UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
CLMMC V anno
Patologia Sistemica VI (M-Z)
AA 2023-24

Liver transplantation

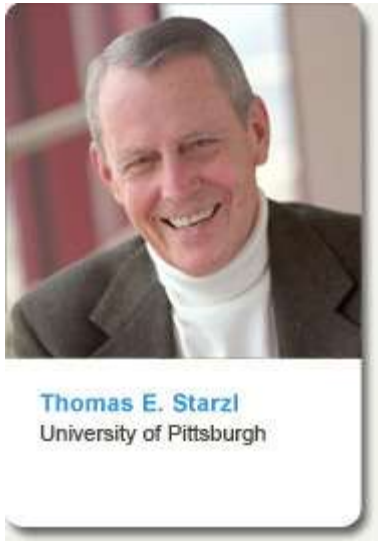
Prof. Stefano Fiorucci
Direttore Scuola di Specializzazione in Malattie apparato digerente
Università di Perugia
Stefano.fiorucci@unipg.it
www.unipg.gastroenterologia.it

Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Liver transplantation

- Liver transplantation is the replacement of the native, diseased liver by a normal organ (allograft The preferred and technically most advanced approach is orthotopic transplantation, in which the native organ is removed and the donor organ is inserted in the same anatomic location.

- Pioneered in the 1960s by Thomas Starzl at the University of Colorado and, later, at the University of Pittsburgh and by Calne in Cambridge, England, liver transplantation is now performed routinely worldwide. Success measured as 1-year survival has improved from ~30% in the 1970s to about 90% today.



Liver transplantation: Italy

- Based on the current level of success, the number of liver transplants has continued to grow each year; in 2010 , 1059 patients received liver allografts in Italy . Still, the demand for new livers continues to outpace availability; in the same period, 1481 patients were on a waiting list for a donor liver.
- From 1992 to 2019, there were 22759 liver transplants with a 5 years survival of 75-80%.

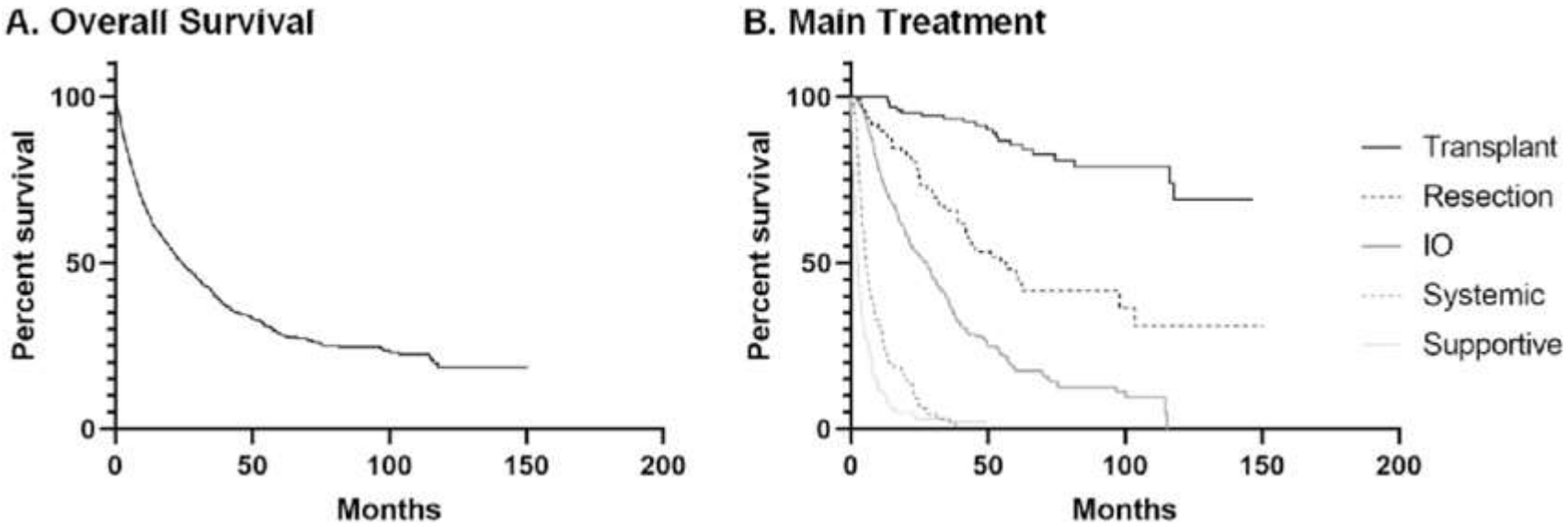
Liver transplantationL: indications pediatric vs adult

TABLE 368-1 INDICATIONS FOR LIVER TRANSPLANTATION

Children	Adults
Biliary atresia	Primary biliary cirrhosis
Neonatal hepatitis	Secondary biliary cirrhosis
Congenital hepatic fibrosis	Primary sclerosing cholangitis
Alagille's syndrome[a]	Autoimmune hepatitis
Byler's disease[b]	Caroli's disease[c]
α_1-Antitrypsin deficiency	Cryptogenic cirrhosis
Inherited disorders of metabolism	Chronic hepatitis with cirrhosis
Wilson's disease	Hepatic vein thrombosis
Tyrosinemia	Fulminant hepatitis
Glycogen storage diseases	Alcoholic cirrhosis
Lysosomal storage diseases	Chronic viral hepatitis
Protoporphyria	Primary hepatocellular malignancies
Crigler-Najjar disease type I	Hepatic adenomas
Familial hypercholesterolemia	Nonalcoholic steatohepatitis
Primary hyperoxaluria type I	Familial amyloid polyneuropathy
Hemophilia	

Liver transplantation

- **Liver transplantation is indicated for end-stage *cirrhosis* of all causes.**
- Patients with nonmetastatic primary hepatobiliary tumors—primary hepatocellular carcinoma (HCC), cholangiocarcinoma, hepatoblastoma, angiosarcoma, epithelioid hemangioendothelioma, and multiple or massive hepatic adenomas—have undergone liver transplantation; however, for some hepatobiliary malignancies, overall survival is significantly lower than that for other categories of liver disease.



Liver transplantation

Contraindications

Absolute contraindications for transplantation include life-threatening systemic diseases, uncontrolled extrahepatic bacterial or fungal infections, preexisting advanced cardiovascular or pulmonary disease, multiple uncorrectable life-threatening congenital anomalies, metastatic malignancy, active drug or alcohol abuse

Liver transplantation

Absolute	Relative
Uncontrolled extrahepatobiliary infection	Age >70
Active, untreated sepsis	Prior extensive hepatobiliary surgery
Uncorrectable, life-limiting congenital anomalies	Portal vein thrombosis
Active substance or alcohol abuse	Renal failure
Advanced cardiopulmonary disease	Previous extrahepatic malignancy (not including nonmelanoma skin cancer)
Extrahepatobiliary malignancy (not including nonmelanoma skin cancer)	Severe obesity
Metastatic malignancy to the liver	Severe malnutrition/wasting
Cholangiocarcinoma	Medical noncompliance
AIDS	HIV seropositivity
Life-threatening systemic diseases	Intrahepatic sepsis
	Severe hypoxemia secondary to right-to-left intrapulmonary shunts (P_{O2} < 50 mmHg)
	Severe pulmonary hypertension (mean PA pressure >35 mmHg)
	Uncontrolled psychiatric disorder

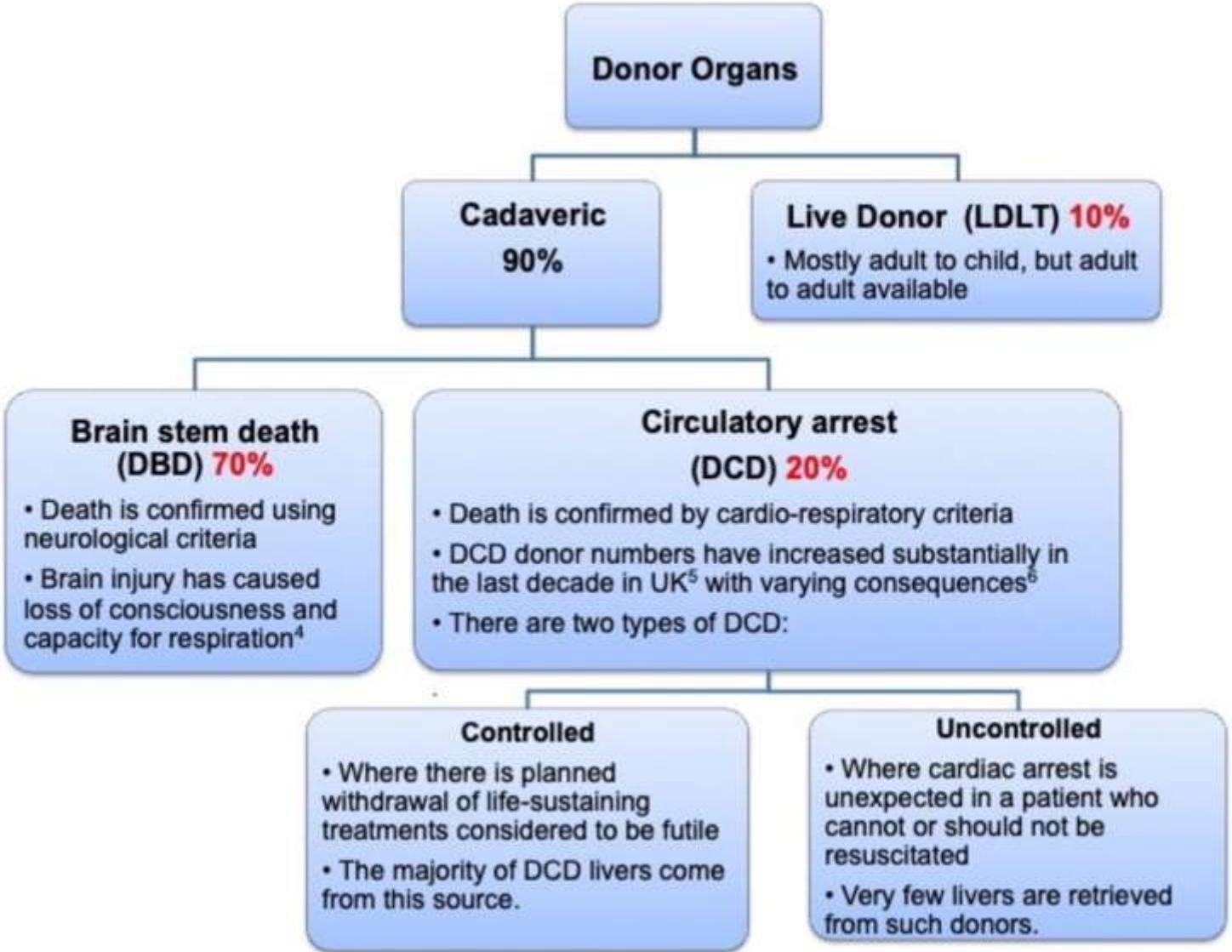
Liver transplantation

Allocation based on MELD score a mathematical model that includes bilirubin, creatinine, and prothrombin time expressed as international normalized ratio (INR)

The Model for End-Stage Liver Disease (MELD) score, on a continuous scale,[b] determines allocation of the remainder of donor organs. This model is based upon the following calculation:

$3.78 \times \log_e$ bilirubin (mg/100 mL) + $11.2 \times \log_e$ international normalized ratio (INR) + $9.57 \times \log_e$ creatinine (mg/100 mL) + 6.43 (X 0 for alcoholic and cholestatic liver disease, X 1 for all other types of liver disease).[c,d,e]

Liver transplantation



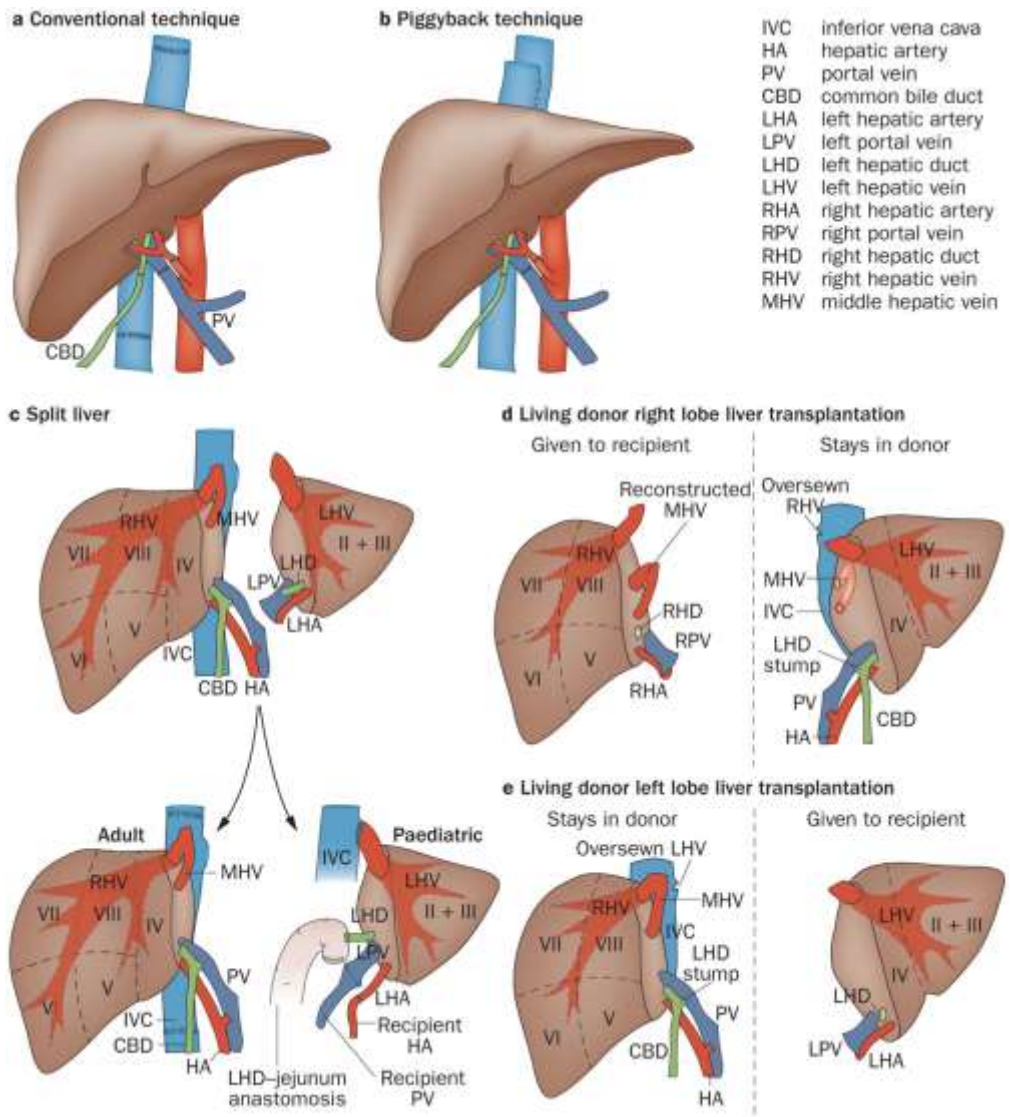
Liver transplantation

Living-Donor Transplantation

- Occasionally, especially for liver transplantation in children, one cadaver organ can be split between two (one adult and one child) recipients. A more viable alternative, transplantation of the right lobe of the liver from a healthy adult into an adult recipient, has gained increased popularity.
- Living-donor transplantation of the left lobe (left lateral segment), introduced in the early 1990s to alleviate the extreme shortage of donor organs for small children, accounts currently for approximately a third of all liver transplantation procedures in children.
- Driven by the shortage of cadaver organs, living-donor transplantation involving the more sizable right lobe is being considered with increasing frequency in adults; however, living-donor liver transplantation cannot be expected to solve the donor organ shortage.

Liver transplantation techniques

Many techniques have been developed for liver transplantation. From the conventional technique first developed by Starzl to partial liver transplantation techniques developed in the 1980s and 1990s, modifications in liver transplantation techniques have improved outcomes and allowed the expansion of the donor pool. a | Conventional, b | piggyback, c | cadaveric split, d | living donor right lobe, and e | living donor left lobe liver transplantation.



Zarrinpar, A. & Busuttil, R. W. (2013) Liver transplantation: past, present and future *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2013.88

Liver transplantation

Calcineurin inhibitors (CNIs) are the mainstay of immunosuppression after liver transplantation. **Tacrolimus** is the most frequently used because of reduced acute rejection rates and better graft and patient survival, compared with cyclosporine.

Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations

Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
Adult kidney transplant patients In combination with azathioprine	0.2 mg/kg/day	month 1 to 3: 7 to 20 ng/mL month 4 to 12: 5 to 15 ng/mL
In combination with MMF/IL-2 receptor antagonist‡	0.1 mg/kg/day	month 1 to 12: 4 to 11 ng/mL
Adult liver transplant patients	0.10 to 0.15 mg/kg/day	month 1 to 12: 5 to 20 ng/mL
Pediatric liver transplant patients	0.15 to 0.20 mg/kg/day	month 1 to 12: 5 to 20 ng/mL

* Note: two divided doses, q12h

‡ In a second smaller study, the initial dose of tacrolimus was 0.15 to 0.2 mg/kg/day and observed tacrolimus concentrations were 6 to 16 ng/mL during month 1 to 3 and 5 to 12

Liver transplantation

- **Both cyclosporine and tacrolimus** are metabolized by the cytochrome P450 IIIA system, and therefore drugs that induce cytochrome P450 (e.g., phenytoin, phenobarbital, carbamazepine, rifampin) reduce available levels of cyclosporine and tacrolimus;
- Drugs inhibit cytochrome P450 (e.g., erythromycin, fluconazole, ketoconazole, clotrimazole, itraconazole, verapamil, diltiazem, nicardipine, cimetidine, danazol, metoclopramide, bromocriptine, and the HIV protease inhibitor ritonavir) increase cyclosporine and tacrolimus blood levels. Indeed, itraconazole is commonly used to help boost tacrolimus levels.
- Like azathioprine, cyclosporine and tacrolimus appear to be associated with a risk of lymphoproliferative malignancies which may occur earlier after cyclosporine or tacrolimus than after azathioprine therapy. Because of these side effects, combinations of cyclosporine or tacrolimus with prednisone and azathioprine—all at reduced doses—are preferable regimens for immunosuppressive therapy.

Liver transplantation

- In patients with pretransplantation renal dysfunction or renal deterioration that occurs intraoperatively or immediately postoperatively, **tacrolimus or cyclosporine therapy may not be practical**; under these circumstances, induction or maintenance of immunosuppression with monoclonal antibodies to T cells, OKT3, may be appropriate
- Rapamycin, an inhibitor of later events in T cell activation, is approved for use in kidney transplantation but is not approved for use in liver transplant recipients because of the association with an increased frequency of hepatic artery thrombosis in the first month posttransplantation.

TABLE 368-5 HEPATIC COMPLICATIONS OF LIVER TRANSPLANTATION

Hepatic Dysfunction Common After Major Surgery	
Prehepatic	Pigment load
	Hemolysis
	Blood collections (hematomas, abdominal collections)
Intrahepatic	
Early	Hepatotoxic drugs and anesthesia
	Hypoperfusion (hypotension, shock, sepsis)
	Benign postoperative cholestasis
Late	Transfusion-associated hepatitis
	Exacerbation of primary hepatic disease
Posthepatic	Biliary obstruction
	↓ Renal clearance of conjugated bilirubin (renal dysfunction)
Hepatic Dysfunction Unique to Liver Transplantation	
Primary graft nonfunction	
Vascular compromise	Portal vein obstruction
	Hepatic artery thrombosis
	Anastomotic leak with intraabdominal bleeding
Bile duct disorder	Stenosis, obstruction, leak
Rejection	
Recurrent primary hepatic disease	

TABLE 368-4 NONHEPATIC COMPLICATIONS OF LIVER TRANSPLANTATION

Fluid overload	
Cardiovascular instability	Arrhythmias
	Congestive heart failure
	Cardiomyopathy
Pulmonary compromise	Pneumonia
	Pulmonary capillary vascular permeability
	Fluid overload
Renal dysfunction	Prerenal azotemia
	Hypoperfusion injury (acute tubular necrosis)
	Drug nephrotoxicity
	↓ Renal blood flow secondary to ↑ intraabdominal pressure
Hematologic	Anemia secondary to gastrointestinal and/or intraabdominal bleeding
	Hemolytic anemia, aplastic anemia
	Thrombocytopenia
Infection	Bacterial: early, common postoperative infections
	Fungal/parasitic: late, opportunistic infections
	Viral: late, opportunistic infections, recurrent hepatitis
Neuropsychiatric	Seizures
	Metabolic encephalopathy
	Depression
	Difficult psychosocial adjustment
Diseases of donor	Infectious
	Malignant
Malignancy	B cell lymphoma (posttransplantation lymphoproliferative disorders)
	De novo neoplasms (particularly squamous cell skin carcinoma)

Liver transplantation

- **Transplant Rejection**
- Despite the use of immunosuppressive drugs, rejection of the transplanted liver still occurs in a proportion of patients, beginning 1–2 weeks after surgery. Clinical signs suggesting rejection are fever, right upper quadrant pain, and reduced bile pigment and volume. Leukocytosis may occur, but the most reliable indicators are increases in serum bilirubin and aminotransferase levels. Because these tests lack specificity, distinguishing among rejection and biliary obstruction, primary graft nonfunction, vascular compromise, viral hepatitis, CMV infection, drug hepatotoxicity, and recurrent primary disease may be difficult. Radiographic visualization of the biliary tree and/or percutaneous liver biopsy often helps to establish the correct diagnosis.

Liver transplantation

- Morphologic features of acute rejection include a mixed portal cellular infiltrate, bile duct injury, and/or endothelial inflammation ("endothelialitis"); some of these findings are reminiscent of graft-versus-host disease, primary biliary cirrhosis, or recurrent allograft hepatitis C. As soon as transplant rejection is suspected, treatment consists of intravenous methylprednisolone in repeated boluses; if this fails to abort rejection, many centers use antibodies to lymphocytes, such as OKT3, or polyclonal antilymphocyte globulin. Caution should be exercised when managing acute rejection with pulse glucocorticoids in patients with hepatitis C virus (HCV) infection, because of the high risk of triggering recurrent allograft hepatitis C.

Liver transplantation

- **Chronic rejection is a relatively rare** outcome that can follow repeated bouts of acute rejection or that occurs unrelated to preceding rejection episodes. Morphologically, chronic rejection is characterized by progressive cholestasis, focal parenchymal necrosis, mononuclear infiltration, vascular lesions (intimal fibrosis, subintimal foam cells, fibrinoid necrosis), and fibrosis. This process may be reflected as ductopenia—the vanishing bile duct syndrome. Reversibility of chronic rejection is limited; in patients with therapy-resistant chronic rejection, retransplantation has yielded encouraging results.

Liver transplantation

- **Survival**
- Currently the 5-year survival rate exceeds 60%. An important observation is the relationship between clinical status before transplantation and outcome. For patients who undergo liver transplantation when their level of compensation is high (e.g., still working or only partially disabled), a 1-year survival rate of >85% is common.
- For those whose level of decompensation mandates continuous in-hospital care prior to transplantation, the 1-year survival rate is about 70%, while for those who are so decompensated that they require life support in an intensive care unit, the 1-year survival rate is ~50%.

Liver transplantation

- For patients who do not fit any "high-risk" designations, **1-year and 5-year survival rates of 85 and 80%, respectively,** have been recorded. In contrast, among patients in high-risk categories—cancer, fulminant hepatitis, age> 65, concurrent renal failure, respirator dependence, portal vein thrombosis, and history of a portacaval shunt or multiple right upper quadrant operations—survival statistics fall into the range of 60% at 1 year and 35% at 5 years

Liver transplantation

- **RECURRENCE OF PRIMARY DISEASE**
- Whether autoimmune hepatitis and sclerosing cholangitis primary biliary cirrhosis recur after liver transplantation is controversial;
- Hereditary disorders such as Wilson's disease and $_1$ antitrypsin deficiency have not recurred
- however, recurrence of disordered **iron metabolism** has been observed in some patients with hemochromatosis.
- In patients with intrahepatic hepatocellular carcinoma who meet criteria for transplantation, 1- and 5-year survivals are similar to those observed in patients undergoing liver transplantation for nonmalignant disease.

Liver transplantation

- As a result of long-term survival after liver transplantation for chronic hepatitis B at 1-year rates between 75 and 90%.
- Further improving the outcome of liver transplantation for chronic hepatitis B is the current availability of such antiviral drugs as lamivudine, adefovir dipivoxil, and entecavir
- lamivudine can be used to prevent recurrence of HBV infection when administered *prior* to transplantation and to treat hepatitis B that recurs *after* transplantation, including in patients who break through HBIg prophylaxis; and to reverse the course of otherwise fatal fibrosing cholesta
- tic hepatitis.
- Currently, most liver transplantation centers combine HBIg plus lamivudine or adefovir, and additional antivirals such as the more recently approved entecavir are being introduced as well.

Liver transplantation

- Recurrence of HCV infection after liver transplantation can be documented in almost every patient if sufficiently sensitive virus markers are used. The clinical consequences of recurrent hepatitis C are limited during the first 5 years after trans
- Benign clinical evolution. No impact on survival.
- histologic studies have documented the presence of moderate to severe chronic hepatitis in more than half of all patients and bridging fibrosis or cirrhosis in ~10%. Moreover, progression to cirrhosis within 5 years is even more common, occurring in up to two-thirds of patients if moderate hepatitis is detected in a 1-year biopsy .
- **velpatasvir /sofosbuvir should be initiated is patients become HCV+**

Liver transplantation

- **Currently, alcoholic liver disease is one of the more common indications for liver transplantation, accounting for 20–25% of all liver transplantation procedures, and most transplantation centers screen candidates carefully for predictors of continued abstinence.**
- Recidivism is more likely in patients whose sobriety prior to transplantation was <6 months.
- For abstinent patients with alcoholic cirrhosis, liver transplantation can be undertaken successfully, with outcomes comparable to those for other categories of patients with chronic liver disease, when coordinated by a team approach that includes substance abuse counseling.

Liver transplantation

- **Posttransplantation Quality of Life**
- Full rehabilitation is achieved in the majority of patients who survive the early postoperative months and escape chronic rejection or unmanageable infection.
- Psychosocial maladjustment interferes with medical compliance in a small number of patients, but most manage to adhere to immunosuppressive regimens, which must be continued indefinitely.
- In one study, 85% of patients who survived their transplant operations returned to gainful activities. In fact, some women have conceived and carried pregnancies to term after transplantation without demonstrable injury to their infants.

Liver transplantation

- Tacrolimus is more potent than cyclosporine, it is also more toxic and more likely to be discontinued for adverse events.
- The toxicity of tacrolimus is similar to that of cyclosporine; nephrotoxicity and neurotoxicity are the most commonly encountered adverse effects, and neurotoxicity (tremor, seizures, hallucinations, psychoses, coma) is more likely and more severe in tacrolimus-treated patients. Both drugs can cause diabetes mellitus, but tacrolimus does not cause hirsutism or gingival hyperplasia.
- Because of overlapping toxicity between cyclosporine and tacrolimus, especially nephrotoxicity, and because tacrolimus reduces cyclosporine clearance, these two drugs should not be used together.
- Since 99% of tacrolimus is metabolized by the liver, hepatic dysfunction reduces its clearance; in primary graft nonfunction (when, for technical reasons or because of ischemic damage prior to its insertion, the allograft is defective and does not function normally from the outset), tacrolimus doses have to be reduced substantially, especially in children