Training courses for pediatric abdominal organ transplantation
Suzdal, June 15-16, 2013

First week after pediatric kidney transplantation

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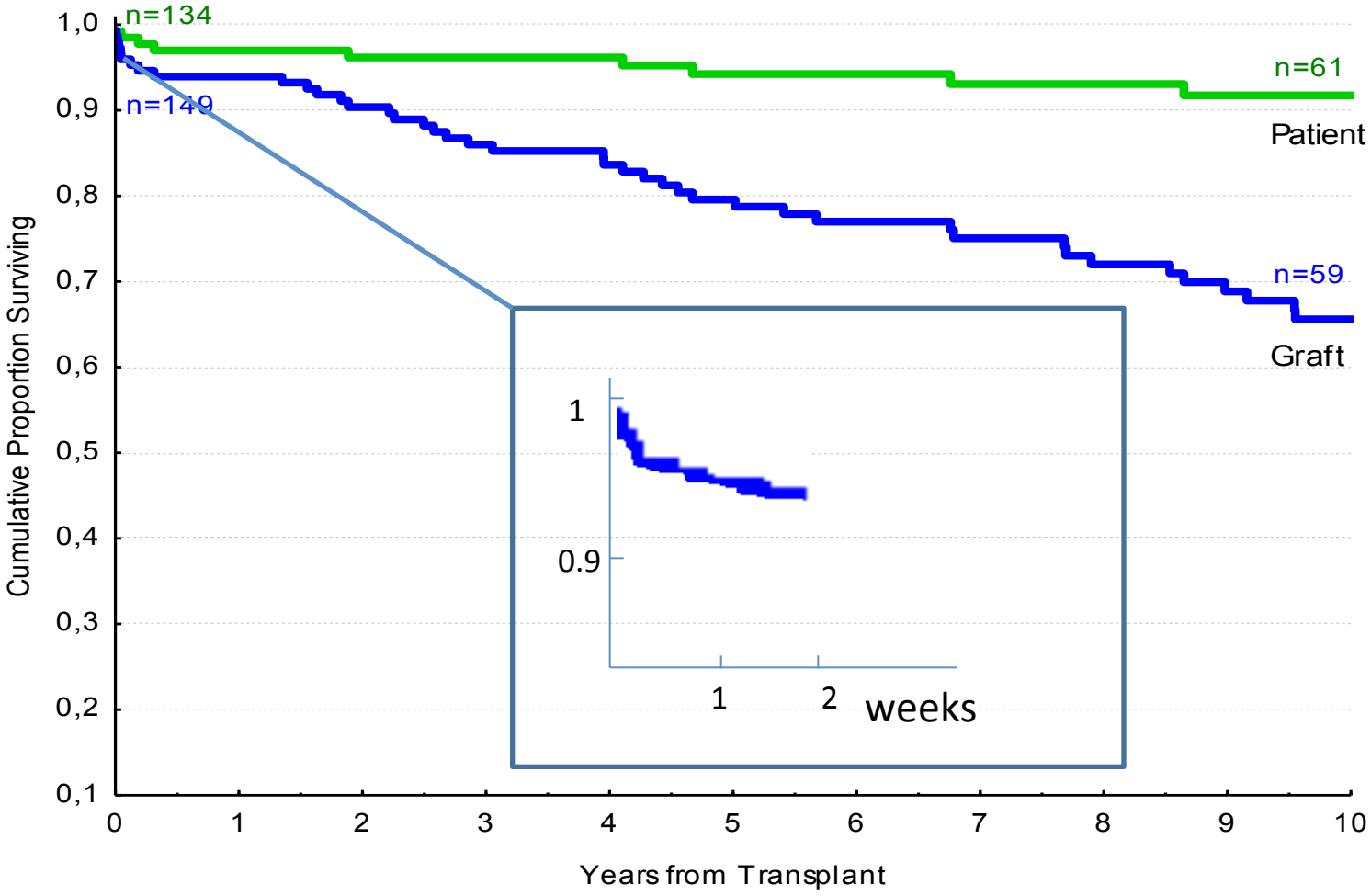
Overview of the lecture

- Introduction
- Nursing orders
- Fluid therapy
- Medications
  - Immunosuppressive therapy
  - Infection prophylaxis
  - Anticoagulation
- Complications
  - Delayed graft function
- Psychological issues
- Take-home messages

Patient and graft survival (KUL)



Peri-operative management

- Nephrologist is present during transplantation
  - follow the surgery
    - Details of operation: vascular problems, bleeding, exact cold ischemia and anastomosis time, color of allograft after re-anastomosis, diuresis, abdominal wall closure problems….
  - follow the anesthesia
    - Details of anesthesia, blood pressure control, fluid/blood/ vasoconstrictor drugs administration, IV access (Jugularis CVL, peripheral IV), CVP (10-15 mm H_2O), medications (methylprednisolone, mannitol 20% 2,5 ml/kg /furosemide 2 mg/kg) …

First hours

- Recovery unit -> ICU unit :
  - young recipient (<2 years), complications during surgery, hemodynamic instability, respiratory problems, need in sedation)

- Recovery unit -> Tx ward

First week post-Tx nursing orders

Lab control	Every 4 hours			Every 12 hours CNI levels 1qd			Every 24 hours	
AV-fistel	Every 4 hours			Every 6 hours			Every 24 hours	
Fluid balance	Every hour	Every 4 hours		Every 6 hours			Decrease frequency of controls depending on the condition of the patient	
Urine output	Every hour (diuresis prior to Tx ?)						Decrease frequency of controls depending on the condition of the patient	
Vital sings	Every hour		Every 2 hours		Every 3 hours		Decrease frequency of controls depending on the condition of the patient	
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

Days of Tx

Pediatric renal Tx protocol Leuven

Other nursing orders

- Patient out of bed: day 1
- Dressing care: when needed
- Bladder catheter care: every 8 hours (bladder catheter out: max day 7)
- CVL catheter care: daily (CVL out: max day 7)
- Wound drain care: daily (out by surgical order when no output)

Fluid management

- Keep patient slightly hyperhydrated, avoid fluid overload

- Maintenance fluid: 20 ml/kg/day
- Replacement fluid: in = out (to adjust at the time of fluid balance)

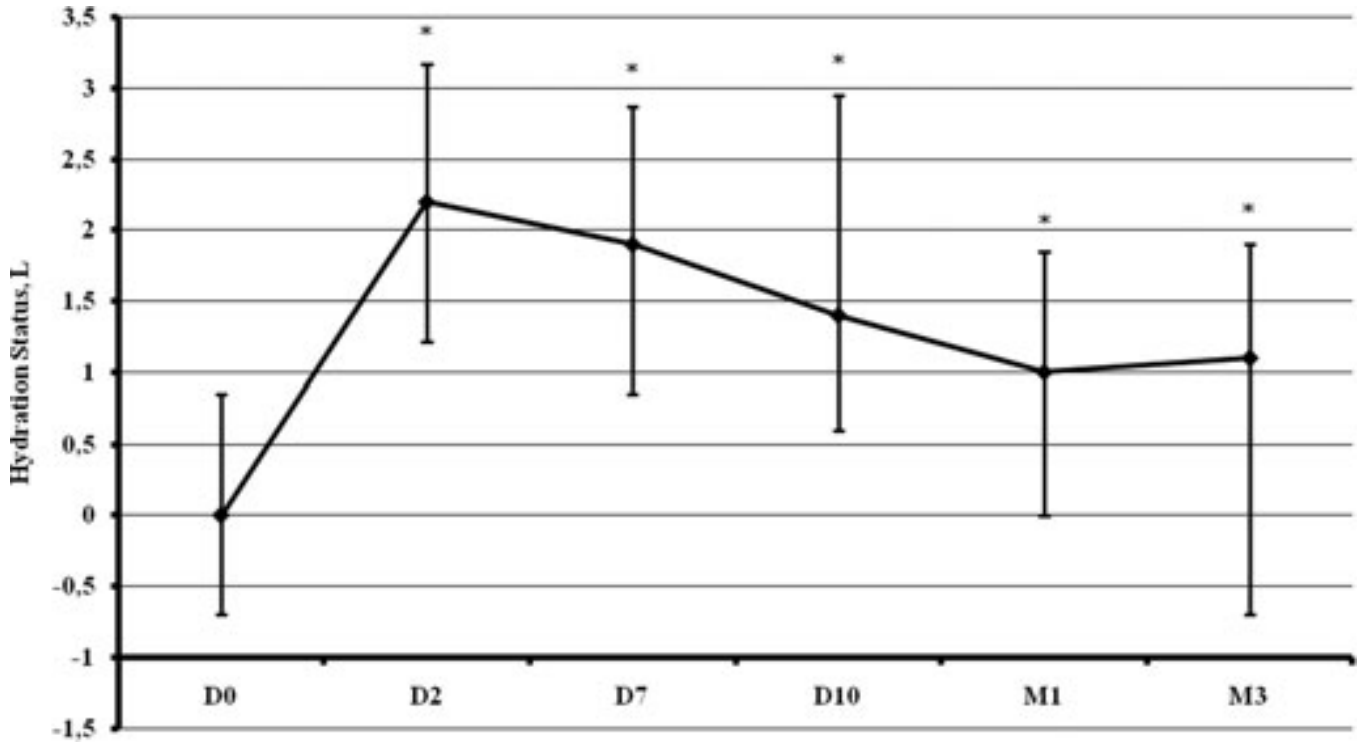
- Fluid composition:
  - glucose 2.5% - NaCl 0.45%
  - Potassium, bicarbonate : depending on laboratory values

- Avoid hyperglycemia!

- Start oral fluid: day 1, when bowel movements are present

Hydration status after renal Tx

N = 50 adult patients, age 50 (47-61) years
Body impendance spectroscopy for measuring ECW



Gueutin et al. Clin Transplant 2011

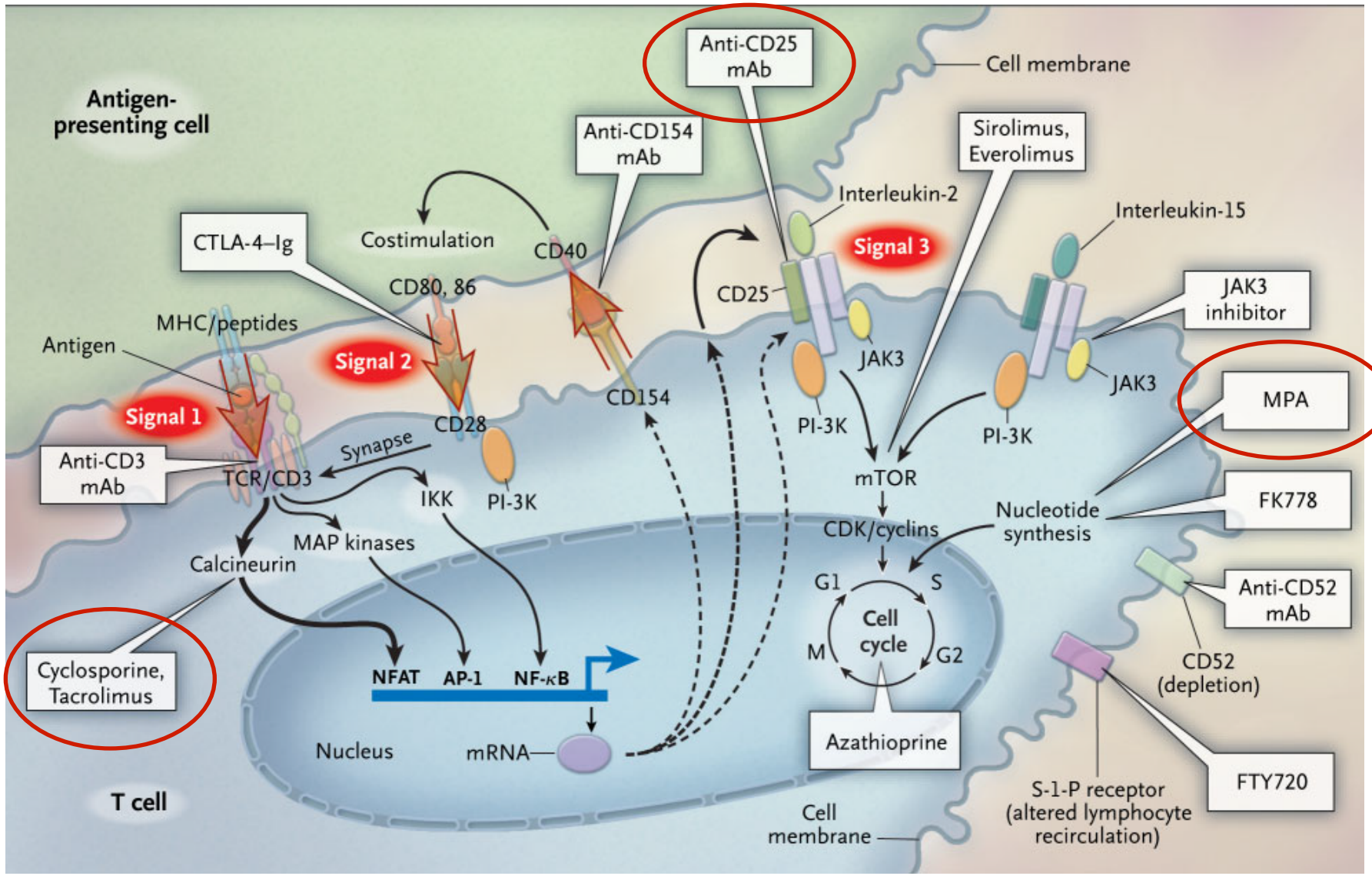
Hydration status depends on graft function

	GFR (ml/min/1,73 m2		
	< 30	30-60	> 60
	N=5	N=19	N=5
Overhydrated n (%)	0 (0)	12 (63)	2 (40)
Normohydrated n (%)	2 (67)	3 (32)	3 (60)
Dehydrated n (%)	1 (33)	1 (5)	0 (0)

Other predictors of hydration status:
PD (NH 75%) versus HD (NH 50%)
Residual diuresis

Gueutin et al. Clin Transplant 2011

Immunosuppressive therapy



Halloran NEJM 2004

Pre-operative immunosuppressive therapy

- Tacrolimus 0.075 mg/kg PO 6 hrs pre-op
- MMF 600 mg/m2 PO or IV 6 hrs pre-op
- Basiliximab IV prior to OK (+ day 4)
  - BW > 35 kg: 20 mg
  - BW < 35 kg: 10 mg

Pediatric renal Tx protocol Leuven

Steroid therapy

– Methylprednisolone:

during OK: 400 mg/m2 in IV

6 hours after reanastomosis: 200 mg/m2

– Prednisolone (mg/kg):

	BW > 20 kg	BW < 20 kg
D0-3	1.25	1. 5
D4-6	1	1.25
D7-14	0.8	1
D15-30	0.6	0.75
M2	0.4	0.5
M3	0.3	0.4
M4-6	0.2	0.3
M7-9	0.15	0.25
M10-12	0.1	0.15
… 1 year	0.075	0.1

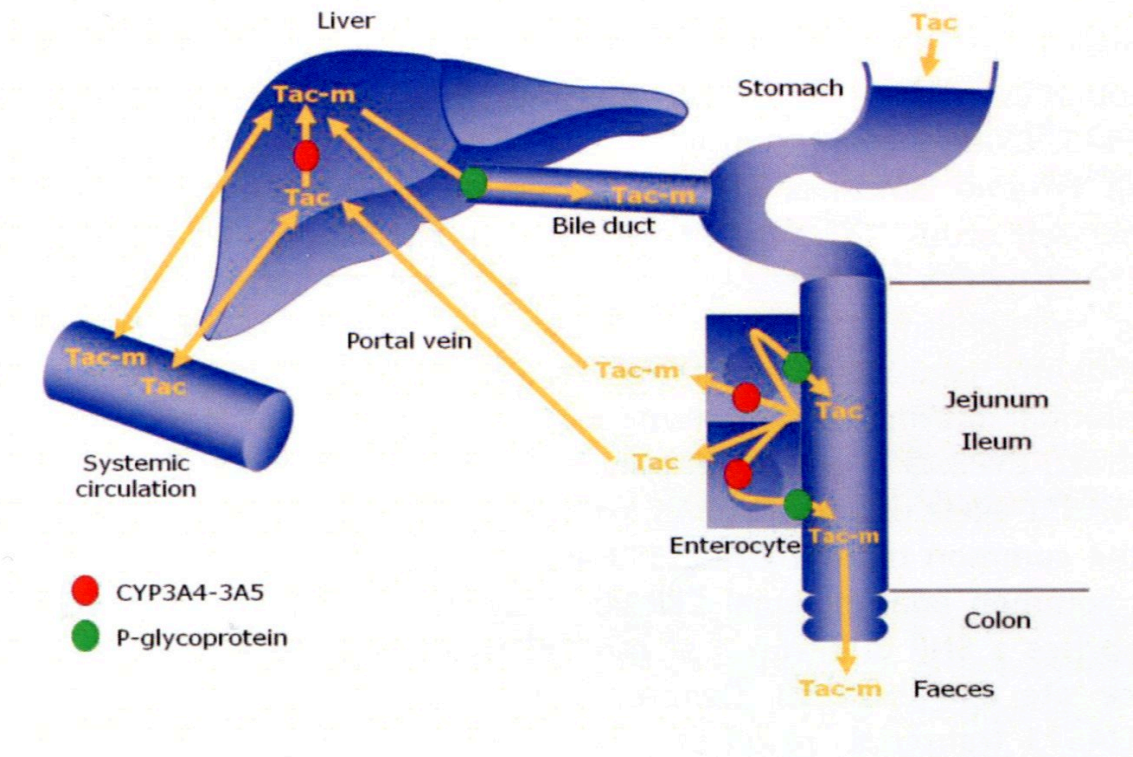
Pediatric renal Tx protocol Leuven

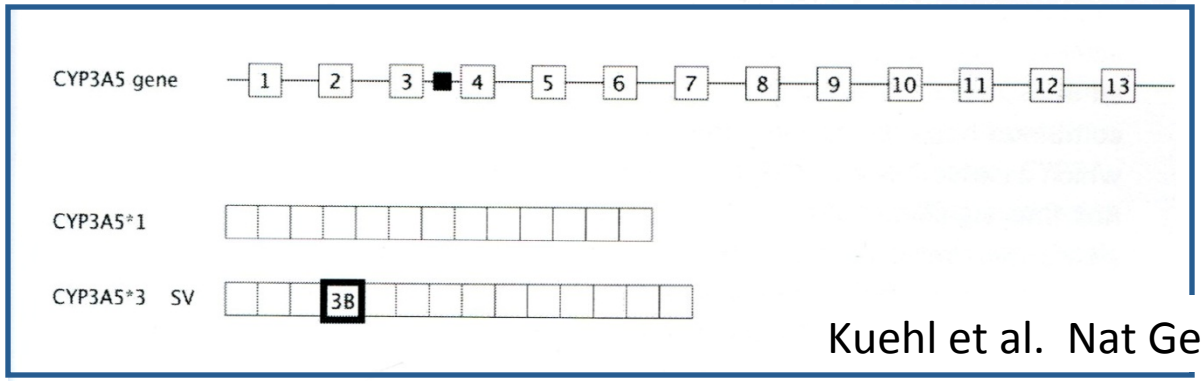
Tacrolimus

- 0.15 mg/kg in 2dd
- Trough levels (C0)
  - D0-30: 10-15 ng/ml
  - D30-180: 7-12 ng/ml
  - D>180: 5-10 ng/ml

Pediatric renal Tx protocol Leuven

CNI (tacrolimus) metabolism



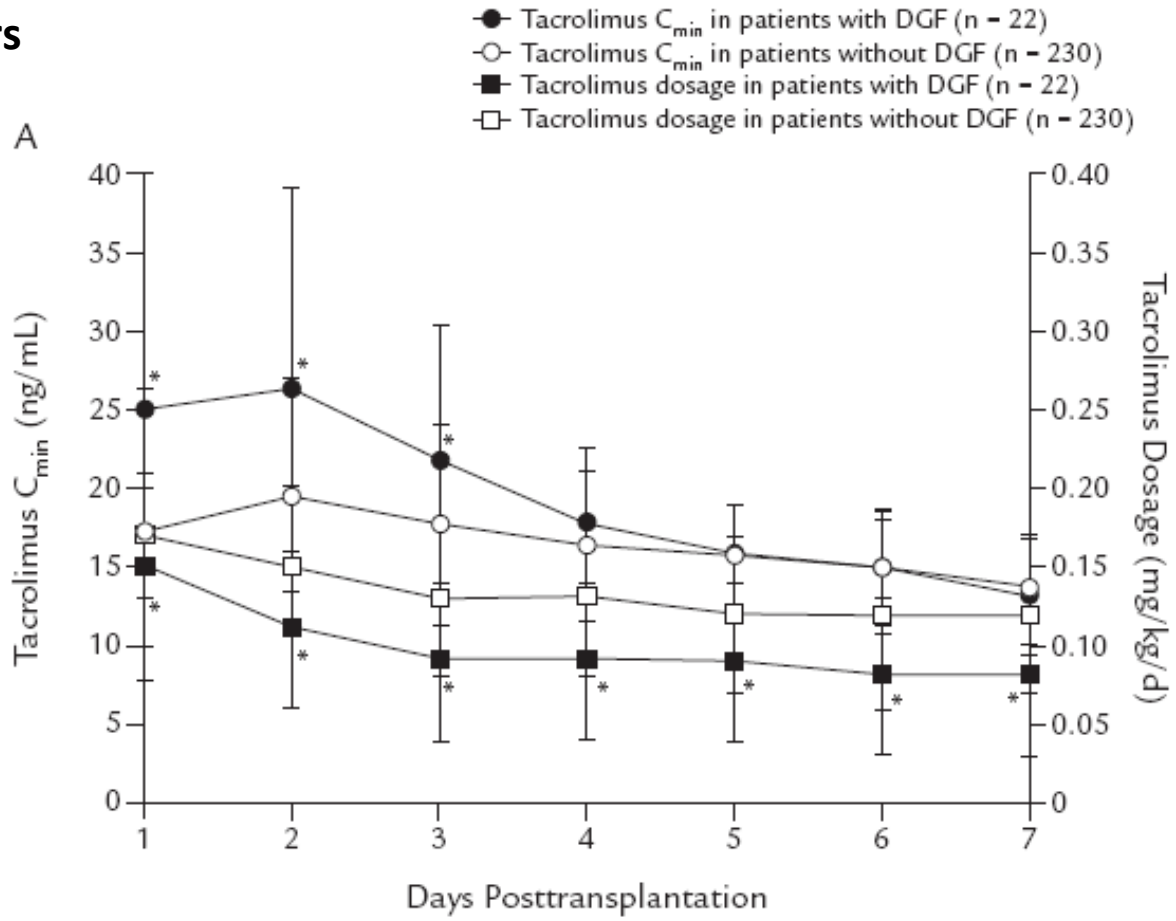


Kuehl et al. Nat Genetic 2001

Tacrolimus doses and trough levels depending on graft function

Non-expressors

CYP3A5*3/*3

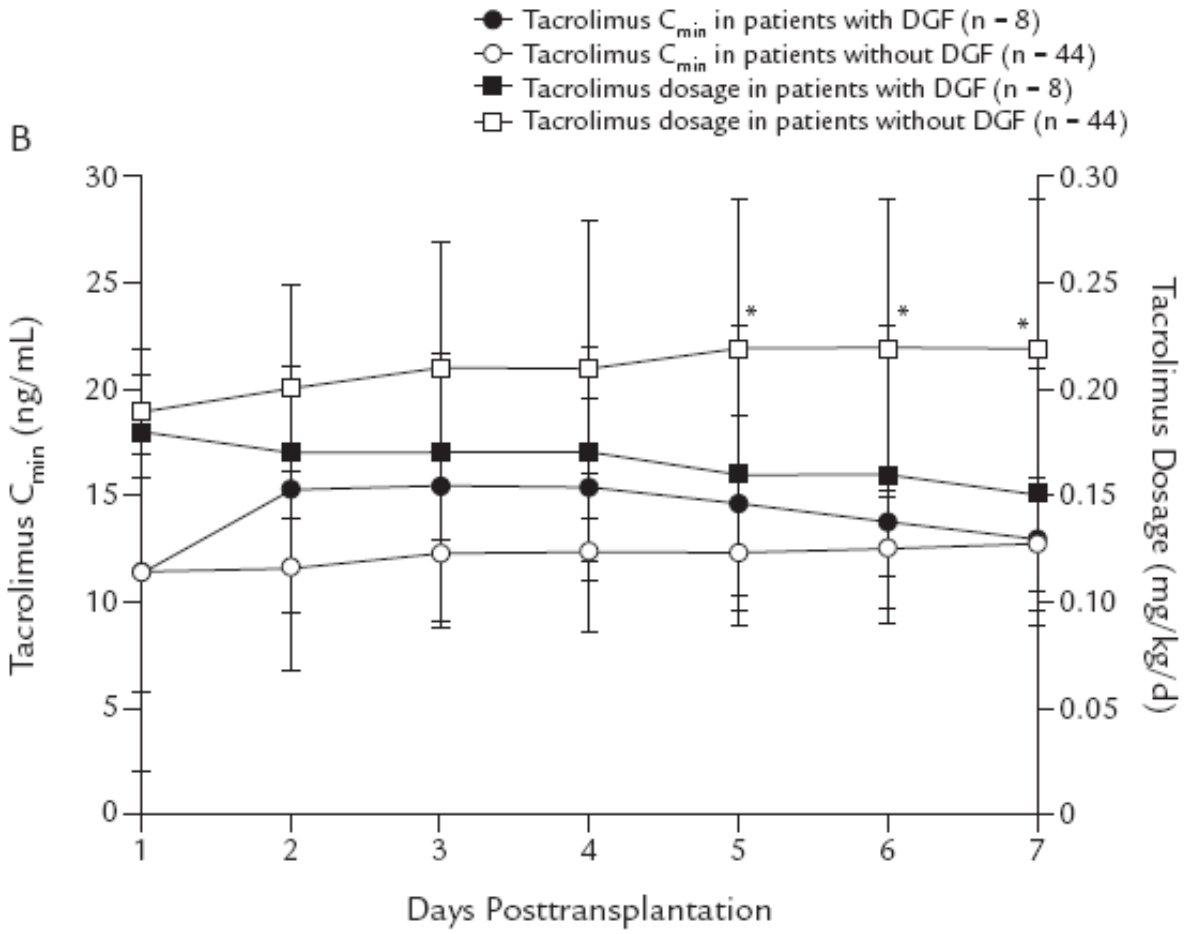


Kuypers et al. Clin Therapeut 2010

Tacrolimus doses and trough levels depending on graft function

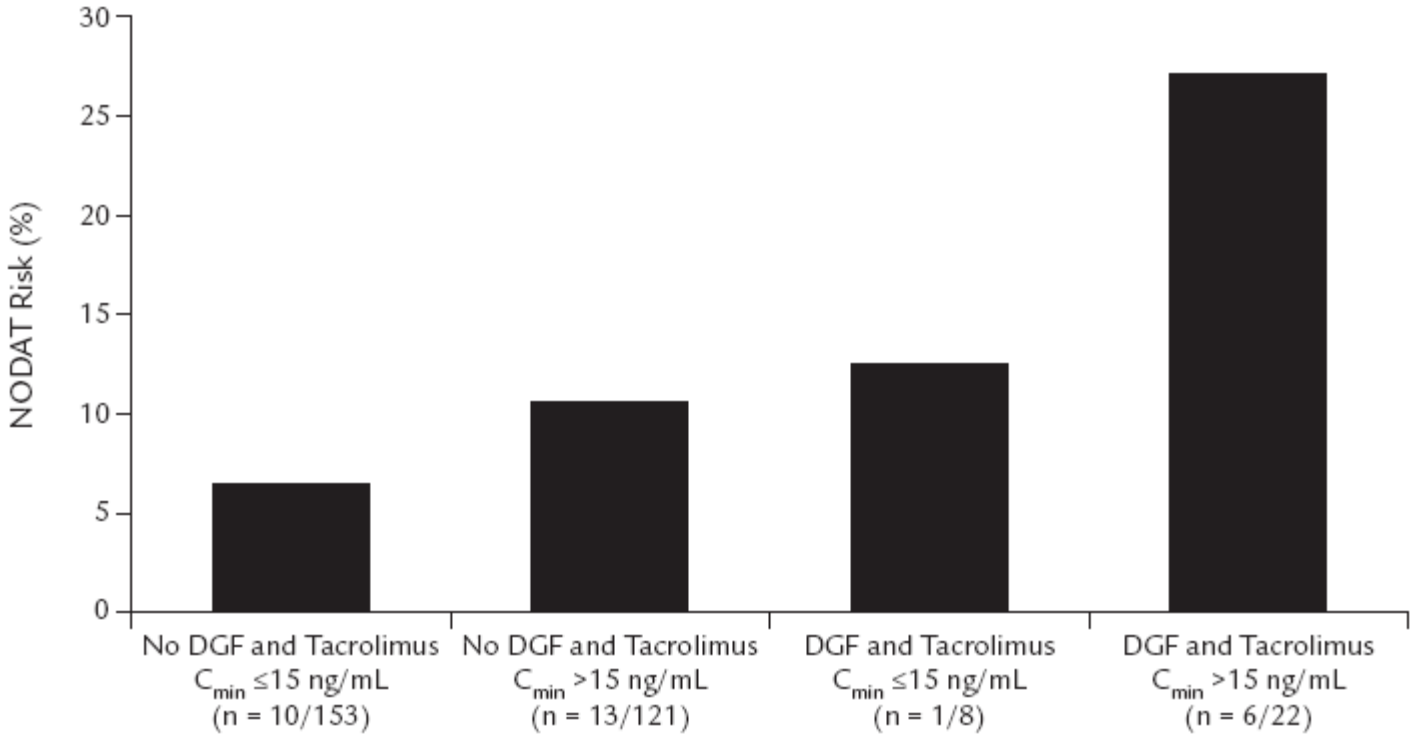
Expressors

CYP3A5*3/*1



Kuypers et al. Clin Therapeut 2010

Newly onset diabetes after Tx depending on graft function



Kuypers et al. Clin Therapeut 2010

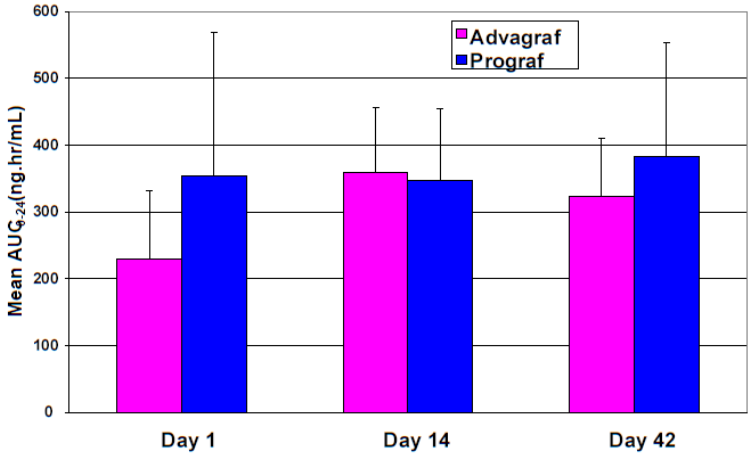
Tacrolimus administration

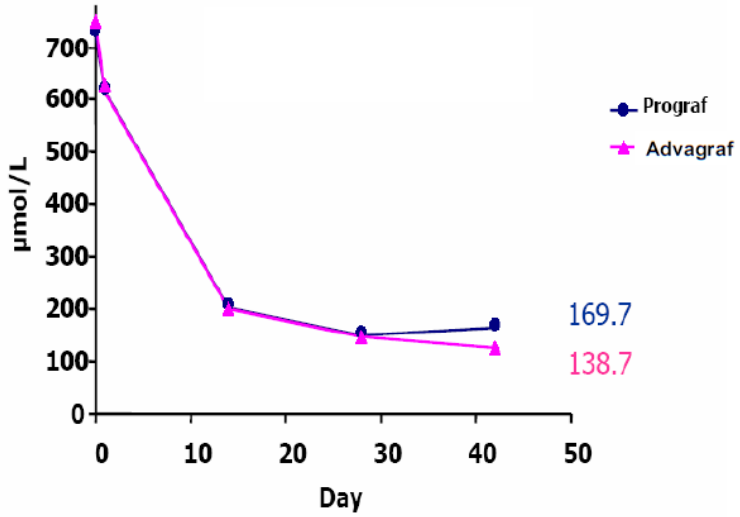
- No pre-operative dose if expected cold ischemia time > 36 hrs

- No post-operative treatment if no function of the graft

Advagraf

Advagraft vs Prograft in *de novo* kidney recipients





Tacrolimus interactions

- ↑ tacrolimus levels:
  - Erythromycin, Clotrimazole, Fluconazole Ketonazole
  - Omeprazole
  - Nifedipine/nicardipine (Hooper et al. Transplantation 2012)

  -….
- ↓ tacrolimus levels:
  - Rifampicin, Clarithromycin
  - …
- Increase risk of toxicity:
  - NSAIDs

Most frequent side effects of tacromilus

- ↓Renal function
- Hyperkalemia
- Hyperglycemia
- Hypertension
- ↑Liver enzymes
- Tremor

Mycophenolate Mofetil (MMF)

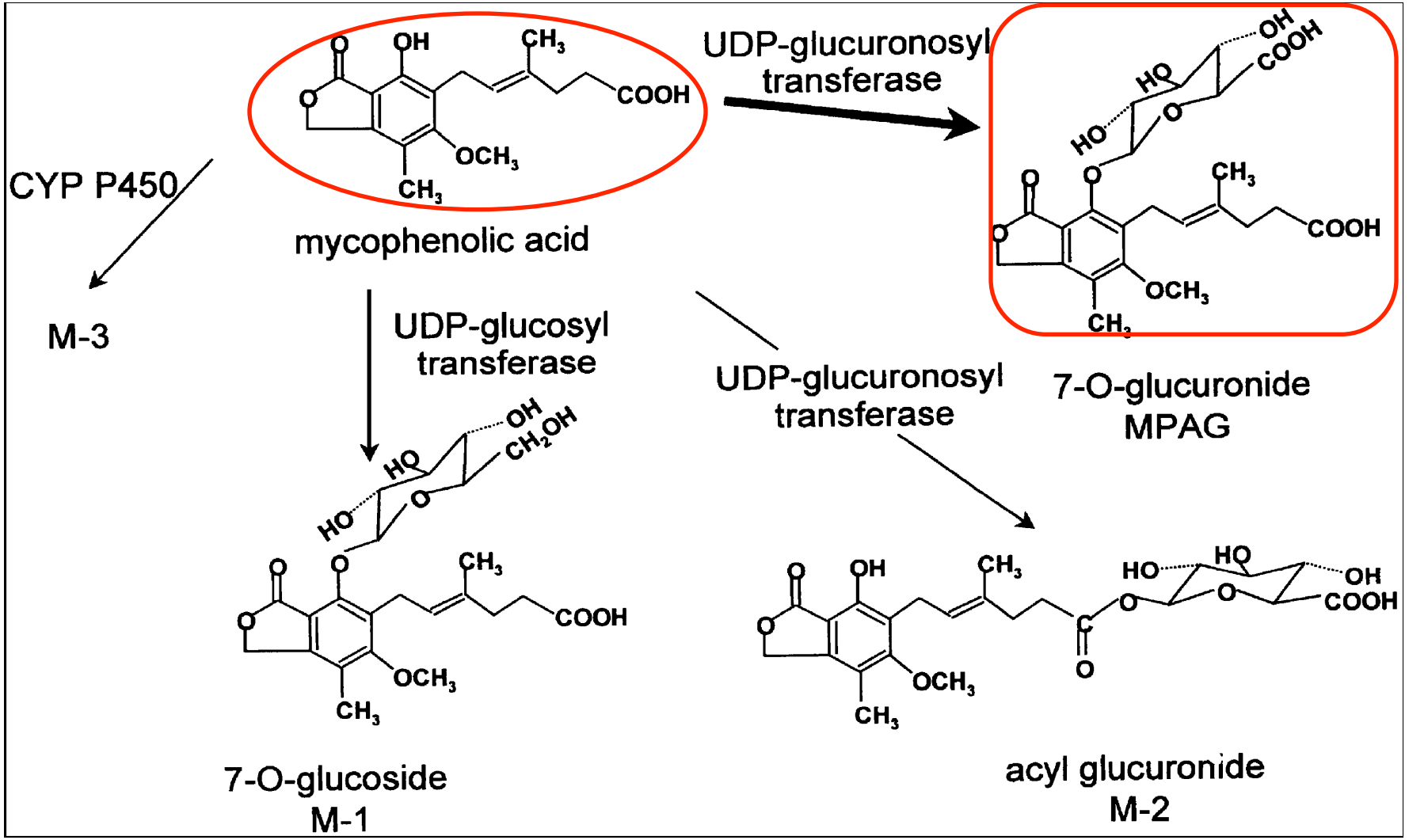
- 600 mg/m2 in x2 doses

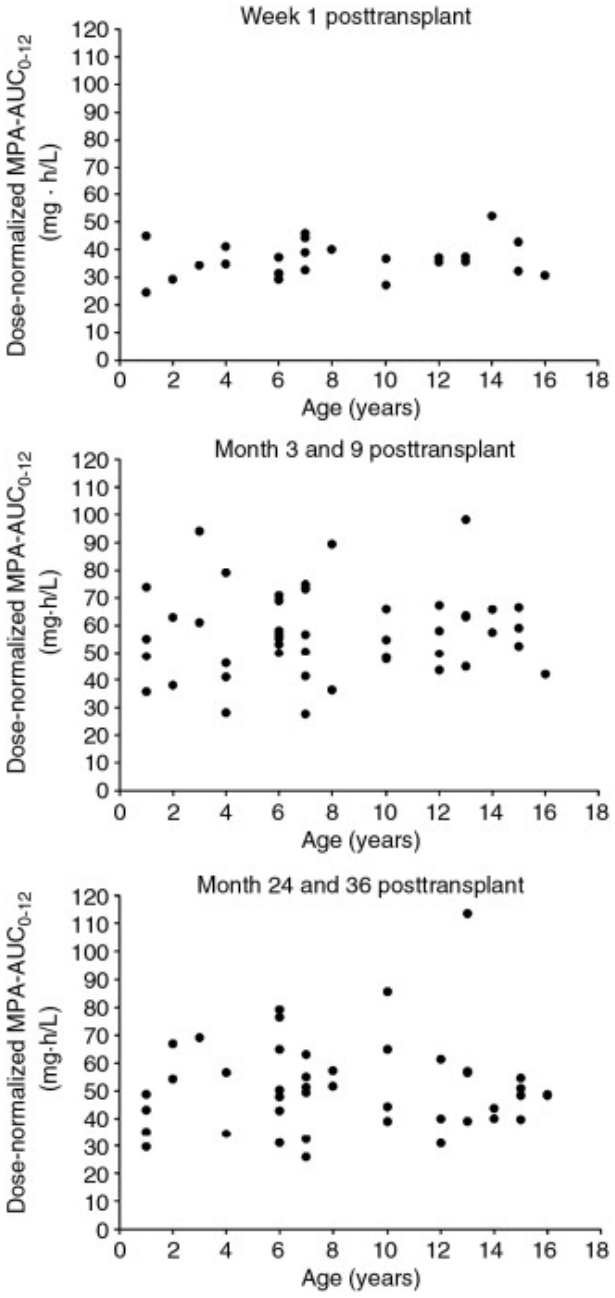
- Trough levels are not representative for exposure

- Monitor side effects
  - effect on bone marrow
  - gastrointestinal complaints

Pediatric renal Tx protocol Leuven

Metabolism of MMF





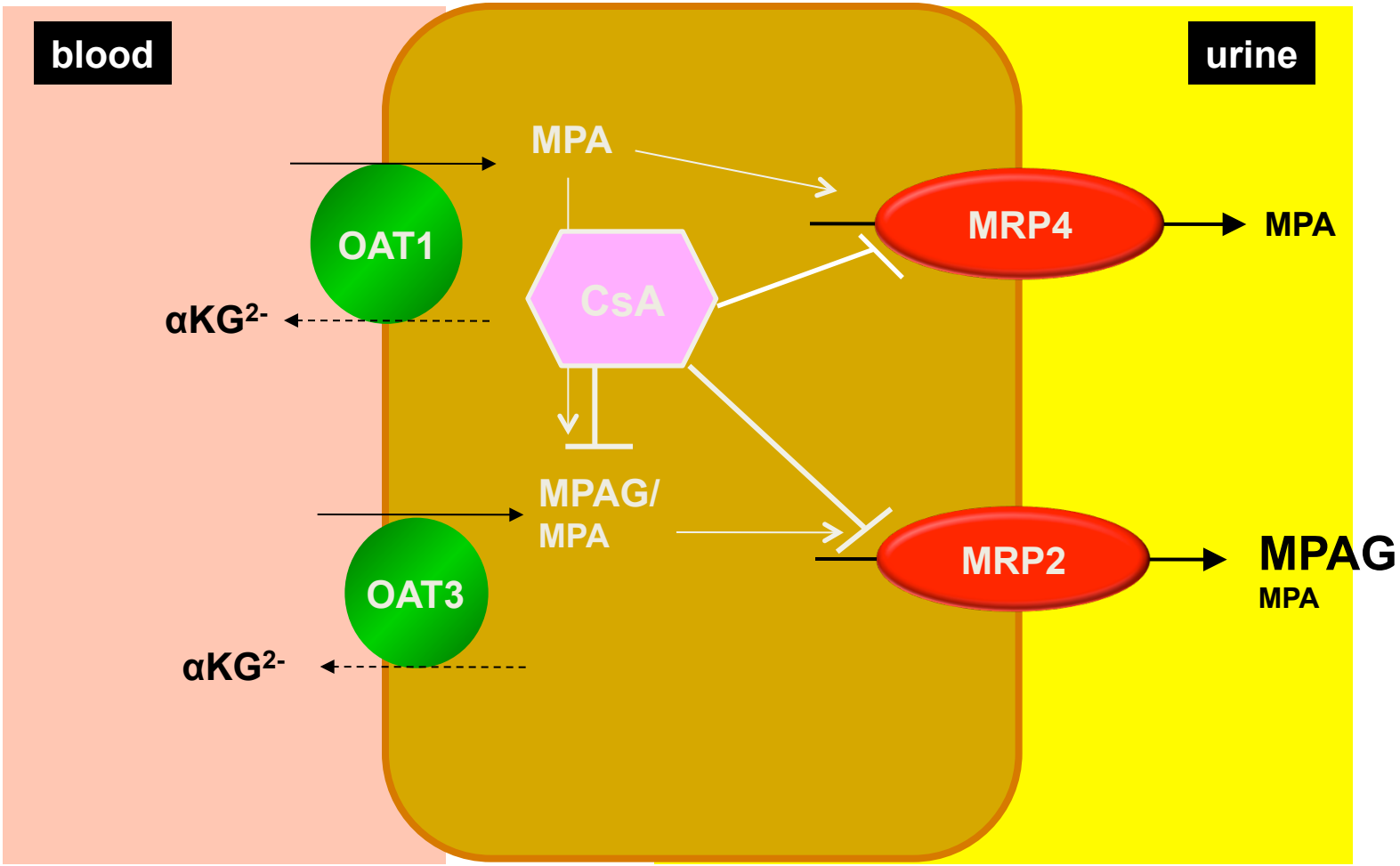
Weber et al. Ther Drug Monit 2008

- **Through levels (C0): not useful**
- **Big variability in drug exposure**
- **Recommended AUC (12 h) > 30 mg.h/l**
- **Frequent under-exposure with current dose regiments**

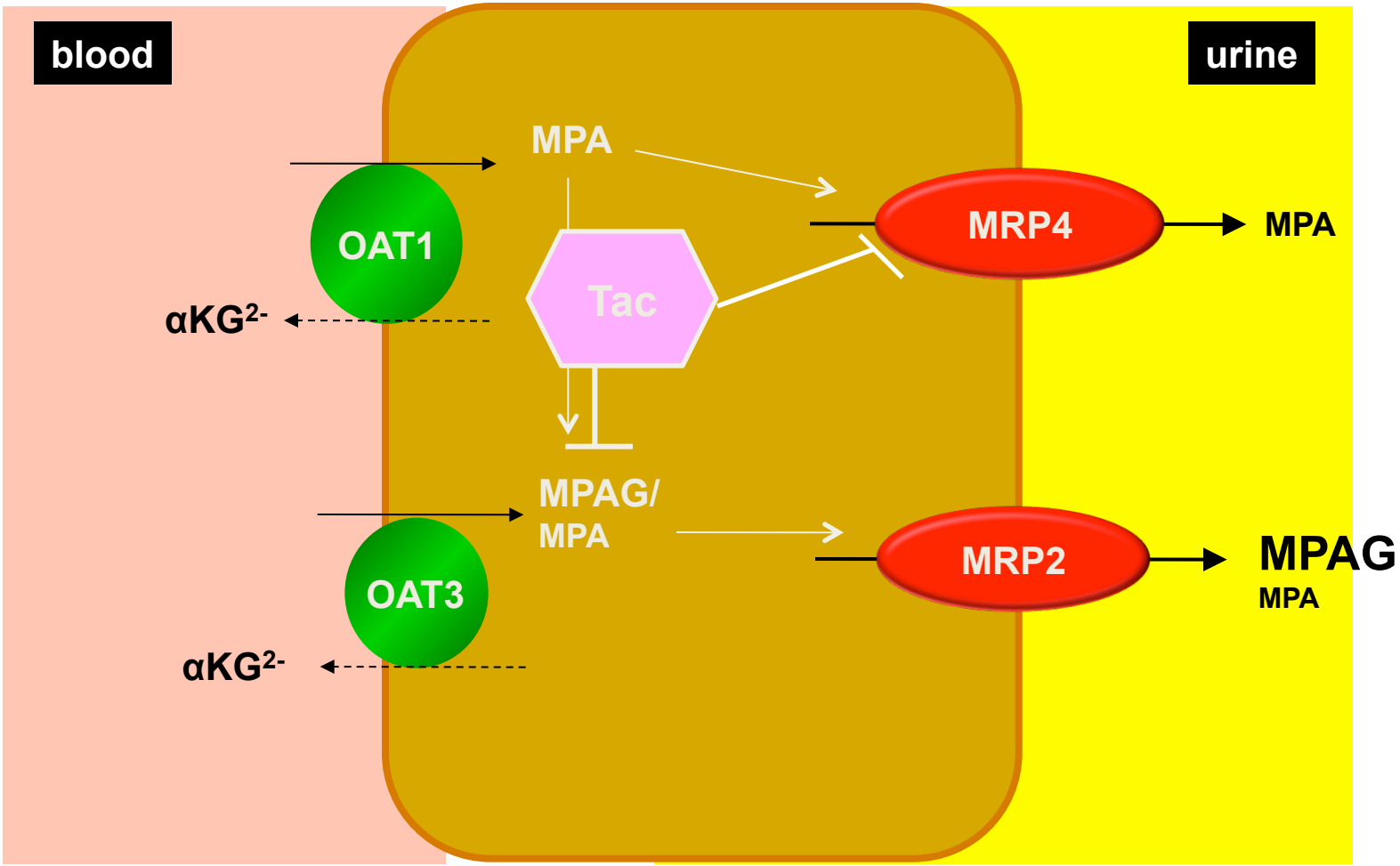
<u>AUC variability:</u>

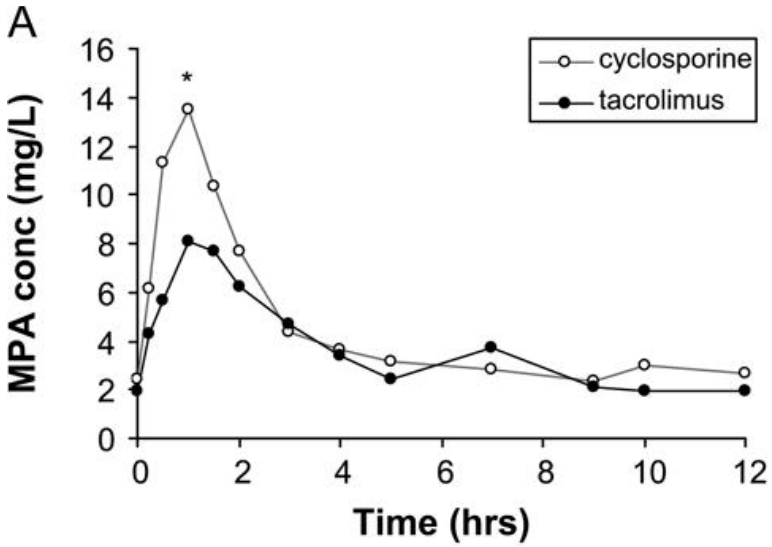
- **Interactions with other drugs (CNI)**
- **Factors interfering with entero-hepatic circulations**
  - **Meal**
  - **Drugs (CsA, inhibits MRP2)**
  - **Diseases**

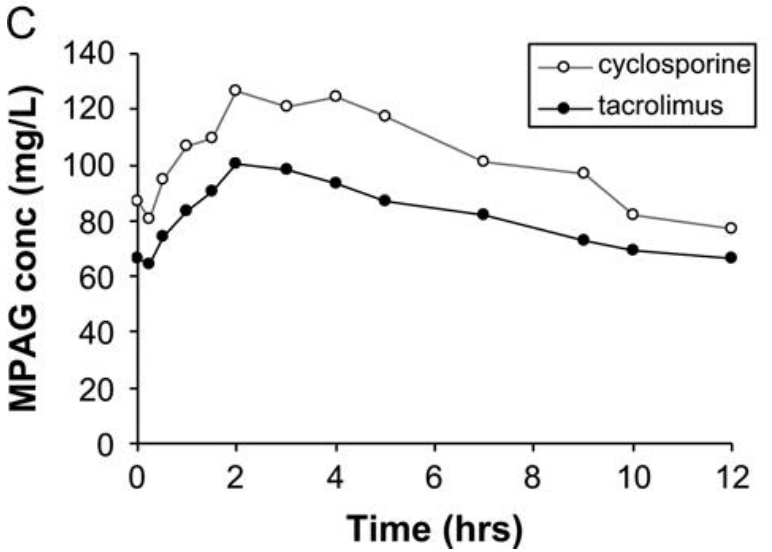
Interactie MMF and CNI



Interactie MMF and CNI





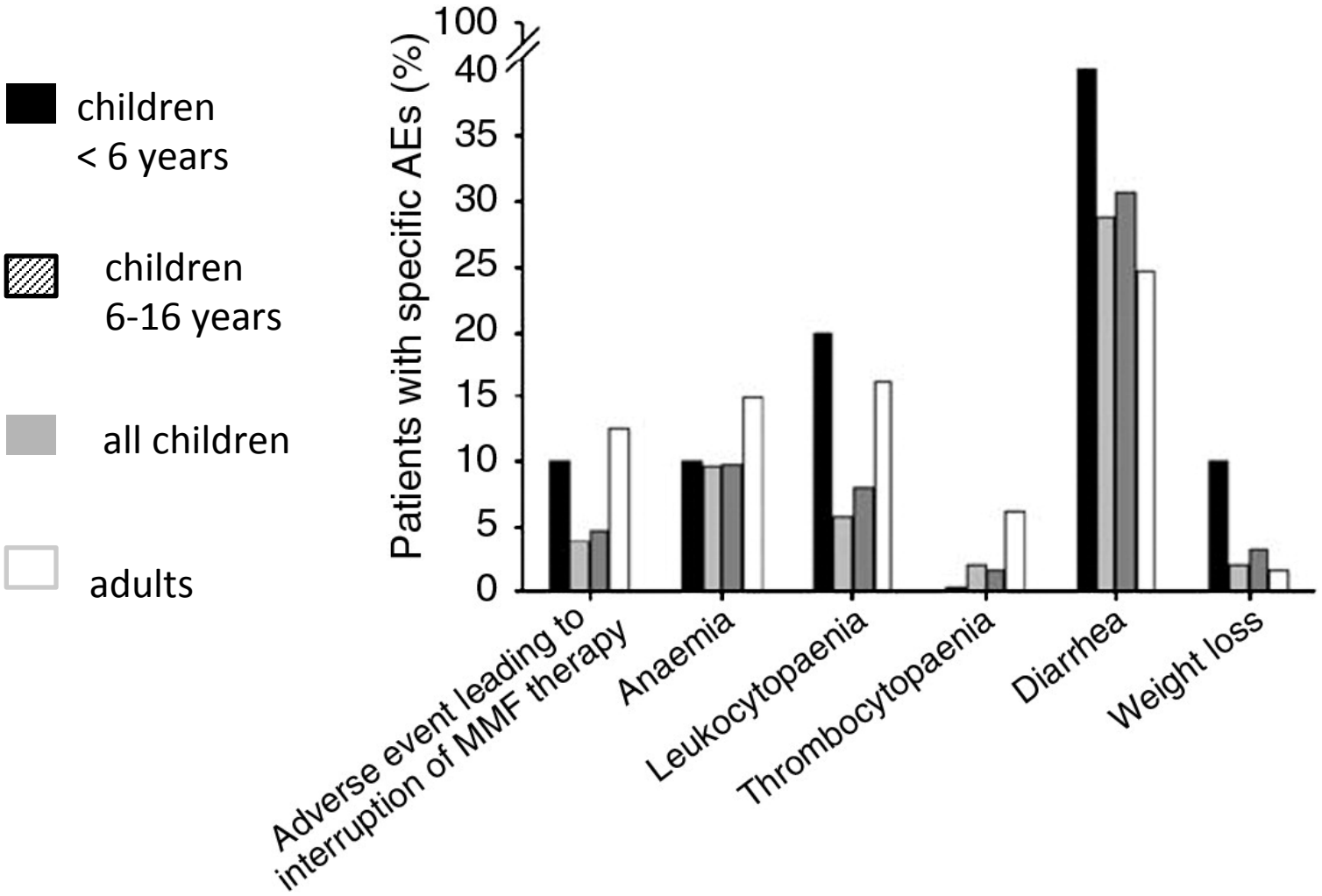


- **Tapering CsA can significantly increase (pre-dose) MPA plasma concentrations**
- **Switching from CsA to tacrolimus increases (pre-dose) MPA plasma concentrations**
- **1-3% free fraction of MPA = active fraction**
  - **Increased free fractions:**
    - **Nephrotic syndrome**
    - **Impaired renal function**

→ Increased risk of toxicity

Patel et al., 2007

Adverse events of MMF



Höcker et al. NDT 2010

Infection prophylaxis

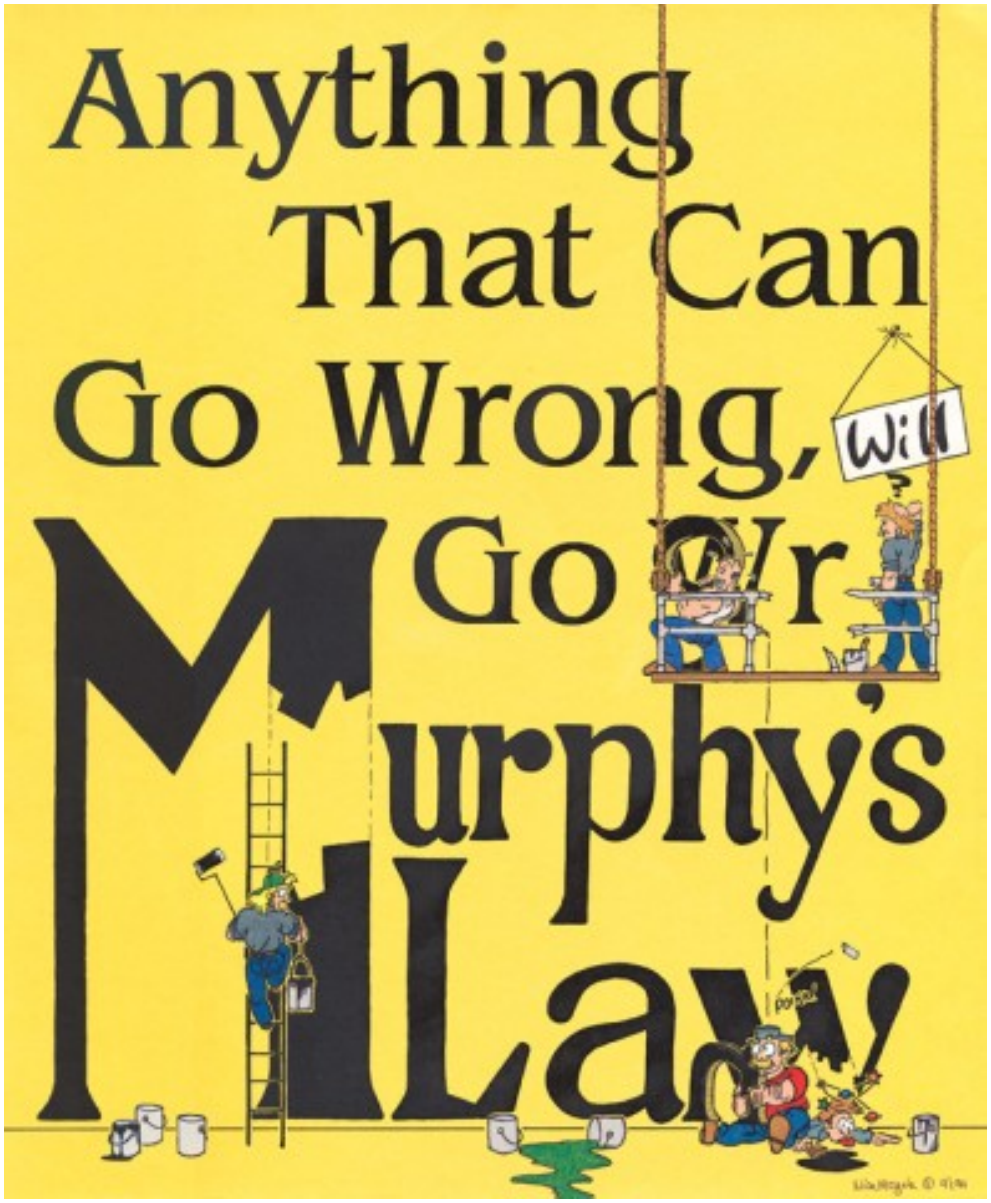
- Cefazoline 50 mg/kg/dose every 8 hrs (before OK, day 0)
- PPC prophylaxis: cotrimoxazole 4 mg/kg/day in x2
- Oral wash: nystatine/chlorohexidine
- CMV prophylaxis:
  - R-/D+: gancyclovor IV (dose adjustment depending on renal function) → after 14 d valgancyclovir PO
  - R+/D+ or D-: acyclovir IV (dose adjustment depending on renal function) → after 6 d acyclovir PO

Pediatric renal Tx protocol Leuven

Prophylaxis of osteoporosis

- Vitamine D3: < 10 kg: 400 IE/day
  > 10 kg: 800 IE/day

- Ca carbonate: < 10 kg: 250 mg/day
  >10 kg - < 40 kg: 500 mg/day
  > 40 kg: 1000 mg/day

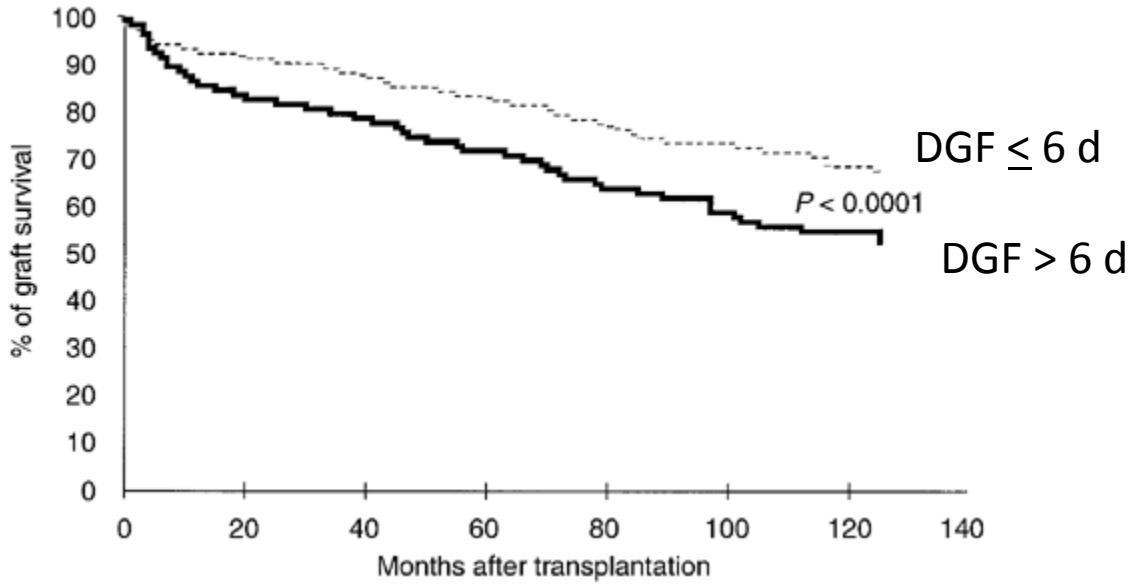

Anything
That Can
Go Wrong,
Will
Go Wr
Murphy's
Law!

Delayed graft function (DGF)

- Post-Tx acute renal failure: anuria or oliguria, increased graft immunogenicity, decreased long-term survival (Perico et al. Lancet 2004)
- Definitions (Yarlagadda et al. NDT 2008):
  - 65 studies (1984-2007)
  - A (75%): DGF = need of
  - B (14%): DGF = failure if
  - C (11%): A+B
- Incidence of DGF (Perico et al. Lancet 2004)
  - Living donor: 4-10%; Deceased donors: 5-50%

- Any need of dialysis post-Tx
- Need of dialysis post-Tx 4 d
- Need of dialysis post-Tx 7 d
- Need of dialysis post-Tx 10 d
- 2 or more dialysis sessions

Effect of DGF on graft survival



Gital-Classe et al. KI 1998

Risk factors for delayed graft function (donor)

- Procurement:
  - Non-heart beating donors
  - Inotropic support of the donor
  - Cold ischemia time (23%↑ for each 6 hrs)
  - Cold storage preservation instead of pulsative perfusion
- Age donor >55 years
- Marginal kidneys (diabetes, hypertension…)

Perico et al. Lancet 2004

Risk factors for delayed graft function (recipient)

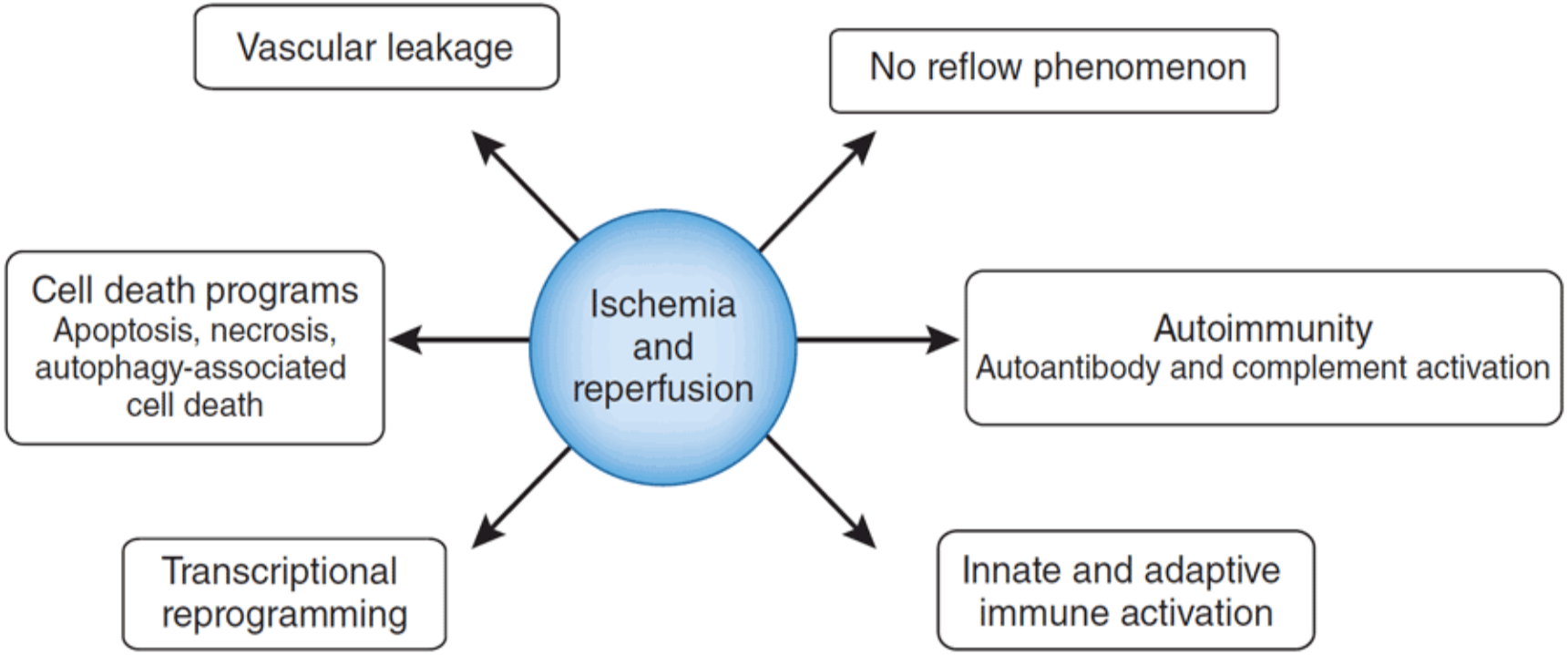
- Prerenal:
  - Hypovolemia (PD<HD<nocturnal HD?)
  - Haemodialysis with UF < 24 hrs before Tx
  - Recipient or donor bodyweight
  - N of previous transplants
- Renal
  - **Acute tubular necrosis**
  - Inherited thrombophilia (factor V Leiden mutations)
  - Antiphosphospholipid AB

  } **Graft thrombosis**

  - Antidonor AB → (**hyper)acute rejection**
  - CNI toxicity
- Postrenal:
  - Ureteral leakage
  - Ureteral obstruction

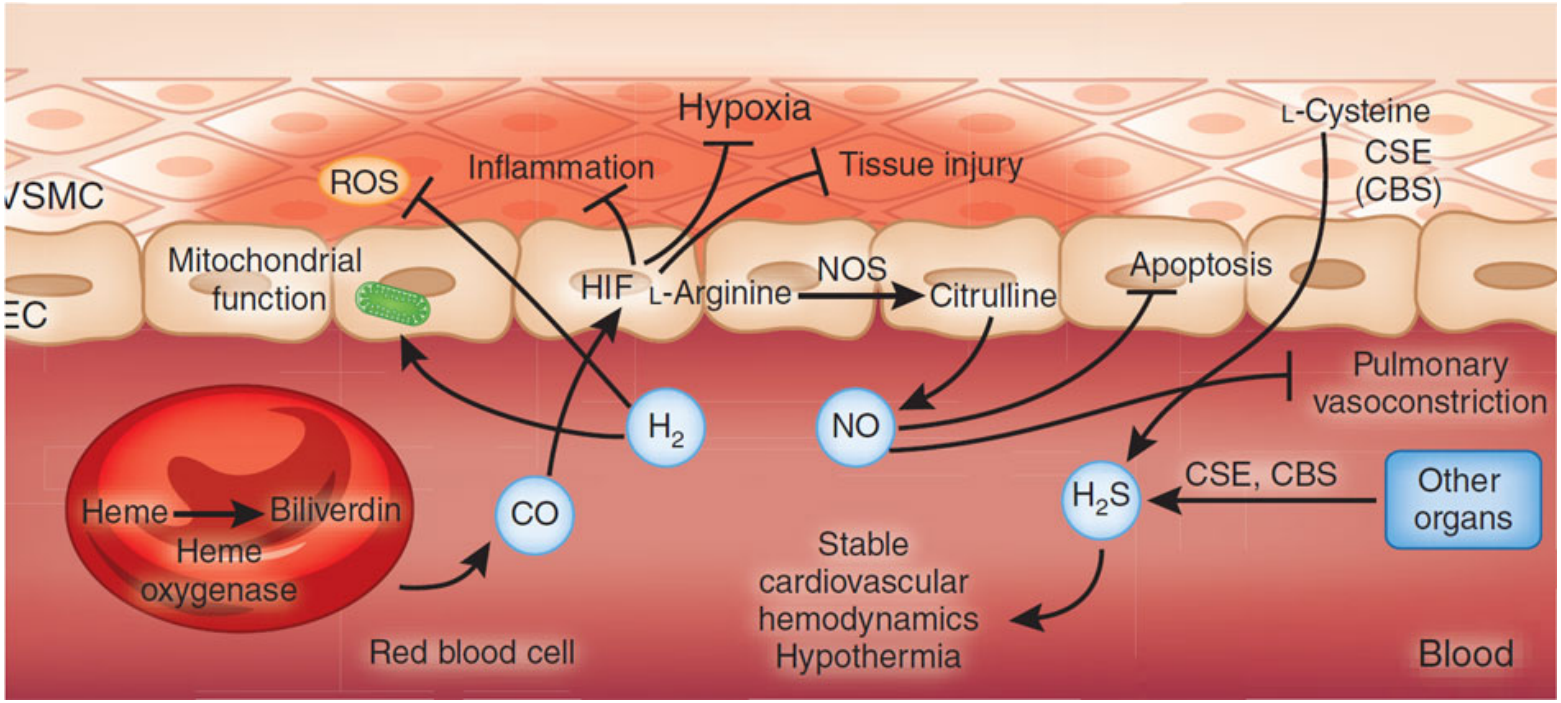
Perico et al. Lancet 2004

Ischemia-reperfusion injury (IRI)



Eltzschig&Eckle Nature Med Rev 2012

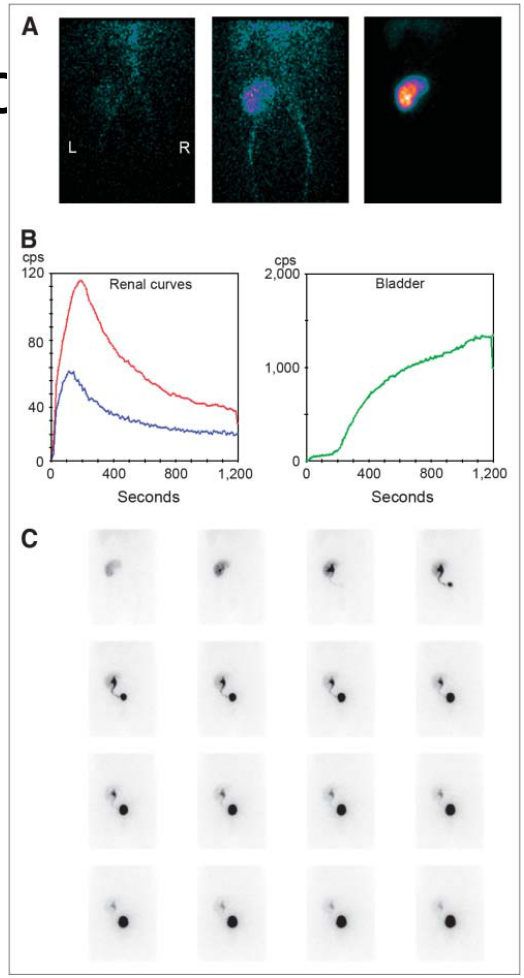
Gates for therapeutic interventions in IRI



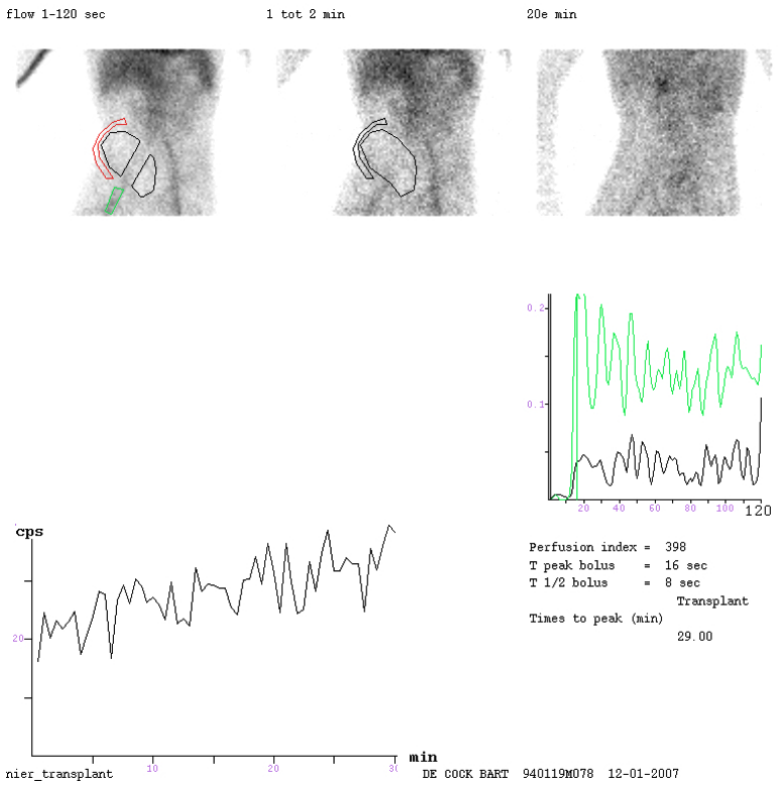
Eltzschig&Eckle Nature Med Rev 2012

Diagnostic strategies in DGF

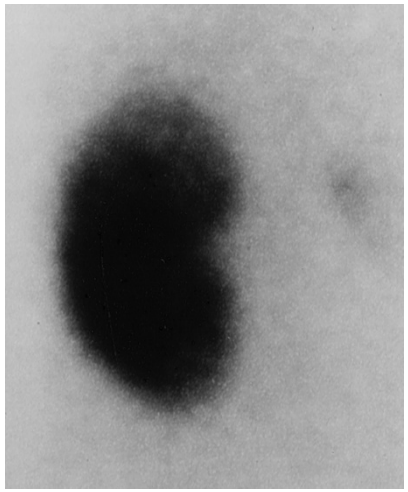
- US + Dc
- MAG-3
- Biopsy



Normal MAG-3



a. renalis thrombosis



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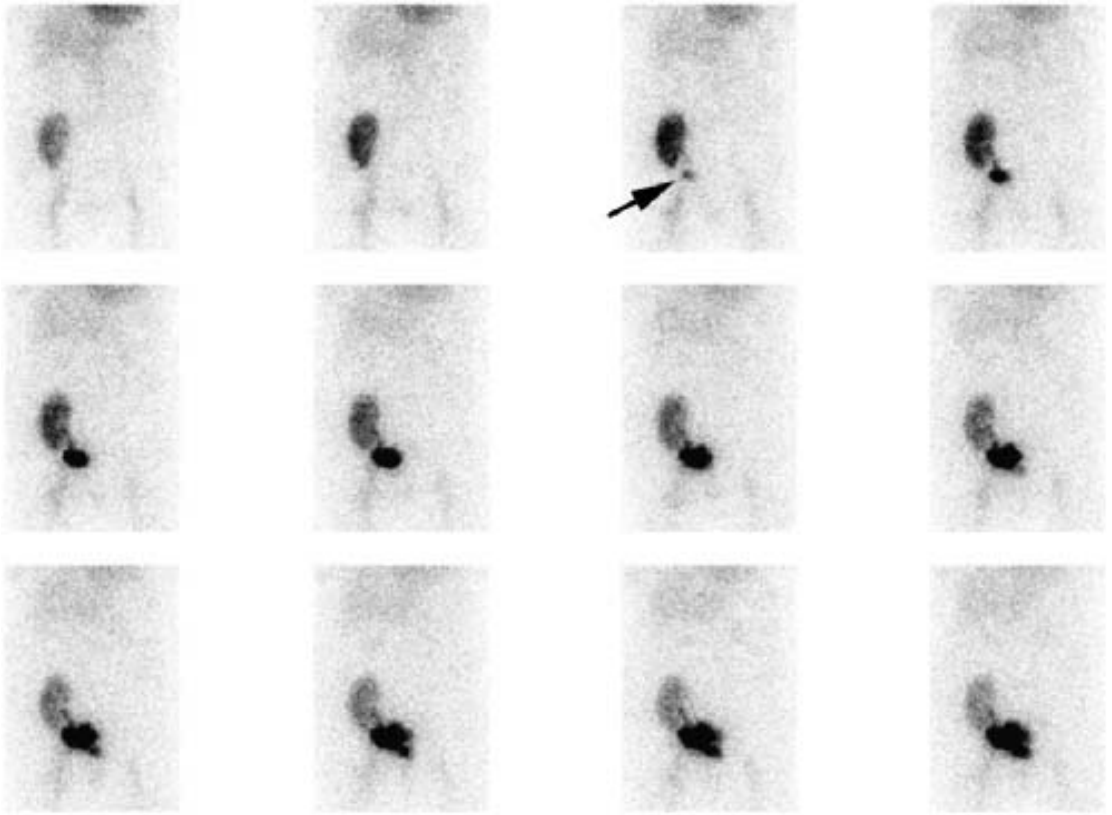
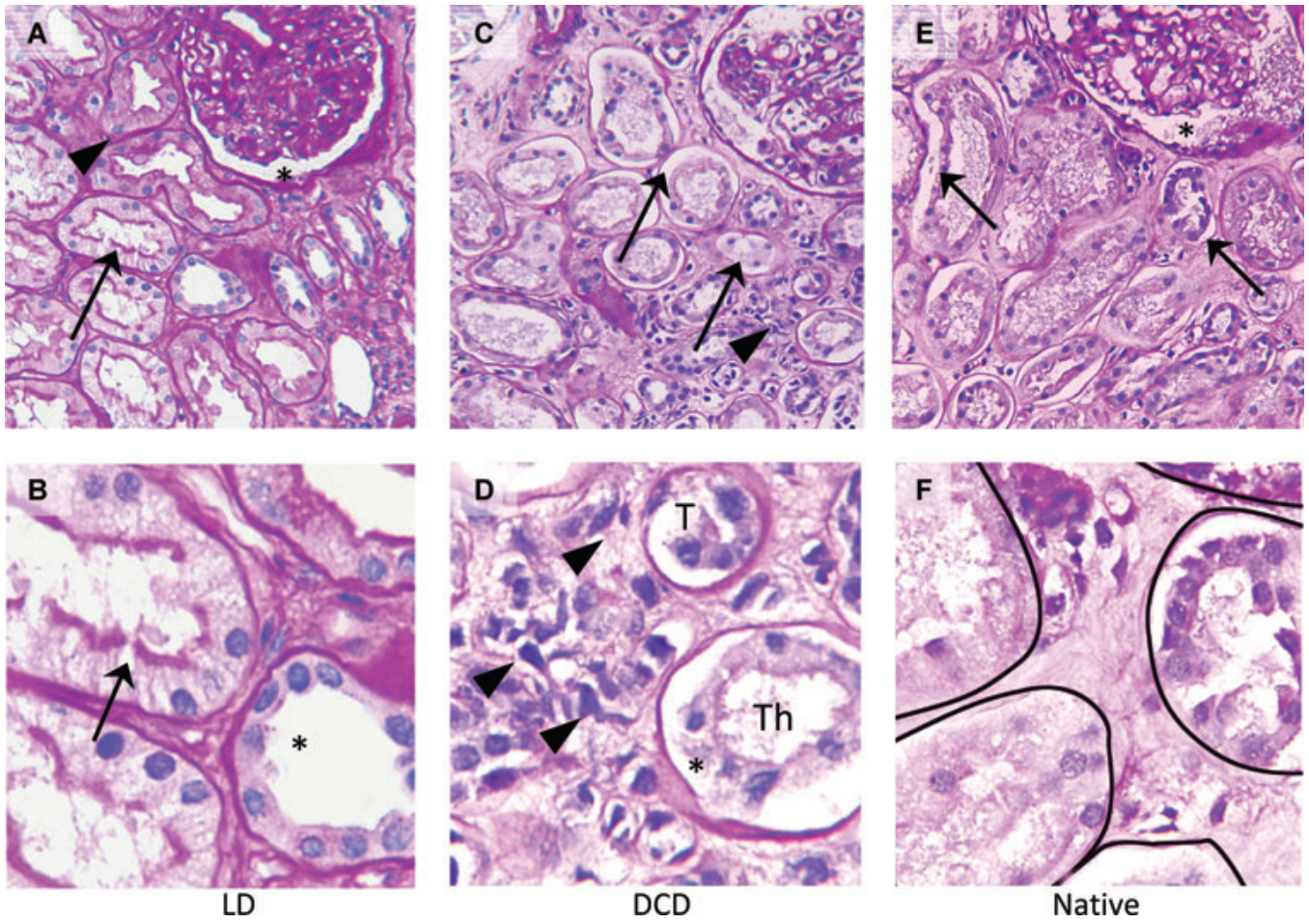


Urine leackage

Histological changes in DGF



Siedlecki et al. Am J Transplant 2011

Prevention of DGR

- Donor factors (best donors for children!, propagate living donation)
- Organ preservation, keep ischemia time as short as possible
- Recipient factors:
  - Avoid hypovolemia, mannitol/furosemide during Tx
  - Thrombosis prophylaxis: enoxaparine 0.5 mg/kg x2 dd SC 10 days
    - Recipient < 5 years
    - En block Tx
    - Disproportion of blood vessels between donor/recipient
    - Vascular problems during Tx
    - Thrombophilia

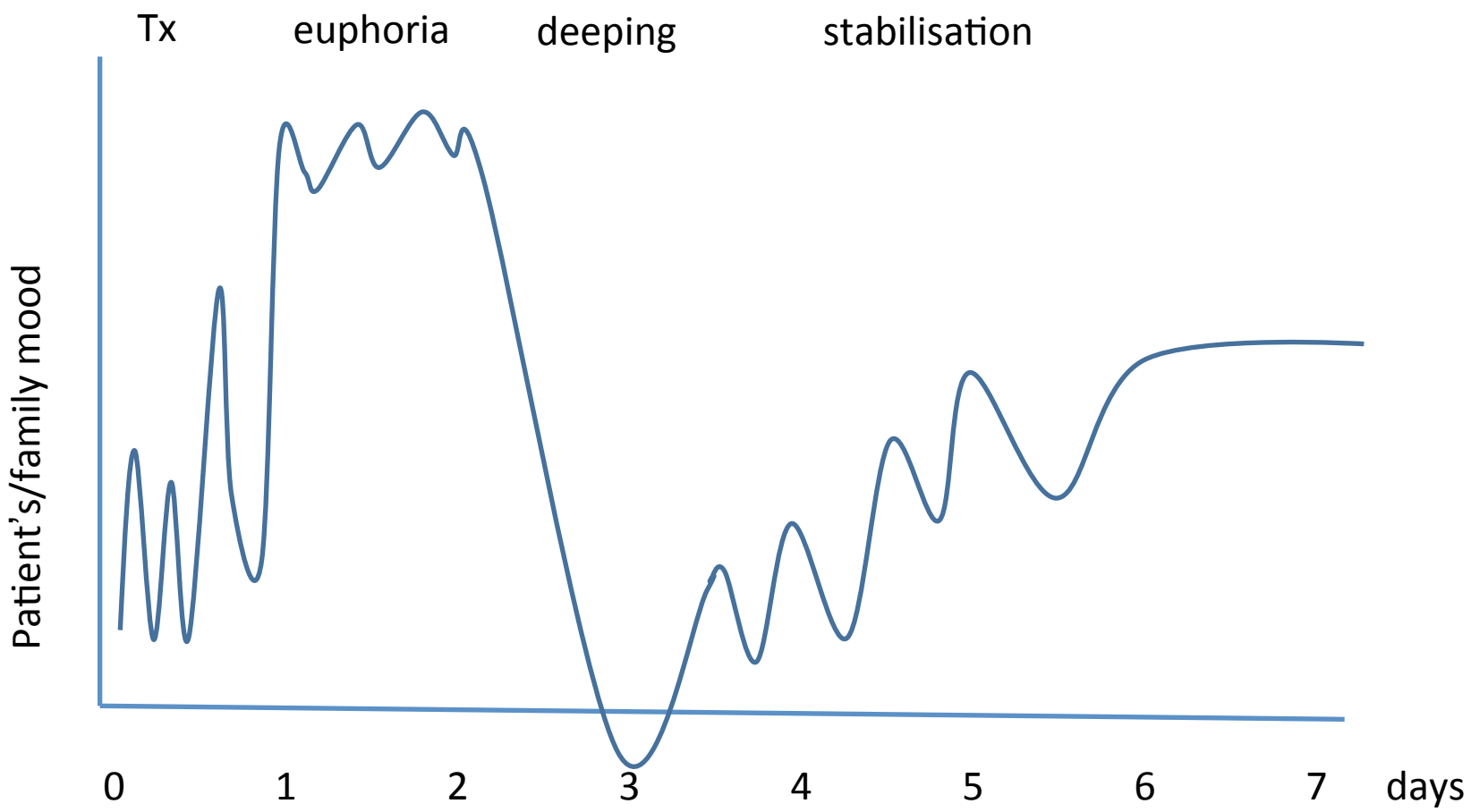
Pediatric renal Tx protocol Leuven

Hyperacute rejection

- Due to allosensitisation

- Extremely rare due to advantages of detection of panel-reactive antibodies and cross-proof prior to Tx

Psychological issues



“Take-home” message

- Детскую почечную Тх следует проводить в специализированных центрах, при участии опытных хирургов и медицинской бригады
- Предварительное обследование пациента имеет важное значение для предотвращения острых (и хронических) осложнений
- «Лучший доноры - для детей“!


PAPA
MAMA
IK
EINDELIJK
KRIJG IK
EEN NIER!
BEDANKT


Pediatric Nephrology Unit
Добро пожаловать в Лёвен!