Liver Transplantation

Ahmad Bashar Abdulkarim, MD, PhD, FACS
Avera Hospital and University
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Transplantation Principle

“To provide an adequate functional cell mass”
Liver Transplantation - **Indications**

- Viral diseases
- Other Primary Liver diseases
- Neoplasms:
  - HCC
  - Cholangiocarcinoma
  - Neuroendocrine tumors

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**Liver Transplantation**

**Surgical Technique**

- Infra-hepatic cava to cava anastomosis. The portal vein is flushed during suturing the cava anterior wall.

- Technique for portal vein reconstruction with a donor iliac vein.
Liver Transplantation

Piggyback technique
Vascular Complications after LTx

- Vascular complications following orthotopic liver transplantation (OLT) seldom occur.
- They are the most feared complications with a high incidence of both graft loss and mortality.
- They compromise the blood flow of the transplant (either inflow or outflow).

Vascular Complications after LTx

- The overall incidence of VCs in adults varies widely among transplant centers worldwide.
  - It is around 7% for deceased donor liver transplantation (DDLT).
  - It is around 13% for living donor liver transplantation (LDLT).

Vascular Complications after LTx

**HAT**

- It is the first cause of primary non-function of the liver transplant, which can lead to allotransplant loss and patient death in the early postoperative period.
- It is the most common vascular complication following LTx.
- Timing:
  - Early (within the first month): 2.9%–4.4%.
  - Late (after the first month): Lower incidence.

**Clinical picture:**
- Depends on the existence of collaterals
- Collaterals could develop in 2 weeks post tx.
  - Early HAT
  - Late HAT

**Treatment:**
- Percutaneous transluminal angioplasty (PTA)
- Intra-arterial thrombolysis (IAT)
- Surgical revascularization
- Re-transplantation (75% of cases)
- Observation


Vascular Complications after LTx

HAS

• Significant HAS is usually defined as a narrowing of the transverse diameter > 50% on angiogram associated with clinical suspicion and a RI < 0.5 (defined by peak systolic flow end diastolic flow/peak systolic flow) and a peak systolic velocity > 400 cm/s detected by DUS.


HA stenosis at the anastomosis site

Vascular Complications after LTx

HAS

• HAS occurs in 2% to 13% of transplants, at the level of the anastomosis (59% of cases), graft HA (41%) or recipient HA (2.6%).

• HAS can progress to HAT in 65% of cases at 6 mo, if untreated.
• The median time to diagnosis is 100 d (range: 1-1220) post LTx.

HA stenosis due to kinking

Vascular Complications after LTx

HAS

• Symptoms: Insidious/ high LFTs..
• Diagnosis: DUS/CT/Angiography
• Risk factors:
  – technical and surgical factors
  – intimal dissection
  – excessive length with kinking and angulation
  – vasa vasorum disruption
  – acute cellular rejection

Vascular Complications after LTx

HAS

• Treatment:
  – PTA with or without stent placement.
  – Surgical revision, or re-transplant.
Vascular Complications after LTx

**HAP**

**Definition:**
- Dilated hepatic artery
- Occurs after iatrogenic injury in most cases
- Causes blood to leak and pool outside the artery wall into surrounding tissue, with a persistent communication between the HA and the resultant adjacent cavity.

**Incidence:** 0.27% - 3%

**Presentation:**
- Hemorrhagic shock
- Fever
- Abd pain

**Risk factors:** infections, infections, infections...

**Diagnosis:** DUS, CT, Angiography

**Treatment:**
- Tie off hepatic artery
- Revascularization
- Endovascular: coiling/stenting

**Prognosis:** >50% mortality

Portal Vein Stenosis

Vascular Complications after LTx

Portal Vein Thrombosis (PVT)

- Incidence: 0.3%-2.6%.
- Early: severe acute liver insufficiency or graft failure.
- Late: clinical symptoms depend on the portocaval collateral circulation existence.
- Timing: day 1-15 (mean: 5 d) post tx.
- Etiology:
  - Redundant vein/kinking
  - Pre tx PVT
  - Splenectomy
  - Use of vein conduit
  - Hypoplastic PV (<5 mm)
  - Large portosystemic shunts

Portal vein thrombosis and cavernous transformation
Vascular Complications after LTx

Portal Vein Thrombosis (PVT)

- **Diagnosis:** DUS
- **Treatment:**
  - Within 72 hr of LTx: Surgical repair and systemic anticoagulation.
  - Day 3 to 30 of LTx: Percutaneous thrombolysis and stent.
  - >30 days with no symptoms: No treatment.
  - >30 days with symptoms: Thrombolysis with TIPS placement.

Liver Transplantation - Technique

TIPS

Vascular Complications after LTx

Caval Vein Complications

- **Incidence:** < 3%.
- **CVC** is represented by stenosis, thrombosis and kinking depending on the type of caval anastomosis (cava resection or Piggyback).
- **Clinical presentation:** lower body edema, hepatomegaly, ascites, pleural effusions, Budd-Chiari syndrome, liver and renal failure, and hypotension, leading to allograft loss and even death.
Vascular Complications after LTx
Caval Vein Complications

• Etiology: technical error in the creation of the anastomosis.
  "Modified-PB with the three-hepatic vein seems to offer better outcomes".

Vascular Complications after LTx
Caval Vein Complications

• Diagnosis: DUS, contrast-enhanced CT and cavography.
• Treatment: Transjugular Percutaneous radiological intervention:
  – It includes angioplasty by balloon dilatation, and
  – stent placement in case of recurrence.
Liver Transplantation

Acute liver failure  Chronic liver disease

Acute Liver Failure

- Acute liver failure (ALF) is characterized by a rapid deterioration of the liver function (international normalized ratio ≥ 1.5) and the development of hepatic encephalopathy within 26 wk of jaundice in a patient with no previous history of liver disease.
- ALF accounts for 7% of indications for liver transplantation in the USA.


Acute Liver Failure

- Prognosis in patients with ALF is highly variable and depends on:
  - The etiology
  - Interval between jaundice and encephalopathy
  - Age
  - The degree of coagulopathy.
Acute Liver Failure - Etiology

- Viral Hepatitis
- Drug-induced (Paracetamol: tylenol, 50% of cases)
- ...
- ...

Acute Liver Failure - Prognosis

- Clichy Criteria (1986)
- King’s College Criteria (KCC) 1989
- Sequential Organ Failure Assessment (SOFA)
- Acute Physiological And Chronic Health Evaluation II (APACHE II)
- MELD
- MELD-M65 (cell death-associated marker)

Acute Liver Failure - Prognosis

- Graft quality and recipient clinical condition were described as the most relevant factors influencing transplant outcome in this setting.

Acute Liver Failure - Prognosis

- Multivariate analysis of variables in the United Network for Organ Sharing (UNOS) database identified four factors associated with poor outcome:
  - recipient age > 50 years,
  - history of life support,
  - body mass index ≥ 30 kg/m², and
  - serum creatinine > 2.0 mg/dL [50].

  “Five-year survival was at 47% for those with all four variables.”


Acute Liver Failure - Prognosis

- One-year survival following LT in ALF patients ranges between 74% and 84%. These results are worse than those of patients grafted for other indications.

- This outcome remains better compared to a 64% one-year survival described in patients in ICU immediately prior to LT, and to 54% observed in patients on mechanical ventilation at the time of organ allocation.

- Most deaths occur in the first three months after surgery, from neurologic complications, MOF, or sepsis.

Acute Liver Failure - Prognosis

- Before the era of advanced critical care and liver transplantation, the mortality of ALF was 80-85%.

- In the transplant era, overall survival in patients with ALF underwent considerable improvement. Still, nearly 30% of patients with ALF die.
Liver Transplant for Acute Liver Failure

• Major causes of post Tx mortality:
  – infections was the most common cause of mortality following LT for ALF.
  – Neurologic complications were reported as the second-most common cause of death following transplantation.

Liver Transplantation for viral hepatitis

• Hepatitis B virus:
  – About 25% of all chronic HBV carriers can develop serious liver diseases, such as chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma.
  – Cirrhosis or hepatocellular carcinoma (HCC) due to HBV infection represented one of the most important indications for liver transplantation in the last ten years (14.4%).

Liver Transplantation for viral hepatitis

• Anti HBV therapy
  – Should be started immediately in patients with HBV decompensated cirrhosis, regardless level of detectable serum HBV DNA and/or ALT activity.
  – Lamivudine: High incidence of viral resistance 15%-25% at year 1, 65%-80% at year 5.
  – Adefovir: Viral resistance 29% at 5 years.
  – Entecavir: 50% of lamivudine-resistant pts get resistance.
  – Tenofovir: Low resistance.

  Bartholomeusz A, Semin Liver Dis 2006; 26: 162.

• Indications for Liver Transplantation in HBV:
  – Presence of HCC within Milan criteria.
  – Decompensated liver function, with or without development of HCC.
  – Acute liver failure or fulminant hepatitis.

• HBV Decompensated Liver Cirrhosis:
  – Tenofovir
  – Entecavir

  Goal: Keep HBV <100,000 copies/ml.
  Higher levels have >50% chance of viral recurrence after OLT.


• HCC and HBV:
  – The incidence of HCC in CHB ranges 2.8% to 6.4%.

Liver Transplantation for viral hepatitis

• Hepatitis D virus:
  – HDV coinfection has a variable prevalence among CHB patients.
  – Treatment options are very limited, because nucleosides used for the treatment of HBV are ineffective.
  – LT often remains the main choice in this setting.

  Lampertico P, J Hepatol 2015; 63: 1238.

Liver Transplantation for viral hepatitis

• Hepatitis C virus:
  – Nowadays, cirrhosis secondary to chronic hepatitis C, with or without hepatocellular carcinoma, is the leading indication for LT worldwide.
  – Recurrent hepatitis C infection of the allograft is universal if HCV is detectable at the moment of transplant surgery.
Liver Transplantation for viral hepatitis

- **Hepatitis C virus:**
  - Approximately 1/3 of the patients with Hepatitis C will progress to liver cirrhosis in the graft within only 5 years after transplantation.
  - Two strategies, including pre-transplant treatment of HCV infection in cirrhotic patients and post transplant treatment of liver graft infection, can be adopted for achieving sustained virological response (SVR).


Liver Transplant and Hepatocellular Carcinoma (HCC)

Hepatocellular Carcinoma (HCC)

- Worldwide,
  - HCC represents the sixth most common cancer.
  - It is the third most common cause of cancer-related deaths.

Forner A, Lancet; 2012; 379: 1245

Hepatocellular Carcinoma (HCC)

Selection of candidates with HCC for LTx:

- The aim of LTx for HCC is to obtain a level of disease-free survival (DFS) similar to that of patients who are transplanted for benign disease.

Forner A, Lancet; 2012; 379: 1245

Radiological criteria for the selection and prognosis of patients with HCC for LT

- Bismuth et al noted that patients transplanted for HCC with up to 3 nodules (each < 3 cm) exhibited the best results.
- In 1996, the Milan criteria:
  - a single lesion < 5 cm or fewer than three lesions, each < 3 cm and without macrovascular invasion or extrahepatic disease.
- resulted in 5-year DFS >75% and a recurrence rate < 15%.


Radiological criteria for the selection and prognosis of patients with HCC for LT

- The University of San Francisco (UCSF) criteria (2001):
  - a single lesion ≤ 6.5 cm in diameter or
  - 2-3 lesions each ≤ 4.5 cm with a total maximum diameter ≤8 cm.
  - similar survival after LTx to that
  - Criticism: Retrospective. Only 24% of pts where outside Milan.

Yao FY, Hepatology 2001; 33: 1384
**Radiological criteria for the selection and prognosis of patients with HCC for LT**

- MRI is emerging worldwide as a leading method for the diagnosis and staging of HCC, and it is the most sensitive method for the detection of small HCCs.

Choi JY, Radiology, 2014; 273: 30

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**Isolated biological criteria for the selection and prognosis of patients with HCC for LT**

- In a multivariate analysis, Mailey et al. classified patients into low (≤ 20 ng/mL), medium (20-399 ng/mL), or high (≥ 400 ng/mL) AFP level groups.
- The medium and high AFP groups were associated with higher mortality.
- AFP level > 1000 ng/mL is a reason for exclusion from the wait list.

Hameed B. et al. Liver Transpl 2014; 20: 945

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**Isolated biological criteria for the selection and prognosis of patients with HCC for LT**

- In Japan, des-gamma carboxy prothrombin (DCP) is well established as a biomarker and is reported to correlate with post-LT recurrence of HCC.


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**Bridging Therapy**

- Bridging therapy is used for patients with HCC who meet the MC and are included on the WL but have the possibility of a delay in LT > 6 mo.
- Purpose:
  - to prevent tumor progression,
  - reduce the recurrence of HCC after LT, and
  - increase post-transplant survival.

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**Downstaging**

- Is used to convert tumors that initially do not meet the transplant criteria into tumors that meet the MC, UCSF criteria....
- The aim is to add the patients to the WL once the tumor has decreased in size.
- Tumors with more favorable histology are more likely to respond to treatment and exhibit a good outcome after LT.

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**Bridging Therapy**

- Indications:
  - Tumors with a diameter greater than 3 cm or
  - patients with more than 1 tumor.

Because these patients are more likely to have recurrence after LTx.
Downstaging

• The eligibility criteria for downstaging should have an upper limit, which can be set as follows:
  – one lesion > 5 cm and up to 8 cm;
  – two to three lesions with at least one lesion > 3 cm and not exceeding 5 cm, with a total tumor diameter up to 8 cm; or
  – four to five lesions with none > 3 cm, and a total tumor diameter up to 8 cm.


Downstaging F/U

• Once the treatment is completed, it is mandatory to follow the “ablate and wait policy”, with close monitoring for at least 3 months before inclusion on the WL.

• This policy will help evaluate the tumor’s behavior and exclude aggressive tumors from LT.


Downstaging

• There is no evidence that patients submitted to downstaging followed by LT have a worse prognosis than those who initially meet the MC.

Downstaging - F/U

• Independent predictors of HCC recurrence:
  – AFP level ≥ 100 ng/mL,
  – a maximum tumor size ≥ 7 cm and
  – a lack of complete necrosis at LT after TACE


Downstaging - F/U

• AFP increase of > 15 ng/mL per month, is the most relevant preoperative prognostic factor for low OS and DFS.

Angiographic image during radio embolization with Y90 to the HCC through the left hepatic artery.

Axial (A) and coronal (B) contrast enhanced CT in the arterial phase demonstrates hyper enhancing hepatocellular carcinoma (marked by arrows).

Axial and coronal contrast enhanced CT in the arterial phase demonstrates hyper enhancing hepatocellular carcinoma (marked by arrows).
Liver Transplant and Immunosuppression

Side effects of immunosuppressive medications
• Cardiovascular disease (CVD) and renal disease: account for 19.3% and 6.8% of non-hepatic causes of death in post-OLT patients, respectively.

Immunosuppression Signal Pathway
• Two-thirds of patients develop metabolic syndrome after LTx.

Immunosuppression Signal Pathway
The liver is rich with parenchymal hepatocytes, but also contains non-parenchymal immune cells that serve as a first barrier to antigens arriving from portal circulation. Hepatic non-parenchymal cells include the largest population of fixed resident macrophages in the body, Kupffer cells, as well as other reticuloendothelial cells. The parenchymal hepatocytes further contribute to immunity by secreting 80%-90% of complement components and pathogen-recognition receptors (PRR), as well as synthesizing membrane-bound PRRs to catch portal antigens.

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Immunosuppression Signal Pathway

- Despite a key role in immuno-regulation, generally, human leukocyte antigen (HLA) histocompatibility has little clinical significance to liver allograft outcome.

Immunosuppression Signal Pathway

- There are three signal pathways targeted by immunosuppressive agents:
  - The first is calcineurin-mediated nuclear factor of activated T-cells activation via the T-cell receptor (TCR) and CD3 meeting an antigen presented on a major histocompatibility complex (MHC) protein.

Immunosuppression Signal Pathway

- the second is a B7/CD28 costimulatory signal required for TCR-MHC complex synapsing,
  - The third signal is mediated by interleukin 2 (IL-2) as a ligand to CD25, through adaptor proteins JAK3 and PI-3K to mechanistic target of rapamycin (mTOR) regulation of cyclin-dependent kinases and cyclins to control the cell cycle.

Immunosuppression Signal Pathway

- Calcineurin inhibitors (CNIs) prevent T-cell activation via an intracellular ??
  - The anti-IL-2 receptor antibodies basiliximab and daclizumab prevent IL-2 receptor activation.

Immunosuppression Signal Pathway

- CNIs have been the mainstay of immunosuppression since they were discovered, and increased 1-year patient and graft survival to greater than 80%.

  CNIs serve to prevent transcription of the autocrine factor IL-2, preventing cell proliferation. These drugs halt the intracellular signal transduction protein that mediates response to antigenic peptides-phosphatase activity of calcineurin, which is an

Immunosuppression Signal Pathway

- Second, there is the non-depleting immunosuppressant, mycophenolate mofetil (MMF). MMF is a prodrug of mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH). Because IMPDH catalyzes the rate-limiting step of de novo guanosine synthesis, both genetic replication and transcription are inhibited.
Immunosuppression Signal Pathway

- The third major class of immunosuppressive drugs are called mTOR inhibitors:
  - This class blocks IL-2-mediated autocrine leukocyte proliferation via inhibition of an intracellular signal transduction mechanism.
  - Thus, mTOR inhibitors are considered non-depleting agents.
  - Everolimus (EVR) and sirolimus (SIR) are the two best-known mTOR inhibitors.

Immunosuppression Signal Pathway

- Depleting immunosuppressant agents are mostly antibody-based. The first monoclonal antibody to be approved for use in humans was OKT3, an anti-CD3 antibody that modulates T-cell activation[46,47]. There are currently a host of biologics directed against T-cell proliferation, these are specific enough that their metabolic impact is significantly less than that of CNIs[48,49].

Immunosuppression Signal Pathway

- Immunosuppressive steroids such as methylprednisone are considered essential to graft tolerance induction.

Thank you

Questions