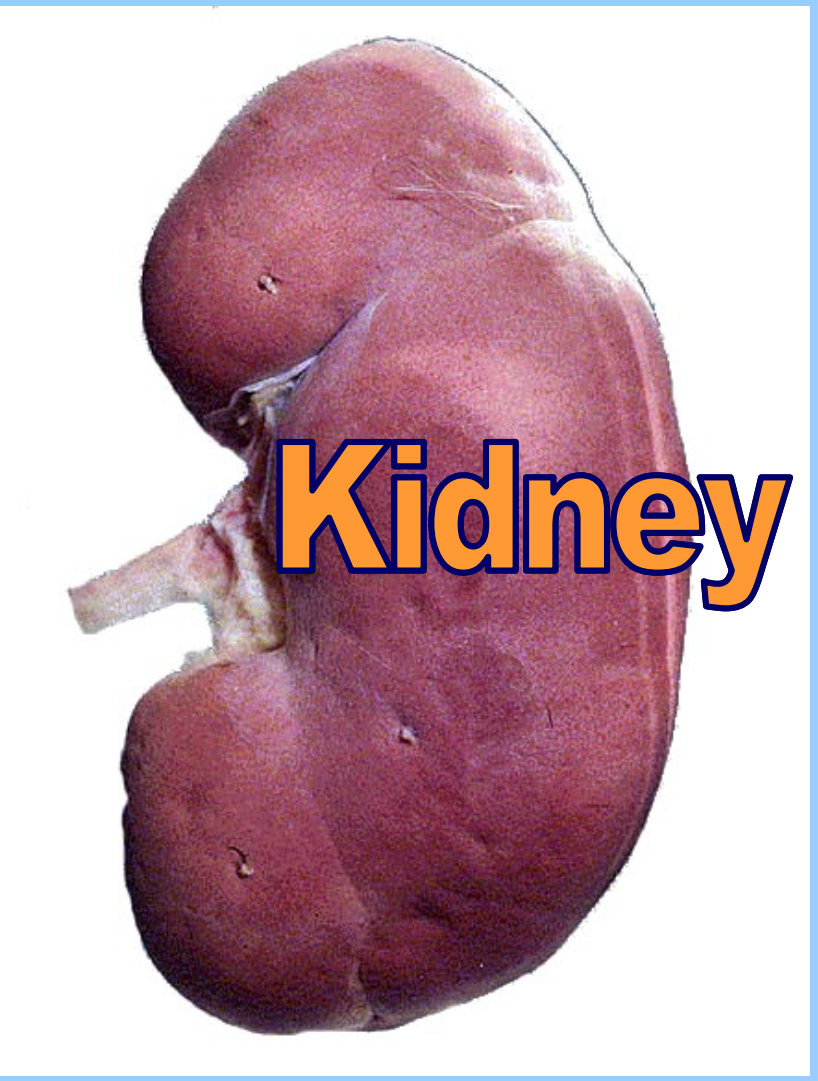


Kidney transplantation

MUDr. J.Svojanovský

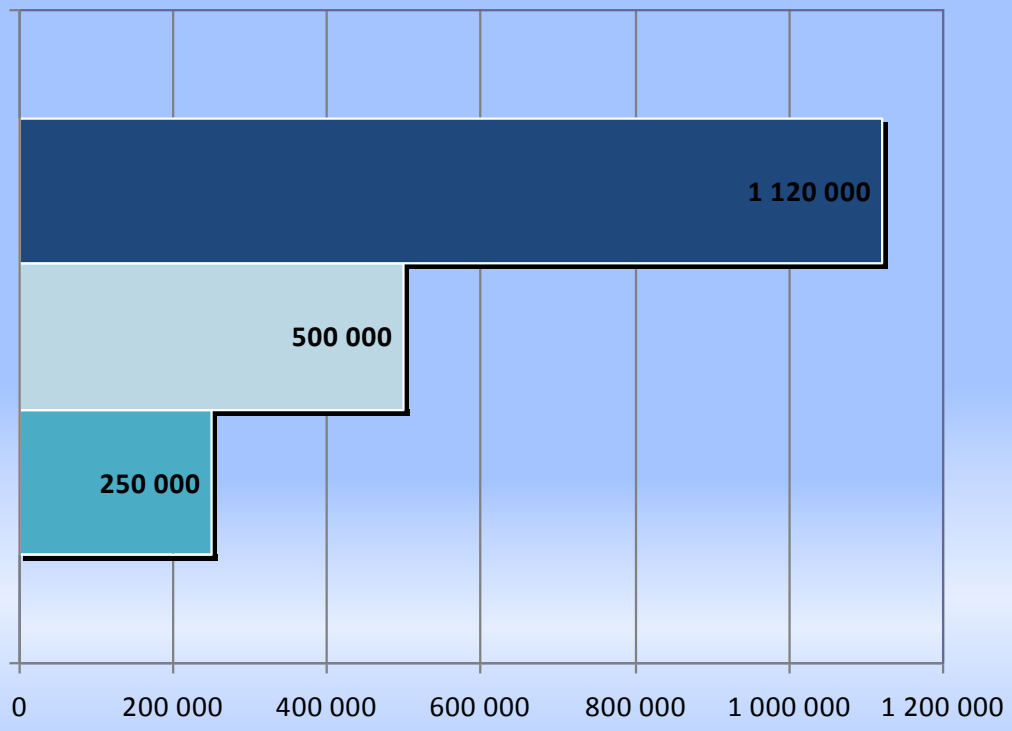
II. interní klinika FN u sv. Anny v Brně

Renal replacement therapy	excrect. function	metabolic/ endocrin.f.	availability
1. EXTRACORPORAL 1.1. hemodialysis 1.2. hemofiltration 1.3. hemodiafiltration	+	–	immediat.
2. INTRACORPORAL 2.1. CAPD 2.2. APD (cycler)	+	–	weeks
3. KIDNEY TRANSPLANTATION	+	+	month-years

Kidney transplantation (Tx)

- **best option for patient with chronic renal failure**
  (recovery of both excrectory and metabolic/endocrine functions)
- **not a life-saving transplant**
  (Tx is one of three options of renal replacement therapy)
- **hardest available**
  (necessity of waiting or searching for suitable donor)
- **most improves the quality of life**
- **most cost-saving**

Comparison of costs (in CZK)



TRANSPLANT DONORS

1. LIVING DONORS

A) GENETICALLY RELATED (parents, sibling, children)

B) GENETICALLY NON-RELATED (spouse, friends, altruistic)

Advantages:

1. ***no waiting for Tx*** (avoidance of prolonged dialysis – time on dialysis may be a risk factor for poorer transplant outcome)

2. ***the best organ quality*** (minimal ischaemic damage of graft, which can cause delayed graft function)

3. ***better graft and patient survival than cadaveric transplantation*** **–** regardless of genetic relationship and HLA mismatch **(genetically non-relat. living donor is better than cadaveric HLA well-matched donor)**

Pre- emptive transplantation (prior to dialysis) – best outcome of all

TRANSPLANT DONORS

- **CADAVERIC (deceased) DONORS**

  organ obtained from someone who has died

Czech republic: 88% cadaveric Tx, 12% living donor Tx

Western countries: 50% cadaveric, 50% living donor

CADAVERIC ORGAN DONATION

1.VOLUNTARY

individual has consented to donate his/her organs after the death
(donor s card, record in driving licence)

2.PRESUMED CONSENT

it is presumed that **ALL ADULT** individuals
AGREE to donate their organs after the death **UNLESS** they have registered an objection
(**Czech Rep**., Austria, France, Portugal)

3.PRESUMED OBJECTION

it is presumed that **ALL ADULT** individuals
DON T AGREE to donate their organs after the death
CONSENT IS REQUIRED FROM FAMILY

CADAVERIC DONOR (part I)

1. PEOPLE WHO ARE BRAINSTEM DEAD
2. BRAIN DEATH = DEATH OF ORGANISM
3. The patient has irreversible BRAIN DAMAGE OF KNOWN CAUSE (head injury, brain haemorrhage, after long resuscitation, drowned people)
4. All efforts have been made to treat the patient condition and any associated problems

CADAVERIC DONOR (part II)

CRITERIA OF BRAIN DEATH

1. **DEEP COMA with no signs of reactivity**
2. **MUSCLE ATONIA**
3. **AREFLEXIA OVER C1**
4. **NO SPONTANEOUS BREATHING**
5. **NO SIGNS OF BRAINSTEM IN BRAIN CAVITY BY BRAIN PANANGIOGRAPHY**

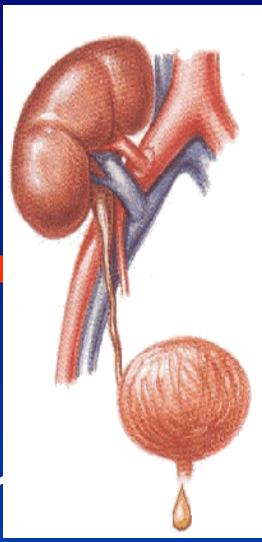
CONTRAINDICATIONS OF ORGAN TAKING

1. WRITTEN OBJECTION DURING THE LIFE
2. THE CAUSE OF DEATH IS NOT KNOWN
3. DONOR HAS:
   hepatitis B/C, HIV +, generalised infection, malignancy, disease of unknown cause

ESSENTIAL CONDITION OF RENAL TRANSPLANTATION

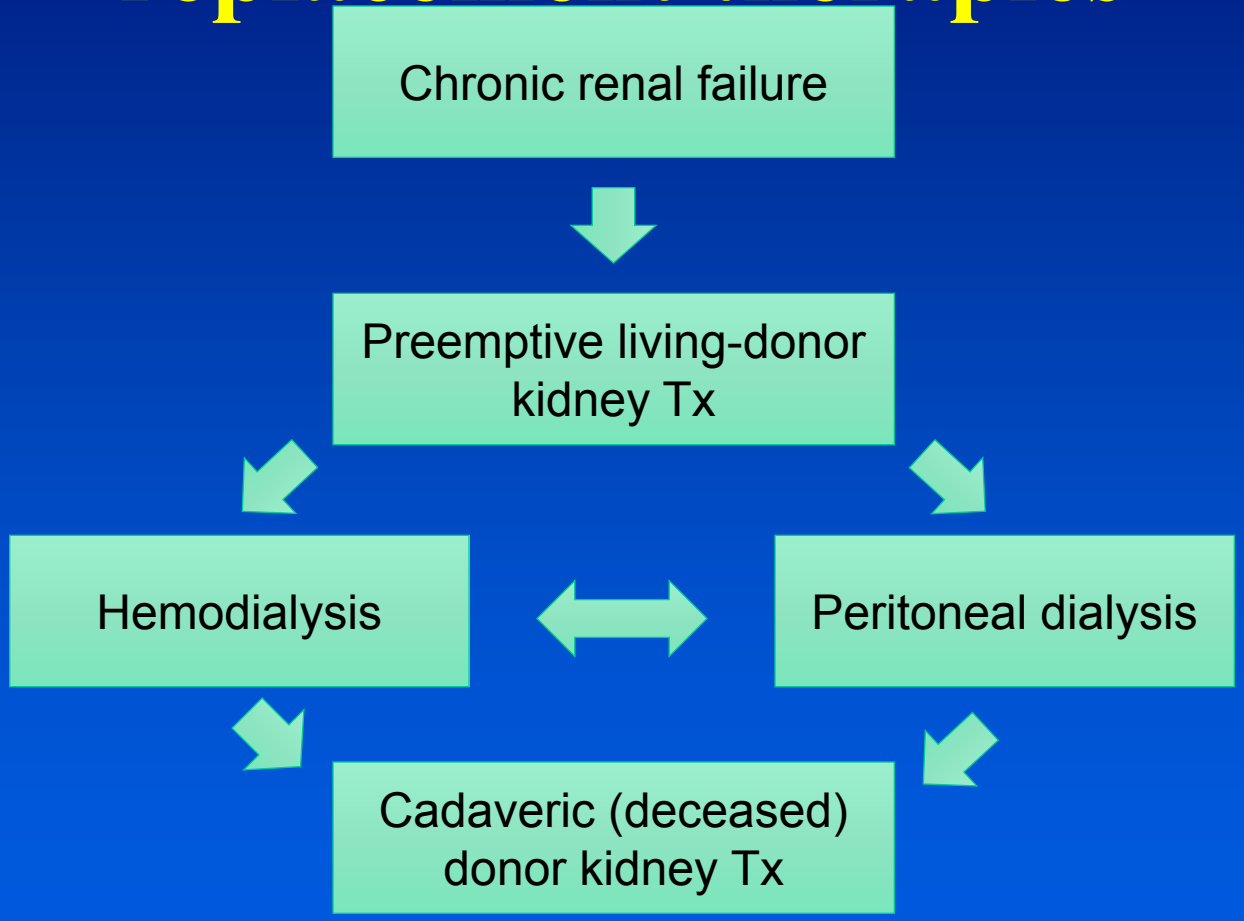
1. DONOR
2. FINDING OF SUITABLE COUPLE RECIPIENT – DONOR
3. MAINTENANCE IMMUNOSUPPRESSION TO PREVENT REJECTION

RECIPIENTS OF KIDNEY GRAFT



- Patient with severe deterioration of renal function (prior to dialysis - pre-emptive living donor or cadaveric Tx) or patient on renal replacement therapy (dialysis method) due chronic renal failure
- without contraindications
- being on waiting list

Chronic renal failure – renal replacement therapies



CONTRAINDICATIONS

1. PERMANENT (CONTINUING)

- non-treatable chronic inflammatory disease
- active chronic liver disease
- malignancy (min. 2 years desease-free)
- non-solvable abnormalities of distal urinary tract (urinary bladder, and urethra)
- serious disease of other systems (e.g. cardiovascular)
- diabetics with progressive foot necrosis

2. TRANSIENT (TEMPORARY)

- acute infection of various origin
- disturbances of haemocoagulation
- acute disease of gastrointestinal tract
- any treatable temporary disease (cardiovascular complications, fracture,..)
- obesity (BMI > 35)

WAITING LIST

- number of identification
- personally dates (name etc)
- blood group
- HLA antigens
- Panel Reactivity Antibodies
  (PRA = antileukocytes ab)
  (scale: 0 – 100 %)

WAITING LIST: BRNO - VČETNĚ DOČASNĚ VYŘAZENÝCH ČEKATELŮ

POŘ.	EV.ČÍSLO	SEX JMÉNO ČEKATELE ABO RODNÉ ČÍSLO DG. POČET TX	BYDLIŠTĚ: ULICE MĚSTO TELEFON	ZAŘAZENÍ VYŘAZENÍ	DATUM MAX VIROLOGIE PROTIL. MAX DATUM AKT PROTIL. AKT	FENOTYP
Kriteria výběru (*-všichni čekatelé):						
Transplantcentrum	-*					
Dialyz. středisko	-*					
EDTA	-*					
ABO	-*					
SEX	-*					
VĚK	-0 -100					
1	2504240	F BRUNCLÍKOVÁ ANNA 0+ 5562231323 10 0	MAROŠOV 166 BRNO-VENKOV 0504/430447	07.12.2000 -	27.12.1999 VHC : CMV: 2 EBV : HIV:- 27.12.2001 HBsAG:- BWR: 0	A :24 25 B :18 44 C : DR:4 15 DQ:
2	2492764	M BYCHOK VASIL 0+ 7901044014 10 0	PALACKÉHO 134 BRNO 0608	01.11.1999 -	25.09.1998 VHC :- CMV: 4 EBV : HIV:- 27.12.1999 HBsAG:- BWR: 0	A :24 26 B :8 51 C :7 DR:1 DQ:
3	2589880	M DIVÁCKÝ ZDENĚK B+ 511122092 10 0	KVĚTNICKÁ 1621 TIŠINOV 411136	11.02.2000 -	29.09.2000 VHC : CMV: 0 EBV : HIV:- 27.12.2001 HBsAG:- BWR: 0	A :1 3 B :8 62 C : DR:12 17 DQ:
4*	2592465	M HRADECKÝ MIROSLAV A+ 370826408 80 0	DĚLNICKÁ 14 BRNO 41224109	- **19.07.2000**	29.06.2000 VHC : CMV: 0 EBV : HIV:- 29.06.2000 HBsAG:- BWR: 0	A :1 32 B :8 44 C : DR:17 12 DQ:
5	2609153	F KLÍVAROVÁ DANUŠE A+ 5652072470 10 0	HÁJEK 9 KLOBOUKY U BRNA 0626/419360	27.02.2001 -	29.09.2000 VHC : CMV: 44 EBV : HIV:- 27.12.2001 HBsAG:- BWR: 34	A :11 26 B :18 38 C : DR:11 12 DQ:
6	2637259	M KNOTEK MIROSLAV B- 6511110287 19 0	SUDICE 31 RAPOTICE 0606/649851, 0509/	26.06.2001 -	28.06.2001 VHC : CMV: 0 EBV : HIV:- 27.12.2001 HBsAG:- BWR: 0	A :2 32 B :50 61 C : DR:11 13 DQ:
7	2592364	F MALÍKOVÁ DANA B+ 6453290382 10 0	MUTĚNICKÁ 11 BRNO 44217558	07.12.2000 -	29.09.2000 VHC : CMV: 0 EBV : HIV:- 27.12.2001 HBsAG:- BWR: 0	A :1 11 B :18 62 C : DR:8 12 DQ:
8*	2647868	M MIKEŠ PAVEL A+ 510305185 41 0	CHUDČICE 208 OKRES BRNO-VENKOV 0504/420840	- **24.10.2001**	23.10.2001 VHC : CMV: 0 EBV : HIV: 23.10.2001 HBsAG: BWR: 0	A :28 29 B :44 51 C : DR:4 11

ASSESMENT OF SIUTABLE COUPLE RECIPIENT - DONOR

1. **compatibility in blood group**
2. **negative result of cross – match**
3. **matching in HLA antigens on locusi A, B, DR**

best matching = full house = 000 MM (rare, e.g. siblings)

worst matching = none conformity = 2,2,2,MM

requirement depends on the titr of PRA

(the highest titr of PRA the better matching is desirable)

e.g. : PRA 80 – 100 %

min. requirement : matching in 3 of HLA antigens

(2 of them on DR locus)

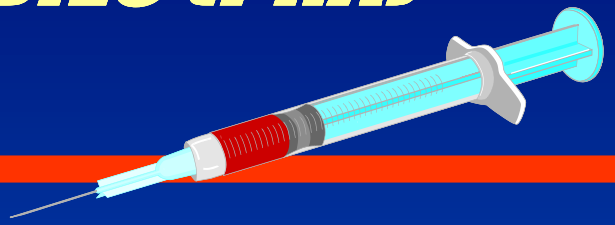
BLOOD GROUP COMPATIBILITY

- 1. „0“ = UNIVERSAL DONOR „AB“ = UNIVERSAL RECIPIENT
  used in living kidney transplant

- 2. BLOOD GROUP COMPATIBILITY
  used in cadaveric kidney transplant

BG	donor		recipient
	0	⇨	0
	AB	⇨	AB
	A	⇨	A
	B	⇨	B

PANNEL REACTIVE ANTIBODIES (PRA) -
detection of anti-HLA antibodies



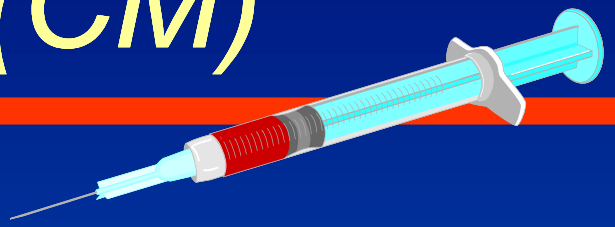
- **Patient serum is incubated with lymphocytes from a panel of representative donors and complement. PRA is expressed as the percentage of donor wells with cell lysis** (PRA 0% means no antibodies , PRA 60% should imply recipient antibodies against 60% of most commonly occuring antigens in that population).

- **Performed each 3 month whilst on waiting list**

- **The higher a patient´s PRA, the higher a risk of hyperacute rejection after Tx**

Sensitization events : previous transplant, pregnancy, blood transfusion, infection

CROSS MATCH TEST (CM)



Lymphocytes from the donor (taking from spleen or lymphatic node) are incubated with serum from recipient in the present of complement. If the cells are killed, specific anti-donor antibodies are present.

Positive CM is contraindication to Tx, because hyperacute rejection could occur.

Cross-match is performed before transplantations.

ASSESMENT OF SIUTABLE COUPLE RECIPIENT - DONOR

1. **compatibility in blood group**
2. **negative result of cross – match**
3. **matching in HLA antigens on locusi A, B, DR**
   best matching = full house = 000 MM
   worst matching = none conformity = 2,2,2,MM

   requirement depends on the titr of PRA
   (the higher titr of PRA the better matching is desirable)
   e.g. : PRA 80 – 100 %
   min. requirement : matching in 3 of HLA antigens
   (2 of them on DR locus)

HLA SYSTEM

I. class — II. class

ANTIGENS

↓

A XX — B XX — **LOCUS** — DR XX (=6Ag)

↓

number and position of o mismatches in A/B/DR represent so called

COMPATIBILITY INDEX

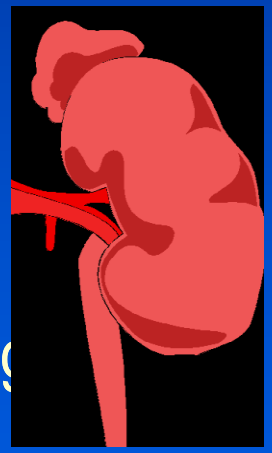
IK		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
A	No. of mismatche	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2
B		0	0	0	1	1	1	2	2	2	0	0	0	1	1	1	2	2	2	0	0	0	1	1	1	2	2	2
DR		0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2

CI	≤	7	when anti HLA-Ab	≥ 80%
CI	≤	15	(= PRA)	20-79%
CI	no limitation			0-19%

PRESERVATION OF CADAVERIC KIDNEYS I.

Simple cold preservation (at 4 st C)

- (the vasculature of the kidney is flushed with a cold solution, which has the similar electrolyte content as intracellular fluid)
- each kidney is then placed in a sterile plastic bag
- a and finally in container surrounded with ice



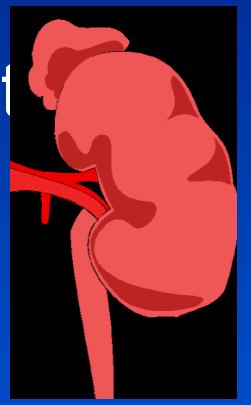
Warm ischemia (in minutes)

period between circulatory arrest and start of cold storag
be close to zero - the procedure takes only sec)

PRESERVATION OF CADAVERIC KIDNEYS II.

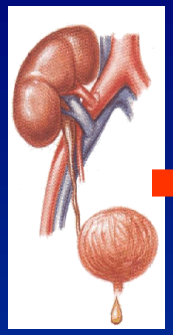
Cold Ischemia (in hours)

time from removing the kidney out of donor s body t
removing it from the box to perform the surgery
most often is 18 – 20 hours



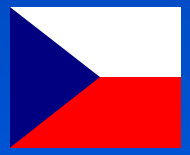
Time of manipulation (in minutes)

time from removing the preserved kidney from the box
to termination of vascular anastomosis and restarting
the blood stem in kidney in the recipient s body
most often 18 – 20 min



History of Tx

- 23.12.1954 monozygotic twins
- 21. 3.1959 dizygotic twins
- 5. 4.1962 cadaveric



- 23.11.1961 living donor (unsuccessful)
- 21. 3.1966 living donor (successful)
- 1972 cadaveric program

- 30.11.1972 cadaveric

1. successful Tx

23.12.1954 Boston

Joseph Murray a Hartwel Harrison

Herrick´s twins

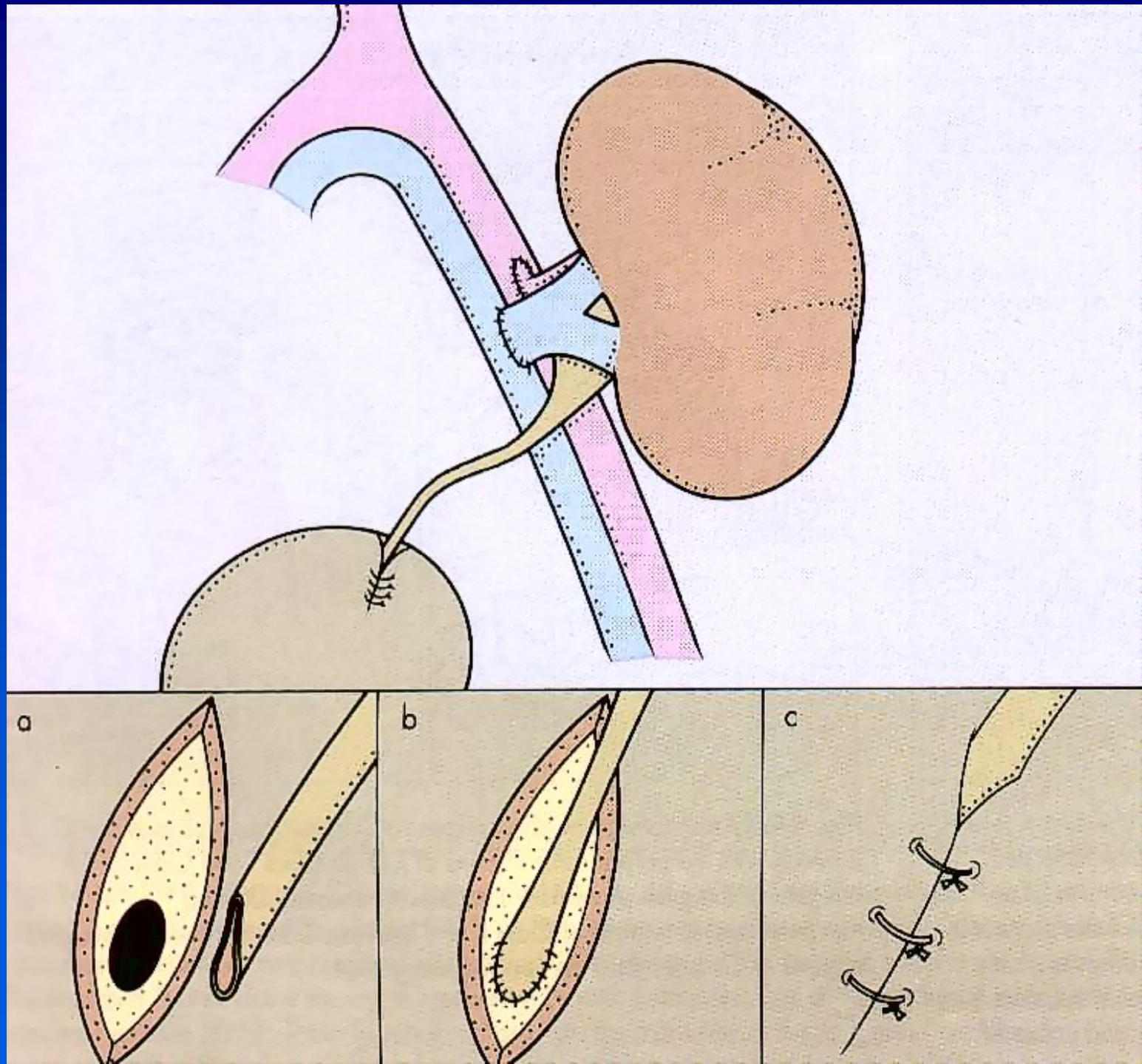
(Richard lived with functional graft 8 years, Ronald died in 79 years with normal kidney function)

SURGICAL TRANSPLANTATION PROCEDURE

Kidney graft is placed **extraperitoneally**
in the right or left **iliac fossa** of the recipients.

Renal arteria and vein are anastomosed
to external or internal iliac vessels.

After the vascular anastomosis is completed,
the ureter is implanted into recipient s urinary bladder. A sub-mucosal tunnel prevents reflux.


a
b
c

EARLY COURSE AFTER KIDNEY TRANSPLANTATION I.

IMMEDIATE FUNCTION

satisfactory urine output + blood concentration of nitrogen metabolities (urea, cretainine) continues to decrease + no supportive dialysis method is necessary.

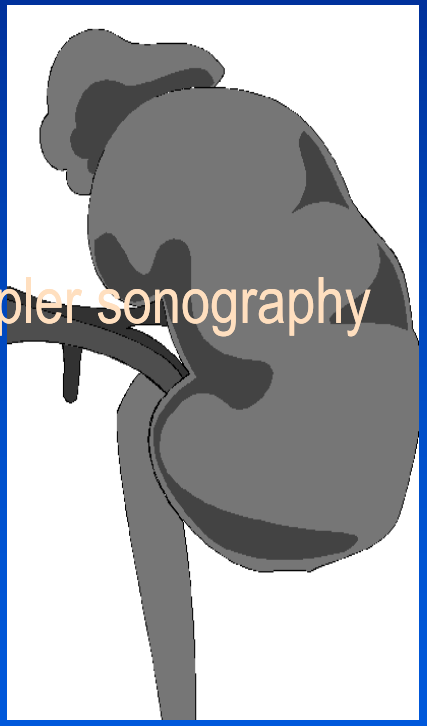
DELAYED FUNCTION

blood concentration of N-metabolities are still raising + supportive hemo- or peritoneal dialysis is therefore inevitable the urine output fluctuates from anuria to 1 L, sometimes even more.
The cause is ATN (injure of ischemic origin).
Renal function usually recovers after 2 weeks.

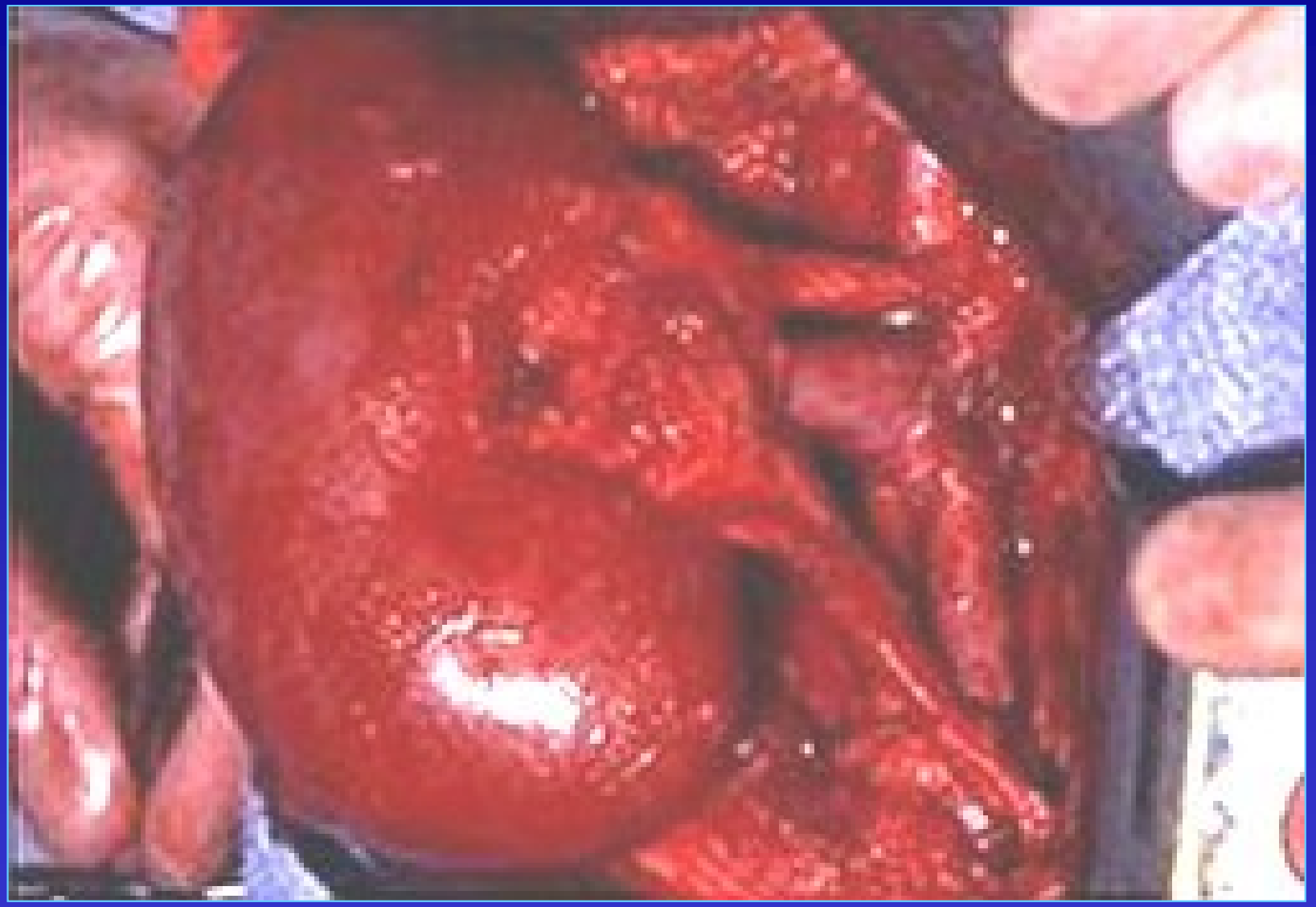
EARLY COURSE AFTER KIDNEY TRANSPLANTATION II.

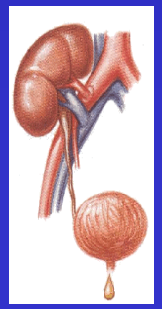
NON-VIABLE KIDNEY

- afunction takes place
- none signs of blood perfusion in the graft by Doppler sonography
  cause: irreversible ischeamic injury of the graft
  early trombosis of the main graft- vessels
  hyperacute rejection

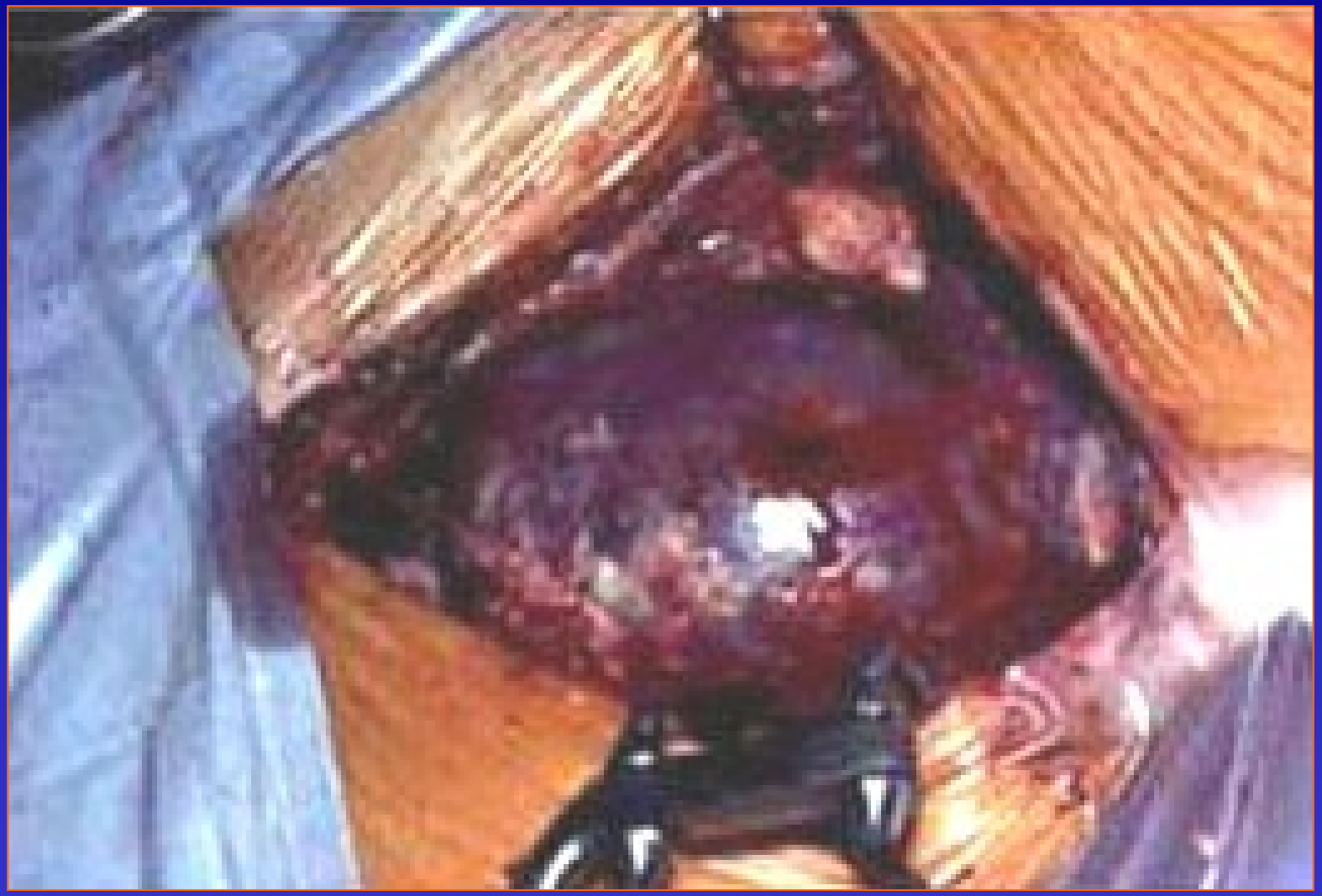


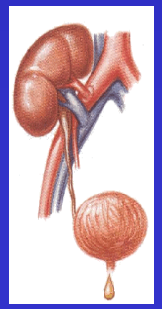
GRAFT HAS TO BEEN REMOVED





transplanted kidney – proper blood perfusion





transplanted kidney – hyperacute rejection

IMMUNOSUPPRESSIVE THERAPY

- *INDUCTION*
- *MAINTENANCE*

IMMUNOSUPPRESSIVE THERAPY

INDUCTION THERAPY

polyclonal Ab: Anti-thymocyte globulin

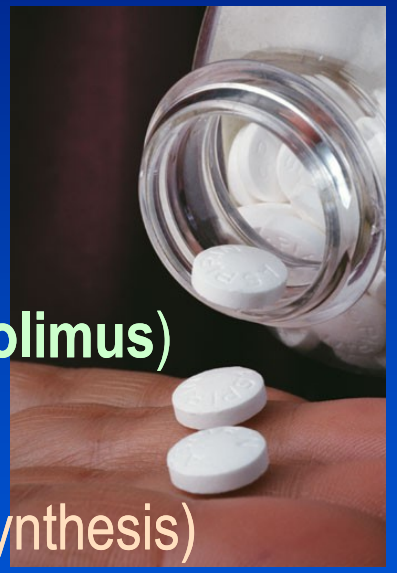
monoclonal Ab : antiCD3,anti CD52, antiCD25

(anti-IL- 2 receptor s Ab:Simulect, Zenapax)

***Indication*:** 1) immunologically high - risk patients
(high level of PRA, second /third grafting)

2) treatment of severe acute rejection

MAINTENANCE IMMUNOSUPPRESSION



combination of

1. **CORTICOSTEROIDS**
2. **CALCINEURIN INHIBITORS (cyklosporin A, tacrolimus)**
3. **ANTIPROLIFERATIVE AGENTS**
   azathioprine (blocks salvage pathways of purine synthesis)
   mycophenolate (blocks de novo synthesis of purines)
4. **„mTOR“ INHIBITORS (sirolimus, everolimus)**

MAIN EFFECTS OF IMMUNOSUPPRESSANTS

CORTICOSTEROIDS
inhibit signals of APCs to Th lymphocytes

CALCINEURIN INHIBITORS
inhibit IL-2 synthesis by blocking the IL-2 gene transcription (pre–receptor IL-2 effect)

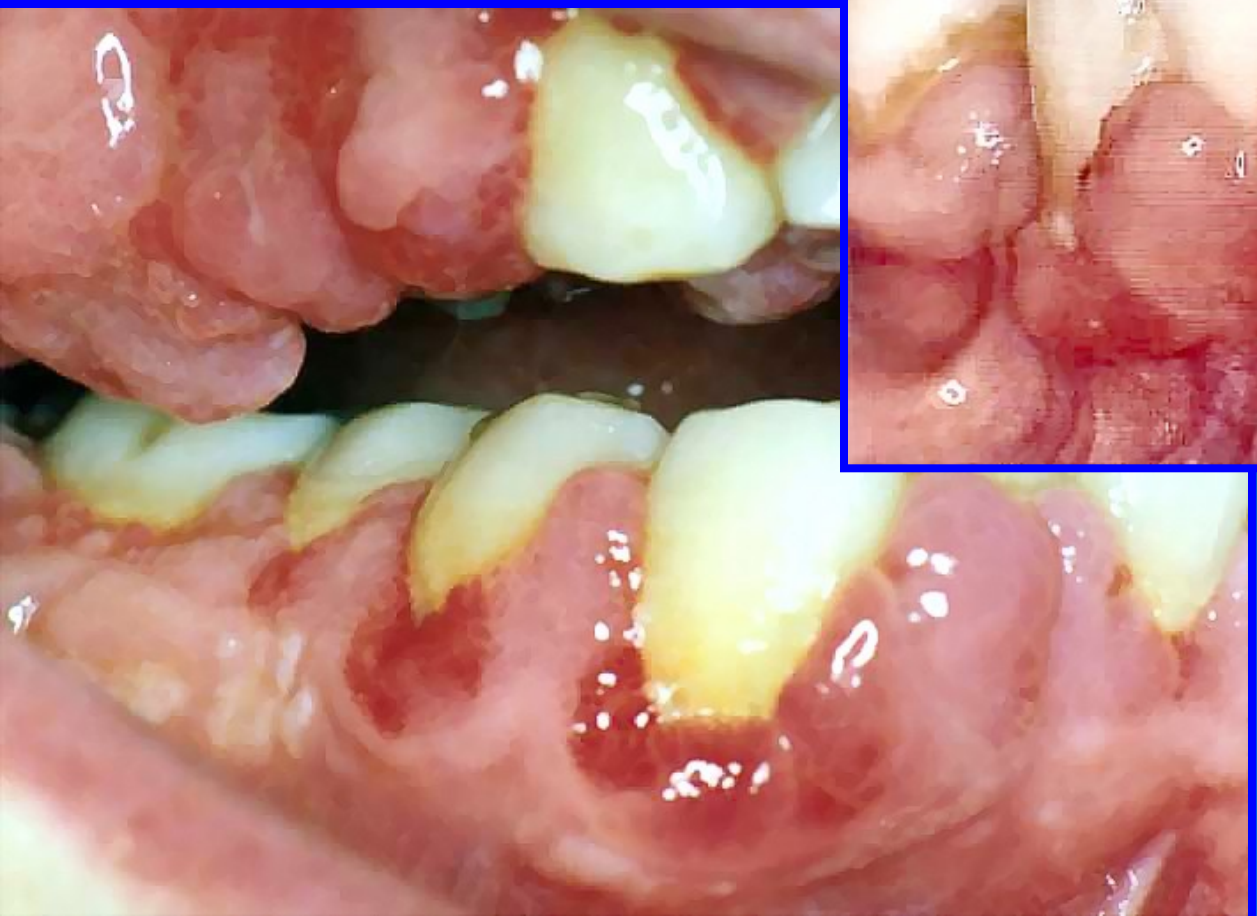
„mTOR" INHIBITORS
inhibit post-receptor IL-2 activation of Th lymphocytes

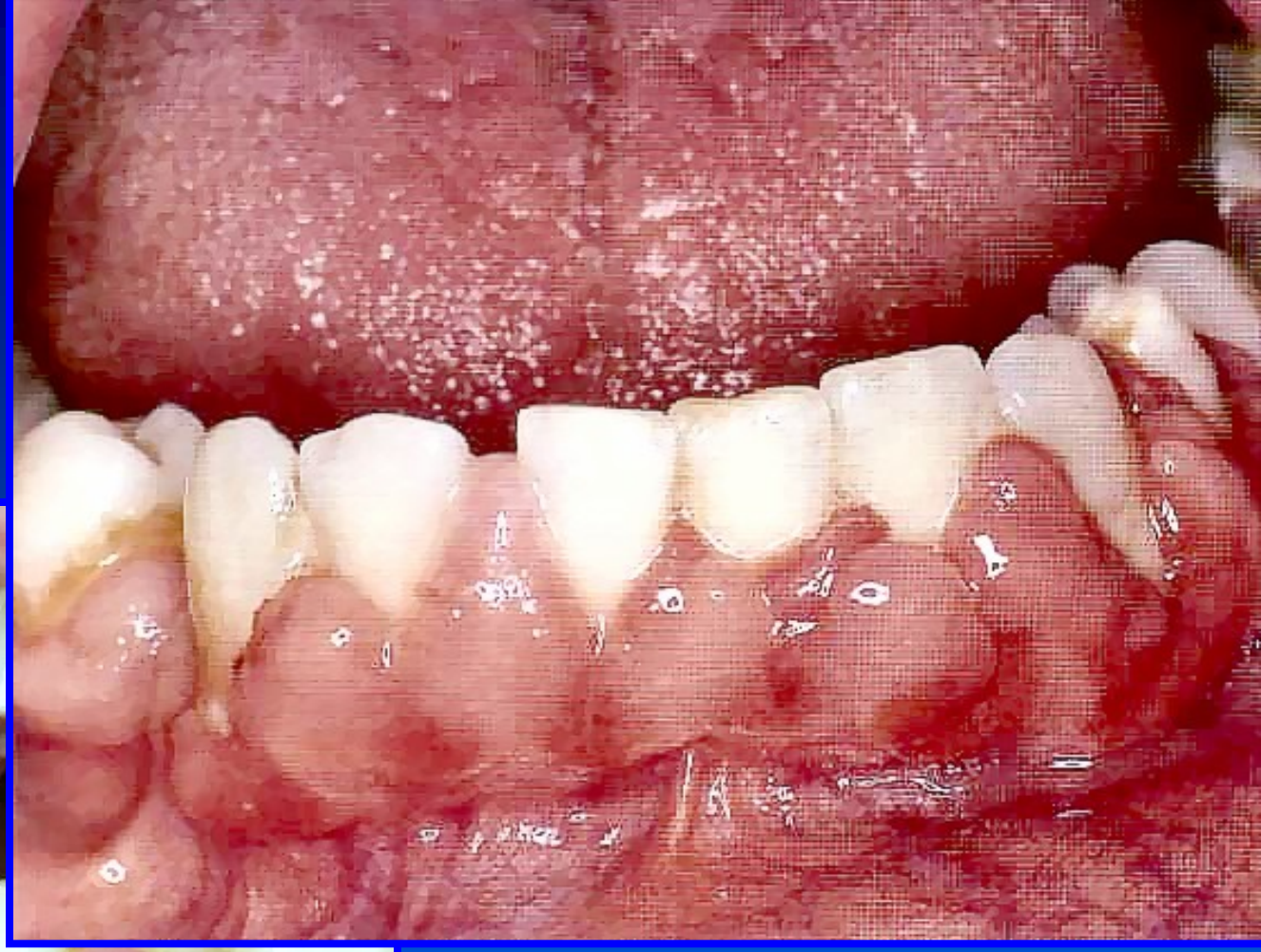
ANTIPROLIFERATIVE AGENTS
inhibit proliferation (dividing) of effectory cells

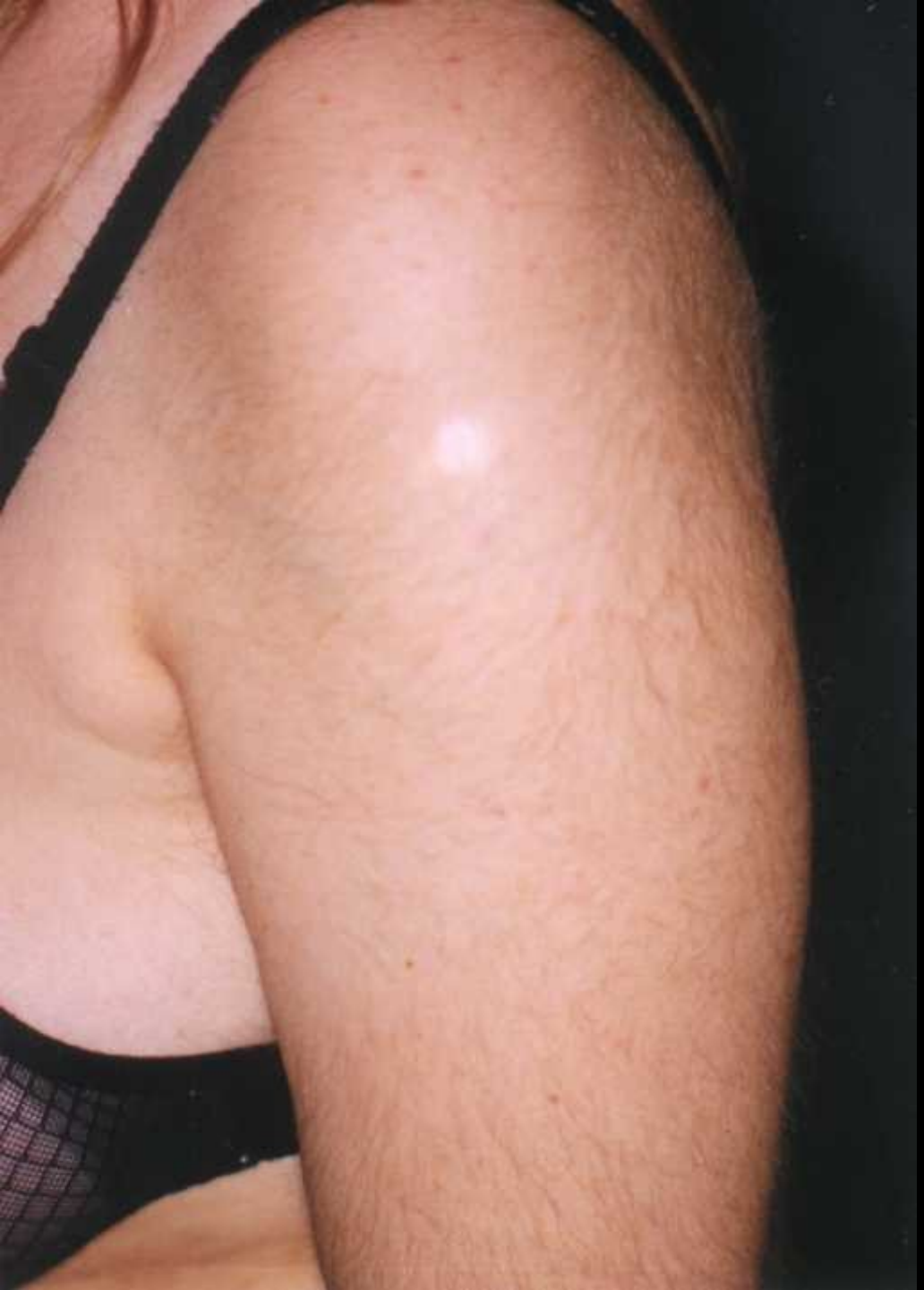
Most common adverse effects of IS

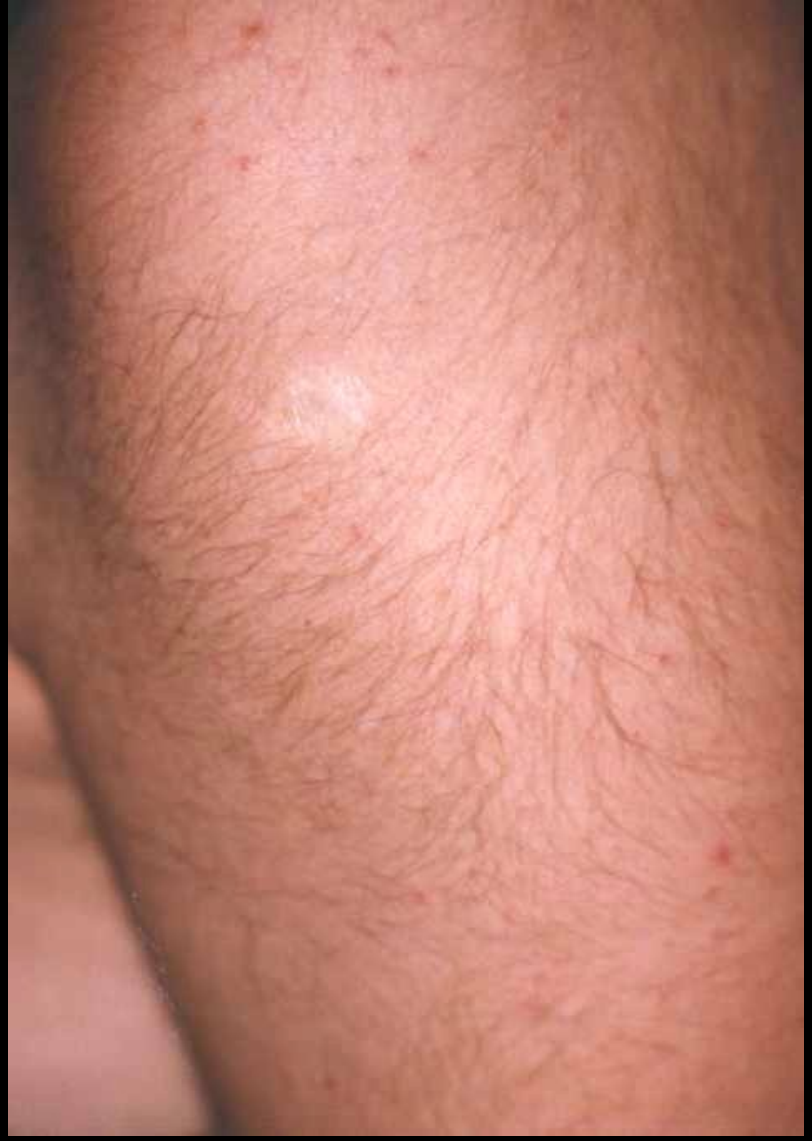
ALL OF THEM	predisposition to infections, risk of malignancy (skin, breast..)
PREDNISON MEDROL	osteoporosis, Cushing habitus, GI problems, DM
IMURAN	bone marrow suppression, hepatotoxicity **!!! MUST NOT BE TAKEN TOGETHER WITH ALLOPURINOL !!! – risk of BM suppresssion**
CELLCEPT	nauzea, vomiting, diarrhoea, leukopenia, trombocytopenia, hepatotoxicity (can be taken with allopurinol)
MYFORTIC	leukopenie, trombocytopenie, hepatotoxicita (can be taken with allopurinol)
SANDIMMUN NEORAL CONSUPREN, EQUORAL	3 H: hypertension + hirsutismus + hyperplastic gingivitis **!!! NEPHROTOXICITY**, neurotoxicity
PROGRAF	hypertension, allopecia, DM **!!! NEFROTOXICITY**, neurotoxicity
RAPAMUNE, CERTICAN	dyslipidemia, anemia, proteinuria

Gingivitis

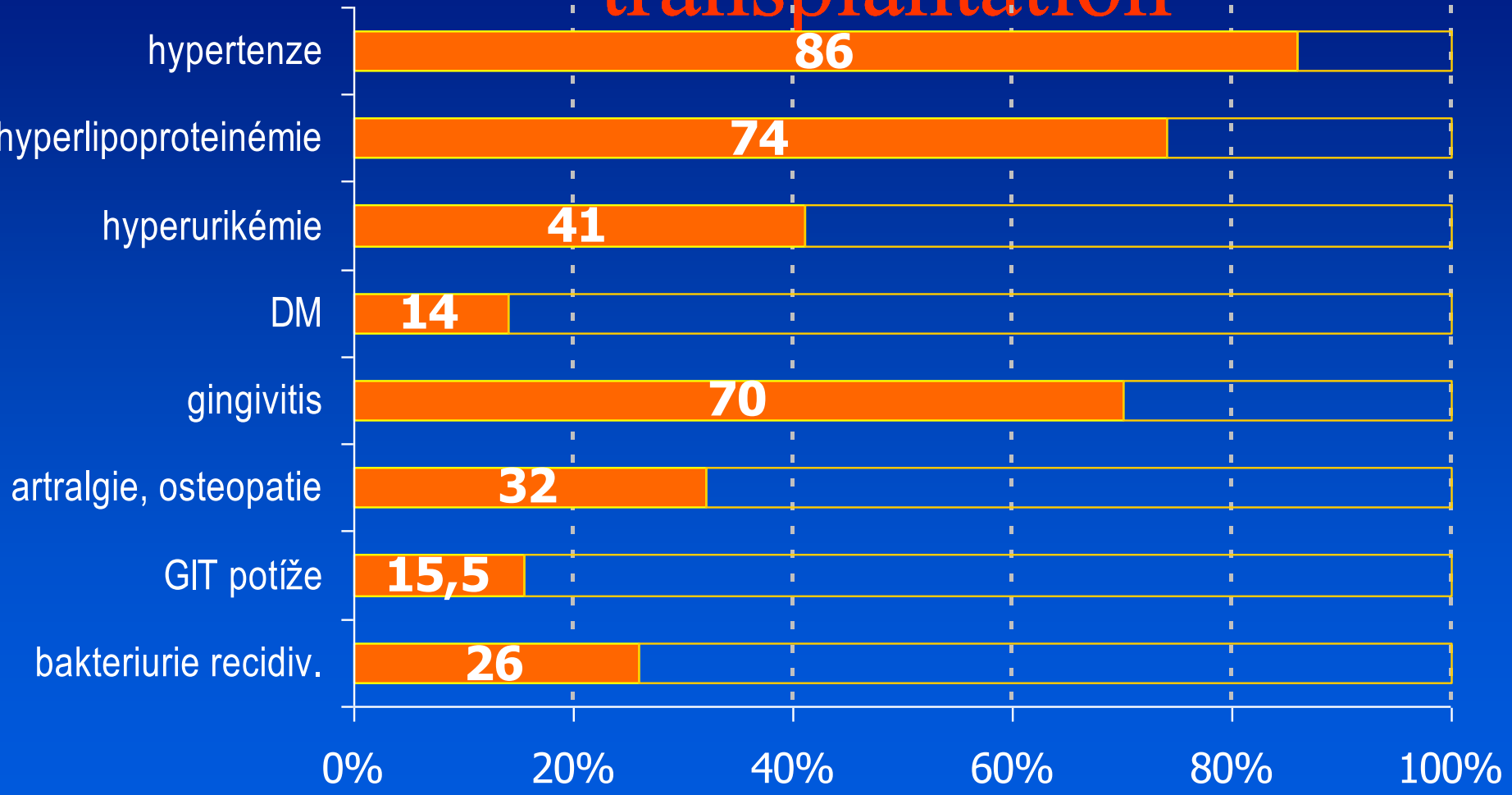








Most common complication after kidney transplantation



Treatment of hypertension after kidney transplantation

TARGET BLOOD PRESSURE 135/80

- **1. Ca-CHANNEL BLOCKERS**
  renoprotective effect in regimes with CNI
  (dilatation of art. afferens in glomerulus)
- **2. ACE-I a AIIA**
  renoprotective, antiproteinuric and antiproliferative effect
- **3. BETABLOCKERS**
- **4. RILMENIDIN, MOXONIDIN**
- **5. OTHERS**

Treatment of hyperlipidemia after kidney transplantation

TARGET: total cholesterol < 5mmol/L
LDL-cholesterol < 2mmol/L
TAG < 2mmol/L

- **STATINS: (esp. fluvastatin, atorvastatin – no metabolization through cP450)**

- **FIBRATS**

Risk of drug interactions

- *During treatment with CyA or Tacrolimus (metabolization through cP450)*

- ***A. Increase level of CyA / Tacrolimus***
  syst. antimycotics (Keto / Flukonazol)
  Diltiazem
  Verapamil
  Erytromycin, Claritromycin
  Amiodaron

- ***B. Decrease level of CyA / Tacrolimus***
  Phenytoin
  Rifampicin
  Carbamazepin

Result of Tx

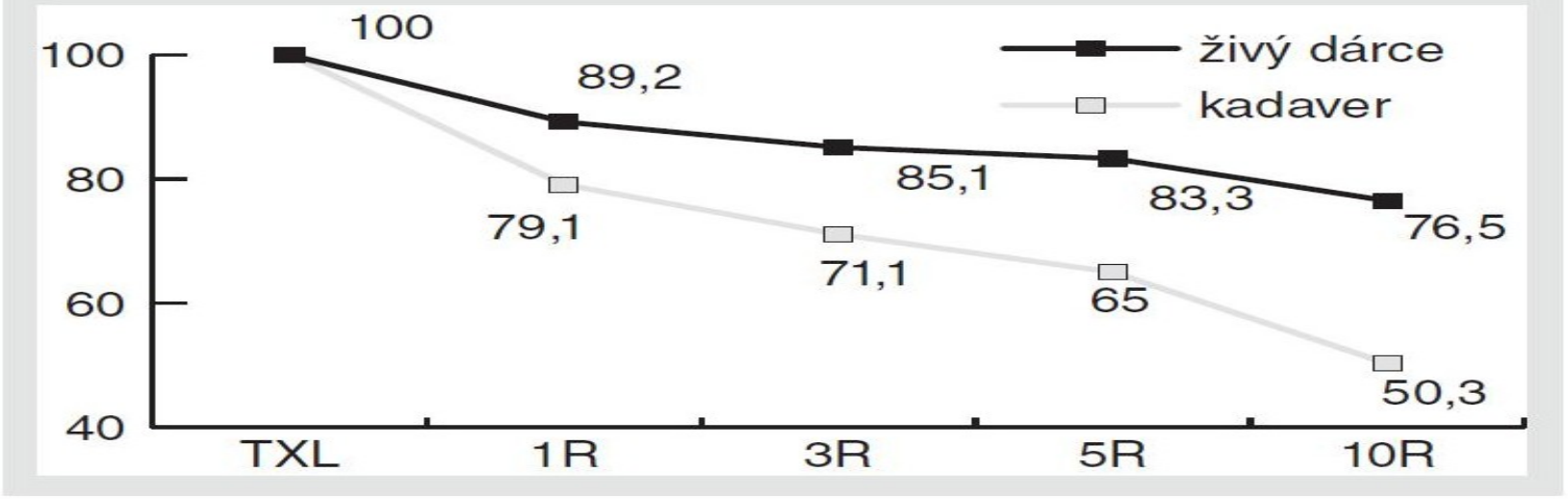
10-years survival:

- recipients: 70-80%
- grafts: 50-70%
- both is better more than 20% in living donor Tx

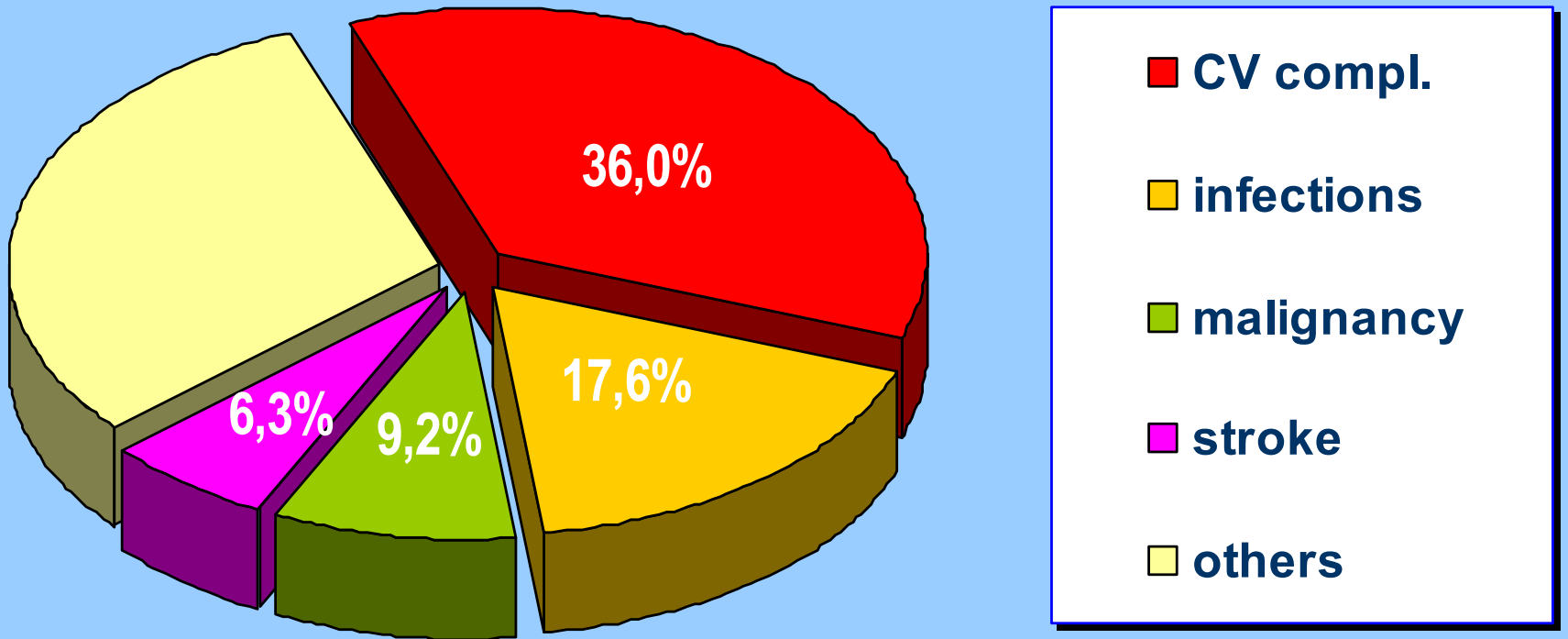
The most common cause of graft failure is death of recipient and chronic allograft nephropathy (CAN, or „chronic rejection“)

The most common causes of death of recipient are cardiovascular complications, infections and malignancy.

Comparison of graft survival from living donor and cadaveric donor



Cause of death in patients with functioning graft



Thank you for your attention