Guidelines for the Management and Control of Kidney Transplanted Patients & 18 Years in the Children's Transplant Centre at Karolinska Institutet
University Hospital

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The kidney transplant children are handled multidisciplinaryly and in collaboration between the section of paediatric nephrology at ALB and the transplant surgery clinic at Karolinska. For the first 3 months after the kidney transplant, the children are primarily to Transplantation and then to paediatric medicine. Treatment of acute conditions (e.g. suspicion of infection, renal impairment), changes to basic medication/immunosuppression, etc. is done in consultation between paediatric nephrologist and transplant surgeon. Within the Children's Transplant Centre at Karolinska, there are 2-4 places of care in department K89 (08-5858 0389).

Barnefrologkonsult is available on standby 24 hours/day and can be reached via child ephrokonsult (08-58587336 or via Avd B78 ALB Huddinge 08-585 803 78). Transplant surgery consultant can be reached daytime on 08-5858 2580, during weekends and during on-call time contact the primary emergency service at Transplantation on 08-5858 7515.

Immunosuppression after kidney transplantation

Immunosuppression in children is based on tacrolimus, mycophenolate mofetil **and prednisolone.**
http://inuti.karolinska.se/Inuti/Var-organisation/Sjukhusdirektor/Sjukhusdirektor-verksamheter/Medicin-Surgery-1/Medicin-Kirurgy-activities/Transplantation Surgery/Om-us/PMGuidelines/.

Note that different immunosuppressive PMs apply to children with normal and increased immunological risk, respectively.

Optimal immunosuppression for the patient in question changes with time after transplantation as well as the clinical situation and must be constantly reassessed. When returning to evaluate whether doses can be reduced, there are signs of overimmunosuppression such as in certain viral infections (BK, CMV, EBV, human papillomavirus), however, overimmunosuppression is usually not considered to occur if only repeated bacterial infections such as UVI.

It is always best if immunosuppression can be administered orally, this is also almost always possible. If this is not possible, the medicines are given via probe or in the case of stagnant bowel or paralysis, intravenously. EV PEG can be used to inflict immunosuppression. In case of doubt about adequate intake of immunosuppression, drug concentrations should be monitored. Please note that IV dosage is different from PO.

If vomiting within 30 min (20 min for oral solution) after oral ingestion of immunosuppression, the dose should be repeated.

Tacrolimus (Adport®, Prograf®, Advagraf®) Dosed according to separate PM as above.
Food intake reduces tacrolimus absorption by up to 40 % which means that the optimal dosage is on an empty stomach.
For practical reasons, tacrolimus may need to be given with food and should then be consistently given in the same way in relation to food intake so that the concentration determinations reflect this and the dosages are adjusted accordingly.
Should not be given with grapefruit, cranberry juice or star fruit (affects absorption).
Adport® can be switched to Advagraf® 3 months after transplantation if necessary, provided that the patient is clinically stable and that no major changes will be made to other medication. Treatment with Advagraf® should be started on a 1:1 (mg:mg) basis for the total daily dose (i.e. the same dose as the current daily dose of Adport®). Advagraf® should be given in the morning. After change of preparation, tacrolimus trough values should be monitored within 1 week. If necessary, dose adjustment is made (same target values for tacrolimus concentration). Optimal therapeutic concentration depends on time from transplantation, number of immunosuppressants, current signs to overimmunosuppression, etc. Please note that different laboratories sometimes use different analytical methods and therefore the recommended dose ranges for therapeutic level may differ depending on the analytical method used.

Interactions can be found under separate heading below.
Side effects: nephrotoxicity (often mild decrease in GFR), hyperkalaemia, hyperuricaemia (may cause gout), hypomagnesaemia, hypertension, diabetes mellitus, diarrhoea and neurotoxicity (especially tremor).
Intravenous preparation may cause more pronounced hypertension.

Tacrolimus concentration:
Month (after transplantation) using specific chromatographic method LC-MS/MS (on average yielding approximately 20 % lower values than previously used immunochemical method).

&1: 8 ng/mL 1-3: 4-8 ng/mL > 3: 4 ng/mL

Mycophenolate mofetil (Mycophenolate mofetil; CellCept®) Dosed according to separate PM as above.

Administered orally divided into 2 doses/day. Concentration analysis can be done via so-called. ‘Area under the curve’ (AUC) for the active metabolite mycophenolic acid (TDM)

monitoring, however, is not routinely used. Measure MMF AUC in case of suspicion of adverse reactions (overimmunosuppression), or in case of suspicion of ineffectiveness (underimmunosuppression) i.e. rejection. Recommended AUC for mycophenolic acid is at Karolinska 95-190 µmol*h. However, it is not certain that TDM for MMF provides any

benefits to patient/transplant survival. Please note that the method for MMF AUC used at Karolinska Hospital is different from that used by most other centres, which is why the recommended reference value for AUC also differs.

Interactions can be found under separate heading below.

Side effects: most common from the gastrointestinal tract for diarrhoea. Not nephrotoxic, but may increase the risk of leukopenia, anaemia and CMV infection. In case of gastrointestinal adverse reactions, dosing 3 times a day may lower the separate dose (same daily dose) or switch to enteric coated MMF (EC-MMF, Myfortic®), please note that the dosage is different from "normal" MMF.

Prednisolone (Prednisolone®)
Dosed according to separate PM as above.

At 3 months post transplant transition to every two-day medication in growing individuals. The total dose should not be reduced directly upon transition to daily medication, but may be reduced, if necessary, after established every two-day medication. The final dose is reached after 6-12 months, depending on the clinical course. The final dose is individual but approximately 5-7.5 mg/m$^{2\text{every other}}$ day.
Some medications can reduce the steroid effect through increased metabolism: ex. rifampicin, phenytoin, and carbamazepine. Increased steroid effect can be seen when combined with: some birth control pills, estrogens, ketoconazole and erythromycin.

Side effects: growth inhibition, susceptibility to infection, Cushingoid appearance, Steroidacne, cardiovascular complications, hypertension, hypergycaemia, aseptic bone necrosis, osteopenia, cataract, blurred vision, impaired wound healing and div. psychological effects (e.g. depression).

Azathioprin (Imurel®, Azathioprin®)
Second-hand preparations and an alternative to MMF. Dosed according to separate PM as above. Side effects: leukopenia, anemia. Liver toxicity, skin cancer and hair loss are also described. The dose is reduced/halfase in leukopenia and may need to be temporarily discontinued depending on the degree of leukopenia. Leucopenin usually recovers within 1-2 weeks.

Long-term immunosuppression after kidney transplantation:
Information on long-term immunosuppression in the case of kidney transplantation to adults can be found on the county council's information portal on medical media issues, see:
http://www.janusinfo.se/Behandling/Expertradsutlatanden/Medicinska-njursjukdomar/Riktlinjer-for-immunosuppression-in-juris transplant/

The need for immunosuppression decreases over time maintenance doses are achieved about.3 months post transplantation at an uncomplicated process. The risk of certain viral infections (BK, CMV, EBV) and malignancies (PTLD, skin tumors) is associated with both the total dose and duration of immunosuppressive therapy. The incidence of skin side effects (warts,

tumours) is likely higher for azahioprin compared to MMF.
The aim of always striving to reduce immunosuppression is to reduce the risk of malignancy and the occurrence of other serious side effects (e.g. nephrotoxicity, hypertension, hyperlipidemia, hyperglycaemia and cardiovascular disease). At the same time, for all renal transplants, there is a lower limit at which rejection occurs (acute or slow onset of chronic transplant nephropathy), in some cases difficult to treat. Where this limit is located in the individual patient case is impossible to know in advance why the need for, as well as the risks of, reducing immunosuppression must always be carefully analysed.

Renal graft biopsy and analysis of donor-specific antibodies (DSAs) may be considered prior to a decision to change basal immunosuppression.

Important interactions with immunosuppressants

Many frequently used drugs can interact with immunosuppression, informing the family to always tell this when in contact with medical care.

Interactions may occur with, among other things:

- macrolide antibiotics (erytomycin, clarithromycin)
- calcium antagonists (verapamil, diltiazem, nifedipine)
- Omeprazole
- imidazole type antimycotics (ketoconazole, fluconazole)
- chloramphenicol
- norethisteron
- levonorgestrel + ethinylestradiol
- methylprednisolone
- midazolam
- lidocaine
- lorokin
- phenytoin
- carbamazepine
- rifampicin
- rifabutin

Certain herbal remedies such as St John’s wort and also grapefruit and cranberry juice and star fruit (carambole) may affect concentrations of calcineurin inhibitors and should therefore not be taken.

Note that almost no kidney transplant patient has a normal GFR why

renal function must always be taken into account when dosing medicines

• Hypertension treatment

Blood pressure is related to height, age and sex.
Hypertension diagnosis should always be made via 24 hours of blood pressure recording, if

repeated blood pressure measurement, see below.

Hypertension is seen in 60-85 % of all renal transplant patients.
Underlying causes:

- Chronic renal transplant dysfunction.
- The basic disease (previously hypertension?)
- Drugs (calcineurin inhibitors, steroids).
- Kidney artery stenosis
- Overweight
- Liquidation
- Age of the donor

Avoid blood pressure swings with pronounced drop in blood pressure. Do not provide temporary blood pressure medication, i.e. of type when prescribed. In asymptomatic hypertension, blood pressure is gradually lowered, not acutely. In symptomatic hypertension, intravenous treatment with good monitoring/monitoring is preferred.

Low-dose AT-II receptor (lorsartan) antagonist is routinely already preoperatively inserted before kidney thx at the transplant surgery clinic, Karolinska University Hospital. There are reports of protective effect against non-HLA-mediated vascular rejections. Furthermore, there is a general renal-saving/renoprotective effect, which is why RAAS blockade is almost always given to patients with renal failure (providing a slower progression of renal failure in adults) — this renal protection effect is likely to exist even for transplanted kidneys. However, there are no studies in children confirming this renoprotective effect, either in chronic renal failure or after kidney transplantation.
Treatment with higher doses of AT-II receptor antagonist and ACE inhibitors (the so-called RAAS blockade) is considered safe in adults even early after kidney transplantation but should be used with caution in children during the first 3-6 months after kidney transplantation.

If hypertensive medication is needed direct Posttransplant Calcium antagonist alt beta receptor blockers are the first choice.
More time after the transplant, see below.

In theevent of a hypertensive crisis (symptomatic hypertension), the patient is treated on BIVA/IVA and given IV treatment according to pages 6-7 of pm for hypertension treatment on the BLF website: http://www.blf.net/nefrolog/dok/
The first choice is usually Labetalol alt. Nitroprusside intravenously.

24 hours of blood pressure registration
Routinely:

- 3 months after transplantation, even when normal “office” blood pressure.
- every year’s inspection.
- as an evaluation of treatment for established hypertension.

Treatment indicated if systolic and/or diastolic day and/or night mean blood pressure > 95 percentile for height, age and sex.
Treatment objectives: under 90 percentile. In adult patients there are studies that prove “as low

as possible" without side effects.

Treatment of hypertension in transplanted patients:

1. Non-pharmacological treatment applies to all patients with hypertension (e.g. diet, exercise, weight, not nicotine, stress reduction, salt reduction, etc.).

2. Pharmacological treatment is controlled by basic disease, degree of hypertension and proteinuria, etc.

    a. RAAS blockade: Ace inhibitors (Enalapril® 0.05-0.1 mg/kg/day divided into 2 doses) or AT II antagonist (Atacand® are not recommended: doses for children, starting dose 2 mg/day in children from school age are used, minor studies using 0.2-0.4 mg/kg and days divided into 2 doses; Cozaar® is an alternative that is easier to dose to smaller children).

    If the patient has already been introduced to a low-dose AT-II antagonist at transplantation, it is appropriate to increase the dose of the existing preparation as stage 1.

    b. Calcium channel inhibitors (Felodipine®, Plendil® Depot) 0.1 mg/kg/day slow-release" preparation 1 dose/day.

    c. Beta-blockers (Metoprolol® 1-2 mg/kg/day "slow-release" preparation one dose/day).

    d. Diuretics (Furosemid 0.5-6 mg/kg/day divided into 2-4 doses, higher doses at worse GFR and/or pronounced proteinuria). First choice in case of liquidation.

Combination therapy using 2-5 antihypertensives may be necessary, however, should first optimise to the full dose of monotherapy before combination therapy, always evaluate compliance.

Minoxidil may cause good blood pressure lowering in some difficult-to-treat patients.

General rule for the introduction of RAAS blockade: in case of impaired renal function, lower starting dose, slower escalation and tighter controls. Follow Creatine, Potassium, Blood Pressure 4-7 days after RAAS blockade and after each dose adjustment.
RAAS blockade is exposed to the risk of dehydration (ex gastroenteritis), rapid renal impairment and possibly prior to anaesthesia (advised with anesthesiologist).

In case of severe hypertension or rapid creae elevation after the introduction of RAAS blockade, consider renal artery stenosis. Also consider nephrectomy of native kidneys in therapy-resistant hypertension in renal transplant patients, discussion with transplant surgeon.

For the recommended dosage see the Swedish Children's Nephrological Association's care programme: http://www.blf.net/nefrolog/dok/hypertoni_utr_beh.doc

Reference values for "office" blood pressure from 6 years: Oscillometric Causal Blood Pressure Normative Standards for Swedish Children Using ABPM to Exclude Casual Hypertension. Krmar *et al*. American Journal of Hypertension 2014. *See Appendix I+ II, at the end of this pm.*

Reference values "office" blood pressure & 6 years: see the Swedish Children's Nephrology Association's Health Care Programme:
http://www.blf.net/nefrolog/dok/hypertoni_utr_beh.doc

Reference values for 24 hours of blood pressure recording: Distribution of 24-h ambulatory blood pressure in children: normalised reference values and role of body dimensions. Wühl *et al.* Journal of Hypertension 2002. *See Appendix III, end of this pm.*

In case of confirmed hypercholesterolaemia (repeated fasting) treatment with statins should be considered.

• Vaccinations

The Swedish Child Vaccination Program is available via link:
http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8825/2008-126-9_20081269.pdf

For update of the preparation options and dosages see FASS.

The patient should, if possible, be fully vaccinated prior to kidney transplantation including BVC's usual vaccination programme (see below) as well as varicella, hepatitis B, pneumococcal and influenza vaccination as a minimum (if the patient's basic disease and current medication allow). Also consider if there is an indication for other vaccines, see below. Start in time to plan the vaccinations. If any, some of the BVC vaccinations ex. MPR may be brought forward to be taken before transplantation.
Live vaccines (varicella, BCG, carbilli, rubella, parotitis, yellow fever) must not be given within 3 weeks prior to transplantation and after kidney transplantation only after a specific opinion including an infection consultant when live vaccines present a certain risk of clinical infection in immunosuppressed patients.

Varicella (Varilrix®, live vaccine)
It is important to have varicella immunity before transplantation. Check the titres. Children who have not undergone varicella infection should be vaccinated before transplantation if basic disease and any treatment permit.
Can be given from 9 months of age, should give 2 doses. The second dose is given no earlier than 6 weeks after the first.
Immunoglobulin and also erythrocyte transfusions may interfer with response to varicella vaccines due to passively added antibodies. At least 1 month should elapse between varicella vaccine and measles vaccine. Also vaccinate non-immunal family members.

Hepatitis A and B (Twinrix paediatric®, killed vaccine)
0.5 ml im. is recommended for children and adolescents from 1 year of age up to and including 15 years of age. The standard primary vaccination schedule consists of three doses, the first being administered at a specified date, the second one a month later and the third six months after the first dose. Possibly booster dose later based on individual assessment. Follow titres.

Influenza A (killed vaccine)
New directives on influenza vaccination to children at risk, including immunosuppressed and patients with GFR & 30 ml/min/1.73$^{m^2}$. These are vaccinated with an ordinary influenza vaccine that also contains protection against H1N1. Children 6-35 months 0.25 ml (half dose), children over 36 months full dose (0.5 ml). Children 6 months to 12 years of age who have not previously been vaccinated with two doses of seasonal influenza vaccine are recommended two doses at > 4 weeks apart.

Pneumococcus (Prevenar®, killed vaccine)
Children between 7 and 11 months of age: two doses, each dose of 0.5 ml, with an interval of at least 1 month between doses. A third dose is recommended in the second year of life.
Children between 12 and 23 months of age: two doses, each dose of 0.5 ml, with an interval of at least 2 months between doses. Children > 24 months of age and adults are given a single dose. Pneumococcal vaccines should be updated every 5 years.

Cervical cancer (killed vaccine)
Recommended. Girls are vaccinated from 9 years of age. Gardasil® is a vaccine for the prevention of especially cervical cancer caused by HPV 16 and 18, but also of genital warts caused by HPV 6 and 11. The primary vaccination series consists of three separate doses of 0.5 mL given according to the following schedule: 0, 2, 6 months.

TBE (killed vaccine) Can be given according to FASS.

Other pre-transplant vaccines
Consider yellow fever vaccine and tuberculosis vaccine before transplantation, both live vaccines, especially if the child's family originates from or often travels to areas where these diseases occur frequently. Infection consultant if the question arises.

When travelling abroad

We advise against travelling abroad during the first 6-12 months Post Transplant (does not apply to nearby destinations with similar infection panorama).
Before traveling later: Travel advice, vaccine review and possible need for prophylactic antibiotics/antimalarial agents should be discussed with infection/vaccination physicians.
Diarrhoea prophylaxis are often given with norfloxacin or equivalent.
Ask the family to discuss planned trips in good time, including for certification, etc.

General vaccination program in Sweden at BVC and school health care

Children born before 2002		
	Age	**Vaccines**
	3 months	DTP I + polio I + Hib I
	5 months	DTP II + polio II + Hib II
	12 months	DTP III + polio III + HibIII
	18 months	MPR IN
	5-6 years	Polio IV
	10 years	DTP IV
	12 years	MPR II
Children born in 2002		
	3 months	DTP I + polio I + Hib I*
	5 months	DTP II + polio II + Hib II*
	12 months	DTP III + polio III + HibIII*
	18 months	MPR IN
	5-6 years	DTP IV + Polio IV
	6-8 years	MPR II
	14-16 years	DTP V
* Since 1 Jan. 2009 also includes pneumococcal vaccine (PCV) at 3.5 and 12 months.		

• Infection in renal transplant patients

Fever, possibly chills, is often the first clinical sign of infection. Renal transplants with unclear fever (> 38.5°Xor > 38 °Cov2 occasions within 24h), general public health and/or chills should always be assessed promptly by an experienced physician, generous with admission and iv. antibiotics

treatment. Antibiotic therapy is initiated with the intention to cover widely but is then controlled on the basis of clinical findings and culture responses to the most optimal therapy.

Note the presence of undertemp may occur in sepsis (also gram-negative). Blood count including LPK with poly/mono, CRP, TPK, crea, u-status, blood cultures and possibly. PAC,

urine and v.b. respiratory tract (bacteria, topical viruses, v.b. fungi), PCR (CMV). In case of respiratory symptoms (or unclear focus), chest X-rays should be considered

Varicella (postexposition prophylaxis for immunosuppressed)
For non-immune patients, post-exposition prophylaxis are given within 72 hours of exposure: p.o. acyclovir 20 mg/kg x4 (max 800 mgx4) for 14 days.
In case of bladder development: emergency Infection Consultant.
If high IgG levels against varicella zoster virus are not routinely given post-exposition prophylaxis but obsess on possible blister formation and if so, an infection consultant.

CMV (cytomegalo virus)
See separate **PM for children** regarding diagnosis, treatment and follow-up of CMV infections in organ transplants: http://inuti.karolinska.se/Inuti/Var-organisation/Sjukhusdirektor/Sjukhusdirektor-activities/Medicin-Kirurgi-1/Medicin- Surgery-activities/Transplantation Surgery/Om-us/PMGuidelines/.

A symptomatic infection with cytomegalovirus (CMV, HHV5) is one of the most common infections after kidney transplantation and affects 10-15 % of recipients. CMV infection is relatively more common in highly immunosuppressed patients (e.g. after induction therapy or rejection therapy). A CMV infection is potentially serious if it is not detected and treated. Therefore, investigations for possible CMV infection (CMV-PCR) should always be included in case of unclear fever or other suspected symptoms in a renal transplant patient.

The infection (usually 1-6 months postoperatively) can be either secondary, i.e. reactivation of a latent CMV infection (70-80 % of cases), or primary. CMV negative recipients (i.e. negative CMV serology, IgG) are at high risk of suffering a primary CMV infection if they are transplanted with a kidney from a CMV-positive donor. Therefore, preoperative immunity to CMV (CMV serology, IgG) is always tested in both recipients and donors. However, with current CMV prophylaxis, the risk of a severe primary CMV infection is small, so any real "matching" with respect to CMV usually does not occur. Three months of postoperative CMV prophylaxis are given today with valganciclovir (Valcyte→) to all CMV negative recipients receiving organs from a CMV positive donor.

Diagnostics are performed using quantitative CMV-PCR. The limit for positive significance is usually set at > 50 viral copies/ml. Serology has a limited value in acute diagnostics but may be positive for IgM. Post-operative monitoring for CMV viraemia is used on certain kidney transplant units, but not routinely at Karolinska University Hospital, Huddinge. CMV virus resistance to various antiviral drugs can be analysed. A primary

After a kidney transplant, CMV infection can run with essentially 3 different clinical processes (with increasing clinical severity):

- CMV viremi

Positive CMV PCR, no actual clinical symptoms. Pre-emptive treatment is usually given with

valganciclovir PO (Valcyte®),follow-up with PCR.

• CMV syndrome
Positive CMV PCR. Most often fever peaks (winding fever) and/or leukopenia but without other symptoms. Sometimes a flu-like symptomatology as well as leukopenia, thrombocytopenia and elevated liver samples are seen. Eradical (curative) with valganciclovir PO (Valcyte→) or in 2a hand ganciclovir IV (Cymevene→)

• CMV infection with organ symptoms
Serious infection (sometimes life-threatening) with organ symptoms either from the renal transplant (nephritis with rising creatinine and transplant dysfunction) or other organs, usually pneumonitis, hepatitis, cystitis, retinitis, encephalitis, myocarditis or gastroenteritis. Therefore, in case of unclear organ symptoms in a transplanted patient with infection, investigation with regard to CMV should always be included. Treatment with ganciclovir (Cymevene®)IV for at least 2 weeks (divided into 2 doses, dose adjustment map renal function), often longer. Treatment can only be stopped when the CMV-PCR is negative.

Pneumocystis disease only affects people with impaired immune systems, e.g. after a kidney transplant (about 5 % if prophylaxis is not given). Pneumocystis almost only causes infection of the lungs, although it can spread to the brain and bones. Patients affected by pneumonia usually have a moderate fever and a moderate dry cough. What dominates the symptom picture is that the patient is getting more and more difficult to get air. Without treatment, mortality is very high. A pneumocystis infection is treated with antibiotics (trimethoprimsulfa, Bactrim→ initially patented and at a high dose). In a patient with immunodefect, after discontinuation of treatment it is common with relapse, which is why treatment often becomes lifelong. Pneumocystis is not yet available in microbiological laboratories. The diagnosis is made by colouring one's sample material (immune morphology/histochemistry on coughing samples, tissue samples) which makes the fungus microscopically visible. In case of negative immunomorphology, PCR analysis is always performed.

However, following the introduction of pneumocystis prophylaxis, no kidney transplant patient has fallen ill in Karolinska. Therefore, all patients undergoing kidney transplantation should receive prophylaxis of pneumocystis with trimetoprimsulfa (Bactrim→). Prophylaxis are usually started before discharge after surgery, but only in the case of good and stable renal transplant function. Prophylaxis are normally given for 3 months postoperatively, in severely immune-inhibited patients, prolonged prophylaxis may be considered to 6 months. Note that creatinine often rises upon initiation of Bactrim→ (for example, avoid putting in prophylaxis for a weekend). In case of failure of transplant function, the dose should be reduced, dose reduction even in the case of significant leukopenia. In case of hypersensitivity to Bactrim®, prophylaxis with pentacarinate (pentamidine) are inhaled every two months. The risk of pneumocystis pneumonia appears to be lower in immunosuppression with MMF.

• Relapse of focal segmental glomeruloscleros following kidney transplantation

20-50 % of renal transplant patients with idiopathic steroid resistant focal segmental glomeruloscleros (FSGS) relapse after transplantation. Secondary FSGS (caused e.g. by HIV, Parvovirus 19, drug toxicity, reduced renal volume and obesitase) does not relapse after transplantation and it is very rare that the genetic forms cause relapse in the transplant. In case of relapse of FSGS post transplantation, proteinuria usually recurs early after transplantation (minutes to a few days) and plasma albumin thus gradually decreases within a few days. However, it is described that relapse of FSGS can come up to 2 years post transplant. In order to interpret the presence of proteinuria after transplantation, knowledge of the level of proteinuria prior to transplantation is required. Most often, proteinuriut secretion from patients' native kidneys decreases after transplantation.

The U-stick and u-alb/create ratio should be followed daily the first month after transplantation in an FSGS patient. However, recurrence of the basic disease FSGS does not always mean a rapid reduction in GFR. Risk factors for relapse are earlier relapses in the transplant (in which case the risk of relapse is 80 % at second transplant), older than 6 years of age at the time of primary infection, non- Hereditary form, short interval between disease onset and terminal renal failure (< 3 years) and findings of mesangial proliferation in renal biopsy.
In the 21st century, different forms of hereditary FSGS forms have been identified through gene mutation determination, primarily: NPHS2, NPHS1, WT1. As may be supplemented by: NPHS3, ACTN4, CD2AP and TRCP6 and INF2. The risk of relapse after transplantation from patients who are homocygotic for the NPHS2 gene is extremely low ~3 %. Heterocygotic forms of NPHS2 have as much relapse risk after transplantation as non-herditary forms. Genetic tests for mutations that cause steroid-resistant nephrosis are becoming increasingly available for clinical use, meaning that genetic mutation analysis should be done on all nephrosis patients reaching chronic renal failure stage 3-5. If suspected recurrence may change immunosuppression, plasmapheresis and/or cyclophosphamide pulsar iv, however, always case for team discussion.

• When Creatine rises/GFR drops

Recontrol creatinine, cystatine C-GFR and tacrolimus concentration (high concentration nephrotoxic).
CRP, urinary status, urine culture.
Clinical symptoms? Dehydration?
Are there signs of infection?
Diarrhea?
Medical Interaction — Re-introduced Medicine? Food?
Compliance Problems?

Recurrence of basic disease? (v.b. U-alb/creatinine quota)

In the case of rapidly rising creatinine (> 10 %) acute complication should be suspected (e.g.

acute rejection, infection, deflux obstruction, nephrotoxicity) and promptly investigated. Check lab samples, cultures, BK-PCR, ultrasonic tx kidney with doppler flows. Question at ultrasound is — circulatory, RI-index, arterial stenosis, urinary fluid obstruction? Acute renal transplant biopsy in connection with the ultrasound examination should be considered (checking bleeding parameters, required insertion and anesthesia?). Kidneyscintigraphy may be considered. Control of donor-specific antibodies (DSA) may be considered

All patients with slowly rising creatine (> 10-20 % at a couple of consecutive revisits) should be investigated with subacute renal biopsy (common histology and immunhistochemistry including C4d and BK virus/SV40). Contact the transplant surgeon for discussion. BK-PCR should be checked. Check the DSA?

- **Risk of malignancy**

The incidence of malignant tumours is 3-5 times increased among renal transplants compared to normal population and skin cancer (ff. squamous cell cancer) is the most common malignancy after kidney transplantation (affects 10 and 40 % of patients). The risk increases over time after the transplant.

Patients should be carefully informed of the risks and the importance of adequate sun protection (cover clothing, avoid sunburn, seek shade, use sunscreen with sufficient SPF> 15). Assessment by skin specialist and skin consultant is included for all patients at each year's check-up. (since 2010 there is a special transplant clinic at the skin clinic in Solna where referrals can be sent electronically). Any ill-considered or difficult to assess skin changes should be immediately assessed by a dermatologist: http://inuti.karolinska.se/Inuti/Var-organisation/Hospital director/Sickhouse director-activities/Medicin-Kirurgi-2/Medicin-Surgery-2-activities/Skin clinic/Skin clinic- activities/Removals1/Tumor reception/Transplantation clinic/
All transplanted patients should have received the information leaflet "skin control after transplantation"

- **Patient Responsibility**

Patient responsibility 0-3 months post-op: Transplant.

Referrals for takeover will be sent in good time.

Patient responsibility > 3 months post-op: Paediatric medicine.

Recommended routine checks after kidney transplantation

> 3 months after NTX 2 times/week sampling, 1 time/week (medical visit).

3-6 Months after NTX 2-4 times/month (medical visit plus sampling).

6-12 months after Ntx1-2 times/month (medical visit plus sampling).

> 1 year after NTX, sampling and frequency of medical visits can be adjusted according to the clinical course, benchmarks:

1-2 years sampling 1 time/month, doctor's visit 1 time/month-1 time/every other month
> 2 years and completely stable progress, sampling and doctor visits every three months (never
more outgles.)
During all controls
Weight, blood pressure, u-stick, u-alb/creaa
Tacrolimus Consec.
HB, LPK, TPK, Na, K, Creaine, Urea, CRP, B-glucose.
The first year also once a month
AST, ALT, LD, ALP, Bilirubin, Gamma GT, B-cells, HbA1c* (in case of increased fB glucose in diabetes). If the patient has an affected kidney function, additional sampling may be considered.

EBV/CMV
EBV PCR 1 time/month first year (in case of EBV negative before transplantation) since v.b.
CMV-PCR v.b., i.e. in case of suspicion of CMV infection (unclear fever, flu-like symptoms, leukopenia, other infection symptoms and liver disorders).

BK virus
BK-PCR is taken post tx at 1 month, 3 months, 6 months and 12 months thereafter vb (i.e. in case of renal dysfunction)
Blood test: BKV-PCR (significantly considered if > 10,000 copies/ml blood but also lower values should in some cases be considered).
Positive PCR is managed according to a special care program, see INUTI/transplant surgery clinic pm (clickable link)

3-month monitoring (3 months after kidney transplantation, performed on paediatric medicine).

Tacrolimus concentration is usually down to maintenance level.
Azathioprin is reduced to 1 mg/kg.

Prednisolone over to every other day (initial increase what and decrease what).
CMV prophylaxis are exposed if nothing speaks against.
Ultrasonic tx kidney (flows, parenchymutes, hydronephrosis).

Carotisdoppler (Intimate Thickness)
Iohexol clearance.
24 hours of blood pressure recording.
Skin Consultant
BK — see above

Sampling:
U-stick, u-alb/creaa.
Tacrolimus Consec.
HB, LPK, TPK, Na, K, Creatinine, Urea, CRP, B-glucose, Ca, P, Albumin, Urat, Standard Bicarbonate, ASAT, ALT, AP, Bilirubin, Gamma GT, PTH (v.b.), f-Kolestrol, f-Triglycerides, LDL, HDL (v.b.), HbA1c (in case of increased fB-glucose alt in diabetes).
Urine culture.

Bactrim is usually discontinued 6 months after transplantation.

Note: many renal transplants have chronic renal failure i.e. renal impairment and must be followed with the usual controls for CKD.

Annual checks

Ultrasonic transplanted kidney including uretary and bladder, native kidneys, liver, spleen, lgll. Iohexolclerance.
Skeletal age: 1 year of verification since every three years (in case of GH treatment annually).
Fenazone and galactose first annual check then only in case of liver disease after washing the liver consultant.
EEG at the first annual check then only in case of pathological.
ECG and Ecocardiography annually in case of hypertension, otherwise every two years.
24 hours of blood pressure recording at least annually.
Skin Consultant (at 3 months ago) every three years + vb.
Endocrine consultant in case of abnormal growth or late/early puberty development.
Eye Consultant initially annually for the first 3 years since v.b.
Dentists (can best be done at home in case of outpatients) annually.
History of miction, urine flow and resurin.

Carotisdoppler at 3 months check and 1 year before transfer to adult.

Sampling:
U-stick, u-alb/creaa.
Tacrolimus concentration.
HB, LPK, TPK, Na, K, Magnesium, Creaine, Urea, CRP, B-glucose, Ca, P, PTH, Albumin, Urat, Standard Bicarbonate, ASAT, ALT, AP, Bilirubin, Gamma GT, f-Kolestrol, f—

Triglycerides, LDL, HDL, 25-OH white D, HbA1c.

Urine culture.
Varicella and hepatitis serology if time negative

Weight/length curve, puberty assessment.
Infection problems.

In case of rising creatinine/sinking GFR investigation as above.

Mark in jl if the patient is at risk of recurrence of basic disease, is retransplanted, has co-morbidity, etc.

Assessment of the skin suit (undressed patient) and vb referral to the skin clinic.

Information call for the child and the family (at each year's check)

Should live a normal life but must have knowledge as described below. Take the opportunity to repeat the information at least every year, ask what the family members themselves know, what they remember of previous information.

•Medication: why, lifelong, regular, compliance, interactions (may only take paracetamol without a doctor's consultant), side effects, storage, regularity. Not health food preparations without having discussed with a doctor.
Do not drink grapefruit or cranberry juice, not star fruit. How is conc. determination made: important with 12 hours of value, etc.

•Dehydration risk: what to do in case of vomiting, diarrhoea: put out Ev. RAAS blockade temporarily mm.

•Rejection reactions: symptoms, risk factors.

•Infections: symptoms, when seeking, to what degree avoid exposure, oral hygiene.

•Mechanical habits.

•Growth, go through growth curve and puberty assessment.

•Lifestyle- how do we prevent cardiovascular disease, diet/motion/weight- encourage physical activity, not smoking, etc.

•Sun protection (sufficiently high sun protection factor (SPF> 15), seek shade, avoid sunburn, not solarium.

•Psychical reactions. Side effect to medicines, life crises, etc. School/comrades.

School, kindergarten?

•Foreign trips — must always be prepared (please tell in good time), if any infection consultant for vaccinations, travel prophylaxis, certificates, where to turn if something happens during the trip.

•Twenty girls info on the future of pregnancy, need for contraception should always be offered gynconsultant.

Need for a dietitian, BUP consultant?

- At the age of 15, start planning for transmission to adult kidney medicine — plan well in advance.

- Clarify who is responsible for sampling, prescriptions, etc. The local doctor/B76 doctor. Contact persons (doctor, nurse) at home and B76/78 respectively.
Who contact in case of acute problems, general questions, certificates, prescriptions, etc.

• Postoperative fluid replacement for kidney transplant children

The guidelines apply to patients under the age of 16 and weighing less than 60 kg. For the rest, the adult guidelines apply.
The patient is planned postoperatively to POP 3-6 hours (longer if special needs). However, children of ≤ 10 kg or 1 year of age are planned for postoperative care at IVA. Postoperative IVA care is also planned in case of complicating conditions where either the nursing or medical conditions for the postoperative care are deemed to require greater resources than can normally be carried out on the postoperative unit.

Below are standard dosages for basal fluid supply and replacement of postoperative timdiures. Decisions on other regimes should be prescribed in particular by the responsible physician.

Som basal vätsketillförsel ges Buffrad glukos 25 mg/ml enligt lista:

Vikt i kg	ml/tim
10	**26**
11	28
12	30
13	31
14	33
15	**35**
16	36
17	37
18	38
19	40

Vikt i kg	ml/tim
20	**41**
22	43
24	45
25	**47**
26	48
28	50
30	**52**
33	55
35	57
37	59

Vikt i kg	ml/tim
40	**61**
45	66
50	**70**
55	74
60	**77**
65	80
70	83

Children under 10 kg or 1 year of age use 10 (or 5) % Glucose with Sodium.
The fluid prescription for these children is done individually.
In addition, as a replacement of the diurese, Ringeracetate ml is given for ml, hour by hour up to 3 ml/kg/h:

Weight in kg	Max diuresis replacement ml/h	Weight in kg	Max diuresis replacement ml/h	Weight in kg	Max diuresis replacement ml/h
6	18	16	48	**30**	**90**
7	21	17	51	33	99
8	14	18	54	35	105
9	27	19	57	37	111
10	**30**	**20**	**60**	**40**	**120**
11	33	22	66	45	135
12	36	24	72	**50**	**150**
13	39	**25**	**75**	55	165
14	42	26	78	**60**	**180**
15	**45**	28	84	> **60**	**200**

The postoperative bleeding of the transplanted kidney is essential, which means that hypovolaemia should be avoided, among other things. Circulation is clinically assessed and good filling and cardiac output are sought as well as adequate blood pressure for age. Normally a CVP of 8-12 cmH_2O is sought. In case of doubt about the circulatory optimisation, doctors should be consulted. For additional volume requirements and adequate Hb, albumin solution 40 (or 50) mg/ml is primarily used. Furosemide is given only on medical prescription (after circulatory optimisation).

Postoperative sampling is done by blood gas analysis of vein blood (Hb, Na, K, Cl, Ca, Standard Bicarbonate & Base excess). Venous blood gas is taken after arrival in postoperative and then every two hours.
Pre- and post-operative sampling in general is governed by routine in the ward or by individual assessment.

For the treatment of chronic renal failure in renal transplant patients see separate pm paediatric nephrosection:
http://inuti.karolinska.se/Inuti/Var-organisation/Sjukhusdirektor/Sjukhusdirektor-verksamheter/Astrid-Lindgren's-Children's Hospital/Astrid-Lindgrens-Children's Hospital/Child Medicine- 1/Child Medicine-Activities/Children's Neurology/For-us-pa- Clinic/PMGuidelines/

Annex I+II: Reference values for "office" blood pressure from 6 years: Oscillometric Causal Blood Pressure Normative Standards for Swedish Children Using ABPM to Exclude Casual Hypertension. Krmar *et al*. American Journal of Hypertension, 2014.

Annex III: Reference values 24 hours ambulatory bltr**.** Distribution of 24-h ambulatory blood pressure in children: normalised reference values and role of body dimensions. Wühl *et al.* Journal of Hypertension, 2002.

Annex IV: Age-Specific Reference Intervals for Indexed Left Ventricular Mass in Children. Khoury *et al*. Journal of the American Society of Echocardiography, 2009.

Annex V: Carotid Artery Intima-Media Thickness and Distensibility in Children and

Adolescents. Doyon *et al*. Hypertension, 2013.

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Version	Date	Change and comment	Responsible
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