Liver transplantation
Indications and contraindications

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What will be discussed?

- What are the indications and contraidications for liver transplantation?

- What are the rules of liver allocation?

Liver transplantation (LTx)

- Start: 1963-67 (Starzl)
- NOW: 10-years survival - 70%
- Main factors influencing survival:
  - Donor factors (age, steatosis of the liver)
  - Recipient: age, primary liver disease (HCC, HCV, ALF), comorbidities
  - Complications after LTx (vessel, biliary, infections, neoplasms, rejection)
  - Immunosuppression
  - Compliance, social support
  - Number of LTx

LTx – risks and benefits

- BENEFITS:
- Survival improvement
- Prevention of long-term complications
- Quality of life improvement

- → assess the severity of the disease (scales: C-P, MELD, King's College criteria, Clichy criteria)

- RISKS:
- Surgery complications
- Immunosuppression consequences
- Recurrent disease

- → exclude contraindications

Indications for LTx

- Decompensated cirrhosis (ALD, AIH, NASH, HBV, HCV) with complications: refractory ascites, variceal hemorrhage, encephalopathy, SBP
  - Hepatocyte dysfunction
  - Hepato-renal syndrome
  - Hepato-pulmonary syndrome
  - Porto-pulmonary hypertension
- Hepatocellular carcinoma (HCC)
- Cholestatic liver diseases (PBC, PSC, congenital)
- Acute liver failure
- Liver-based metabolic conditions with systemic manifestations (Wilson disease, cystic fibrosis, hemochromatosis, alpha1-antitripsine deficiency)

Indication for LTx in children

- Cirrhosis connected to billiary atresia or familial cholestasis:
  - progressive familial intrahepatic cholestasis (PFIC): defects in biliary epithelial transporters type 1, 2, 3, Allagille syndrome
- Liver-based metabolic conditions :
  - Wilson disease
  - Cystic fibrosis
  - Hemochromatosis
  - alpha1-antitripsine deficiency
  - Familial amyloid polyneuropathy
  - Hemochromatosis
  - Tyrosinemia
  - Glycogen storage diseases (type I and IV)
  - Acute intermittent porphyria (AIP)

Rare indications for LTx

- Budd-Chiari syndrome
- *Hepatic epithelioid hemangioendothelioma*
- Hepatoblastoma
- *Hereditary hemorrhagic telangiectasia*
- Hepatic metastases of neuroendocrine tumors (NET)
- Large hepatic adenomas

Child-Pugh classification of severity of cirrhosis

Points assigned	1	2	3
BILIRUBIN (mg/dl)	1-2	2-3	>3
ALBUMIN (g/dl)	>3,5	2,8-3,5	<2,8
INR	INR< 1.7	INR 1.7-2.3	INR>2.3
ENCEPHALOPATHY	none	I-II	III-IV
ASCITES	absent	slight	moderate
class	**A: 5-6**	**B: 7-9**	**C: 10-15**

Prognosis without LTx

- Child-Pugh
- One-year survival:
  - C (> 10p.)– 45%
  - B (7-9p.)– 80%
  - A (5-6p.)– 100%

MELD (MELD-Na, MELD 3.0) - model of end-stage liver disease

- **MELD:**
- INR
- bilirubine
- creatinine
- HD in the last week: 2x or CVVHD ≥24h

- Na → **MELD-Na**
- MELD 12, but if serum Na 125 mmol/L → MELD-Na = 23

- **MELD 3.0** : sex, creatinine, INR, bilirubine, albumin, Na

- MELD>10 → refer the patient to transplant center
- Transplantation:
  - MELD≥15, urgent: MELD≥25
  - Child-Pugh: B or C

What lab tests will you order to determine the stage of liver cirrhosis?

According to Child-Pugh:

- Bilirubin
- Albumin
- INR

According to MELDNa:

- Bilirubin
- Creatinine
- INR
- Na

- **According to MELD 3.0:**
- As above + albumin

Standard MELD exceptions

- Hepatocellular carcinoma
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Hepatorenal syndrome
- Familial amyloid polyneuropathy*
- Primary hyperoxaluria type 1
- Cystic fibrosis if FEV1<40%
- Hilar cholangiocarcinoma (special centers)
- HAT (occuring within 14 days of liver Tx, but not meeting criteria for urgent status)

- *Before transplantation: tafamidis, patisiran, inotersen

Other medical conditions that may be important in LTx candidate

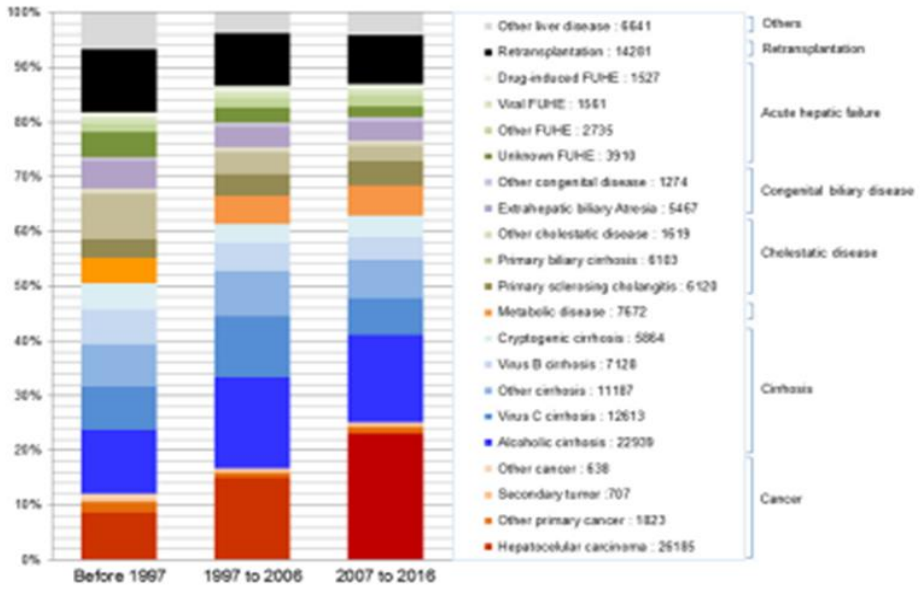
- Intractable pruritus in a patient with PBC
- Recurrent cholangitis in PSC
- Chronic bleeding due to portal gastropathy
- Refractory ascites, SBP
- Refractory variceal hemorrhage
- Refractory hepatic encephalopathy
- Cahexia

Hepatocellular carcinoma (HCC)

- Standard MELD exception
- Milano criteria:
  - 1 up to 5cm
  - max.3 up to 3cm
  - no angioinvasion
  - no meta
- *up to seven?, San Francisco?*
- Others?
- Before LTx: transarterial chemoembolization (TACE), radiofrequency ablation (RFA)
- Before LTx – chest CT, bone scintigraphy, PET-CT

Changes in indications for LTx according to european registries (ELTR)

2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation



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Hepatopulmonary syndrome

- Standard MELD exception
- Frequency: 5-30% candidates for LTx
- Pulmonary vessels dillatation or a-v shunts
- Hypoksemia, platypnea, orthodeoksja
- SAT<96% , PaO2<70mmHg,alveolar-capillary gradient> or = 15 mmHg
- Enhanced echocardiography, scintigraphy (after chest X-ray, CT, lung function tests)
- 5-yr survival:
  - LTx – 76%
  - No LTx – 26%
- PaO2<60mmHg – urgent LTx!
- Prolonged reconvalescence after LTx

Porto-pulmonary hypertension (PPHTN)

- Standard MELD exception
- Definition:
- 1. mean pulmonary artery pressure (mPAP) >25 mmHg at rest
- 2. pulmonary capillary wedge pressure (PCWP) <15 mmHg
- 3. in a patient who has coexisting portal hypertension

- Frequency: 4-8% LTx candidates
- Fatigue, shortness of breath, later – chest pain, syncope
- Morbidity:
  - MPAP>35mmHg → 50%
  - MPAP>50mmHg → 100%

- Echocardiography: RVSP >45mmHg → right heart catheterization
- hepatic vein catheterization → portal hypertension

- beta-blockers and transjugular intrahepatic portosystemic shunts (TIPS) are potentially harmful

- LTx contraindicated if mPAP >45-50mmHg (?)
- **If mPAP<35mmHg after the vessel dillatation (epoprostenol?)→ LTx**

Hepatorenal syndrome

- Standard MELD exception
- Arterial vasodilatation in the splanchnic circulation, which is triggered by portal hypertension (NO, etc.)
- Diagnosis:
  - Rise in serum creatinine meeting criteria for AKI
  - Normal urine sediment, minimal proteinuria (less than 500 mg per day)
  - Na urine concentration < 10 mEq/L
  - Other reasons for AKI excluded
  - No improvement after hydration and albumin infusion 1g/kg, and diuretics withdrawal
- Treatment: norepinephrine, vasopressin, terlipressin,
- LTx if there is no liver function improvement

Indications for LTx & KTx

- CKD and GFR<30 ml/min or > 30% glomerulosclerosis in kidney biopsy
- Hepatorenal syndrome
- HD or HF > 8 weeks
- Primary oxaluria

- Autosomal recessive polycystic kidney disease (ARPKD)
- Autosomal dominant polycystic kidney disease (ADPKD) - in rare cases of large liver

Special candidates for LTx

- Hepatitis B or C:
- Goal: **no replication** before LTx
  - HCV – DAA
  - HBV – NA

HCV
direct- acting antiviral agents - DAA

Drug	Mechanism of action
Sofosbuvir SOF Dazabuvir DSV	NS5b polymerasis inhibitors
Symeprevir SMV Parytaprevir PTV Grazoprevir GZR Asunaprevir ASV Glecaprevir	NS3 proteasis inhibitors
Daklatazvir DAC Ledipasvir LDV Ombitasvir OBV Elbasvir ELB Velpatasvir Pibrentazvir	NS5a replication complex inhibitors

HCV treatment - DAA

- Combined
- SVR
  - F1-F2: 95-100%
  - F4: 80-85%
- Duration 8-12 weeks (up to 24 weeks in cirrhosis)

Prevention of HBV recurrence before LTx

- Nucleoside (Lam, ETV, LdT) and nucleotide (TDF, ADV) analogs
- The best to start theraphy - entecavir (ETV)
- In Lam/ETV resistance - tenofowir (TDF)
- HBV DNA monitoring!

- Continue entecavir or tenofovir after LTx

Special candidates for LTx

- PSC – IBD in 60-80%, risk of colorectal ca, CCC (colonoscopy, cholangio-MRI, Ca 19-9, biopsy during ERCP)
- ALD – abstinence - minimum 6 months, risk of esophageal cancer
- Wilson disease:
  - neuropsychiatric symptoms
  - hemolytic anemia
  - cardiomyopathy
  - hypothyroidism, hypoparathyroidism
- NASH – cardio-vascular risk, CKD
- hemochromatosis, apha-1-antitripsine deficiency, tyrosinemia, porphyria – increased HCC risk
- apha-1-antitrypsine deficiency – lung examination
- serious cholestasis - osteoporosis

Acute liver failure (ALF)

- Definition: hepatic encephalopathy occurs 8 weeks after the begining of acute liver disease, with elevated INR, illness duration <26 weeks
- Etiology
  - acetaminophen (paracetamol) poisoning
  - idiosyncratic drug reactions (halotan)
  - mushroom poisoning
  - B, D, A viral hepatitis
  - AIH
  - Wilson disease
  - Budd – Chiari syndrome (veno-occlusive disease)
  - acute fatty liver of pregnancy, HELLP syndrome
  - ischemic hepatitis
  - HAT, PGNF
  - sepsis
- Early transfer to transplant center (before severe coagulopathy and increased intracranial pressure occurs), even without confirmation of etiology
- Young people!

Probability of spontaneous recovery in acute liver failure (ALF)

- Degree of encephalopathy
- Age
- Etiology of ALF (acetaminophen, HAV, ischemia, pregnancy-related
- vs. HBV, AIH, Wilson disease, Budd-Chiari syndrome, cancer)
- Prognostic models:
  - **King's College criteria**
  - **Clichy criteria**

King's College Criteria for LTx

- For acetaminophen-induced ALF:
- 1. arterial pH < 7,3
- or
- 2. all:
- A) PT > 100s (INR>7)
- B) III/IV grade of encephalopathy
- C) creatinine > 3,4mg/dl

King's College Criteria for LTx

- For other than acetaminophen-induced causes of ALF:
- I. age <10 or >40 years
- II. duration of jaundice before development encephalopathy greater than 7days
- III. PT>50s (INR>3,5)
- IV. bilirubin > 18 mg/dl
- V. unfavorable disease etiology (halotan, Wilson disease)
- VI. PT>100s (INR>7)
- 3 criteria from I-V or only VI

Clichy criteria for LTx in case of viral etiology of ALF

- Encephalopathy III/IV
- Serum factor V:
  - Age <30 years - <20%
  - Age > 30 years - < 30%

What criteria do we use in case of acute liver failure

- acetaminophen-induced? →King's College Criteria for acetaminophen-induced ALF

- other than acetaminophen-induced? → King's College Criteria

- of viral origin? → Clichy criteria

Contraindications for LTx in ALF

- **Resistent brain oedema with sustained intracranial pressure > 50 mmHg**

- Intracranial bleeding
- High NA doses
- Hemodynamic instability

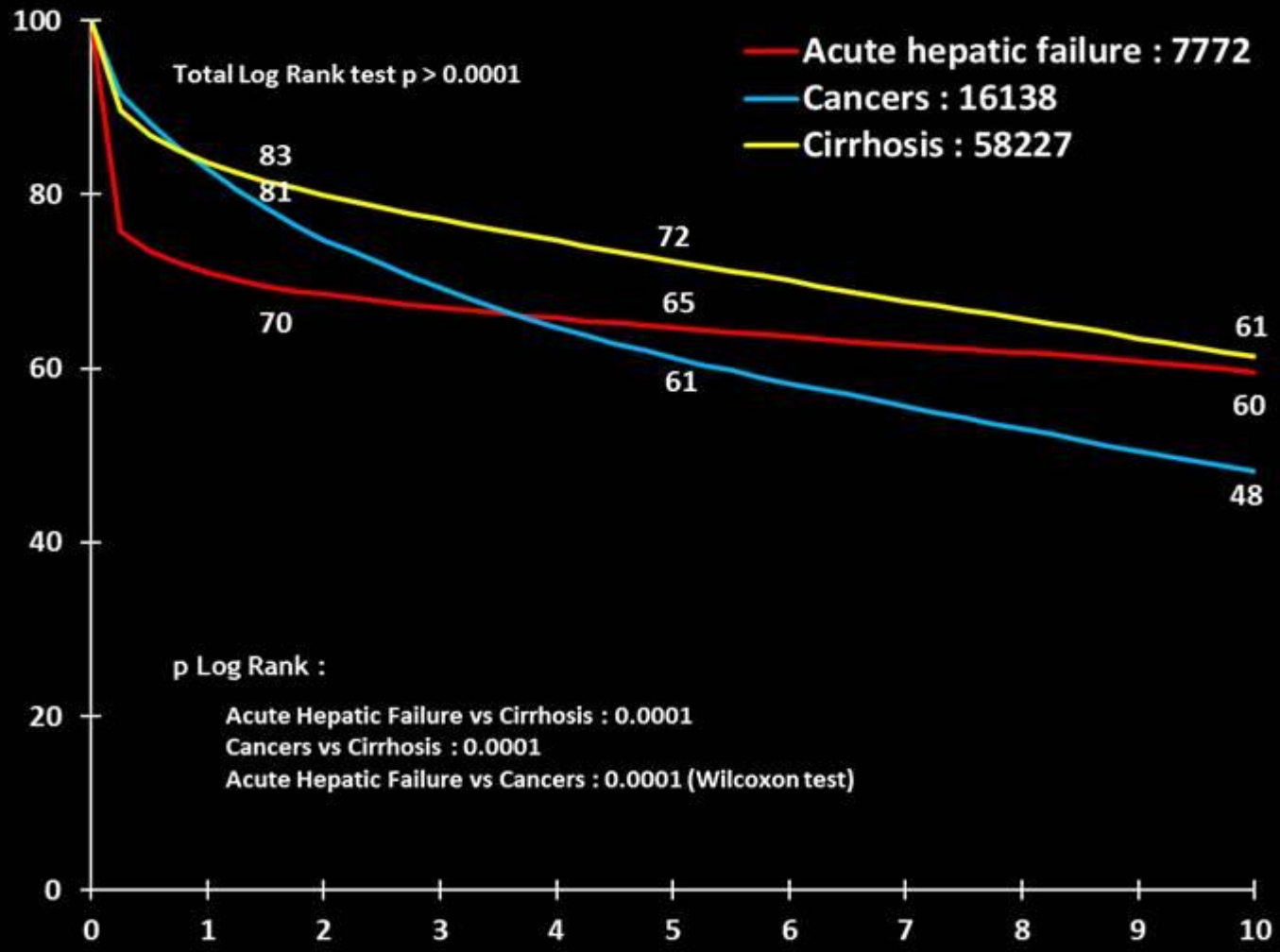
Prognosis in ALF

- Spontaneous recovery – 40%
- Survival after LTx: - 1 year – 70-80%

Patient Survival according to the Indication

01/1988 - 12/2013

12/2013



Contraindications for LTx

- Untreated neoplasms, HCC with metastases
- Cardiopulmonary disease that cannot be corrected and is a prohibitive risk for surgery
- AIDS
- Uncontrolled sepsis
- Anatomic abnormalities that preclude LTx or massive portal thrombosis
- Intrahepatic cholangiocarcinoma
- Hemangiosarcoma
- Nonadherence with medical care
- Lack of adequate social suport

- **Relative :**
  - Age > 65-70 y
  - BMI > 40

PRENTRANSPLANT EVALUATION

- **Diagnosis**, LFTs, creatinine, comorbidities
- **ABO-Rh blood typing**
- HBV DNA, HCV RNA, HAVAb, CMV, HIV, AFP
- Cardiopulmonary evaluation (ECG, cardiac stress testing, SPECT, echocardiography, coronary angiography, pulse oximetry, blood gas, transthoracic contrast-enhanced echocardiography, pulmonary function testing, chest radiograph, chest CT)
- Cancer screening: abdominal CT or MRI, skin examination, colonoscopy (> 50y, PSC), pap smear, PSA, mammography
- Infectious disease evaluation (cultures, oral examination, etc)
- Hepatic imaging and HCC staging
- Upper endoscopy
- Bone densitometry
- Psychosocial evaluation (alc – min. 6 months abstinence)

Allocation criteria

- Blood group (ABO) – identical or compatibile
- MELD (PELD < 12 years), MELDNa, Child – Pugh score
- Weight (maximum difference 10%)
- Waiting time
- The result of crossmatch is known frequently after LTx and does not influence allocation

The shortage of available donor

- Split
- Living donor
- Expanded criteria donors
- Non heart beatting donor (NHBD)
- Domino (donor: familial amyloid polyneuropathy before LTx)

THANK YOU