric KTx is correct?

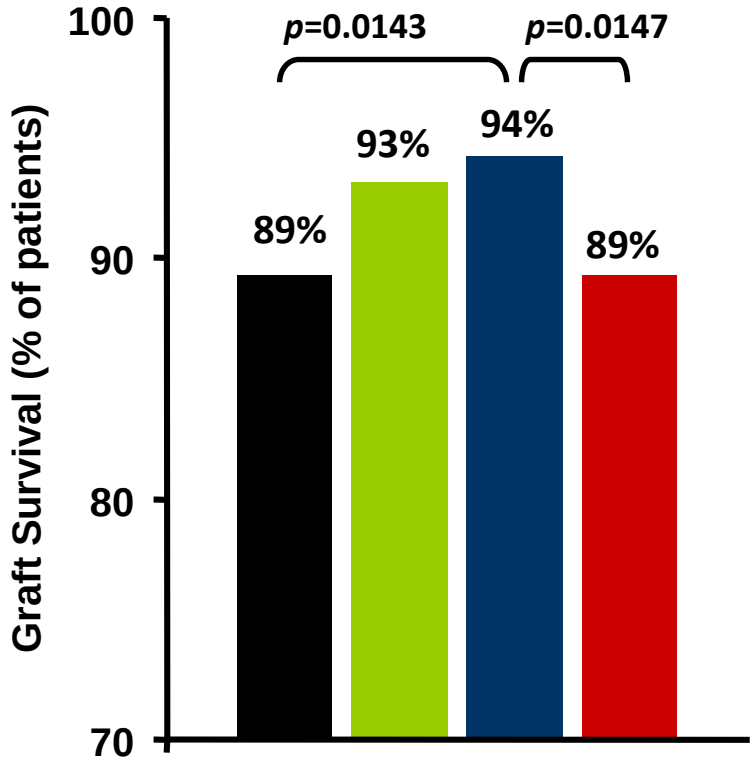
1. Higher tacrolimus oral bioavailability, but lower total body clearance in pediatric patients compared to adults.
2. Pediatric patients require approximately 1.5 – 2-times the dosage of tacrolimus given to adults in order to achieve similar systemic exposure.
3. Infants require more intense immunosuppressive therapy than older children.
4. MMF is well tolerated in all infants after kidney transplantation.

SYMPHONY: GFR and Graft Survival in Patients on MMF at 1 Year

GFR



Graft Survival



- Normal-dose CsA
- Low-dose CsA
- Low-dose TAC
- Low-dose SRL

Ekberg H, N Engl J Med 2007

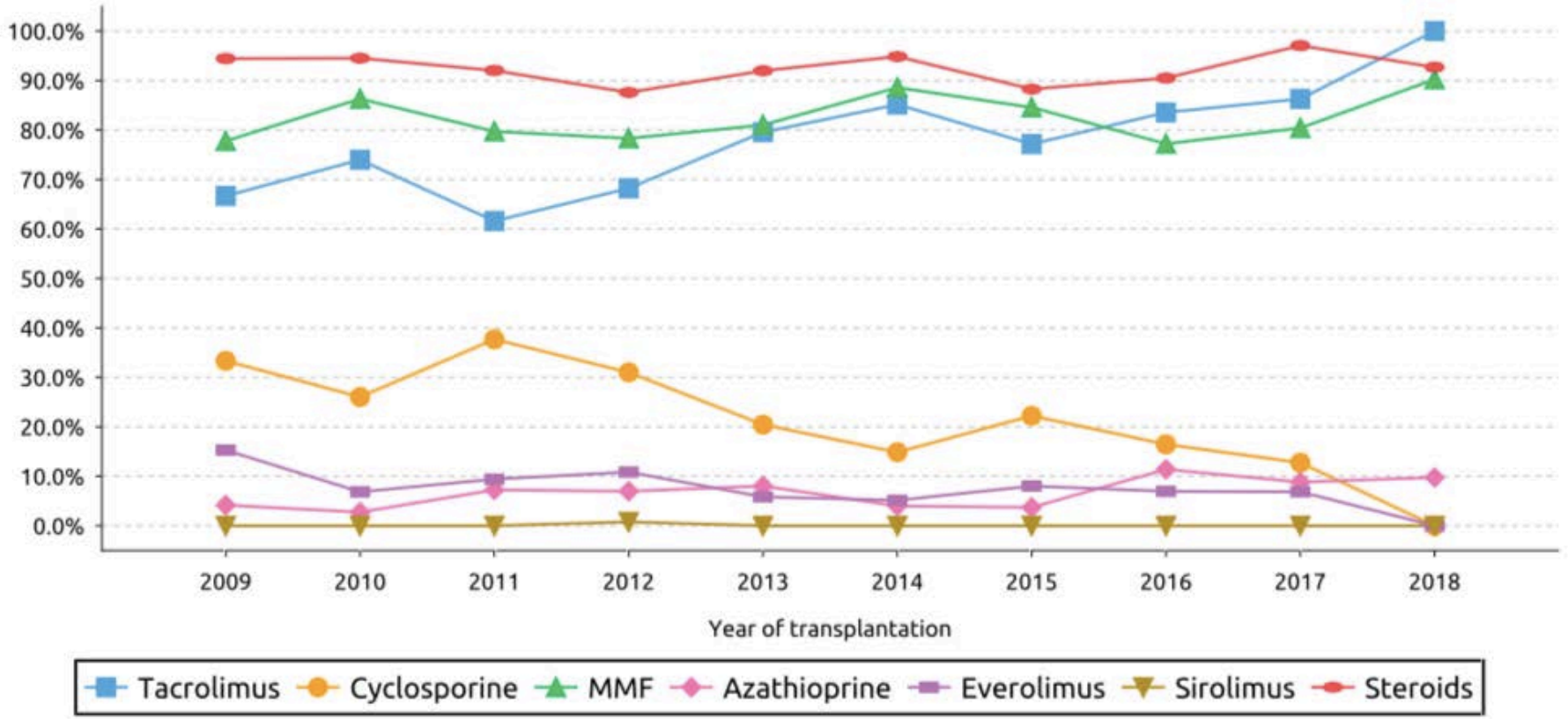
Which immunosuppressive drugs are currently used?

TABLE 2 Percent drug utilization—day 30 post-transplant (patients with functioning grafts)

	Transplant era 1996-2001	Transplant era 2002-2007	Transplant era 2008-2017
Prednisone	97.8	82.4	59.7
Cyclosporine	71.8	15.5	3.1
TAC	23.9	78.9	92.7
MMF	52.5	77.0	87.7
Aza	26.6	3.1	4.9
Sirolimus	3.6	13.4	0.5

The 2018 report of the NAPRTCS
Pediatric Transplantation 2019;23:e13597

Immunosuppressive maintenance therapy at day 30 post-transplant (n=1187)



CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

Which immunosuppressants are currently combined?

TABLE 3 Percent drug utilization—post-transplant (patients with functioning grafts)

	Transplant era 1996-2001				Transplant era 2002-2007				Transplant era 2008-2017			
	30 d	1 y	3 y	5 y	30 d	1 y	3 y	5 y	30 d	1 y	3 y	5 y
Prednisone/CsA/MMF	35.4	38.1	30.6	22.4	9.7	8.6	7.9	7.5	1.7	1.9	0.5	0.7
Prednisone/CsA/Aza	23.1	17.7	14.2	8.9	0.8	0.8	0.6	0.7	0.1	0.2	0.3	0.4
Prednisone/CsA	10.7	4.4	3.8	3.5	1.5	0.8	0.3	0.8	0.4	0.3	0.2	0.0
Prednisone/TAC/MMF	14.3	19.6	24.4	30.1	51.3	49.6	44.2	42.1	48.9	41.7	38.6	33.1
Prednisone/TAC/Aza	2.3	4.9	6.5	6.9	1.7	2.4	2.7	3.9	2.0	2.3	4.3	6.3
Prednisone/TAC	4.2	5.0	6.7	6.9	4.1	5.8	6.7	6.2	2.9	8.2	8.0	6.7
TAC/MMF	0.4	1.1	1.7	2.5	10.7	9.4	11.5	13.1	33.8	27.3	26.5	27.5
Other combination	9.5	9.2	12.0	17.3	20.1	22.7	26.0	25.8	10.1	18.1	21.6	25.3

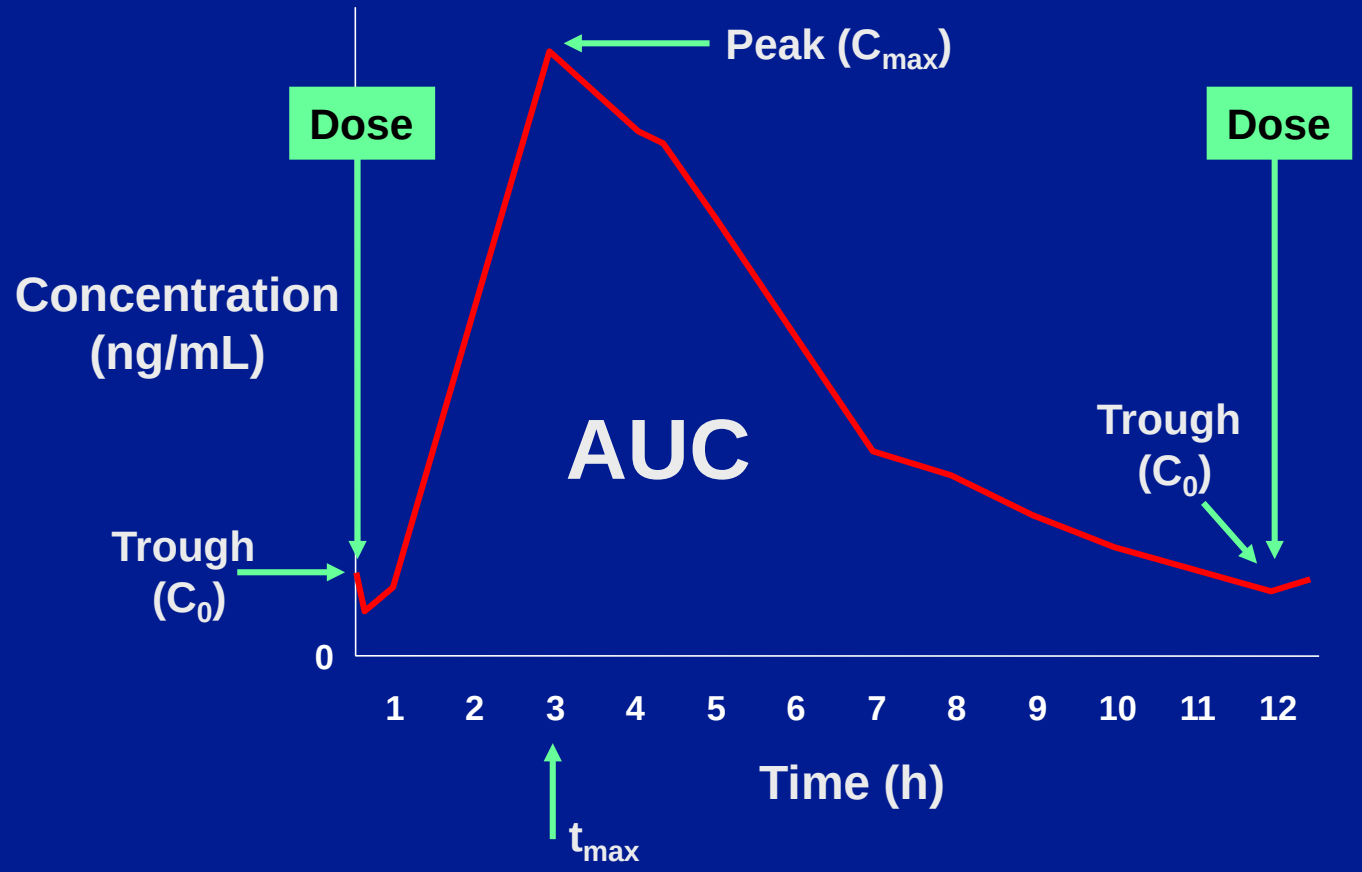
The 2018 report of the NAPRTCS
Pediatric Transplantation 2019;23:e13597

Pharmacokinetics of tacrolimus in children

- Simular oral bioavailability, but higher total body clearance in pediatric patients compared to adults.
- Pediatric patients require therefore approximately 1.5 – 2-times the dosage of tacrolimus given to adults in order to achieve similar systemic exposure.
- However, significant variability in tacrolimus dosing requirements **within** the pediatric patients population (infants, children, adolescents)
- Hence, more precise dosing recommendations for these different pediatric subgroups are required.

Measuring Total Drug Exposure

Area Under the Time-Concentration Curve (AUC)



Correlation of Tacrolimus PK-parameters with Tacrolimus-AUC_{0-12} in Pediatric Transplant Recipients

Author	Period after Rtx	Number of patients	Correlation (r^2) of C_0 with AUC_{0-12}	Best (r^2) individual time point	Best (r^2) abbrevia-ted PK Profile
Wallemacq 97	initial, liver	16	0.81	-	-
Filler 02	stable, renal	53	0.56	C_4 r^2=0.83	C_0,C_1,C_2,C_4 r^2=0.96
Kim 05	initial, renal	30	0.55	C_2 r^2=0.85	(C_0+C_2)/2 r^2=0.92

Target tacrolimus AUC

- Consider immunological and infectiological risk of individual patient
- Week 1 – 4 (early phase post-transplant): 150 – 200 µg x h/L
- Month 1 – 3: 120 – 150 µg x h/L
- > Month 3 (stable phase): 75 – 150 µg x h/L

Scholten EM et al 2005; Lee and Butani 2007

Specific immunosuppressive strategies

- Minimization of glucocorticoids (steroids)
  because of main side effects: suppression of length growth and cosmetic changes
  - Steroid avoidance
  - Early withdrawal (after about 4 days post-transplant)
  - Late withdrawal (after approx. 6 – 12 months post-transplant)
- Minimization of calcineurin inhibitors
  - Comedication with MMF
  - Comedication with mTOR inhibitors (everolimus)
- *Calcineurin inhibitor-free immunsuppression?*

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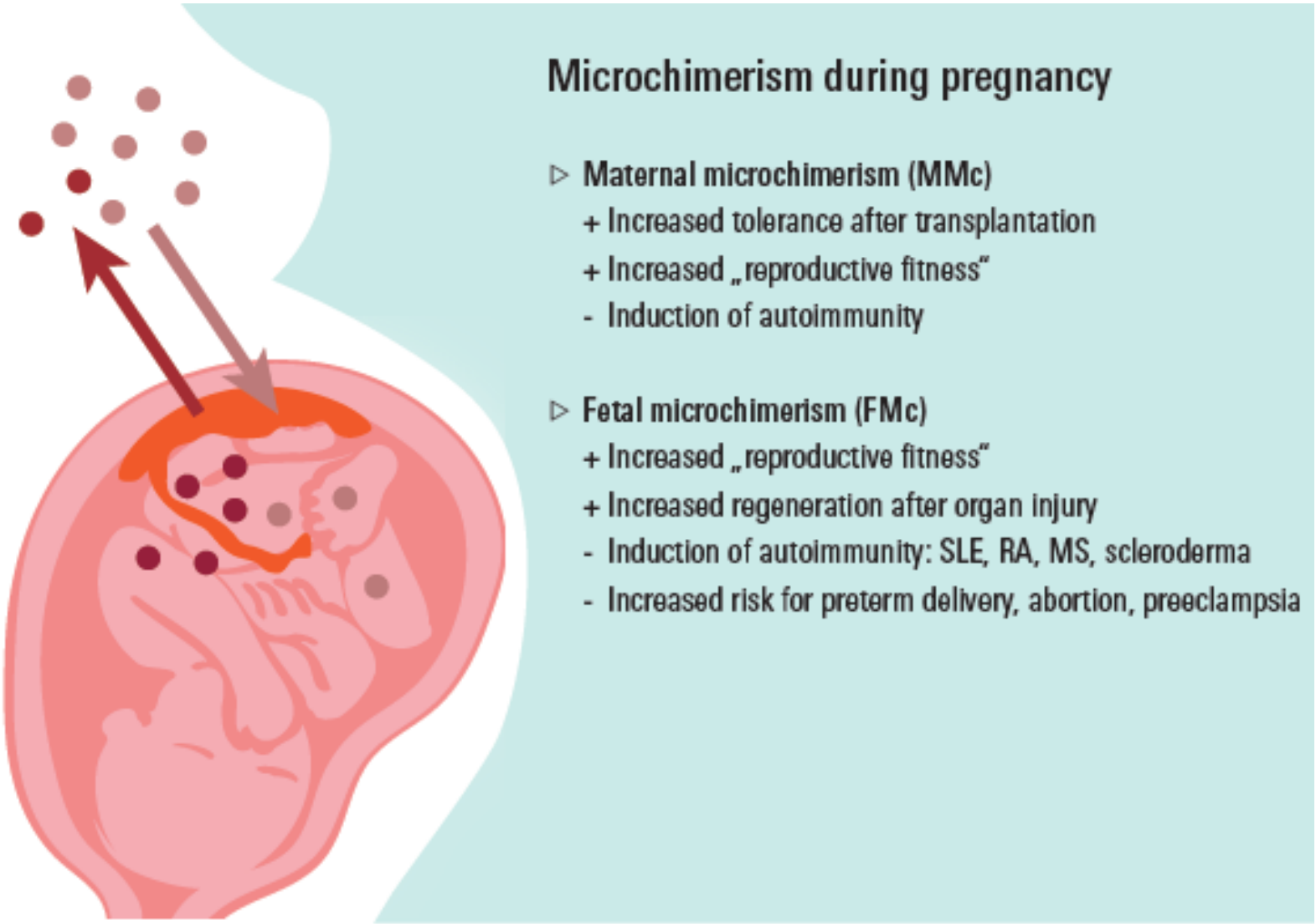
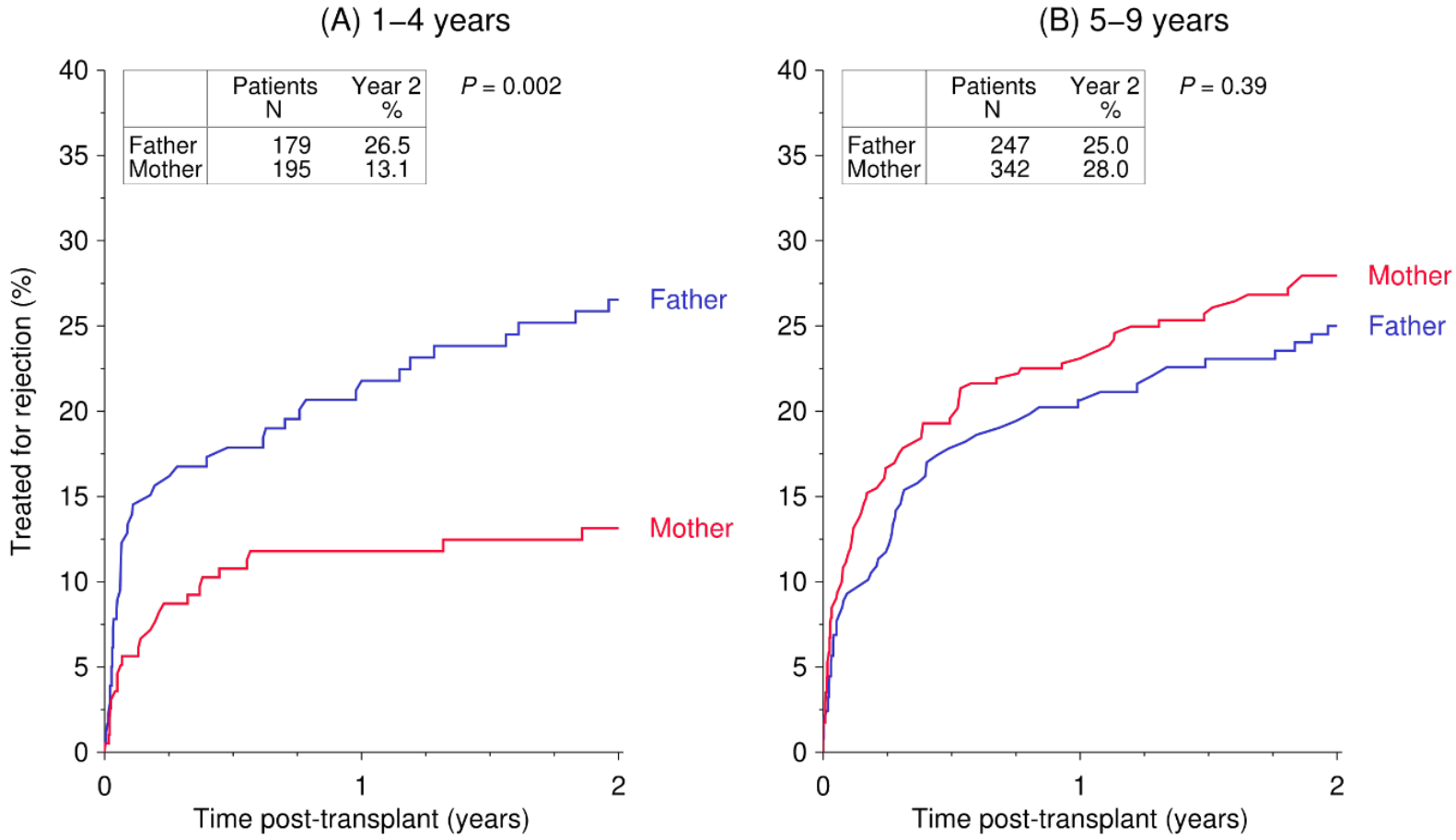
Microchimerism: The bi-directional transfer of cells between mother and child through the placenta



Rate of treated kidney allograft rejection in 1–4- and 5–9-year-old children

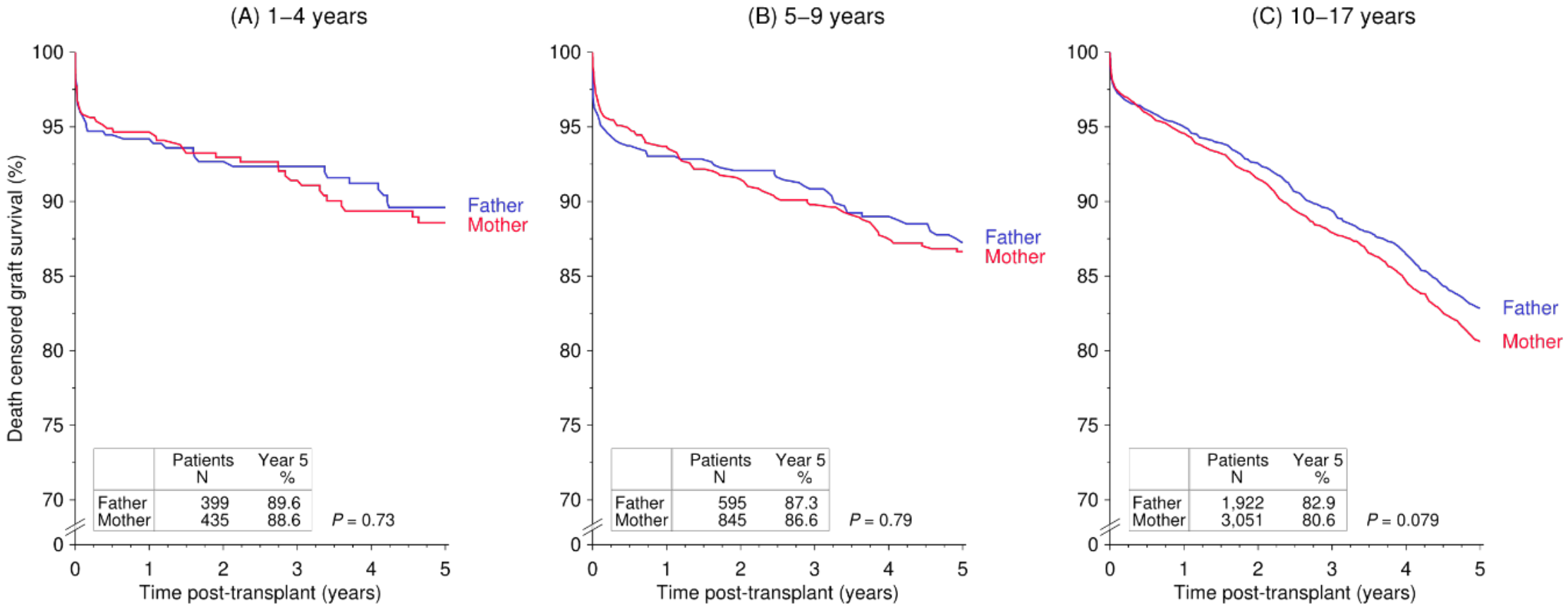
Living donor-kidney transplantation either from the mother or the father



Engels G *et al*, Pediatr Transplant. 2022

5-year death-censored graft survival in children

Living donor-kidney transplantation either from the mother or the father



Engels G *et al*, Pediatr Transplant. 2022

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9. Specific outcome

Prophylaxis of infections

- Ceftriaxone (Rocephin®) 50 mg/kg b.w./day i.v. as a single dose perioperatively (max. 2 g), until drains are removed.
- Nystatin (CandioHermal®) suspension: for 1 week posttransplant
- CMV chemoprophylaxis with (Val)-ganciclovir: D+/R-, D+/R+, D-/R+ and thymoglobulin therapy
- Pneumocystis jirovecii-pneumonia prophylaxis with trimethoprim-sulfamethoxazole for at least 6 months posttransplant

Overview

1. Overall outcome
2. Donor selection
3. Transplant surgery
4. Prevention of thrombosis
5. Fluid management
6. Immunosuppressive therapy
7. Microchimerism
8. Infectious prophylaxis
9. Specific outcome

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CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

ORIGINAL ARTICLE

CrossMark

Outcome of renal transplantation in small infants: a match-controlled analysis

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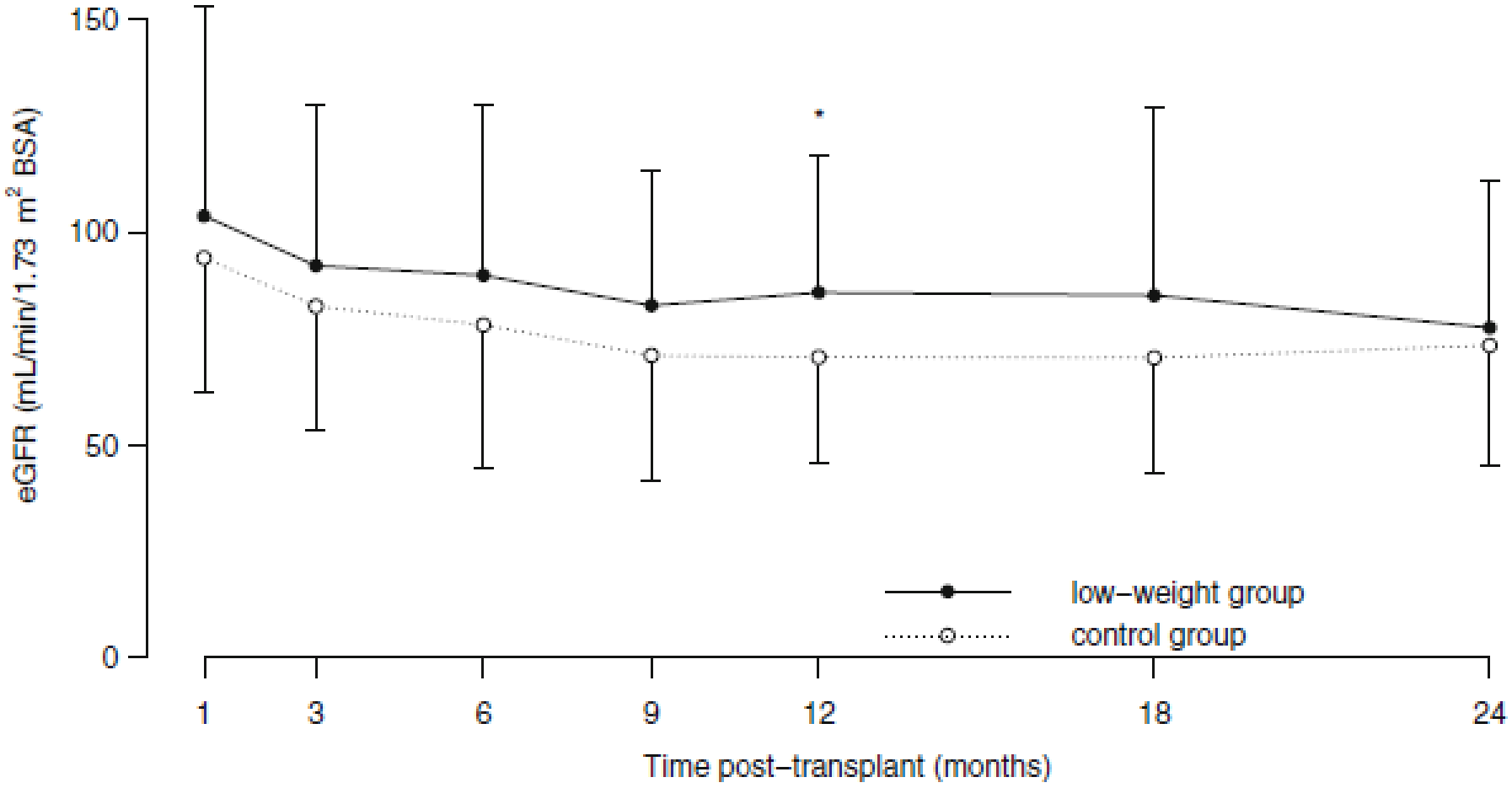
Methods

- Multicenter, retrospective, match-controlled cohort study on infants weighing less than 10 kg at time of engrafting (low-weight group [LWG], n=38) compared to a matched control group (n=76) with a body weight of 10–15 kg,
- Using data from the first 2 years post-transplant derived from the CERTAIN Registry.

Results

- Patient survival was 97 and 100% in the LWG and control groups, respectively (P = 0.33), and death-censored graft survival was 100 and 95% in the LWG and control groups, respectively (P = 0.30).
- Estimated glomerular filtration rate at 2 years post-transplant was excellent and comparable between the groups (LWG 77.6 ± 34.9 mL/min/1.73 m^2; control 74.8 ± 29.1 mL/min/1.73 m^2; P = 0.68).

Mean eGFR over 2 years posttransplant for the low-weight group (n=34) and control group (n=72)



Results and Conclusions

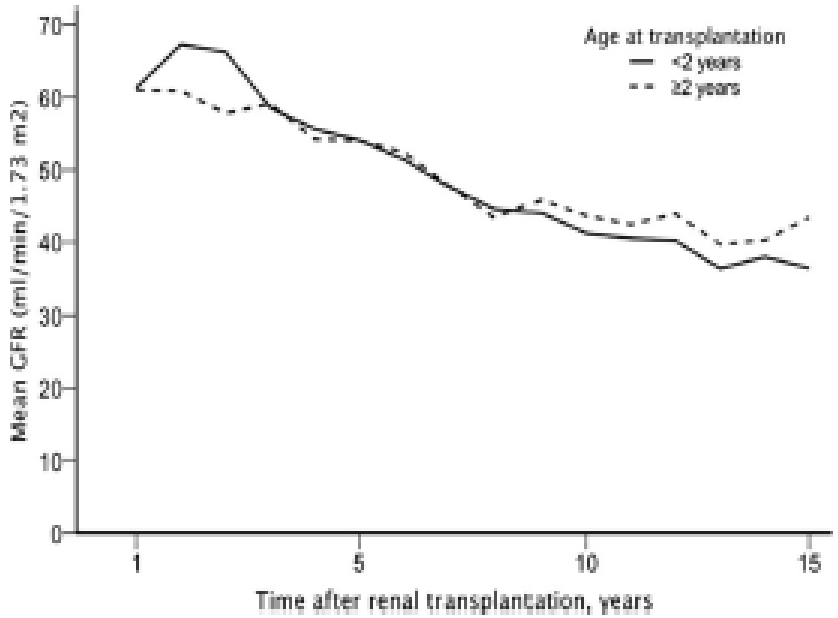
- The overall incidences of surgery-related complications (LWG 11%, control 23%; P = 0.12) and medical outcome measures (LWG 23%, control 36% ,P=0.17) were not significantly different between the groups.
- The medical outcome measures included
  - transplant-related viral diseases (LWG 10%, control 21%; P = 0.20),
  - acute rejection episodes (LWG 14%, control 29%; P = 0.092),
  - malignancies (LWG 3%, control 0%; P = 0.33)
  - arterial hypertension (LWG 73%, control 67%; P =0.57).
- These data suggest that RTx in infants is a feasible option, at least in selected centers with appropriate surgical and medical expertise.

Conclusions

- Tx in small children remains challenging and requires multidisciplinary expertise because of the potentially higher complication rate.
- Complications range from thrombosis of graft artery or vein, huge size difference of graft and recipient, and difficult ureteral anastomosis in small children with congenital anomalies of the kidney and urinary tract.
- Furthermore, small children represent a particularly vulnerable population regarding fluid and blood pressure management and immunosuppressive medication in the first weeks or months after Tx.

Important long-term issues in infant kidney transplantation

- Graft function
- Viral surveillance
- HLA antibody surveillance
- Growth
- Motor development
- Neurocognitive development
- Cosmetic side effects of the immunosuppressive medication
- Bone health
- Metabolic risk factors



Jalanko H et al, Pediatr Nephrol 2016

- Quality if life
- Pubertal development
- Adherence to medication
- Structured transition to adult care

Thank you for your attention!

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22/11/22

Thrombotic thrombocytopenic purpura (TTP)
Paul Coppo (Paris, France)

01/12/22

IPNA Webinar: Clinical Practice Reccomendations for the diagnosis and Management of children with SSNS

Winter Break

24/01/23

Cystinuria
Pietro Manuel Ferraro (Rome, Italy)

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