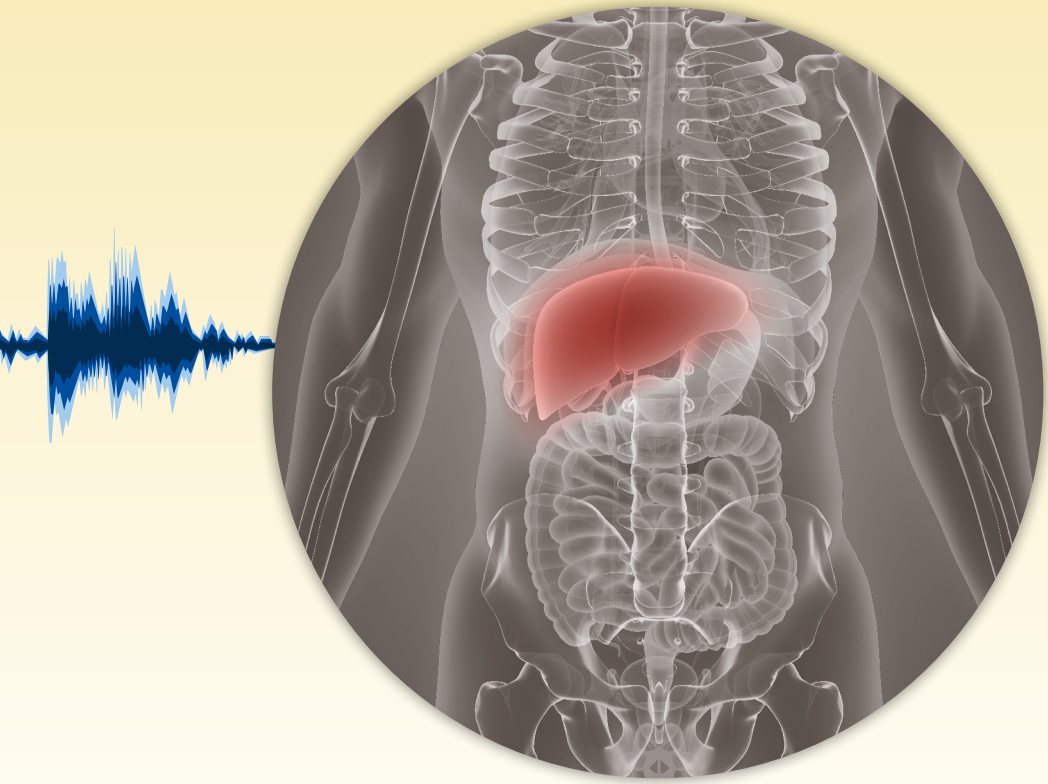
Severe Liver Diseases and Liver Transplantation

Prof. Dr. Kerstin Herzer



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Foreword

In 1983, liver transplantation was approved by the U.S. Food and Drug Administration (FDA) for the treatment of end-stage liver disease and soon became accepted as the standard of care. Since that time, advances in surgical techniques, organ preservation, and pharmacological immunosuppression have driven continuous improvements in 1-year survival following liver transplantation. Liver transplantation has become a routine procedure in Germany over the last 30 years, with liver transplant programs currently available at more than 20 hospitals.

Post-operative outcomes are determined not only by the patient's status prior to transplantation, his or her underlying disease, management of the underlying disease, comorbidities, the quality of the donor organ, but also from qualified and standardized post-transplant care.

To date, there are no high-level guidelines on the topic of post-liver transplant care in Germany. This booklet is intended to provide supporting information for the prevention and treatment of advanced liver disease and for successful outcomes before and after liver transplant. The recommendations in this text are based on scientific data as well as the author's personal experience from clinical practice.

The advice of a hepatologist or transplantation center should be sought in case of specific questions.

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1 Cirrhosis

Development, consequences, and prognosis

Cirrhosis develops as the result of chronic stress or damage to the liver. At its onset, cirrhosis has a clinically silent and asymptomatic presentation which progresses over several years or even decades. During this stage, cirrhosis is considered to be compensated.

Initially, damage to the liver leads to increased scar tissue formation in the liver which is still reversible. As the disease progresses, hepatocytes are replaced by scar tissue. This process is irreversible and impedes the ability of the liver to function properly.

While this chronic course can often be successfully prevented or at least delayed by appropriate early therapy and lifestyle changes, cirrhosis itself is not curable.

Cirrhosis is the end stage of a process characterized by nodular remodeling of the parenchyma with bridging fibrosis, cellular activation, vascular changes, and infiltration by inflammatory cells leading to the gradual loss of hepatic structure and increasing hepatic impairment. The complications of cirrhosis can be major, including the accumulation of water in the abdomen (ascites), impairment in brain function (hepatic encephalopathy, HE), bleeding from varicose veins in the stomach or esophagus (variceal bleeding), and even liver cancer (hepatocellular carcinoma, HCC) in very unfavorable cases. The detoxification and synthetic functions of the liver (albumin, coagulation factors) are reduced, and blood circulation is disrupted by elevated portal venous pressure, causing blood to become backed up in the spleen and the entire venous system of the gastrointestinal tract, including the veins of the esophagus. These processes play a major role in the development of the complications of cirrhosis.

Treatment strategies exist for many of the potential complications. In recent decades, the prognosis for cirrhosis could be improved greatly by an expansion of the treatment options for the underlying conditions leading to cirrhosis. Conversely, patients' life expectancy drops sharply with complications of cirrhosis (decompensated cirrhosis). The quality of life and life expectancy of

cirrhosis patients can be improved by thorough prevention and treatment of both the underlying disease and any complications. It should also be reviewed whether liver transplantation is indicated and feasible.

Finally, the individual outcomes of cirrhosis also depend on the etiology of the patient's disease. Chronic hepatitis C virus (HCV) infection has diminished as a cause of cirrhosis in recent years thanks to improved treatment options, making alcoholic steatohepatitis (ASH) the most common cause followed by non-alcoholic steatohepatitis (NASH) and cryptogenic liver diseases.

The initial strategies for managing these varied causes is to specifically prevent their underlying disorders. For cases of compensated cirrhosis, addressing the causal underlying disorder is the primary strategy, for example by treating HCV infection, ceasing alcohol consumption, or treating an autoimmune liver disease. These steps may prevent or delay disease progression.

At later stages of cirrhosis and especially in patients with advanced decompensated cirrhosis, treatment focuses on managing complications.

Complications of cirrhosis and their treatment

Ascites is the most common complication of cirrhosis. About 5–10% of cirrhosis patients develop this complication each year. Ascites has a multifactorial etiology and appears to be caused by a combination of portal hypertension and liver failure.

The presence of ascites is a major detriment to quality of life and is associated with a worse prognosis. When ascites becomes clinically detectable, treatment should be initiated with the goal of reducing its quantity and managing its symptom, not complete reversal of ascites.

This goal can be achieved by prescribing diuretics or by non-pharmacological management consisting of reducing sodium intake (max. 2 g/day equivalent to 87 mmol sodium), ensuring adequate protein intake (1.2–1.5 g/kg BW/day) with sufficient caloric energy (30–35 kcal/kg BW/day), and paracentesis. As secondary hyperaldosteronism plays a central role in renal sodium retention, the

oral aldosterone antagonist spironolactone (starting dose 100 mg/day) should be the first choice of diuretic prescribed. A loop diuretic (furosemide, torasemide) can be additionally prescribed, although these drugs are inferior to spironolactone when prescribed alone.

For patients with refractory or recurring ascites, the requirement and feasibility of liver transplant or TIPS (transjugular intrahepatic portosystemic shunt) should be reviewed.

The potential secondary complications of ascites include spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS), both of which are associated with increased mortality.

Spontaneous bacterial peritonitis (SBP) is defined as detection of > 250 polymorphonuclear leukocyte (PMN) cells, i.e. granulocytes, per mm^3 ascites. More than one-third of all hospitalized patients with cirrhosis develop SBP.

While the prevalence of SBP is only about 3.5% in outpatients with clinically asymptomatic ascites, it is higher among hospitalized patients with a prevalence of up to 36%. SBP can exacerbate existing complications of cirrhosis and increase the likelihood of new onset HRS and HE. Left untreated, SBP is associated with greater mortality.

Primary antibiotic prophylaxis can be administered in cases of ascites with low protein levels (< 1.5 g/dl). The German Society for Digestive and Metabolic Diseases (DGVS) recommends primary prophylaxis with antibiotics for patients who also fulfill one of two additional criteria (1. severe liver failure, e.g. Child-Pugh score > 9 with bilirubin > 3 mg/dl or 2. kidney failure with serum creatinine > 1.2 mg/dl, urea > 25 mg/dl or sodium < 130 mmol). Cirrhosis patients with gastrointestinal bleeding (with or without ascites) should also always be given antibiotics as primary prophylaxis. Daily norfloxacin should be administered continuously as primary prophylaxis, although the semi-synthetic antibiotic rifaximin can be given in rare cases when indicated.

Once SBP is diagnosed, treatment must begin at once. Patients should initially be prescribed a third-generation cephalosporin (ceftriaxone) as empiric therapy. Albumin is also recommended on the day of diagnosis and every 3 days thereafter in addition to antibiotic therapy.

Hepatorenal syndrome (HRS) is one of the most severe complications in patients with advanced-stage cirrhosis and ascites, and is associated with high mortality. It is defined as potentially reversible renal impairment in cirrhosis patients and is subclassified into two forms. Type 1 HRS is characterized by rapidly progressive kidney failure (doubling of serum creatinine to > 2.5 mg/dl in less than 2 weeks). Type 2 HRS is frequently accompanied by treatment-refractory ascites and exhibits moderate kidney failure (serum creatinine 1.5–2.5 mg/dl) with slow progression. Because the rapidly progressing type 1 has a 3-month mortality of over 90%, prevention and treatment of HRS is a daunting task. Volume expansion using albumin can be performed if renal function does not improve after discontinuing either diuretics or other nephrotoxic medicines. However, administration of albumin alone only improves renal function in a small percentage of patients, while case-control studies have shown the combination of terlipressin plus intravenous albumin to be superior. TIPS insertion has been shown to improve renal function in type 1 and 2 HRS as well as prolong overall survival, and therefore should be considered for all patients with HRS.

Another common complication of cirrhosis is **hepatic encephalopathy (HE)**. Up to 21% of cirrhosis patients already have HE at the time of their diagnosis, and about half will experience an HE episode over the course of the disease. HE is linked to high mortality, with 64% of patients dying within 1 year. An additional challenge of this condition is the fact that some of the consequences of HE are irreversible, and sustained cognitive deficits in learning and memory must be expected in some patients even after initial improvement.

The standard treatment for HE is to address its trigger, the most common of which are infections (SBP, urinary tract infections), gastrointestinal bleeding, electrolyte imbalance, and dehydration.

Lactulose is recommended as the first-line pharmacological treatment option for overt HE (oHE). It can be given orally or, if not possible, rectally.

Administration of rifaximin can be considered (off-label) in combination with lactulose in rare cases or if lactulose is not tolerated, although there is no study data confirming its benefit in this setting.

Intravenous branched-chain amino acids can also be given during an acute phase of HE or oHE, although oral administration is not recommended. While L-ornithine L-aspartate reduces the ammonia concentration in blood, a decrease in ammonia levels alone does not provide any indication of clinical effectiveness. Following an initial episode of HE, approximately 60% of patients suffer a second episode. For this reason, secondary prophylaxis with rifaximin in combination with lactulose is recommended. Other poorly absorbed antibiotics such as paromomycin and neomycin pose a risk of severe adverse effects, including ototoxic and nephrotoxic effects, if taken long-term.

Herbal medicines for cirrhosis treatment

Herbal medicines have been shown to be effective treatments for hepatobiliary disorders for many years. The majority of these herbal medicines have been described by Commission E, a committee which advises the German Federal Institute for Drugs and Medical Devices (BfArM) on traditional herbal medicines.

Herbal medicine can be a useful component of a treatment plan for hepatobiliary disorders when prescribed in a targeted manner.

Silymarin is a component of milk thistle seeds that stabilizes the membrane of hepatocytes, thereby protecting them from the influx of toxins into the cytoplasm of the cells. This mechanism yields a positive effect on the outcomes of several disorders, including fatty liver, toxic liver damage, and viral hepatitis as well as cirrhosis due to its antifibrotic effects. Standardized treatment with milk thistle extract can slow the progression of liver damage and alleviate its symptoms. The extract has especially potent effects against acute death cap poisoning, and has also been observed to greatly improve the survival rates of patients with cirrhosis, fatty liver, and steatohepatitis.

Beetroot (*Beta vulgaris*) has been shown to have similar effects as milk thistle. The primary active substance in this plant is glycine betaine, which like methionine is an essential hepatoprotective amino acid. It plays a role in the methylation cycle in hepatocytes by acting as a methyl donor, which promotes hepatocyte regeneration. Glycine betaine has been shown to have protective and

anti-inflammatory effects against a number of inflammatory liver diseases, although no prospective, placebo-controlled clinical trials have been conducted to confirm its efficacy in advanced fibrosis and cirrhosis.

2 Liver transplantation

An indication for liver transplantation should always be considered when a patient is diagnosed with cirrhosis. In 1983, liver transplantation was approved by the U.S. Food and Drug Administration (FDA) for the treatment of end-stage liver disease and soon became accepted as the standard of care. Since that time, advances in surgical techniques, organ preservation, and pharmacological immunosuppression have driven continuous improvements in 1-year survival following liver transplantation. Liver transplantation has become a routine procedure in Germany over the last 30 years.

Nonetheless, mortality has become high for individuals on the waiting list for a liver transplant. According to the annual report of the German Organ Transplant Foundation (DSO), 19% of the 1,385 patients registered on the German liver transplant waiting list in 2018 died before transplantation. There was a negative trend in the number of deceased organ donors between 2010 and 2017, and again in 2019 following an increase in 2018. Hence, care and stabilization of patients on waiting lists is of great importance. Furthermore, post-operative outcomes are in large part determined by the patient's condition before transplantation as well as by management of the patient's underlying disease, qualified and standardized post-transplant care, and a number of other factors.

Preparation for transplantation

Before patients can be placed on a liver transplantation waiting list, a transplantation center must evaluate the patient's need for a transplant and rule out any contraindications. This requires extensive laboratory tests, imaging procedures (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]) and tests to determine general suitability for surgery (ECG, lung function, chest X-ray). Contraindications for liver transplantation include portal vein thrombosis, advanced hepatocellular carcinoma (HCC) greater than > 5 cm, extrahepatic malignancy, uncontrollable infections, severe disease in other organs, and mental disorders associated with poor compliance.

The countries of Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Slovenia, and the Netherlands have formed an international consortium to distribute donated organs (Eurotransplant). Each transplantation center in these member countries can access the Eurotransplant database and enter information on organ donors and potential organ recipients. In the event of an organ donation, an algorithm is used to select the most suitable recipient for the organ. This algorithm incorporates the factors of urgency, expected outcome, blood group, age, and many others. It also aims to keep organ exchange balanced between the countries. The Eurotransplant consortium attempts to evaluate urgency in an objective manner using several tools, including calculation of the MELD (Model of End-stage Liver Disease) score to assess the severity of liver disease. This formula incorporates the laboratory parameters of total bilirubin, international normalized ratio (INR), and serum creatinine. The MELD score can range from 6 to 40 points and provides an indication of the likelihood that a patient will survive the next 3 months. The higher the MELD score, the greater the likelihood of death.

The feasibility of transplantation is determined based on the results of various tests known as the evaluation process. These tests are intended to rule out certain health risks that may severely jeopardize the success of transplantation, such as cardiovascular disorders, cancer, and inflammatory disorders. The tests include ECG, Holter ECG, chest X-ray, upper endoscopy, colonoscopy, abdominal ultrasound, and examinations by an ENT specialist, dentist, urologist/gynecologist, and dermatologist. The required tests are typically coordinated by a central transplantation physician, who compiles the findings when complete. Once the findings have been compiled, an interdisciplinary team of physicians decides whether the patient can be placed on a liver transplantation waiting list.

An interdisciplinary transplantation committee at the transplantation center makes the final decision of whether to place a patient onto a waiting list, maintain the patient on the list, and possibly register the patient.

The transplantation centers forward the requisite data to the Eurotransplant coordination center.

The Eurotransplant foundation is responsible for distributing donated organs among the eight European countries listed above and thus collaborates closely with the organ donation organizations, transplantation centers, laboratories, and hospitals.

A patient may be denied if the risks of transplantation are deemed to be greater than the benefits and/or the patient is not able to handle the physical and mental stress of transplantation. Moreover, there are other specific medical situations which represent contraindications for transplantation: malignant cancer, severe atherosclerosis, acute or chronic infections, HIV positivity, or acute alcohol or drug abuse.

The transplantation center also reports any acute diseases such as febrile infections, myocardial infarction, pulmonary embolism, depression, or a major worsening of global health status to Eurotransplant in order to indicate that a patient is temporarily not suitable for transplantation. In this situation, the patient is not removed from the waiting list but is switched to a "passive" status in which he or she is temporarily not eligible for an organ. Once the patient has stabilized sufficiently, the center reports that the patient can be switched back to the "active" list and become eligible for donated organs again.

Periodic visits to the transplantation center are necessary during the waiting period so that the assigned physician can evaluate the patient's current health status and report his or her current blood test results to Eurotransplant at regular intervals. Patients on a transplantation waiting list should be within contact at all times, which is most easily achieved by a mobile telephone kept on day and night. Patients should always notify the transplantation center about any upcoming vacations so that the patient can be placed into passive status in Eurotransplant while traveling.

When the phone call comes, the patient should travel to the transplantation center as soon as possible. The call often comes at night, and a bag should always be kept prepared with all items necessary for a hospital stay. A means of transport to the transplantation center should be available at all times.

It is crucial that patients not eat or drink after receiving the phone call, including no chewing gum or nicotine. The opera-

tion cannot be performed if the patient/recipient of the organ is not sober.

Post-transplant care

Following liver transplantation, the transplant recipient should visit a qualified center at regular intervals in close coordination with his or her primary care physician. Until recently, each site devised its own post-transplant care regimen individually. A guideline is now in development for Germany that will issue recommendations for all aspects of post-transplant care. The important topics for post-transplant care are optimization and tailoring of the immunosuppressive regimen, managing any complications or recurrence of the underlying disease, and regular cancer screening to detect cancer at an early stage.

Complications

The probability of certain complications after transplantation changes over time. In the early post-transplantation phase, surgical complications, vascular occlusion, primary non-function, or hyperacute rejection may occur.

Biliary complications, opportunistic infections (primarily CMV infection), or acute cellular rejection may emerge in the initial months after transplantation.

The objective during the first year after transplantation is to reduce or prevent complications due to the adverse effects of immunosuppressants as well as preventing chronic rejection. Recurrence of the underlying disease (autoimmune hepatitis [AIH], primary sclerosing cholangitis [PSC], hepatocellular carcinoma [HCC]) is also possible.

The long-term risk of developing cancer is also greater and must be anticipated. Specifically, the risk of skin cancer is much greater due to immunosuppressive therapy, and accordingly regular screenings (at least every 6 months depending on skin type) by a specialist are recommended. Patients with fever and B symptoms must also be monitored for PTLD (post-transplant lymphopro-

liferative disease), as lymphomas are the second-most common type of cancer after liver transplantation. The risk of gynecological/urogenital cancer as well as colorectal cancer is also higher. Regular cancer screening is thus of major benefit to transplant recipients.

Medications and immunosuppression

Pharmacological therapy is a central factor in post-transplant care, particularly immunosuppression. It requires regular monitoring and must be tailored to each patient.

The serum levels of the immunosuppressive drug administered (cyclosporine A, tacrolimus, sirolimus, everolimus) must be checked on a regular basis. On the day of testing, the morning dose should not be taken until **after drug levels have been measured**!

Drugs that modify cytochrome P_{450} (CYP)3A4 should not be administered!

Because numerous drugs are degraded via CYP3A4, they should only be prescribed after consulting with the transplantation center. Combinations of these drugs can lead to a toxic rise or even a critical drop in drug levels in the body.

Several different immunosuppressive drugs are now available with different adverse effect and tolerability profiles. Accordingly, different drugs or drug combinations are suitable for different patients based on their risk profiles.

Medications should be taken regularly every 12 or 24 hours regardless of specific drug. Should a patient forget to take one dose, the full dose can still be taken up to 6 hours after the normal time. If a dose is forgotten completely, the next dose can be increased 1.5-fold one time only.

Most of the immunosuppressive agents used in liver transplantation are critical-dose drugs, meaning their levels must be monitored regularly. The dosage is guided by the trough levels measured in the morning before the morning dose is taken. The target is higher trough levels in the first 3–6 months following transplantation, after which the dosage can usually be reduced over time.

Calcineurin inhibitors (CNI) tacrolimus and cyclosporine A

The CNIs tacrolimus and cyclosporine A typically represent the standard of care for immunosuppressive therapy. It must be noted that cyclosporine A and tacrolimus are available in various pharmaceutical formulations with different trade names. If switching to a different cyclosporine product is unavoidable, drug levels must be monitored closely to ensure comparable exposure to the new drug, which may be absorbed and metabolized differently, and to prevent rejection reactions.

Common adverse effects of CNIs	
– Increased risk of infections – Increased risk of cancer – Kidney disease – Hyperkalemia – Arterial hypertension – Neurotoxicity (psychomotor agitation, tremors, polyneuropathy)	– Elevated cholesterol and triglycerides – Diabetogenic effects – Hypertrichosis – Gingival enlargement – Bone turnover disorders

Target trough levels	
Tacrolimus:	
Months 1–3:	7–9 ng/ml
Months 4–6:	5–7 ng/ml
> 6 months:	~ 5 ng/ml, in combination with MMF or mTOR inhibitor
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 or mTOR inhibitor

Mycophenolate mofetil (MMF)

MMF is frequently administered in combination with a CNI in order to reduce the target level and thus the adverse effects of the latter. The pharmacologically similar drug mycophenolic acid (mycophenolate sodium) is currently only approved in Europe for kidney transplant.

Common adverse effects of MMF	
– Abnormal blood counts (esp. leukopenia and anemia but also thrombocytopenia) – Gastrointestinal adverse effects (gastritis, diarrhea, bloating) – Headaches	– Increased risk of infection – Increased risk of cancer – Wound healing complications (MMF should be temporarily discontinued for major surgery, consultation with a transplantation center is recommended)

It is not necessary to measure drug levels; normal dosage: MMF 2 x 500–1,000 mg/day or mycophenolic acid (not approved in Europe for liver transplant recipients) 2 x 720 mg/day. Dose modification may be necessary in the event of changes in blood counts.

mTOR inhibitors everolimus and sirolimus

The mTOR inhibitors everolimus and sirolimus are potent immunosuppressants that can generally be administered in combination with a CNI after liver transplant. While everolimus has been approved in Europe in combination with tacrolimus for liver transplantation since mid-November 2012, sirolimus is still only approved for kidney or heart transplant patients. It can therefore only be administered to liver transplant recipients in exceptional cases in the setting of compassionate use or in the context of clinical trials.

The advantages of mTOR inhibitors over CNIs are their very low nephrotoxicity and absence of neurotoxicity in particular. There is also evidence that the incidence and/or recurrence rate of cancer after transplant is lower since the mTOR inhibitor drug class has antiproliferative effects.

The target levels of mTOR inhibitors must also be measured before the drug is taken.

Common adverse effects of mTOR inhibitors	
– Aphthous stomatitis, exanthema, acne, pruritus – Hypertriglyceridemia, hypercholesterolemia – Abnormal blood counts (esp. anemia, leukopenia)	– Gastrointestinal symptoms (diarrhea, nausea, anorexia) – Increased risk of infection, especially wound and urinary tract infections – Wound healing complications – Non-infectious pneumonitis

Target trough levels	
Everolimus:	5–8 ng/ml
Sirolimus (not approved in Europe post-liver transplant):	5–8 ng/ml
Is typically combined with a CNI, in which case the target levels for mTOR inhibitors drop to 3–5 ng/ml	

Systemic steroids

Steroids should be avoided to the greatest extent possible in long-term therapy due to their side effects. The value of steroids after liver transplant remains for the first 3 months after surgery to stabilize organ function and prevent rejection. High-dose steroids are also considered the standard of care for a rejection reaction.

Topical steroid budesonide

Budesonide is a topical corticosteroid that is nearly completely absorbed in the gut and exhibits a first-pass effect of 85–90% in the liver. In other words, only 10–15% of the absorbed drug enters systemic circulation where it can cause the adverse effects typical of steroids.

Budesonide is approved in Europe for the treatment of auto-immune hepatitis (AIH; without cirrhosis!). Budesonide may be a valuable treatment option in the liver transplant setting if AIH recurs in the transplanted liver.

Azathioprine

Azathioprine is a precursor to 6-mercaptopurine, which inhibits DNA and RNA synthesis in T and B lymphocytes. The limiting factor for this drug is bone marrow toxicity leading to leukopenia, as well as hepatotoxicity in some patients. Azathioprine is typically combined with other drugs.

The clinical applications for azathioprine have been largely replaced by the introduction of mycophenolate mofetil (MMF) and mycophenolate sodium, which are more effective, lymphocyte-specific drugs. Nonetheless, azathioprine remains valuable for liver transplant patients for treating AIH recurrence or inflammatory bowel disease (IBD).

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is a bile acid which occurs naturally in bile and can be therapeutically enriched to enhance the hydrophilic component of bile. This enrichment alters the ratio of bile acids and phospholipids, resulting in less aggressive hydrophobic bile acid effects and protection against the harmful effects of hydrophobic bile acids.

Bile secretion does not completely return to normal during the first few months after liver transplantation. A high ratio of bile acids to phospholipids can damage the biliary epithelia and potentiate harmful effects caused by other mechanisms such as preservation injury. This is thought to be preventable by the long-term use of UDCA following liver transplantation.

While the use of UDCA is established for the treatment of the cholestatic liver disease of primary biliary cholangitis (PBC), this drug has also been shown to exert beneficial effects after liver transplant, particularly with regards to preventing recurrence of PBC. UDCA has a generally positive impact on stabilizing and maintaining transplant function following liver transplantation.

Lifestyle factors

Nutrition

The following is always recommended:
– adequate liquid intake
– adequate intake of high biological value protein (animal- and plant-based)
– a fiber-rich and vitamin-rich diet
– adequate plant-based fats with sufficient omega-3 fatty acids
– magnesium, vitamin C/iron, zinc supplementation as needed

Foods potentially contaminated with microbes are not recommended:
– raw meat or raw fish, shellfish
– raw, cold, or stale food
– oil- or fat-rich foods (mayonnaise, eggs, sandwiches)
– ice cubes, ice cream, opened cold drinks
– foods packaged in plastic wrap

Several special nutritional issues must be kept in mind during the early phase after liver transplantation: Obesity should be avoided, including through adequate physical activity! It is just as important to avoid additional factors that promote atherosclerosis (e.g. smoking!).

The dietary recommendations are primarily applicable during the first 3 months after transplantation but also during the first 6–12 months depending on post-transplant developments. By year 1 after transplantation, the immunological situation has stabilized sufficiently that patients can usually transition to a normal, healthy, and balanced diet. A Mediterranean diet is particularly recommended.

However, foods and other substances which interfere with the metabolism of immunosuppressive drugs (grapefruit, St. John's wort) must be permanently excluded from the diet.

Physical therapy and dietary counseling should be performed consistently to counteract the loss of capabilities associated with the patient's pre-transplant chronic liver disease.

Vaccinations

All patients should be vaccinated against hepatitis A and B as well as pneumococcus prior to transplantation. Patients who did not receive these vaccinations should receive them post-transplant, if necessary using a double dose since vaccination response is hampered by immunosuppression. In general, all inactivated vaccines can be feasibly administered under immunosuppression, even though many patients do not develop robust protection. Live vaccines should only be administered in rare, exceptional cases!

The following vaccinations are recommended:
– influenza vaccine: annually
– pneumococcal vaccine: booster every 5 years
– adequate protection and booster as needed: tetanus, diphtheria, hepatitis A and B
– in rare, justified cases: tick-borne encephalitis (TBEV), meningococcus, rabies, polio (oral vaccine contraindicated!)

Contraindicated:
Measles, mumps, rubella, chickenpox, typhus, yellow fever, tuberculosis

General tips on self-management after liver transplantation

Sun

An important adverse effect of immunosuppressive drugs that emerges only years after use is skin cancer: Various types of skin cancer are observed in 40–60% of patients over a period of 20 years after transplantation. Unprotected exposure to sunlight represents the major cause of skin cancer, and the risk of developing skin tumors increases dramatically through the combination of immunosuppressants and sunlight exposure! Patients are thus recommended to avoid direct exposure to sunlight and to protect themselves appropriately from the sun, specifically using sunscreen with a high sun protection factor (SPF) as well as by covering exposed parts of the body and wearing a head covering. Cancer screening at 1- to 2-year intervals by an experienced dermatologist should also always be recommended to patients.

Travel

Since immunosuppressive therapy must be given at higher doses during the first year after transplantation to prevent rejection, the risk of an infectious disease is higher during this time. Patients should thus restrict their travel more during the first year after transplantation than in subsequent years. Vacations should be limited to destinations and countries with moderate climates, adequate hygiene standards, and sufficient basic medical care: primarily countries in Europe and North America. Countries in the Middle East, Africa, Southeast Asia, and Latin America represent high-risk areas even after the first year post-transplant.

Transplant recipients should be advised not to swim in tropical waters or walk barefoot and to avoid unprotected sexual contact.

Physical activity

Improving cardiovascular function and stability are primary goals following transplantation. Once wound healing is complete, moderate resistance training can be started to build muscle strength. Moderate aerobic exercise should be recommended as soon as possible, and can start with simply walking. Speed and distance should be guided by recommendations from the patient's doctors and physical therapist.

Building up muscle strength is almost always necessary and can be achieved by moderate strength exercises.

Activities that could lead to blunt abdominal trauma (liver tearing!), such as martial arts, should be avoided.

Endurance sports (walking, running, bicycle riding) is recommended for conditioning the cardiovascular system and preventing metabolic issues (obesity, diabetes). In addition to restoring strength and endurance, post-transplant exercise helps balance a patient's metabolism, since many immunosuppressive drugs can unfavorably impact sugar and fat metabolism.

There is also mounting evidence that physical activity can help prevent or alleviate chronic fatigue.

Patients should be encouraged to join an exercise group led by an experienced trainer. A multi-week rehabilitation program at a medical rehabilitation clinic is also highly recommended, since the staff can address questions about nutrition, exercise, and disease-specific questions in great detail.

3 Rehabilitation of patients with advanced liver disease or post-liver transplant

Muscle loss strongly affects both the outcomes of chronic diseases, including of the liver, as well as post-transplant outcomes. A chronic disease deeply restricts the afflicted individual not only physically but also mentally due to his or her often horrendous body self-image or anxieties.

Patients' self-empowerment can be enhanced by professional support, as is often provided at an inpatient rehabilitation center. Over a 3-week program, patients are closely supported and assisted by physicians, exercise therapists, psychologists, and nutritional experts, instructed on sensible daily routines, and aided in working through the emotional aspects of their disease. These activities can be especially helpful for individuals who did not engage in regular exercise or physical activity before their liver transplant by improving and stabilizing their mental and emotional capabilities, thereby positively impacting their condition.

Like rehabilitation following a liver disease, rehabilitation following liver transplant takes a holistic approach based on five pillars:

1: Physical stabilization
Exercise and daily physical activity reduce the risk of suffering from fatigue and help fight fatigue in those who already experience it. The effects of sarcopenia are improved, the body becomes stronger again, and anxiety and depression become less intense.

2: Mental stabilization
Psychotherapeutic group sessions help patients process topics relating to processing their disease and difficulty adjusting, which frequently afflict transplant recipients. Tips on handling stress and relaxation exercises can help reduce sleeping disorders as well as the physical consequences of stress and tension, such as high blood pressure and metabolic disorders.

3: Nutritional advice
Nutritional interventions improve both muscle strength and help counteract sarcopenia. They can also have a positive impact on imbalances in sugar metabolism such as prediabetes or existing diabetes.

4: Advice on dealing with the disease
During rehabilitation, seminars are held to emphasize the importance of regular follow-ups and screening visits. These seminars also address general questions about life after or with the disease. For transplant recipients, all key questions regarding post-transplant care are addressed.

5: Education about medications (especially immune modulators)
Patients are provided practical tips for the medications they routinely use, the effects of these medications, and their key adverse effects, which bolsters patients' compliance and willingness to take their medications as prescribed. For example, adequately educating patients about their immunosuppressive drugs reduces the risk of injury to the transplant. Periodic monitoring of blood levels of immunosuppressive drugs is a central pillar of post-transplant care.

Evidence-based rehabilitation can make a major contribution to stabilizing the patient's liver disease and toward successful long-term transplant outcomes. Only about 30% of all liver transplant recipients in Germany are able to work full-time or part-time again after transplantation. This percentage could be increased if more patients would undergo rehabilitation following transplant. It has also been shown that patients who take part in a rehabilitation program have significantly better transplant survival.

4 Post-transplant treatment plan (overview)

Frequency of visits/coordination with primary care physician

Post-transplant outpatient care takes place at a liver transplant specialist's office once or twice per week during the first 4 weeks after surgery, and once per week thereafter for stable patients.

During the first 6 months after transplantation, the patient should maintain close contact with his or her transplantation center and visit it for follow-ups every 4 weeks. After the first 6 months, patients in stable condition are recommended to visit the center every 3 months. These intervals can be rescheduled after the first 2 years.

The serum levels of the immunosuppressive drug administered (cyclosporine A, tacrolimus, sirolimus, everolimus) must be checked on a regular basis. On the day of testing, the morning dose should not be taken until **after drug levels have been measured**!

The following laboratory parameters should also be monitored:

- Liver enzymes (AST, ALT, AP, GGT, bilirubin)
- Coagulation (INR)
- Kidney parameters (creatinine, urea, uric acid, electrolytes)
- Blood counts
- Infection parameters (leukocytes, CRP)
- CMV-DNA PCR
- Monitoring of sugar and fat metabolism: HbA1c, cholesterol, LDL, HDL

Other parameters should be monitored as appropriate for the patient's underlying condition, comorbidities, immunosuppressive therapy, other medicines, time since liver transplantation, and clinical condition.

Special follow-ups are required for patients with the following conditions:

- Viral hepatitis (HCV, HBV)
- Cancer (HCC, NET)
- Primary biliary cholangitis (PBC)
- Primary sclerosing cholangitis (PSC)
- Autoimmune hepatitis (AIH)
- Alcoholic steatohepatitis (ASH)

Serology

In addition to laboratory tests and clinical examinations, patients' serology should also be tested at regular intervals for viral infections. For patients with active or resolved hepatitis B or C, viral serology (HBsAg and/or anti-HCV-IgM) should be tested at 3-month intervals. Furthermore, CMV infection or reactivation of latent CMV in the donor organ can lead to complications in immunosuppressed patients if not detected and treated. Regular testing for CMV by PCR is accordingly advisable for all patients following liver transplantation.

Cancer screening after liver transplantation

The risk of developing cancer is increased after transplantation due to the requirement for immunosuppression. The incidence of cancer is approximately four-fold higher among transplant recipients compared with the general population. The primary reasons for this increase are:

- aggressive immunosuppression during the initial post-transplant period
- much greater sensitivity of the skin to UV rays (sunlight)
- susceptibility to certain viral infections associated with a risk of developing lymphoma, such as Epstein-Barr virus (EBV)
- direct tumorigenic effects of the administered drugs themselves

Regular follow-ups/screening should thus be carried out lifelong for all patients after transplant in order to detect new cases of cancer as early as possible:

Abdominal ultrasound	Every 6 months
Whole body skin inspection	Every 12 months
Women: gynecology exam with Pap smear	Every 12 months
Men: urology exam with PSA	Every 12 months
Colonoscopy	Every 3–5 years after liver transplant, more frequently if polyps are known or follow-ups based on histology and guidelines; annually for patients with IBD

Specific diagnostic tests for patients with HCC:

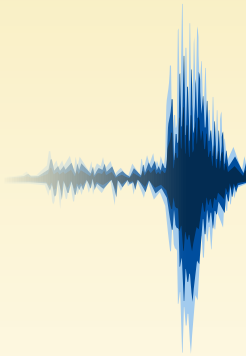
Abdominal CT, possibly MRI, with AFP after 6, 12, and 24 months. Abdominal ultrasound and testing for the cancer marker AFP should be performed every 6 months thereafter.

Other recommended examinations:

Dental check-up	Every 6–12 months
Bone density measurement	Every 2–3 years

Overview of recommended post-liver transplant treatment plan

Cancer screening:	
Annual dermatology examination for early detection of skin cancer Annual gynecology examination for women Annual urology examination for men Annual ENT examination, especially for smokers Abdominal ultrasound every 6 months Regular colonoscopy for early detection of colorectal cancer: every 3–5 years or annually for patients with PSC/IBD	
Other recommended examinations:	
Annual ophthalmology check (some drugs lead to glaucoma, cataract, or changes in visual acuity) Dental examination every 6 months	
Vaccinations:	
Generally recommended: In certain cases: Contraindicated:	Influenza, tetanus, diphtheria, pneumococcus Tick-borne encephalitis (TBEV), meningococcus, rabies Measles, mumps, rubella, chickenpox, typhus, yellow fever, tuberculosis



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