General Transplant

- LTE should begin when r/o death from transplant is less than risk of dying from their original liver dz (\^MELD >15)
  - End Stage Cirrhosis 75%
    - HCV 55%
    - Alcohol 20%
    - NASH/Cryptogenic 15%
    - HBV, AIH, PBC, PSC 10%
  - T2 HCC 15%
  - Acute Liver Failure 5% = Status 1
  - Cirrhotic Complications (variceal bleeding, HRS/HPS, etc)
  - Certain Metabolic Disorders (familial amyloidosis, hereditary oxalosis, inborn errors of metabolism)
  - Mts (pancreatic neuroendocrine tumors)
- Pre-Work-Up to assess for contraindications (comorbidities and >65yo)
  - Match: Size and ABO Blood Type (HLA haplotype is not needed!!!!!)
  - CV/Pulm: TTE w/ PA pressure, R/L cath to rule out significant cardiopulmonary morbidity
  - Onc: pts must be >2yrs out maybe longer for CRC, Breast Cancer, Melanoma
  - MS: DEXA
  - ID: HIV (controversial, some centers have done it w/ good success), active infection (pts are made Status 7)
  - Psych: substance abuse (EtOH >6mo), poor support system, demonstration of non-compliance
- Approach
  - <20: Stay at home
  - 20-30: Stay in Dallas (35 = 60% 3mo mortality)
  - 30-40: Stay in Hospital
- Epidemiology
  - 10% die on list each year
  - 5000 transplants per year w/ 18,000 on list
  - these numbers are actually worsening!!!
  - 6% are alive after 5yrs post-transplant
- UNOS stratifies using the Model for End stage Liver Disease (MELD) Score
  - Based on who is sickest via MELD score (eg. the sicker you are the higher on the list you are) NOT waiting time (eg. the longer you are on the list the higher you move up) or utilitarian reasons (eg. younger pts get transplants sooner than older pts) like most other organs
    - NB livers ranking was originally based on waiting time and Child Score but the problem is that ascites and HE is subjective and waiting time does not necessarily have an effect on survival hence the MELD score was developed
    - NB eventually the system will be modified recognizing the increase r/o death in pts w/ pulmonary dz, etc
  - MELD
    - 0.36xlog(TB) + 0.95xlog(Cr) + 1.12xlog(INR) + .643 and Dialysis > twice in the past week prior to measuring Cr
    - MELD was originally developed to estimate 90d survival in pts who had undergone TIPS
    - 90d survival (y axis) vs MELD (x axis) generates an inverse sigmoid curve where the steepest part of the curve is b/t 18-32 therefore <18 and >32 is pretty flat
    - 90d mortality is 2% for MELD <9 and 71% for MELD >40 and 15% for MELD 15 which is equivalent to 90d mortality following OLTx
    - score ranges from 6-40
    - If each variable (INR, TB, Cr) were 1 the biggest/smallest multiplier is INR/TB hence INR is the most important variable and TB is the least important
    - You can raise Cr/INR by giving pt lasix/coumadin but no one ever does this
    - Pt is given 22 extra points if HCC/HPS/PPS
    - a recent NEJM article showed that the addition of the severity of hypoNa to MELD aka MELDNa is a better predictor of mortality but the problem is that Na can be manipulated w/ meds
- Types
  - Orthodromic Liver Transplant – OLT (whole liver from brain dead cadaver, interestingly the most challenging part is removal of the cirrhotic liver h/c adhesions, bleeding, etc, split single cadaveric liver can be done for two recipients but this approach is very challenging, left goes to child and right goes to adult)
  - Living Donor Liver Transplant – LDLT (represents only 5% of transplants in 2004, using right lobe from living donor, best prognosis in those with MELDs <25, increases donor pool but there is a risk to donor and higher incidence of biliary complications in the recipient h/c of the exposed cut side of the liver, therefore not done much anymore except in pediatric pts and in India, NB you can remove up to 80% of liver and still retain adequate liver function, after 1mo each half of liver nearly regenerates completely in both patients)
- Prognosis
  - 65% at 10yrs (best w/ alcohol/cholestasis and worst w/ HCV)
  - 10% need retransplantation
- Follow-Up
  - who follows these patients? Transplant surgeons → hepatologists → PCP
  - Visits: weekly x2mo, biweekly x2mo, yearly x1yr
- Things to Focus On: (1) follow liver function, (2) assess for the development of complications, (3) maintain effective immunosuppression while minimizing side effects, (4) social circumstances and QOL
- Early On: monitor HD, neurologic status and bile flow
- LFTs will be high directly post-op 2/2 graft ischemia, reperfusion injury, etc but should improve everyday and if not then a work-up is needed w/ liver bx
- Ascites resolves over days to weeks but if longer consider a vascular complication
- HE resolves w/in days but if longer consider metabolic causes esp uremia and electrolyte imbalance, infection, residual HE, medication SE, hemorhage/infarct
- Pregnancy (menstruation returns to normal 1-2mo after transplantation, pregnancies have more complications therefore it is recommended to wait >1yr before getting pregnant)

**Immunosuppresion**
- History/Future: Corticosteroids (1950s) and Azathioprine (1960s) → Antilymphocyte Globulin (1970s), Cyclosporine (1980s), FK506 (1990s), Mycophenolate Mofetil, Rapamycin, OKT3 → creating less nephrotoxic immunophilin inhibitors eg. FK778, WHI P154, LEA29Y, FTY720 → creating tolerance of the transplanted organ is the holy grail
- Induction (1mo): Intra-Op Corticosteroid Bolus + T-Cell Antibody ONLY if autoimmune condition (eg. AIH, PBC, PSC)
  - **T-Cell Antibody** (destroy and prevent function of T-cells)
    - CD52: alemtuzumab (Campath)
    - NB IL-2: basiliximab (Simulect), daclizumab (Zenapax) is no longer available

**Immunophilin Inhibitors** (bind and inhibit immunophilins in T-cell lymphocytes which in turn prevent them from activating calcineurin/mTOR which normally induce expression of IL-2: TNF-alpha, IFN-gamma therefore immunophilin inhibitors keep T-cells in a quiescent state)
- Calcineurin Inhibitors (CNIs): cyclosporine CyA (Neoral, NB Sandimmune is an older version that had variable absorption) or tacrolimus–TAK/FK506 (Prograf) NB tacrolimus is 100x the potency and both derived from fungi
  - PK/PD: absorbed in jejunum, widely distributed, metabolized by liver P450-3A (increase levels (CCBs, Azoles, Macrolides, Allopurinol, Reglan) vs decrease levels (AEDs, Rifampin)), t1/2 of ~1d, follow 12hr trough levels but some are now checking 2hr peak levels; also check CMP/FLP periodically
    - **Cyclosporine Trough Levels**
      - 0-6wks: 150-200ng/mL checking Qwk
      - 6wks-1yr: 100-150ng/mL checking Q2wks
      - >1yr: 50-100ng/mL checking Q4wks
    - **Tacrolimus Trough Levels**
      - 0-6wks: 8-15ng/mL checking Qwk
      - 6wks-1yr: 4-8ng/mL checking Q2wks
      - >1yr: 3-5ng/mL checking Q4wks

- SEs (HTN is less common while DM is more common w/ tacrolimus)
- **Most Important Ones**
  - Neurotoxicity w/ hypoMg/hyperK (most important, 1/3/10% develop ESRD at 1/5/10yrs, 2/2 vasoconstriction on renal artery, increased risk if pt had HRS, early on reversible but later on if chronic then CKD can occur, Bx: interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, Tx Approach: decrease CNIs and increase MMF or switch CNIs to mTOR inhibitor or consider kidney Tx)
  - HTN complicated by Posterior Reversible Encephalopathy Syndrome (PRES)
  - CNS (tinntus, paresthesias, tremors, hallucinations, confusion, migraines, insomnia, dysarthria, seizures)
- **Less Important Ones**
  - Endo (metabolic syndrome w/ dyslipidemia/hyperglycemia)
  - Derm (hypertrichosis/gingival hyperplasia)
  - GI (N/V)
  - Heme (thrombocytopenia)
  - Rheum (myalgia/arthralgia)
  - ID (opportunistic infection esp w/ PCP/CMV)
    - Bactrim forever
    - Valcyte 6wks
- mTOR (mammalian Target Of Rapamycin) Inhibitors: sirolimus/rapamycin (Rapamune), everolimus/SDZ-RAD (Certican)
  - PK/PD:
- Rapamune Trough Levels
  - 0-4wks: 8-10ng/mL
  - >4wks: 4-6ng/mL

- SEs: NO nephrotoxicity but hepatic artery thrombosis, pancytopenia, dyslipidemia, oral ulcers, interstitial pneumonitis, diarrhea, wound dehiscence, infection, arthralgias

- Antimetabolites (inhibit de novo purine synthesis or competes w/ purines → impaired DNA replication esp in lymphocytes b/c all other cell lines have salvage pathways)
  - Inosine Monophosphate Dehydrogenase Inhibitor: mycophenolate mofetil-MMF (CellCept) is a prodrug that is converted to mycophenolic acid-MPA (Myfortic)
    - SEs: GI toxicity, myelotoxicity/hepatotoxicity but less than purine analogues
  - Purine Analogue: Azathioprine (Imuran) is a prodrug that is converted to 6-mercaptopurine-6-MP (Purinethol) (refer to IBD notes) NB rarely used
    - Rejection: Increase Maintenance Meds → High Dose Corticosteroids (1g OD tapered over several days) if no improvement

- T-Cell Antibody
  - Multiple T-cell Ags: anti-thymocyte globulin (Atgam from horse, Thymoglobulin from rabbit)
    - SEs: First Dose Cytokine Release Syndrome (F, chills, tachycardia, GI distress, bronchospasm, hypotension, ameliorated w/ preTx steroids/Benadryl/Tylenol), Lymphopenia
  - NB anti-CD-3: muromonab-OKT3 (Orthoclone) is no longer available

- Transplant Related Complications
  - Any Time
    - Immunosuppressive Side Effects (refer)

- Opportunistic Infection: vaccinate except live vaccines
  - CMV: used to be a major cause of M&M during the first 14wks following transplant b/f effective Px (gancyclovir iv x100d post-op), presenting as asymptomatic viremia to multiorgan involvement especially graft, GI tract, skin, lung, heart
  - PCP: Bactrim
  - Any Bacterial/Fungal Infection: most frequent cause of death first month post LTx hence all recipients get abx for 1-2weeks post op

  - 1st Week
    - Hyperacute Rejection: actually very rare, 2/2 preformed antibodies, Tx: retransplantation
    - Primary Graft Nonfunction (PNF): <10%, manifested by persistent elevated INR/AT, HE, poor bile production thru T-tube, Tx: retransplantation as Status 1
    - Hepatic Artery Thrombosis (HAT): <10%, looks just like PNF, distinguish by US-Doppler/Angiography, later on can result in intrahepatic biliary strictures w/ cholangitis and abscess, Tx: surgical thrombectomy to retransplantation
    - Portal Vein Thrombosis

  - 2nd Week – 3rd Month
    - Acute Cellular Rejection (ACR) (usually asymptomatic however occasionally HM/TPP, Labs: increased AP/GGT followed by AST/ALT after initial normalization post transplant, Tx: biliary and vascular T-lymphocyte inflammation resulting in destruction of bile ducts and venules, highest risk in pts transplanted for AIH/PBC, once difficult to distinguish from recurrent dz, Tx: refer above and in most cases it can be reversed

  - >3rd Month
    - Chronic Rejection (CR) (asymptomatic, Labs: slowly increasing cholestatic LFTs, Tx: ductopenia and obliterative foamy cell arteriopathy, Tx: unlike ACR steroids/OKT3 are not very effective rather tacrolimus appears to be marginally effective therefor unlike ACR CR has a poor prognosis)
    - De Novo Neoplasia (skin cancer, PTLD, solid organ is controversial)
    - Dz Recurrence
      - HCV
        - General: viral levels drop to undetectable levels after transplant and then begin to rise 6d after Tx peaking at ~20x pre-transplant levels at 2mo resulting in nearly 100% recurrence
        - RFs: older age of donor/recipient, pre-Tx HCV viral load, use of high dose immunosuppression, black female, ischemia time, CMV infection, previous HCV Tx, rapid steroid taper
        - Course: variable however it tends to progress faster to cirrhosis compared to non-transplanted pts (30% at 5yrs w/ 2/3 decompensating w/in 3yrs)
          - NB do liver 8x to exclude ACR
          - NB this all results in higher allograft dysfunction and decreased survival
          - NB a rapid recurrence w/ graft loss is 2/2 “fibrosing cholestatic hepatitis” seen in 5% of pts 1-3mo after transplant w/ graft failure in 3-6mo and death in 1yr, pathogenesis is unclear, suggestive labs (very high RNA levels, TB >6, ALP >5xULN) and 8x (hepatocyte ballooning, no inflammation, cholangiolar proliferation w/ ductopenia)
What do you do? (NB HCIG is shown to not be helpful and if all else fails then re-transplant but this is controversial)

- (1) Pre-Tx Prophylaxis (theory is that clearance of virus before Tx eliminates r/o recurrence post-Tx however most pts are too ill for treatment but if not then treat)
- (2) Post-Tx Prophylaxis (only 60% of pts are eligible 2/2 cytopenias and renal insufficiency, treatment is usually started 1-4wks post-Tx, presently only done in few cases)
- (3) Post-Tx Treatment at time of dx of acute hepatitis (SVR much lower compared to non-transplanted pts)

- HBV: Nucleoside Analogue (eg Lamivudine) prior to Tx then continue along w/ HBIG after transplant, prior recurrence was >80% but now it is <20%
- PBC/PSC/AIH: <15%, despite being immunosuppressed autoimmune conditions can recur, these pts are kept on lifelong steroids and given a T-cell antibody early on, sometimes difficult to make dx as autoimmune markers can persist after transplant and thus cannot be used to make a dx of recurrence and Bx are non-specific, importantly though clinical recurrence is rare, NB de novo AIH can occur esp in the pediatric population

- **Biliary Complications** (10-25%, higher risk in living related Tx and choledocho-jejunostomy anastomosis instead of duct-to-duct)
  - Bile Leaks w/ Biloma (first month post Tx)
    - At anastomosis, cystic duct remnant, T-tube site if present
    - 2/2 technical problem, ischemia
    - Tx: (refer to bile leaks after cholecystectomy)
  - Strictures (first several months post Tx)
    - Anastomotic (5%)
      - Occurs later after transplant
      - single/short/anastomotic
      - 2/2 technical problem, fibrosis, local ischemia, bile leak
      - dilatation then progressive plastic stents or metal stent
    - Non-Anastomotic (10%)
      - Occurs early after transplant
      - long/multiple/intrahepatic
      - 2/2 ischemia from HAT/prolonged cold/warm ischemia times/donation after cardiac death or chronic rejection, ABO incompatibility
      - Tx: retransplantation b/c graft loss is seen in up to 50% of pts

- Stones, Sludge, Casts
- Papillary Stenosis w/ SOD
- Lymphoma
- CMV Cholangitis