GENERAL PROTOCOL LIVER TRANSPLANTATION

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A. Immediate pre-transplantation period

❖. Preparation before starting the surgical procedure

- Medical history review.
- Review that you have informed consent from Signed Transplantation, Blood Bank and Biobank
- Check drug allergies.
- Weight, Size, Physical Exploration, satO2
- Sampling (pharyngeal, rectal, urine) for culture of bacteria and fungi
- PCR Coronavirus SARS Cov 2
- Enema with physiological saline serum (100 to 200 cc depending on age, or 10 ml/kg)
- Bath with chlorhexidine gel
- Analytical: blood count, coagulation, ions, liver biochemistry, PCR, venous gasometry, cross-testing
- Sample for HLA (Tube will be collected by the Transplant Coordinator)
- Peripheral venous channeling
- Glucosalin 1/5 (less than 1 year) or glucosalin 1/3 (over 1 year) at baseline needs
- Absolute diet
- Medication:
  - ❖ Ranitidine i.v. 1.5 mg/kg/dose (maximum 50 mg) every 6 hours, or Omeprazole iv 1 mg/kg/dose every 12 hours.
  - ❖ Nistatin 1 oral dose: 25,000 IU/kg
  - ❖ Perioperative antibiotics: plan to start to receive 1 dose before going to the O.R.
  - ○ Antibiotic prophylaxis depending on the patient's pretransplantation situation (entry with previous antibiotherapy, stable situation at home...) and microbiological history (check if previous carrier of multidrug resistant bacteria). The overall objective is to cover Gram positives, Gram negatives and anaerobics.
  - ○ Standard in a patient not carrying multidrug resistant bacteria and without other risk factors: Vancomycin iv 10 mg/kg every 6 hours (diluted at a maximum concentration

5 mg/ml SG5 % or SSF and infusion time: 60-90 minutes + Piperacillin-Tazobactam (Piperacillin dose 100 mg/Kg/6-8h iv, maximum 4 gr/6h).

- In patient carrying resistant bacteria, betalactamase or carbapenemase VIM/OXA48:
  Vancomycin iv 10 mg/kg every 6 hours + Meropenem (20 mg/kg dose every 8 hours may be sufficient for betalactamases, 40 mg/kg/dose for carbapenemase). Amikacin (15 mg/kg/dose every 24 hours) should be evaluated as a function of sensitivity.

Comment on the history, analysis and peculiarities of the child with the anesthesiologist

Attach a treatment sheet for the intraoperative period, to continue ranitidine/omeprazole and antibiotics during the surgical act. Add instruction of methylprednisolone 10 mg/kg (maximum 500 mg) to infuse iv in the operating room after portal revascularisation.

Take the O.R. and deliver the anesthesiologist's assistant nurse the RNAlater container to store sample of explante liver (before deposited in formalin). Collect the sample and bring tube to consultation refrigerator Hepathology

B. POSTOPERATIVE

1. Measures of infection prophylaxis Prophylaxis of bacterial infection

Isolation

- personal with mask
- wash hands with soap, and then apply hydro-alcoholic solution

- Sampling for culture (peritoneal drained fluid, bronchial aspirate, urine, blood culture) every 3 days the first week, then according to clinical indication
- Rectal smear every week (surveillance of resistant bacteria)

- nistatin 25,000 IU/kg/dose every 6-8h oral (hospitalisation period)

Antibiotherapy:

- Conventional patient: continue for 5 days with a pattern initiated at the preoperative and intraoperative time. Monitor Vancomycin levels to avoid nephrotoxicity.
- Subsequently reassess prolonged duration or change according to complications or microbiological findings.
- In patients with special risk circumstances such as intraoperative bowel perforation, and new Roux, biliary leakage or with clinical or analytical data of infection, evaluate Piperacilin-Tazobactam change by Meropenem and prolongation of duration. Subsequent modifications according to microbiological findings.

Prophylaxis of fungal infection:

—Patient without special circumstances: do not administer (only give Nistatina oral, all admission)

- Patient at risk*: Micafungina 1 mg/kg/day x7 days or for the duration of the risk situation
- risk of fungal infection: delayed closure of abdominal wall (mesh), polytransfusion by intraoperative or postoperative haemorrhage, dialysis, severe renal failure, intestinal perforation, foreseeable prolonged antibiotherapy.

Prophylaxis of Pneumocystis jirovecii

The most risky period is from month 1 to 6.

- Oral sulfamethoxazole-trimethoprim (trimethoprim 5 mg/kg/day distributed every 12h continuously from day 21.
- Minimum duration: Six months. We usually keep it 2 years.
- Re-administered in periods of increased immunosuppression

Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) prophylaxis

In all patients, from the immediate postoperative period (start at 48 h post-transplantation, after recovery of thrombopenia).

Duration of prophylaxis: until the end of month 6.

Start: Ganciclovir iv 5 mg/kg/dose (maximum 250 mg) every 12 h for 15 days (adapt to

GEF), followed by oral Valganciclovir: dosage: 7x body surface x FGE (maximum 900 mg), every 12 hours

Controls: DNA quantification of CMV and EBV at 30 days, 3 rd month and 6th month. After completion of prophylaxis: every 3 months, indefinite checkup

Antiviral prophylaxis will be re-administered or maintained longer while the patient receives severe immunosuppression (such as rejection) or maintains an unrecovered general condition.

Treatment of CMV infection:
Criterion: DNA-CMV greater than 10e5: always try. DNA CMV greater than 10e3: specify whether or not you are treated according to the time of follow-up and symptoms.

- If there are symptoms (cytopenia, rash, pneumonitis, or hepatitis): reduce immunosuppression, and administer Ganciclovir iv until symptom resolution followed by oral valgancyclovir, until 2 months. Add gammaglobulin antiCMV if there is pneumonitis.
- If there are no symptoms: Valganciclovir 1 month (confirm DNA-CMV undetectable).

Treatment of EBV infection:
DNA-EBV> 2.4x10e4 copies/ml: reduce immunosuppression by decreasing tacrolimus level to <4 ng/ml. If it persists elevated or is greater than 10e5 tacrolimus reduction to 2-3 ng/ml.
Add valgancyclovir to DNA-EBV less than 2.4x10e4 copies/ml

- If there are symptoms (amigdalar hypertrophy, adenoidal hypertrophy, diarrhoea, adenopathies, pneumonitis, splenomegaly, or fever): perform a biopsy to rule out lymphoproliferative syndrome, which would require according to histological degree and depending on organ involvement: decrease tacrolimus, remove tacrolimus, give rituximab, or chemotherapy.

2. Thrombosis Prophylaxis Measurements

Avoid Hb >12 g/dL

- Target Hb 8-10 g/dL in immediate post-transplantation
- Replenish abdominal drainage with seroalbumin from the absence of active bleeding
- Quantify antithrombin (on 1st day): administer 1 dose (AT = (100- patient AT activity) x Weight) if the value of AT is <70. If PPP matches less than 40 % plasma 10 cc/kg should also be administered.

Patients at standard risk

In the absence of active bleeding, with platelets >50.000/µL and APP>40 % (without plasma): start sodium heparin in continuous infusion (10 U/Kg/hora:240-300 U/kg/day) TTPA target: ratio 1-1.5 or antiXa 0.2-0.4

- Duration of heparin: 10-15 days, according to patient's recovery status
- Change to acetylsalicylic 2-3 mg/kg/day (if Plt >50,000) or dipyridamole 1 mg/kg/dose every 8 hours at 10-15 days, end at 30 days.

Patients at increased vascular risk (complex suture, fine gauge, portal stenosis, arterial pattern parvus tardus, large graft):

- heparin sodium iv in continuous infusion 300 IU/kg/day, target TTPA ratio 1-1.5, or antiXa 0.2-0.4

- followed by: low molecular weight heparin (HIBOR every 24 hours subcutaneous, anti-Xa-regulated dose) until end of risk (flow pattern recovery), or until the end of month 1.
- If the hepatic artery is at risk, heparin may be replaced by acetylsalicillic 2-3 mg/kg/day orally. If the risk is porta or suprahepatic: low-weight heparin is preferable, if there is

difficulty in administration replacing with acetylsalicylic 2-3 mg/kg/day

3. **Prophylaxis of digestive bleeding**

Omeprazole 1 mg/Kg/dose every 12 hours or Ranitidine 1.5 mg/kg/dose iv every 6 hours.

4. **Immunosuppression**

- **Standard**
  Intraoperative: Methylprednisolone 10 mg/kg (max 500 mg) in postoperative graft reperfusion: corticoid combination+ basiliximab+ tacrolimus

- **Renal impairment:**
  Corticoid+ basiliximab and tacrolimus (decreased in level 2-5 ng/ml less than standard
  Association of mofetyl-mycophenolate 600 mg/m² or 20-30 mg/kg/day (distributed every 12 hours)

- **Cardiomyopathy, multiple food allergy:**
  Replacement of tacrolimus with cyclosporin microemulsion

Dosing of immunosuppressants

Corticoid (methylprednisolone)

Children under 30 kg:

- 10 mg/kg intraoperative.
- Day 1 to 6: 2 mg/kg/day.
- Day 7 to 13: 1 mg/kg/day.
- Day 14 to 20: 0.7 mg/kg/day.
- Day 21 to 28: 0.5 mg/kg/day.
- Month 2: 0.3 mg/kg/day.
- Month 3: 0.2 mg/kg/day
- From the 6th month: change to alternate days (0.2 mg/kg every 48 h)

children over 30 kg:

- 10 mg/kg intraoperative max 500 mg
- Day 1 to 6: 0.7 mg/kg/day.
- Day 7 to 13: 0.4 mg/kg/day.
- Day 14 to 20: 0.25 mg/kg/day.
- Day 21 to 28: 0.2 mg/kg/day.
- Month 2 and 3: 6 mg day.

From 3 months: change to 6 mg every 48 hours

Tacrolimus

Tacrolimus granulated formulation for GNS or oral administration in children, diluted in water. Do not administer other oral medications or foods from 1 hour before to 1 hour postdose.

- Start in the first 2 h post-transplantation: 0.07 mg/kg per nasogastric probe (painted 1 h).
- Next dose at least 6 h later, to adjust convenient schedule to extraction of levels.

- 1st day: 0.15 mg/kg/day divided into 2 doses
- Successive doses according to level.
- Daily level control in valley.

Tacrolimus Desired level (total blood immunoassay, ng/mL)

- weeks 1 and 2: **12** mg/L (10 to 15);
- semanas 3 y 4: **10** mg/L (de 8 a12);
- meses 1 a 3: **8** mg/L (de 6 a10);
- meses 4 a 12: **6** mg/L (de 4 a 8);

- posteriormente **4** mg/L (de 2 a 6).

antiIL2R (Basiliximab)

Dosage: to day 0 and day 4 post-transplantation

- 10 mg i.v. if weight is <35 kg
- 20 mg if the weight is >35 kg

Alternative and complementary drugs in special situations:

cyclosporine microemulsion

• Start in the first 2 h post-transplantation: 10 mg/kg per nasogastric tube, 1 h clamped probe. Next dose adjusted to the appropriate schedule for removal of levels at least 6 h after the first dose:
• Day 1: 15 mg/kg/day distributed every 12 hours.
• Successive doses according to level.
• Daily level 2 h post-administration control (C2).

Desired level (total blood, ng/mL):
• Days 1 to 14: valley: 250-350; C2: 1000-1200.
• Weeks 3 to 12: 200-300 valley; C2: 800-1000.
• Subsequently: valley 150-200; C2: 600-800.
• Long-term (from 9th month): valley 100; C2: 400-600.

Mycophenolate

15 mg/kg every 12h or 600 mg/m^2 every 12h, oral
Fixed dose, decrease if there is cytopenia, or if MMF is used as an immunosuppression supplement with tacrolimus decrease.

Sirolimus

Desired level: 4-8 ng/ml

5 .Antibiotic prophylaxis in procedures

- Performing liver biopsy

Cefotaxima 100 mg/Kg/day (start before the procedure and another dose 8 h later).

- Interventionist radiology

—Central access: teicoplanin 10 mg/kg/day or vancomycin 10 mg/kg every 6-8h for 24 hours.
—Transhepatic access: according to the patient's microbiological history: standard: theicoplanin (or vancomycin) + piperacillin-tazobactam for 24 h.

6 . Analysis and routine examinations in the early postoperative period

- 1st and 2nd days:

- Surveillance: hemodynamics, bleeding, alkalosis, hypocalcaemia, hypokalaemia, primary failure
- Chest X-ray (special attention to the position of the endotracheal tube, catheters, and probes).

- Hepatic Doppler ultrasound: daily, special attention to arterial and portal flows.
- Analytical: arterial gasometry with ions, ion calcium and hematocrit every 6 hours, blood count, coagulation, transaminases and bilirubin every 8-12 h.
- Immunosuppressant level: I'm diary.
- Samples for bacteriological study of all locations.

- 3 rd to 7th days:

- Surveillance: infection, rejection, arterial thrombosis, hydroelectrolytic balance.
- Hepatic Doppler ultrasound: day-to-day.
- Chest X-ray: daily if it continues intubated.

- Analytical: arterial or venous gas, ion calcium, blood count, liver biochemistry, ions and coagulation every 12 hours.
- Immunosuppressant level: I'm diary.
- Samples for bacteriological study: every 2 days.
- Liver biopsy if the course of transaminases and bilirubin does not follow the characteristic descent into normal.

- Second week

- Surveillance: rejection, infection.
- Hepatic Doppler ultrasound: weekly.
- Complete analytical and immunosuppressant level: I'm diary.
- Bacteriology: weekly.

- 3 rd and 4th weeks

- Surveillance: infection, changes in the pharmacokinetics of immunosuppressants.
- Hepatic Doppler ultrasound: weekly (vigilance via bile, abdominal collections and cutting area if the graft is reduced).
- Complete analytical and immunosuppressant level: every 3 days.
- Bacteriology: weekly.

- 2nd month

- Surveillance: viral infection.
- Doppler ultrasound: every 15 days.
- Analytical and immunosuppressant level: every 15 days.
- DNA quantification of EBV and CMV: monthly.

7. Routine follow-up in external consultation.

- Anamnesis and general physical examination.

- Every 3 months
- Medication compliance.
- Intercurrent processes.
- Medication in intercurrent processes (special attention to drugs that may interact with anticalcineurins, such as macrolides).
- Weight and stature development.
- Psychomotor development and school learning, hearing and vision
- Specific liver symptoms (prurito, etc.)
- Routine vaccination check-up.
- Data on possible drug toxicity: Cushing, hair, tremor, polydipsy, nicturia (enuresis), blood pressure.
- Data of possible lymphoproliferative process associated with EBV: adenopathies, poor nasal breathing, amigdal hypertrophy, salivary gland hypertrophy, diarrhea, organomegaly.

- Analytical data and other explorations

Every 3 months:

—Hemogram, general biochemistry (glycaemia, ions, creatinine, venous gasometry, cholesterol, triglycerides, transaminases, GGT, bilirubin, uric, alkaline phosphatase, immunosuppressant level, DNA quantification of CMV and EBV, sediment).

Every 12 months:
—Abdominal ecograph, hepatic Doppler.
— Annual flu vaccination

- Other controls

- Specific follow-up in the Nutrition Unit of transplanted children

with an age of less than 2 years, and for all those severely pretransplanted (follow-up of previous

support measures such as enteral night feeding and consideration of its post-transplantation duration).

- Specific follow-up in the Nephrology Service to patients with renal impairments prior to transplantation and those who have elevated serum creatinine or high blood pressure or proteinuria after transplantation. Consideration of angiotensin convertase inhibitors, thiazides, growth hormone and erythropoietin (EPO) by the Nephrology specialist.

- Specialist hearing and ophthalmological control, based on background

8. Main rules in monitoring

—Avoid drugs with interaction with ciclosporin/tacrolimus.

—Monitor compliance with immunosuppression.

Promote normal integration of the child into all activities of his or her age, but avoid day-care in children under 3 years of age and school trips or camps for children and adolescents, unless there is an adult responsible for administering the medication.

—Special care of processes with vomiting or diarrhoea: they induce renal failure easily (the ability of urinary concentration is decreased), in children with tacrolimus diarrhoea increases the blood levels of the drug. Hospitalise and ensure the entry of basal i.v. contributions for age (and 20 cc/kg more for possible tubulopathy), adding more contributions (oral or i.v.) to replenish the sustained losses.

—Adrenal insufficiency prophylaxis if concomitant severe pathology or surgeries. Increase doses of steroid temporarily on a preventive basis, so that they receive the physiological production of cortisol (i.e.: 6-9 mg/m²/day, oral: 10-15 mg/m²/day) multiplied by 3, or its equivalent in another preparation of corticoid. Return to the patient's previous dose of steroid as soon as the stress situation passes.

—Monitor continued protection against Pneumocystis (various valid regimens with cotrimoxazole (daily every 12h, or 3 times a week once a day), HBV, HV, influenza, Haemophilus, pneumococcus and meningitis.

—Monitor renal function (glomerular filtering and proteinuria). Modify immunosuppression in patients with compromised renal function: (FGE<70 ml/min)

Immunosuppression regimen for patients with renal function involved in mid-long-term follow-up:

Mycophenolate mofetil (MMF) 300 mg/m² every 12 hours the first week, then 600 mg/m² every 12 h (decrease if leucopenia).
After one week of MMF at full dose: progressive decrease of the calcineurine inhibitor to achieve a level of 30-50 % less than baseline over 3 weeks.