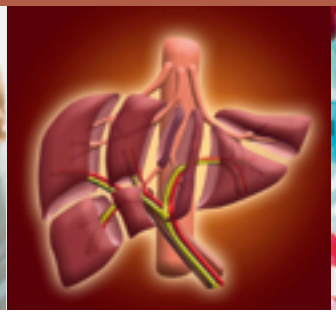
Aftercare Following Liver Transplantation

Pharmacological Therapy – Complications – Lifestyle


Recommended Practices for Cooperation Between the Primary Care Provider and the Transplant Center

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Publisher

DR. FALK PHARMA GmbH

Leinenweberstr. 5
79108 Freiburg
Germany

www.drfalkpharma.com

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3rd edition 2018

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Orthotopic liver transplantation in patients with end-stage liver disease was first approved as an appropriate modality at a consensus conference of the National Institutes of Health (USA) in June 1983. Over the ensuing three decades, the one-year survival following liver transplantation has been further improved by advances in surgical techniques and organ preservation, as well as in pharmacological immunosuppression. Over the same period, liver transplantation has become a routine procedure in Germany, where more than 20 centers offer liver transplantation programs. The post-operative course depends on many factors, including patients' condition prior to transplantation, the underlying disease and its management, potential comorbidities and the quality of the donor organ. Of overriding importance, however, is qualified and standardized aftercare.

Guidelines defining the standard of care following liver transplantation have yet to be adopted in Germany. The present brochure is intended to serve as a support for the most important topics in the aftercare of patients following liver transplantation. The statements and recommendations are based on research data and the personal experience of the authors.

Specific questions should be addressed to a transplant center.

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1. Aftercare Protocol

Transplantation aftercare should be rooted in close cooperation with patients' primary care provider

Frequency of Aftercare at the Transplant Center/Cooperation with the Primary Care Provider

During the first four post-operative weeks, ambulatory aftercare is scheduled once or twice a week for appointments with a physician experienced in liver transplantation. Patients in stable recovery will then be scheduled for weekly appointments.
Patients remain in close contact with the transplant center for the first months and are seen for aftercare every four weeks. After the first half-year, it is advisable, even for patients in stable recovery, to present to the transplant center for follow-up every three months. Once two years have passed, intervals can be gradually lengthened.

It is important to regularly monitor serum levels of the respective immunosuppressant (cyclosporine A, tacrolimus, sirolimus, everolimus). Patients should be reminded on the day scheduled for the laboratory visit to take their morning medication dose only **after the blood sample has been drawn**.

In addition, the following laboratory parameters should be monitored:

- Liver enzymes (AST, ALT, AP, γGT, bilirubin)
- Coagulation parameters (INR)
- Renal parameters (creatinine, BUN, uric acid, electrolytes)
- Blood count
- Infection markers (white blood count, CRP)
- Metabolic parameters: HbA1c, cholesterol, LDL, HDL
- CMV DNA PCR

Monitoring of other laboratory parameters depends on the nature of the underlying disease, complications and associated disorders and the particular form of immunosuppression, in addition to patients' other medications, the time elapsed since the transplant surgery and patients' current clinical condition.

The following disorders require careful monitoring of specific laboratory parameters:

- Viral hepatitis (HCV, HBV)
- Malignant tumors (HCC, NET)
- Primary biliary cholangitis (PBC)
- Primary sclerosing cholangitis (PSC)
- Autoimmune hepatitis (AIH)
- Alcohol abuse (ASH)

The basic monitoring protocol is supplemented by testing individually tailored to patients' underlying disease and current status

Serology

In addition to routine laboratory and clinical monitoring, patients' viral status should also be regularly assessed. Patients with active or resolved hepatitis B or C are advised to undergo viral serology testing at intervals of three months (HBsAg or anti-HCV-IgM, respectively). CMV reactivation or infection under immunosuppression can cause complications, when not detected and not treated. Therefore, all patients' laboratory monitoring should include polymerase chain reaction (PCR) testing for cytomegalovirus (CMV).

The risk of malignancy is increased in transplant patients and requires regular screening examinations

Tumor Screening after Transplantation

Due to the obligatory immunosuppression patients face an increased risk of malignant disease following transplantation. In fact, transplant patients exhibit rate of developing tumors that is about four-fold that of the normal population. The most important causes of this phenomenon include:

- Rather high levels of immunosuppression in the early post-transplant phase
- High sensitivity of the skin to UV radiation (sun)
- The development of certain viral infections associated with lymphoma induction (e.g. Epstein-Barr virus [EBV])
- A direct tumor growth-promoting effect of the pharmaceuticals themselves

Because of this risk, every patient undergoing transplantation requires long-term follow-up that regularly monitors for, and detects at an early stage, the development of malignant disease:

Abdominal ultrasound	every 6 months
Dermatological whole body check	every 12 months
Female: Gynecology	every 12 months
Male: Urology with PSA	every 12 months
Colonoscopy	Every 3–5 years following transplantation; more frequently with polyps; follow-up according to histology and guidelines; patients with PSC/IBD need annual colonoscopy

Special diagnostics in patients with HCC:

At 6 ,12 and 24 months, CT or MRI of the abdomen and alpha-fetoprotein (AFP); subsequently, abdominal ultrasound and AFP every six months.

Further recommendations for follow-up:

Dental examination	every 6–12 months
Bone density measurement	every 2–3 years

Recommended Aftercare Monitoring Examinations Following Liver Transplantation

Cancer screening

Yearly dermatological examination for early detection of skin tumors
Yearly gynecological examination in women
Yearly prostate/urological examination in men
Yearly ENT examination, especially in smokers
Abdominal ultrasound every 6 months
Regular colonoscopies for early detection of tumors of the colon every 3–5 years; yearly in patients with PSC or IBD

Additional examinations

Yearly ophthalmological examinations (some medications can cause changes in vision, glaucoma or cataract)
Dental examinations every 6 months

Immunizations

Generally recommended:	Influenza (flu), tetanus, diphtheria, pneumococcus
Individual (as needed):	Early summer meningoencephalitis (FSME), meningococcus, rabies
Contraindicated:	Measles, mumps, German measles, chickenpox, typhoid, yellow fever, tuberculosis

This and other educational materials for patients are available for downloading at:
www.ursofalk.com/handout

2. Immunosuppressants: Mechanisms of Action, Side Effects and Target Levels

Immunosuppressive therapy is a central factor in transplantation aftercare. It requires regular monitoring and must be adapted to the individual patient's needs

A variety of immunosuppressive agents are available today, each with its own side effect profile and individual tolerability. This allows the clinician to match the most appropriate agent or agents to the patient's needs and risk profile.

Depending on preparation, the immunosuppressive medication should be taken regularly every 12 or 24 hours. If a medication dose should be unexpectedly overlooked, patients may still take the full dose up to six hours past the regular administration time. If a dose is completely missed, patients may compensate by increasing their next regular dose to 1.5 times the regularly prescribed dose.

The majority of immunosuppressive agents administered to patients undergoing liver transplantation are considered "critical-dose drugs" whose serum concentrations must be regularly monitored. The prescribed dose is determined by trough levels, which are measured in blood drawn prior to patients' morning medication dose. Higher trough levels are maintained over the initial three to six months following transplantation; thereafter, dosages can be gradually reduced in most cases.

Calcineurin Inhibitors (CNIs): Tacrolimus and Cyclosporine A

The calcineurin inhibitors (CNIs), tacrolimus and cyclosporine A, are usually considered to represent the standard agents for immunosuppressive therapy for patients undergoing liver transplantation. Both cyclosporine A and tacrolimus are available in a variety of pharmaceutical formulations and marketed under a number of different brand names. Because pharmaceutical preparations may differ in terms of their absorption and metabolism, patients in whom a change in cyclosporine preparation is unavoidable must be closely monitored in order to assess the impact of the new preparation on serum concentrations. This is crucial in order to minimize side effects and prevent rejection reactions.

Common Side Effects of CNIs:

- Increased risk of infections
- Increased risk of malignancies
- Renal insufficiency
- Hyperkalemia
- Arterial hypertension
- Neurotoxicity (psychomotor agitation, tremor, polyneuropathy)
- Elevated cholesterol and triglyceride concentrations
- Diabetogenic effects
- Hypertrichosis
- Gingival hyperplasia
- Disturbances of bone metabolism

Mycophenolate-Mofetil (MMF)

Mycophenolate-mofetil (MMF) is commonly used in combination with CNIs with the objective of reducing the target concentrations of these agents and thus avoiding side effects. Mycophenolate sodium, a pharmacologically similar agent, is currently approved only for use as an immunosuppressant in patients undergoing renal transplantation.

Common Side Effects of MMF:

- Hematological changes (especially leukopenia and anemia, also thrombocytopenia)
- Gastrointestinal side effects (gastritis, diarrhea, meteorism)
- Cephalgia
- Increased risk of infections
- Increased risk of malignancies
- Delayed wound healing (if larger surgical procedures are planned, MMF should be interrupted; we recommend consultation with a transplant center)

Target serum concentrations (trough levels)

Tacrolimus:

Months 1–3:	8–10 ng/ml
Months 4–6:	5–7 ng/ml
> 6 months:	~ 5 ng/ml; in combination with MMF: 2–4 ng/ml

Cyclosporine A:

Months 1–3:	100–120 ng/ml
Months 4–6:	80–100 ng/ml
> 6 months:	50–80 ng/ml; in combination with MMF: 40 ng/ml

Serum levels of MMF do not require monitoring. Typical dosing for MMF is 1000 mg bid, for mycophenolate sodium (not approved for liver transplantation) 720 mg bid. The dose may need to be adjusted in response to hematological changes.

Target serum concentrations (trough levels)

Everolimus:
Months 1–6: 8–10 ng/ml
> 6 months: 3–8 ng/ml

Sirolimus (not approved for use with liver transplantation):
Months 1–6: 8–10 ng/ml
> 6 Months: 3–8 ng/ml

It is recommended that mTOR inhibitors should be given in combination with low-dose CNI. In these cases, target concentrations for mTOR inhibitors are reduced to 3–8 ng/ml even in the early phase after liver transplantation and CNI concentration must be adjusted appropriately

mTOR Inhibitors: Everolimus and Sirolimus

The mTOR inhibitors, everolimus and sirolimus, are potent immunosuppressants that can in principle be administered following liver transplantation in combination with CNIs. Everolimus has been approved since mid-November 2012 in combination with low-dose CNIs for immunosuppression in patients undergoing liver transplantation. Sirolimus is approved only for use in patients undergoing kidney or heart transplantation. Its use, therefore, remains restricted to clinical studies and to individual, exceptional cases after liver transplantation for which approval must be obtained from the patient's health insurance carrier.

Advantages of the mTOR inhibitors in comparison with conventional CNIs include their very low nephrotoxicity and absence of neurotoxicity. In addition, there is evidence that the incidence and/or recurrence rate of malignancies following transplantation is lower, owing, perhaps, to the antiproliferative properties of the mTOR inhibitors as a group.

Monitoring of target concentrations (trough levels) prior to the morning medication dose is required.

Common Side Effects of mTOR Inhibitors:

- Aphthous stomatitis, skin eruptions, acne, pruritus
- Hypertriglyceridemia, hypercholesterolemia
- Hematological changes (especially anemia, leukopenia)
- Gastrointestinal symptoms (diarrhea, nausea, anorexia)
- Increased risk of infection, especially wound infections and urinary tract infections
- Delayed wound healing
- Non-infectious pneumonitis

Systemically Acting Steroids

Because of their considerable side effects, use of steroids for long-term therapy should be avoided whenever possible. Steroids have, however, retained their value in the aftercare of liver transplantation for stabilizing organ function and preventing rejection during the first three months after surgery. High-dosed steroids remain the standard therapy for patients experiencing an acute organ rejection.

Steroids have retained their value in the early phase following liver transplantation but less during patients' subsequent clinical course

Budesonide: A Topically Acting Steroid

Budesonide is a topically acting glucocorticoid that is almost completely absorbed in the bowel and exhibits a high first-pass effect in the liver of 85–90%. Hence, only 10–15% of the absorbed steroid reaches the systemic circulation and may cause steroid-typical side effects.
Budesonide is approved for treatment of autoimmune hepatitis (AIH). It must not be given to patients with cirrhosis. In liver transplantation aftercare, budesonide may have a role as a therapy option in patients with recurrent AIH in the transplanted liver or for treatment of de-novo AIH.

Azathioprine

Azathioprine, as a precursor to 6-mercaptopurine (6-MP), inhibits the synthesis of DNA and RNA in T- and B-lymphocytes. Limiting its application are its bone marrow toxicity with resulting leukocytopenia and, in some patients, hepatotoxicity. Azathioprine is customarily given in combination with other agents.
The introduction of the more effective, lymphocyte-specific agents mycophenolate-mofetil and mycophenolate sodium has significantly reduced the clinical use of azathioprine. Azathioprine has, however, retained a significant role in liver transplant patients for treatment of recurrent autoimmune hepatitis and of de-novo AIH in the transplanted liver.

Azathioprine is used to treat recurrent AIH

3. Dealing with Side Effects and Medical Complications Due to Immunosuppressants

Renal Insufficiency

- Adequate fluid intake is essential!
- Reduction of CNI dose by addition of MMF
- Switching to an mTOR inhibitor
- Avoidance of other nephrotoxic agents

Neuropathy

- Reduction of CNI dose by addition of MMF
- Switching to an mTOR inhibitor

Hypertension

- Attempt to control first with a beta-blocker (e.g. bisoprolol, metoprolol) or, in patients with diabetes or mild renal insufficiency, with an ACE inhibitor and, if needed, a diuretic (risk of hyperkalemia).
- If a calcium channel blocker is selected, amlodipine is preferred as it does not interact with immunosuppressants, but not infrequently causes ankle edema (nitrendipine is an alternative).
- Regular monitoring of blood pressure!
- Treatment of additional risk factors (obesity, diabetes, hyperlipoproteinemia)

Diabetes mellitus

- Insulin appears to be the most reliable approach (constant control, no interaction with immunosuppressants)
- Glimepiride is the most preferred oral antidiabetic agent
- Metformin is often contraindicated due to reduced renal function
- Regular blood glucose and hemoglobin A1c monitoring
- Discontinue corticosteroids
- Weight control, nutrition counseling, increased physical exercise

Hyperlipidemia

- The HMG-CoA reductase inhibitors pravastatin and fluvastatin are most suitable for reducing serum cholesterol concentrations because they are not metabolized by cytochrome P450 3A4 (CYP 3A4). Monitor creatine kinase due to risk of rhabdomyolysis.
- Discontinue corticosteroids
- Weight control, nutrition counseling, increased physical exercise

Osteoporosis

- Regular bone density measurements
- Supplementation of vitamin D 1000–2000 IU/day
- Bisphosphonates (e.g. alendronate 70 mg/week)
- Discontinue corticosteroids
- Increase physical exercise
- Sufficient calcium intake by nutrition/supplement

For more detailed information we may refer to practice guidelines of the respective boards.

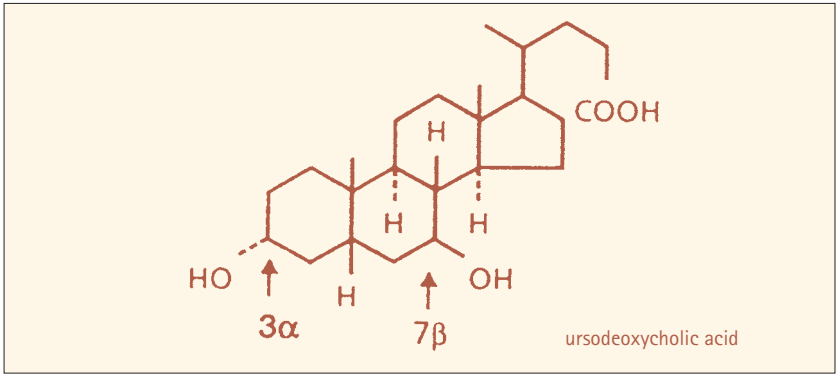
Medical Complications Associated with Immunosuppressants

	Calcineurin inhibitors (CNIs) *Tacrolimus Cyclosporine A*	**Mycophenolate-mofetil (MMF)**	**mTOR inhibitors** *Sirolimus Rapamycin Everolimus*	**Methyl-prednisolone = Glucocorticoids**
Nephrotoxicity	++	–	+/–	–
Neurotoxicity	++	–	–	+/–
Diabetes mellitus	++	–	–	++
Hyperlipidemia	++	–	++	+
Bone marrow toxicity	–	++	–	–
Osteoporosis	+	–	–	+++
Hypertension	+++	–	–	++
GI tract	–	+	+/–	–

4. Ursodeoxycholic Acid in Liver Transplantation

UDCA has a positive effect on transplant graft function following liver transplantation

Ursodeoxycholic acid (UDCA) is a bile acid that occurs naturally in the bile. It can be therapeutically enriched and, by promoting the hydrophilic components in the bile, affects the balance between bile acids and phospholipids. As a result, the bile is less aggressive chemically and this protects against the damaging effects of hydrophobic bile acids.



ursodeoxycholic acid

Bile secretion in the transplanted liver does not completely normalize during the first few post-operative months. A high ratio of bile acids to phospholipids may damage the bile duct epithelium and intensify other deleterious influences, such as preservation damage. Adding ursodeoxycholic acid (UDCA) to patients' long-term regimens following liver transplantation may protect against this.

UDCA has long been an established agent for treating the cholestatic liver disease, primary biliary cholangitis (PBC). Moreover, it has recently been shown that UDCA reduces the risk of recurrence after liver transplantation. It is very likely that this bile acid has a beneficial effect following liver transplantation.

5. General Complications Following Liver Transplantation

The post-operative course of patients undergoing liver transplantation is impacted by certain complications that are specific for the respective post-operative period.

Days–Weeks	Month(s)	Years
Post-operative complications – Anastomoses	**Recurrence of the underlying disease**	
	Medication toxicity	
	Bile duct complications	
Acute rejection		**Chronic rejection**
Infections – Nosocomial bacterial infections – Candida and Aspergillus	**Infections** – Opportunistic infections, especially viruses (CMV, EBV, HHV–6, adenovirus)	**Malignancies**

6. Differential Diagnosis of Transplant Graft Dysfunction

In the first days following liver transplantation

- Thrombosis of the hepatic artery or portal vein
- Primary transplant graft failure (preservation damage)
- Hyperacute rejection (secondary to preformed antibodies in ABO incompatibility, very rare)

Up to three months after liver transplantation

- Acute rejection
- Bile leak
- Infection by opportunistic pathogens

More than three months after liver transplantation

- Chronic rejection
- Ischemic-type biliary lesions (ITBL)
- Bile duct strictures
- Recurrence of the underlying disorder (viral hepatitis B/C/D, AIH, PBC, PSC)
- Infectious diseases secondary to viruses (CMV [cytomegalovirus], HSV [herpes simplex virus], VZV [varicella-zoster virus], EBV [Epstein-Barr virus], adenoviruses) or mycoses

Rejection

Acute

- Incidence 30–50%; acute rejection is rare after the first four weeks
- Clinical signs: often begins with fever, feeling unwell, fatigue, jaundice; frequently clinically inapparent
- Laboratory: usually an increase in liver enzymes or increased AP/γGT, followed by the transaminases, sometimes starting with an increase in bilirubin
- Treatment: high-dose prednisone (500–1000 mg IV/day for 3–5 days), together with increase in the CNI dose
- The diagnosis is confirmed histologically

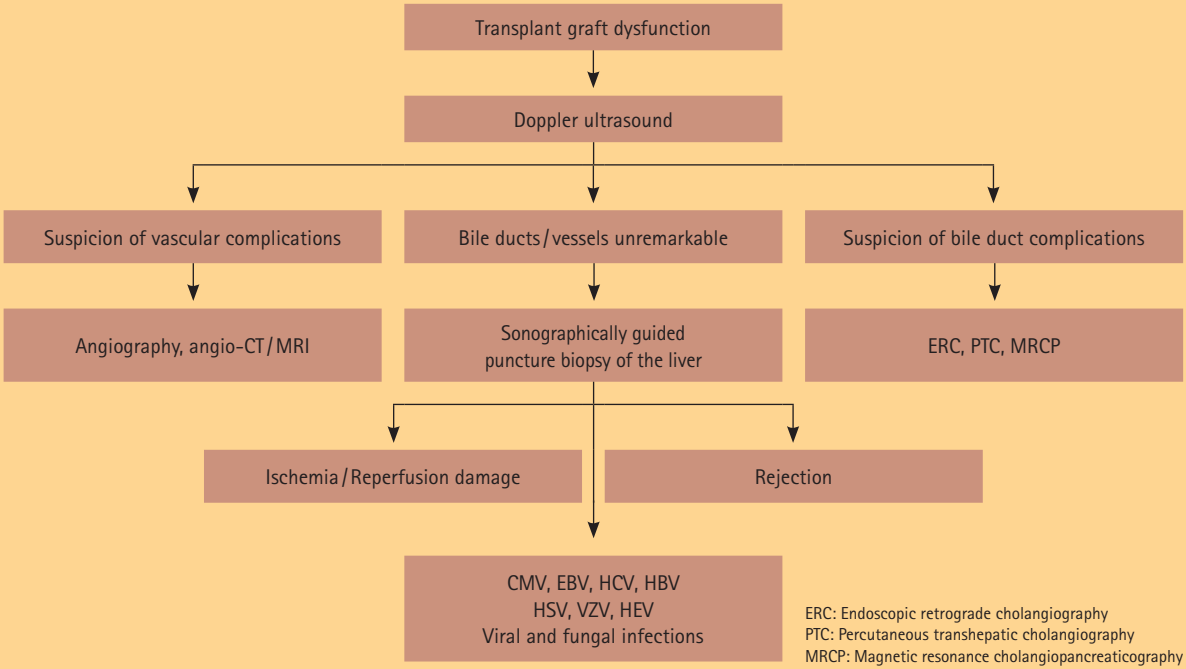
Chronic

- Incidence low; rarely occurs before month 3, usually after month 6
- Clinical signs: usually inapparent, jaundice may occur
- Laboratory: very gradual increase in cholestasis parameters (differential diagnosis includes: bile duct strictures with or without cholangitis, recurrence of PBC/PSC)
- The diagnosis is confirmed histologically (loss of the smaller bile ducts, obliterative angiopathy)
- Therapy: intensification or change of immunosuppression; retransplantation if needed

Info-Box

Post-operative Complications

Post-operative transplant graft complications are detected by signs of transplant graft dysfunction, including increased liver enzymes, reduction in bile production and drop in hepatic synthetic parameters. The dysfunction may be of vascular, biliary or parenchymal origin. The work-up of transplant graft dysfunction is based on the following algorithm:



ERC: Endoscopic retrograde cholangiography
PTC: Percutaneous transhepatic cholangiography
MRCP: Magnetic resonance cholangiopancreaticography

The risk of CMV infection or reactivation depends on the CMV status of both the recipient and donor

Infections

CMV Infection

Infection with the cytomegalovirus (CMV) is the most common infection affecting organ transplant recipients in the first four post-operative months. Causes include CMV-positive donor organs and blood products, and the re-activation of an endogenous infection secondary to the immunosuppressive therapy. CMV-seronegative transplant recipients of a CMV-seropositive donor organ face the greatest risk. The infection may lead to a variety of complications, including CMV hepatitis, CMV colitis and CMV retinitis. Therapy: valganciclovir 900 mg twice a day until PCR negative; if unsuccessful or in cases of viral resistance, ganciclovir (5 mg/kg body weight IV; dose adjusted in renal insufficiency!) as monotherapy or in combination with foscarnet or cidofovir.
In case of renal insufficiency or severe side effects, CMV immunoglobulin (CMV-Ig) may be administered.
In order to prevent reactivation, patients can be offered prophylactic administration of valganciclovir 450 mg twice a day for three months (100 days) for those with high risk. Here, too, the dose must be adjusted according to patients' creatinine clearance.
In all other cases the CMV DNA should be monitored continuously during the first 12 months and every three to six months in the following. Monitoring is essential to detect an infection in time and to prevent the development of a CMV disease.

Detection of viruses and fungi

CMV, HSV, VZV, EBV: quantitative PCR of EDTA blood or relevant body secretions
Adenoviruses: quantitative PCR or antigen detection
Aspergillus, Candida: culture, antigen and antibodies in serum, smear

Therapy

CMV: valganciclovir 900 mg po bid or ganciclovir 5 mg/kg body weight IV every 12 h until PCR negative or CMV-Ig; control of CMV DNA every two weeks
HSV: aciclovir 500 mg IV tid; if unsuccessful, foscarnet or cidofovir
EBV: therapy attempt with aciclovir (or cidofovir), reduction of immunosuppression
Adenovirus: combination therapy with ribavirin and cidofovir (strict indication!)
Aspergillus: caspofungin (if liver function is poor), otherwise voriconazol
Candida albicans: fluconazol, in cases of resistance, caspofungin
Candida, all other cases: caspofungin or liposomal amphotericin B

Standard diagnostics in cases of fever following transplantation

History/clinical examination/urine analysis/laboratory findings/chest x-ray; abdominal ultrasound; blood cultures/drainage fluid; consider CT of thorax and abdomen.
Empirical antibiotic therapy: e.g. tazobactam 3 x 4.5 mg or meropenem 3 x 1 g; if fungal infection suspected, liposomal amphotericin B or caspofungin IV, switch to fluconazole if Candida albicans (**Caution**: Frequent monitoring of immunosuppressant levels is required!)
Further specialized work-up of fever: bronchial lavage for Pneumocystis jirovecii
Important differential diagnoses: rejection reaction, drug reaction, other opportunistic infections, post-transplantation lymphoproliferative disorder (PTLD)

Recurrence of the Underlying Disease

All diseases that lead to liver transplantation may recur

HBV

Pre-operative antiviral therapy with a nucleos(t)ide analogue should be continued for at least three months. The viral load should whenever possible be suppressed below the detection threshold. During the transplant surgery, patients receive 10,000 IU of hepatitis B immunoglobulin (HBIG) intravenously followed by 2000 IU daily for the first seven post-operative days. Patients continue to receive infusions of 10,000 IU every two months (target anti-HBs titer > 100 IU/ml). In addition to the intravenous immunoglobulins, patients require lifelong daily administration of a nucleos(t)ide analogue (lamivudine, entecavir, tenofovir). Because steroids stimulate HBV replication, post-operative immunosuppression should transition away from steroids as soon as possible.

For further information see
www.aasld.org/publications/practice-guidelines-0
www.easl.eu/research/our-contributions/clinical-practice-guidelines

HCV

Patients with HCV-associated liver cirrhosis practically always experience HCV reinfection of the transplant graft. About 20% of patients develop cirrhosis of the transplanted liver within five years. As with hepatitis B, steroid-free immunosuppression should be achieved as soon as possible. Since introduction of IFN-free therapeutic strategies, treatment of HCV infection or recurrence after liver transplantation has become significantly more efficient and safe. The appropriate combination of direct-acting antivirals (DAAs) and the duration of treatment depend on genotype, pretreatment, kidney function and general condition of the patient. Treatment should only be performed in collaboration with an experienced transplant center.

For further information see
www.aasld.org/publications/practice-guidelines-0
www.easl.eu/research/our-contributions/clinical-practice-guidelines

AIH

Autoimmune hepatitis (AIH) is reported to recur in the transplanted organ in 10–30% of cases, depending on the study. Diagnosis should be based on the characteristic histological and serological findings and laboratory analysis for AIH. Treatment is quite effective with adaptation or change of immunosuppression.

For further information see
www.aasld.org/publications/practice-guidelines-0
www.easl.eu/research/our-contributions/clinical-practice-guidelines

PSC

Disease recurrence affects about 10–20% of PSC patients undergoing liver transplantation. Recurrence of PSC is very difficult to distinguish from bile duct damage secondary to other causes or from chronic transplant graft rejection. Elevated serum AP, γGT and bilirubin concentrations may signal disease recurrence. Further work-up includes imaging of the biliary tract using magnetic resonance imaging (MRCP), direct endoscopic examination of bile ducts (ERC) and transplant biopsies.

For further information see
www.aasld.org/publications/practice-guidelines-0
www.easl.eu/research/our-contributions/clinical-practice-guidelines

PBC

Recurrence of PBC is quite rare and occurs in about 5–10% of cases. Recurrent PBC is treated as is the primary disease with UDCA. However, recent data prove a significant reduction of the risk of PBC recurrence by early administration of UDCA.

For further information see
www.aasld.org/publications/practice-guidelines-0
www.easl.eu/research/our-contributions/clinical-practice-guidelines

Nutritive-Toxic Liver Cirrhosis

Relapse of alcohol abuse and of nutritive-toxic liver disease secondary to dietary causes occurs in 10–15% of cases even when abstinence is maintained for at least six months. Patients benefit from regular counseling regarding nutritional habits and the importance of adequate physical exercise as well as from psychosomatic support (compliance groups) and optimum control over metabolic factors (diabetes mellitus, hyperuricemia, lipid metabolism).

HCC

The recurrence of hepatocellular carcinoma (HCC) depends heavily on patients' tumor stage at the time of transplantation. Regular abdominal ultrasound examinations and monitoring of patients' AFP levels every six months are recommended. In the first three years after liver transplantation, CT scan of the chest and the abdomen may be performed every six months to exclude tumor recurrence.

De-Novo Malignancies

The risk of developing de-novo tumors in patients undergoing immunosuppressant therapy following liver transplantation must not be underestimated. The ongoing improvements in pharmacological immunosuppression leading to ever increasing patient and transplant graft survival contribute to the constantly growing risk of malignant disease. Thus, the incidence of malignant disease following liver transplantation depends not only on the underlying disease that led to transplantation and to the associated immunosuppression, but also on the length of post-operative observation. The risk of de-novo tumor development following liver transplantation has been estimated at 10%, 24%, 32% and 42% at 5, 10, 15 and 20 years, respectively. This is three- to four-fold higher than the respective incidences in an otherwise comparable non-transplanted population. The most common neoplasms include skin tumors, such as epithelial basal cell carcinomas (BCC, basaliomas) and squamous cell carcinomas (SCC, spinaliomas), followed by lymphatic diseases (post-transplantation lymphoproliferative disorder, PTLD) and tumors of the ear, nose and throat, and of the urogenital tract. This risk is reflected in aftercare algorithms and must also take into consideration patients' individual risk factors.
In particular patients with PSC and inflammatory bowel disease (IBD) should receive annual colonoscopy. All other patients should receive colonoscopy every 3–5 years or dependent on results.

Post-Transplantation Lymphoproliferative Disorder (PTLD)

Up to 10% of all patients undergoing organ transplantations develop post-transplantation lymphoproliferative disorder (PTLD). The individual risk is affected by the following factors: patient's age, presence of Epstein-Barr virus (EBV) infection at the time of transplantation, and immunosuppressant therapy. Children and patients who were EBV-negative prior to transplantation have a higher risk of developing PTLD. Symptoms are mostly non-specific and may include fever, fatigue, night sweats, weight loss and signs of tonsillitis, sinusitis or otitis media; or it may resemble infectious

PTLD is an important differential diagnosis in cases of unclear fever following liver transplantation

mononucleosis. Many patients exhibit at least one manifest tumor that resides outside the lymph nodes and can cause symptoms such as pain, bleeding or neurological deficits. Therapeutic options include reducing pharmacological immunosuppression, a combination chemotherapy that includes the monoclonal anti-CD20 antibody, rituximab, and adoptive immunotherapy. With this last strategy, leukocytes are obtained from tumor patients after several days of receiving interleukin-2 (IL-2). These leukocytes are then incubated in vitro for several days in the presence of high IL-2 concentrations and then re-injected into the patient's blood stream.

De-Novo Autoimmune Hepatitis

This form of autoimmune hepatitis occurs following liver transplantation secondary to a non-immune mediated liver disease. The disease manifests as acute hepatitis with elevated liver enzymes, especially the transaminases, and is associated with hypergammaglobulinemia. As a rule, autoantibodies (ANA, LKM-1) are detectable. Treatment consists of steroids (e.g. budesonide or prednisone) and azathioprine. Calcineurin inhibitors possess only limited efficacy.

7. Drug Interactions

Many drugs are metabolized by CYP 450 3A4. These agents should only be prescribed after consulting with a transplant center. Combinations of these agents may result in a toxic increase or critical drop in serum concentrations.

Use of pharmaceuticals that interact with CYP 450 3A4 should be avoided

Elevated concentrations:

- Macrolide antibiotics (e.g. clarithromycin, erythromycin)
- Clindamycin
- Tetracyclines
- Calcium channel blockers (diltiazem, nicardipine, verapamil) with the exception of amlodipine and nitrendipine
- Antifungals (azoles: fluconazole, ketoconazole, itraconazole)
- Protease inhibitors (e.g. indinavir, telaprevir)
- HMG-CoA reductase inhibitors with the exception of fluvastatin and pravastatin
- Estrogen, testosterone and progesterone preparations (Caution: reduced reliability of oral contraceptives!)
- Others: danazol, metoclopramide, bromocriptine, cisapride, allopurinol, grapefruit juice

Reduced concentrations:

- Rifampicin
- Antiepileptics (carbamazepine, phenytoin, phenobarbital)
- Others: octreotide, ticlopidine, protease inhibitors

Potentiation of nephrotoxicity:

- Antibiotics: gentamycin, tobramycin, vancomycin, cotrimoxazole
- Antifungals: ketoconazole, itraconazole, amphotericin B
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Other drug interactions can be reviewed under:
www.druginteractions.org

8. Nutrition

- Grapefruit juice and high-fat diets increase the effects of CNIs!
- Saint John's Wort reduces the effects of CNIs!

Basic general recommendations:

- Adequate fluid intake
- Diet high in fiber and vitamins, but low in fat
- Substitution with magnesium, vitamin C, iron, zinc as needed
- Maintenance of normal body weight and adequate physical exercise
- Avoidance of risk factors for arteriosclerotic vascular disease (e.g. tobacco smoking)

Consuming potentially contaminated, bacteria-containing foods is not recommended:

- Raw or undercooked meat or fish and sea food
- Uncooked, cold foods that have not been kept refrigerated
- Oily or greasy foods (mayonnaise, eggs, sandwiches)
- Ice cubes, ice cream, opened soft drinks
- Foods packed in cellophane or plastic wrappers

Specific dietary requirements should be observed especially in the early phase following liver transplantation.
In the following, regular training and nutritional education is highly recommended to prevent metabolic diseases and to regain performability.

These dietary recommendations apply primarily to the first three months following transplantation but may, depending on patients' clinical course, extend to the first six to 12 months. After one year, the post-transplant immunological situation has sufficiently stabilized such that patients can, as a rule, transition to a normal, healthy and balanced diet.

Recommendations regarding foods and other substances that interact with the metabolism of immunosuppressants (e.g. grapefruit, Saint John's Wort) should be observed lifelong.

In general, guided exercise and nutritional education are highly recommended to reverse the loss of physical effectiveness caused by chronic liver disease preceding liver transplantation.

9. Immunizations

All patients should be immunized prior to transplantation against hepatitis A and B, as well as against pneumococci. If this has not been done, it should be supplied after transplantation. It may be necessary to administer a double vaccine dose because the immune response is compromised as a result of the immunosuppression. In general, all immunizations using inactivated vaccines can be administered during immunosuppression, although many patients do not develop full immunity. Live vaccines should only be used in exceptional cases.

Live vaccines are contraindicated after liver transplantation

Recommendations are:

- Yearly flu shots
- Pneumococcal vaccine – booster every 5 years
- Adequate immunization and/or booster against: tetanus, diphtheria, hepatitis A and B
- In individual cases: early summer meningoencephalitis (FSME), meningococci, rabies, polio (oral vaccination contraindicated!)

Contraindicated:

Measles, mumps, German measles, chickenpox, typhoid, yellow fever, tuberculosis

Please see board recommendations for detailed recommendations for vaccinations in immunocompromised patients.

10. Dental Care

Antibiotic prophylaxis, e.g. with ampicillin, a cephalosporin or ciprofloxacin, should be performed prior to a planned dental procedure or extraction. It is recommended to begin 12 hours prior to the procedure and continue for three days following the initial dose.

11. Pregnancy

About half of all women who suffer with chronic liver diseases and undergo liver transplantation during their childbearing years experience amenorrhea (absence of menstruation) during the initial period after surgery. In nearly all cases, however, sexual functioning normalizes within a few months following successful liver transplantation.
It remains a topic of continued discussion, however, whether and how the required immunosuppressant medications affect both the developing child and the mother.
While azathioprine has known teratogenic effects and should therefore be discontinued in women desiring to conceive, it would appear that the rates of fetal abnormalities and miscarriage are no higher than those of the general population in women treated with cyclosporine A or tacrolimus during pregnancy. Nevertheless, every pregnancy following liver transplantation should be considered a high-risk pregnancy. Thus, the following requirements should be met:

1. Stable transplant graft function and at least 12 months elapsed since transplantation.
2. A conscious decision for parenthood and inclusion of the domestic partner following comprehensive discussion with the responsible transplantation specialist.
3. Regular interdisciplinary monitoring during the pregnancy.

12. Back Home After Liver Transplantation: General Advice

Sunlight

An important side effect of immunosuppressants that only occurs many years after these medications have been administered is the development of various kinds of skin cancer. In fact, some form of skin cancer is observed in 40–60% of patients within 20 years of transplantation. One significant cause for this development is unprotected exposure to sunlight. The risk of developing skin cancer increases significantly as a result of a combination of immunosuppressants and exposure to sunlight. Thus, patients are advised to avoid direct exposure to sunlight and to use appropriate protective measures, including topical sunscreen lotions with high sun protection factor (SPF), clothing that covers exposed areas of skin and wearing a hat. In addition, patients should undergo preventive examination by an experienced dermatologist once or twice a year.

Adequate protection against sunlight is crucial for patients under immunosuppression!

Travel

During the first year after transplantation, patients receive higher doses of immunosuppressant medication to reduce the risk of organ rejection. This is associated with a higher risk of infectious diseases. For the same reason, restrictions on travel are greater during the first year. Patients are advised to restrict travel to destinations and countries with a moderate climate and adequate hygienic and healthcare infrastructure. This applies especially to countries in Europe and North America. High-risk areas for patients under immunosuppression (both during and after the first year) include the Near East, Africa, southern Asia and Latin America. Patients are advised to avoid bathing in tropical waters and going barefoot. Unprotected sexual contact should be strictly avoided.

Physical exercise
Exercise and sports are a basic recommendation for patients following transplantation although, especially in the early months after surgery, overexertion should be avoided. Moderate strength training can begin following primary wound healing. Endurance sports such as walking, hiking and cycling are recommended for conditioning the cardiovascular system and preventing metabolic problems (obesity, diabetes). Patients should be advised to join an exercise group under the guidance of a skilled trainer.

Gardening
Potting soil contains extremely high numbers of micro-organisms. Direct contact should therefore be avoided during the first months after transplantation.

Domestic animals
Animals are carriers of a variety of pathogens that, especially in patients receiving immunosuppression, may result in problematic infections. Hence, contact with domestic animals should be avoided, especially during the first year after transplantation.

General recommendations
Public transportation and swimming pools should be avoided during the first year after transplantation. Tobacco smoking should be avoided in any case. Absolute abstinence from alcohol, especially in patients undergoing liver transplantation due to alcohol-related disorders, should continue lifelong.

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U13e 3-6/2018 POP