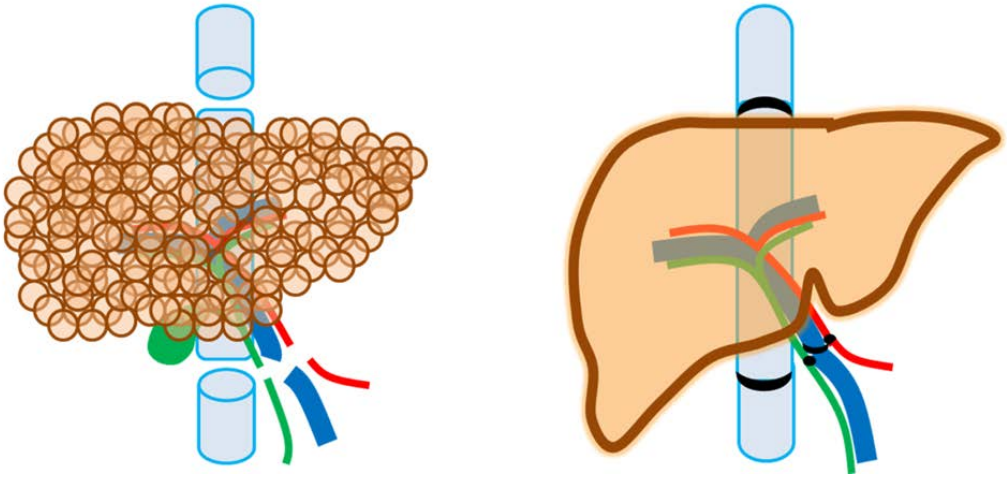
Chapter 15. Liver Transplantation

15.1 Indications, Surgical Techniques and Outcomes

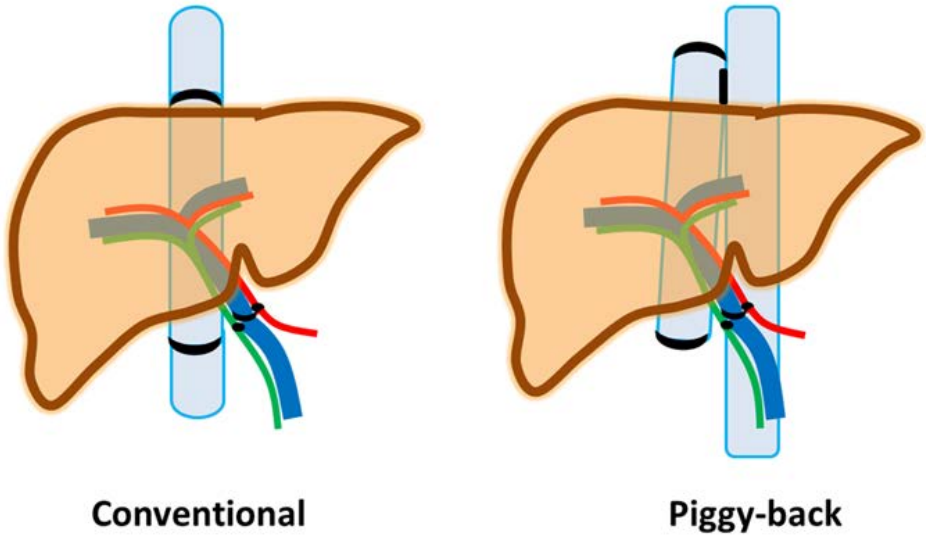
- **Indications**
  - In Canada there are approximately 600 LT per year
    - 95% are for cirrhosis and 5% are for acute liver failure
  - 90% are done in adults
    - 35% have HCV
    - 25% are transplanted for HCC
    - ETOH is second most common indication (6 months abstinence required)
    - NAFLD is rapidly increasing as an indication
  - 10% are done in children (<18 years old)
    - Most common indication is biliary atresia (45%)
- **Source of donors**
  - Donation after brain death (DBD), donation after cardiac death (DCD), live donation (LDLT)
  - Demand > supply = long wait-times and approximately 20% waitlist mortality
- **Organ allocation**
  - Patients are listed according to ABO blood group (and size)
  - Acute liver failure has highest priority (national sharing in Canada)
  - Children receive priority
  - MELD-Na is used to rank patients with cirrhosis (sickest first policy)

- MELD exemption points are granted to HCC patients and others (e.g. HPS or POPH) to ensure they get an organ in time

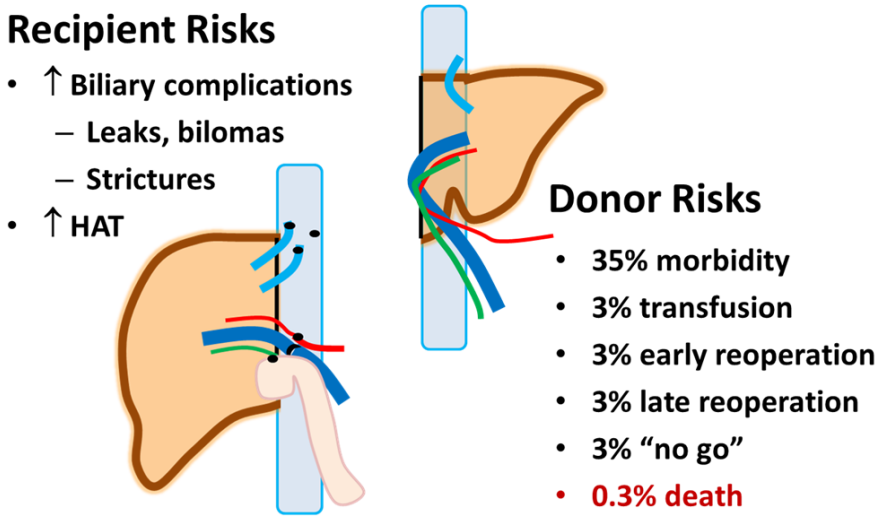
- **Surgical techniques**
  - Diseased liver is removed and new liver is put in place with anastomoses of portal vein, hepatic artery, bile duct and hepatic veins



  - Two techniques – conventional (IVC interposition) or piggyback



- Two types of biliary anastomosis
  - Duct-to-duct (see above)
  - Rou-en-Y (loop of bowel is brought up to the liver) is used in **live donor liver transplant** (see below) and in PSC patients where the diseased bile ducts must be removed
  - **Live donor surgery** is associated with increased risk to the recipient (smaller connections) and also has risks for the donor



- **Outcomes**
  - Patient survival after adult LT is excellent
    - 1 year = 90%
    - 5 year = 75%
    - 10 year = 60%
    - 15 year = 50%
    - 20 year = 30%

- Patient survival after pediatric LT is also excellent with slightly lower one year survival (87%) but better long-term survival (73% at 20 years) in Alberta, Canada
- Most patient enjoy an excellent quality of life and return to work full-time

15.2 Immunosuppression and Complications

- **Immunosuppression** required to prevent acute cellular rejection (ACR) by targeting the T cell
  - Induction is given at time of LT
  - Maintenance is given long-term
    - Drugs have many side-effects
    - Must balance risk of rejection versus complications from immunosuppression
- Since first LT in 1963 drugs have become more potent
- ACR now occurs in <25% and is most common in first 6 months after LT
- **Acute cellular rejection (ACR)**
  - Usually no symptoms
  - Increase of ALT, AST, ALP, with or without ↑ bilirubin, and occasionally ↑ WBC
  - Pathologic diagnosis (Banff criteria) – each graded 0 → 3 on rejection activity index (RAI)
    - portal inflammation
    - bile duct injury
    - endothelitis (inflammation in blood vessels)
  - Treatment = solumedrol IV x 3 days and ↑ maintenance immunosuppression
  - ACR has no impact on survival

- 20% of LT recipients develop tolerance (don't need immunosuppression) but it is currently impossible to identify these patients

- **Corticosteroids**
  - Blocks T cell and antigen presenting cell (APC) cytokine production
  - 80% of centers use steroids at time of LT
    - However, only 25% of patients are on prednisone at 1 year
  - 20% of LT programs are steroid-free using IL2-R blockers + CNIs + MMF
  - Side-effects
    - Cosmetic changes
    - Mental status changes
    - Hypertension (HTN)
    - Lipid abnormalities
    - ↓ wound healing
    - Diabetes
    - Myopathy
    - Osteoporosis
    - Fluid retention
    - Cataracts

- **Calcineurin Inhibitors (CNIs)**
  - **Cyclosporine (CyA**) – 10% of LT
    - Isolated in 1973 from soil fungus (Tolypocladium inflatum)
    - Given at 10 – 15mg/kg dosed twice daily (BID)
    - Trough levels target
      - 1^{st} year → 250 – 300 ng/mL
      - Year 2+ → 100 – 200 ng/mL
      - If renal dysfunction → 40 – 100 ng/mL

- **Tacrolimus (FK506)** – 90% of LT
  - Isolated in 1984 soil fungus in Japan (Streptomyces tsukubaensis)
  - Given at 0.1 – 0.15 mg/kg dosed BID or tacrolimus-ER once daily
  - Trough levels target
    - 1^{st} year $\rightarrow$ 8 – 12 ng/mL
    - Year 2+ $\rightarrow$ 5 – 8 ng/mL
    - If renal dysfunction $\rightarrow$ 3 – 5 ng/mL
- **CNI side-effects**
  - Renal dysfunction (50% at 5 years $\rightarrow$ can go on to dialysis or kidney transplant)
  - $\downarrow Mg^{++}$, $\uparrow K^{+}$
  - Neurologic – tremor, headache, seizure
  - HTN (50% at 5 years) [CyA > FK506]
  - Hyperlipidemia [CyA > FK506]
  - Diabetes (25% at 5 years) [FK506 > CyA]
  - Nausea, vomiting, diarrhea
  - Hirsutism (excessive hair) [CyA]
  - Hair thinning or loss [FK506]
  - Gingival hyperplasia [CyA]
- **Cancer risk** is increased with immunosuppression (20% at 5 years)
  - Non-melanoma skin cancer is very common
  - Throat cancer (if LT done for alcohol, especially if still smoking)
  - Colon cancer (if LT done for PSC)

- Post-transplant lymphoproliferative disease (PTLD) is seen in 2-4% adults and more common in children (EBV related)

- **Sirolimus (Rapamycin**) – <10% LT
  - From soil of Rapa Nui (Streptomyces hygroscopicus)
  - Has anti-tumour properties → used in HCC patients and those who develop skin cancer
  - Can be used for CNI induced renal disease
  - Dosed once daily for trough levels of 5-10 ng/mL
  - Side-effects
    - ↑ hepatic artery thrombosis (HAT), therefore usually not used in first month
    - Anemia
    - Hyperlipidemia
    - Mouth ulcers
    - Interstitial lung disease
    - Peripheral edema
    - Proteinuria
    - Wound dehiscence (should find an alternative before elective surgery)
- **Anti-metabolite drugs** (no drug level monitoring)
  - **Azathioprine**
    - Dosed 50-150 mg once daily
    - Rarely used now except transplant for AIH or PSC with IBD
    - Side-effects include low WBC and pancreatitis

- **Mycophenolate mofetil (MMF)** – 80% of LT
  - Dosed at 1000 mg BID
  - Allow for lower levels of CNIs
  - MMF + Prednisone can be used to avoid CNIs in patients with renal dysfunction
  - Side-effects include bone marrow suppression, nausea, diarrhea, abdominal pain
    - Avoid in pregnancy

- **Drug – Drug Interactions**
  - CyA, FK506, and sirolimus are metabolized by CYP 3A4
  - Some drugs induce CYP 3A4 (e.g. phenobarbital) and can ↓ immunosuppression levels and thereby ↑ risk of ACR
  - Many drugs are metabolized by CYP 3A4 (e.g. clarithromycin, fluconazole) and therefore can ↑ immunosuppression levels leading to toxicity (e.g. renal dysfunction from CNIs)
  - Grapefruit juice is metabolized by CYP 3A4 in the brush border of the intestine
    - When CyA, FK506, or sirolimus are taken with grapefruit juice, less of the drugs will be metabolized in the small intestine leading to ↑ drug levels and possible toxicity

- **Other Complications**
  - **Infectious complications**
    - Very Early = bacterial post-op infections (e.g. urinary tract infections)
    - Early = viral infections (CMV or EBV) or pneumocystis jirovecii pneumonia (prophylaxis is given with TMP-SMX for six months)
    - Late = community acquired infections

- **Allograft dysfunction**, as indicated by increased liver tests, should be investigated with viral studies for CMV & EBV, Doppler US to look for HAT, ± biopsy to rule out ACR or recurrent disease, ± MRCP to look for biliary strictures
  - PNF = primary non-function
  - ACR = acute cellular rejection
  - HAT = hepatic artery thrombosis (early HAT leads to graft loss and late HAT leads to biliary strictures)
  - PTLD = post-transplant lymphoproliferative disease
- **Biliary complications** ("Achilles heel" of LT)

  NOTE: strictures are more common with DCD donors
- **Recurrent disease**
  - HCV recurrence is universal (80% develop hepatitis → accelerated progression)
  - AIH, PSC, PBC recur in one-third
  - HCC recur <15% within Milan criteria (single HCC < 5cm or 3 HCC each < 3cm) but is higher with extended criteria (e.g. TTV115 & AFP400)
  - ETOH recidivism is a problem although return to problem drinking is uncommon

Summary of LT Complications

	0-1 months	1-6 months	>6 months
Infectious	<u>Bacterial</u> Wound, UTI, Pneumonia, Abscess	<u>Virus / Others</u> CMV, EBV PJP	Community acquired infections
Allograft dysfn	PNF ACR HAT	ACR Recurrent HCV HAT	Recurrent disease Chronic Rejection PTLD
Biliary	Leaks Collections	Strictures	Strictures
Recurrent disease	Uncommon	HCV ETOH	HCV, AIH, PSC, PBC, HCC, ETOH

Abbreviations: ACR = acute cellular rejection; AIH = autoimmune hepatitis; CMV = cytomegalovirus; EBV = Epstein Barr virus; ETOH = ethanol (alcohol); HAT = hepatic artery thrombosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; PBC = primary biliary cirrhosis; PJP = pneumocystis jirovecii pneumonia; PNF = primary non-function; PSC = primary sclerosing cholangitis; PTLD = post-transplant lymphoproliferative disorder; UTI = urinary tract infection

Abbreviations

ACR – acute cellular rejection

AIH – autoimmune hepatitis

APC – antigen-presenting cell

BID – twice daily

CMV – cytomegalovirus

CNIs – calcineurin inhibitors

CyA – cyclosporine

DBD – donation after brain death

DCD – donation after cardiac death

EBV – Epstein Barr virus

ETOH – ethanol (alcohol)

FK506 – tacrolimus

HAT – hepatic artery thrombosis

HCC – hepatocellular carcinoma

HCV – hepatitis C virus

LDLT – live donation

MMF – mycophenolate mofetil

PBC – primary biliary cholangitis

PSC – primary sclerosing cholangitis

PJP – pneumocystis jirovecii pneumonia

PNF – primary non-function

POPH – porto-pulmonary hypertension

PTLD – post-transplant lymphoproliferative disease

RAI – rejection activity index

TMP/SMX – trimethoprim/sulfamethoxazole (Bactrim®)

UTI – urinary tract infection

References

1. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl* 2013; 19(1):3-26.
2. Martin P, DiMartini A, Feng S, et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; 59(3):1144-1165.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol* 2015; 64(2):433-485.