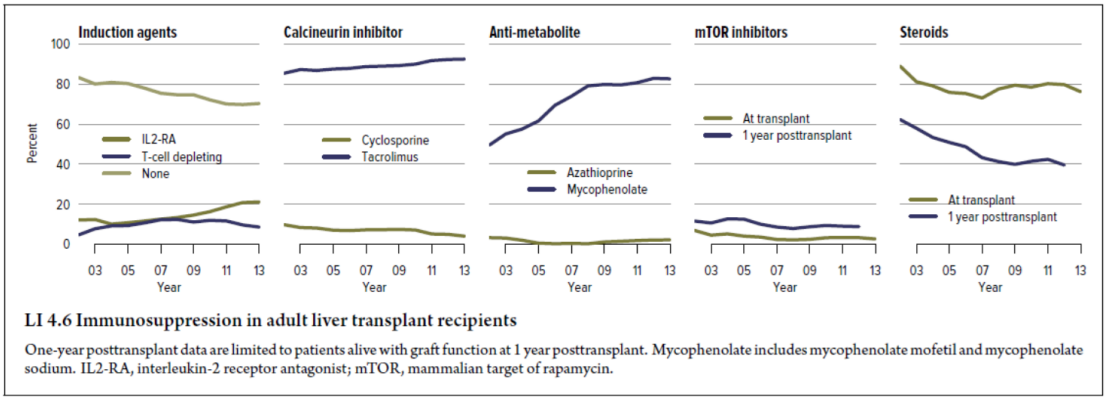
Immunosuppression and Rejection

Josh Levitsky, MD, MS
Professor of Medicine
Division of Gastroenterology and Hepatology
Northwestern University Feinberg School of Medicine

Immunosuppression and Rejection in LT

- Mechanism of Action and Pharmacokinetics of Immunosuppressive Medications
- Perioperative drug toxicity
- Immune Complications (rejection, GVHD, alloimmune/de novo autoimmune diseases)

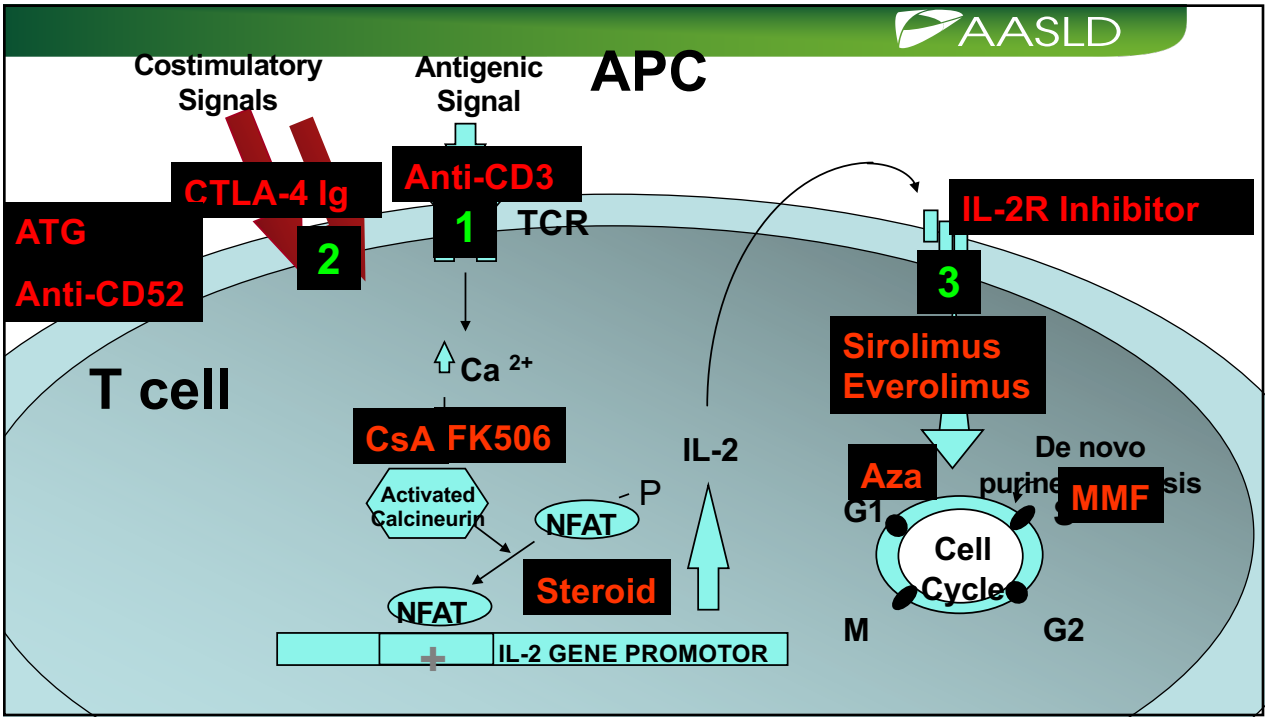
INDUCTION AND MAINTENANCE IMMUNOSUPPRESSION



LI 4.6 Immunosuppression in adult liver transplant recipients

One-year posttransplant data are limited to patients alive with graft function at 1 year posttransplant. Mycophenolate includes mycophenolate mofetil and mycophenolate sodium. IL2-RA, interleukin-2 receptor antagonist; mTOR, mammalian target of rapamycin.

Kim et al, AJT SRTR Report



Cyclosporine

- Most effective against T cell-dependent immune mechanisms
- Forms a complex with cyclophilin and this binds calcineurin.
- Inhibition of Ca2+ dephosphorylation of NFAT (Nuclear factor of activated Tcells)
  - Prevents NFAT entering the nucleus
- Inhibits antigen-triggered signal transduction in T lymphocytes by blocking lymphokine production (IL-2,3,4,5; IFN)
- Excreted in bile
- ½ life = 8 hours (range 5-18 hours)

FK-506 (Tacrolimus)

- Another bacterial derivative (Streptomyces)
- Binds to FKBP-12 (immunophilin)
- Forms a complex and inhibits calcineurin phosphatase.
- 1994 (US multicenter study group; comparison with sandimmune) – less rejection and steroid-resistant rejection
- Like CSA, it has Cytochrome P450 metabolism but is about 20-25x more potent
- Excreted in bile
- ½ life = 11 hours

CNI side effects

- Nephrotoxicity (Early reversible, Late irreversible)
- Neurotoxicity (TAC>CyA) – ranges from seizures, PRES, HA, tremors
- Diabetes (TAC>CyA)
- Hyperlipidemia, Hypertension
- Hair loss (TAC), gain (CyA)
- Rare: HUS (TAC>CyA)

CNI Renal Sparing Studies

- Delay and reduction of CNI exposure minimizes AKI but typically requires antibody induction
- Early (1-6 months post-LT) CNI reduction, typically in combination with non-nephrotoxic agents, may improve/stabilize renal function
- There is evidence that MMF and concurrent reduction in CNI therapy results in improvement of renal function even when performed > 1 year post-LT
- The liver allograft provides partial immunologic protection of a simultaneous renal allograft from the same donor.

Levitsky, O'Leary et al. AJT 2016

Mycophenolate Mofetil

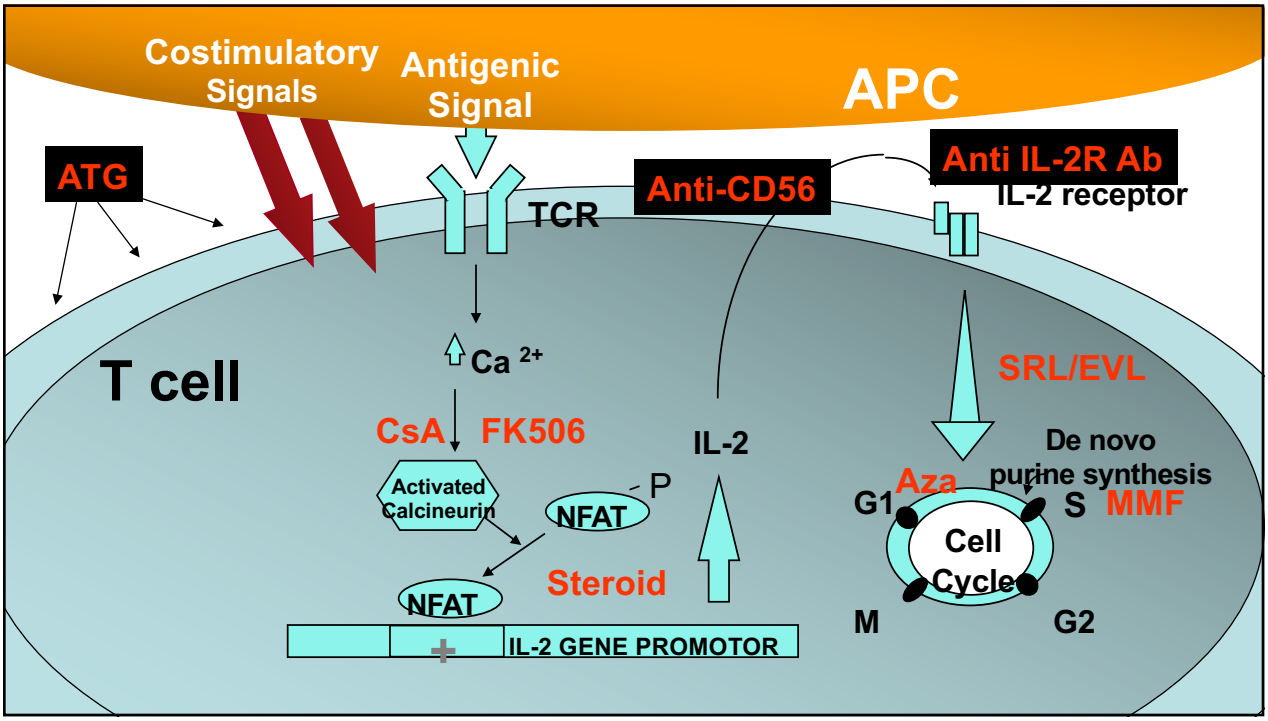
- Active form mycophenolic acid
- Noncompetitive inhibitor of Inosine monophosphate dehydrogenase
- Interferes with guanine nucleotide synthesis and thus purine synthesis
- Potent inhibitor of B and T cells
- Main side effects GI, marrow suppression, GVH-like gut lesion
- Stop if considering pregnancy (teratogenic)

Sirolimus/Everolimus

- Inhibits mTOR (cell cycle regulatory protein)
- Like Tacrolimus, also bind to FKBP
- Unlike Tac, the mTOR FKBP complex - no calcineurin inhibition
- The calcineurin inhibition action of CSA and FK leads to increased endothelin and TGF-β (mediators of acute and chronic renal injury)
  - Not with mTOR (opposite)
- Sirolimus – black box warning for increased risk of HAT and death in LT recipients
- Everolimus – indicated in combo with low dose tac > 30 days post-LT to spare renal function

mTOR-I Side Effects

- Pancytopenia
- Impaired wound healing
- Hepatic artery thrombosis
- Hypertriglyceridemia
- Other SE (oral and GI ulcers, edema, proteinuria, rare pneumonitis)
- Side effects often high trough dependent
- SRL ½ life = 63 hours
- EVL (BID) ½ life = 30 hours
- Excreted in bile



Immunosuppression Summary

- Centers start with CNI (Tac >>> CSA)
- 25% use induction (ATG, IL-2R antagonist), mainly for renal sparing
- >50% use adjunctive MMF at the onset
- 90% use corticosteroids with taper by 3-6 months; steroid-free much less common (induction + CNI + MPA)
- mTOR-I increased utilization after 1-3 months for renal sparing

Assay Methods for Drug Levels

- Drugs are concentrated in RBCs
- CNIs, mTOR: immunoassays (ELISA)
- Standard of care
  - Pre-dose trough levels
  - Poor correlation with degree of over- or under-immunosuppression

Pharmacogenomics: Drug Metabolism

- CNIs, mTOR inhibitors, steroids all metabolized by the cytochrome P450 3A family (3A4, 3A5)
  - intestinal, liver, T/B /NK cells, monocytes
- Substrates for the efflux transporter P-GP
  - multidrug resistance-1 gene (MDR1/ABCB1)

Interactions between Immunosuppressive Agents and Other Medications
Drugs that *increase* CNI and mTOR trough concentrations (block CYP3A4/5):
Macrolides: clarithromycin, erythromycin, azithromycin Antifungals: fluconazole, ketoconazole, itraconazole, voriconazole, clotrimazole Calcium channel blockers: verapamil, diltiazem, nifedipine Others: metoclopramide, danazole, HIV/HCV protease inhibitors, grapefruit juice
Drugs that *decrease* CNI and mTOR trough concentrations (induce CYP3A4/5):
Antibiotics: rifampin, rifampicin, rifabutin Anticonvulsants: phenytoin, phenobarbital, carbamezapine Others: St. John's Wort

Rejection

- Acute Rejection (T cell Mediated Rejection: TCMR)
  - Early, classic
  - Late, atypical
  - Management
  - New data that acute rejection is associated with higher risk of graft failure and death, incrementally worse with time from transplant*
- Chronic Rejection
  - Vascular; Ductopenic
  - Management
- Antibody Mediated Rejection (AMR)

*Levitsky, Goldberg et al. Clin Gastro Hep 2017 Apr

Classic acute TCMR

- Generally 5-30 days, 10-20% of patients
- Higher in autoimmune patients, females, young age, DR mismatches, retransplant
- Rare clinical manifestations unless late diagnosis - fever, abdominal pain, ascites, leukocytosis, eosinophilia
- Biochemical abnormalities non-specific (GGT)

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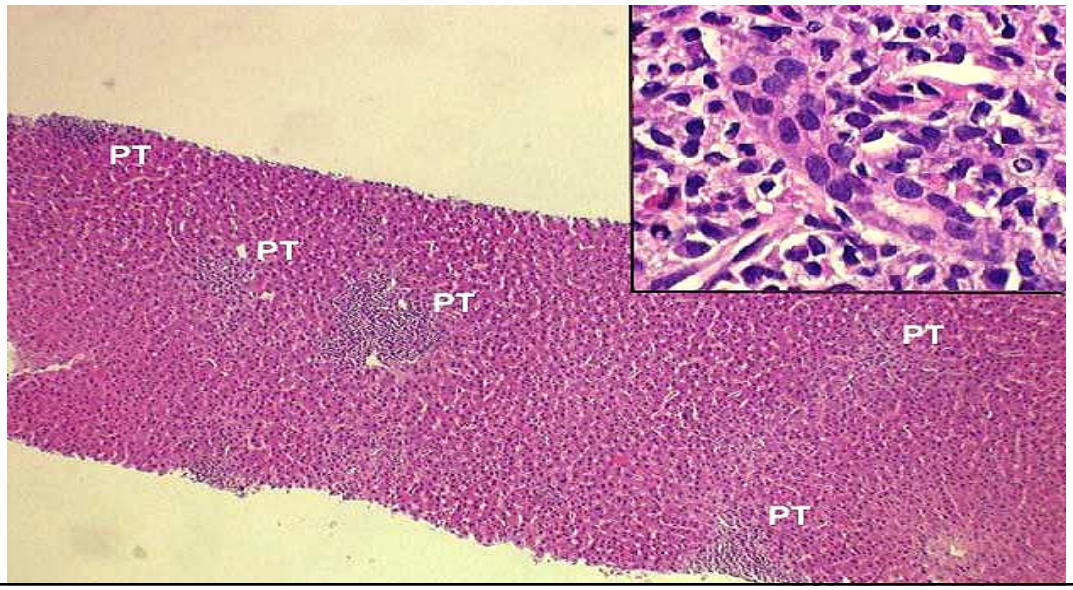
MILD TCMR = <50% of portal tract involvement



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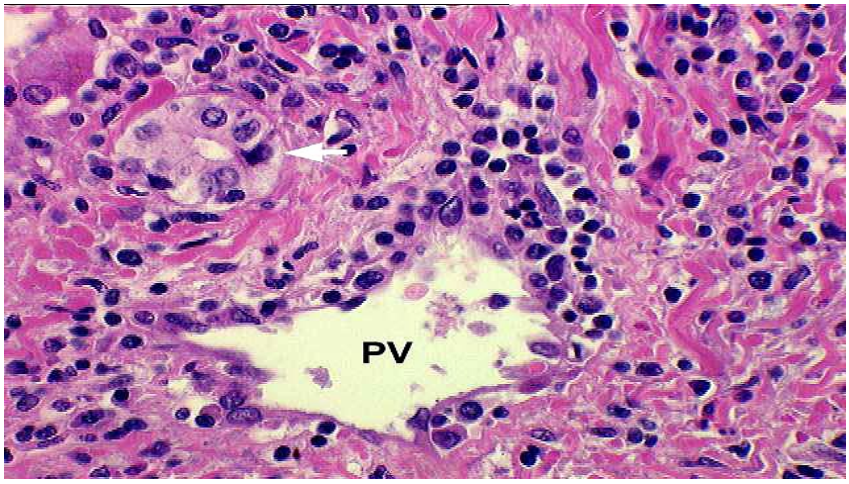
TCMR ENDOTHELITIS AND DUCT INJURY



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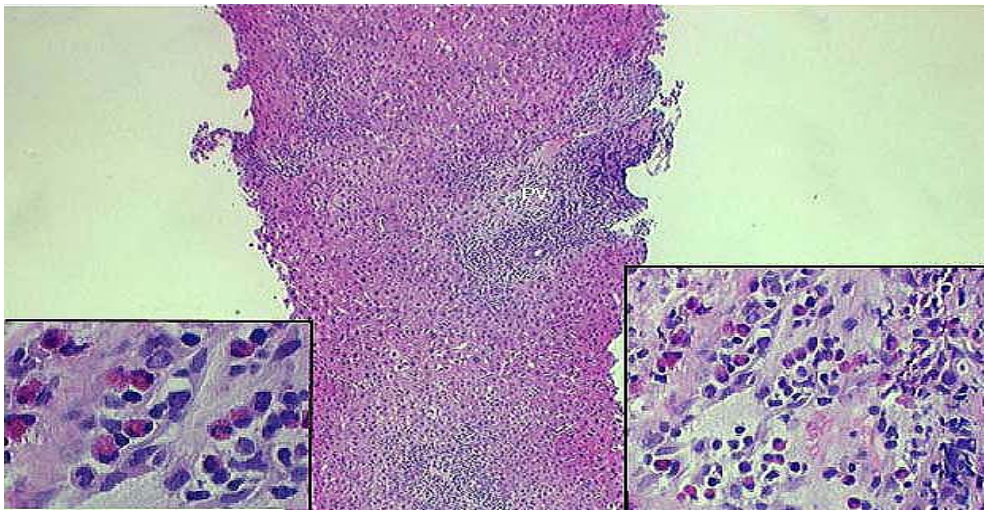
MODERATE TCMR = >50% portal tract involvement



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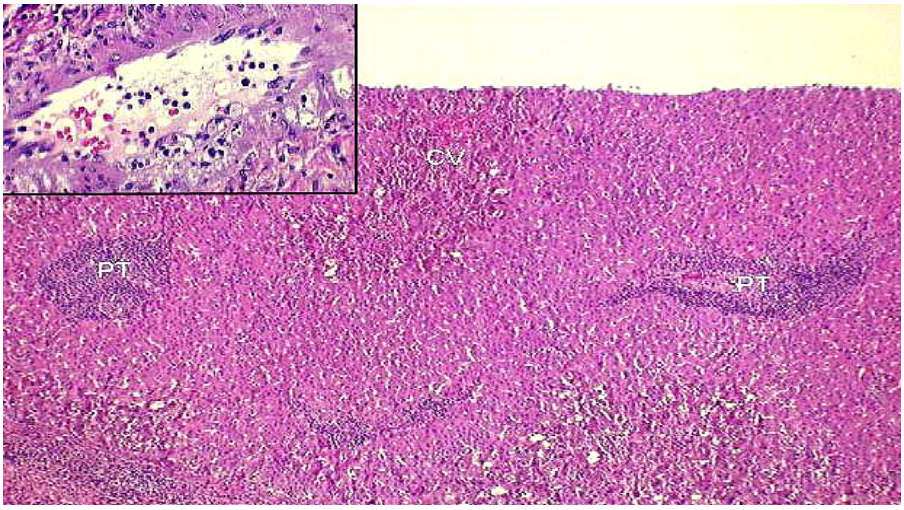
SEVERE TCMR = >50% portal tract involvement with central vein involvement/necrosis



Management of TCMR

- Mild TCMR can be treated with increased maintenance immunosuppression without steroids
- Treat with corticosteroids for moderate to severe TCMR
  - Severe histological and clinical AR – consider initial ATG
- ATG for refractory cases and consider AMR (C4d staining and DSA testing)
- Investigate the reason for TCMR
- Optimize underlying immunosuppression if inadequate
- If already optimized at the time of TCMR, add on 2nd agent
- Consider long term prednisone in autoimmune patients and others with at least 2 episodes or a severe TCMR

Charlton, Levitsky et al. ILTS consensus statement. Transplantation 2018 May

Chronic Rejection

- Indolent, progressive obliterative arteriopathy + intrahepatic cholangiopathy/loss
- 5% of liver recipients and rarely reversible
- Rise in cholestatic enzymes
- Occurs typically in the following patients:
  - Multiple TCMR bouts
  - Severe TCMR with centrilobular necrosis
  - Noncompliance
  - Under-immunosuppression

CR

- Need 8-10 portal tracts (>2 cm piece)
- Minimal criteria for CR are any of following:
  - bile duct loss affecting greater than 50% of the portal tracts
  - the presence of bile duct atrophy/pyknosis, affecting a majority of the bile ducts, with or without bile duct loss
  - foam cell obliterative arteriopathy

Prognosis of CR

- Associated with allograft failure:
  - bile duct loss >50 % of portal tracts
  - severe (bridging) perivenular fibrosis
  - foam cell clusters within the sinusoids
  - Severe hyperbilirubinemia
    - Graft failure median TB 25.5 vs. resolution 4.6*
    - If persistent and associated with synthetic dysfunction or portal HTN, not reversible

*Blakolmer et al. *Am J Surg Pathol* **23** (1999)

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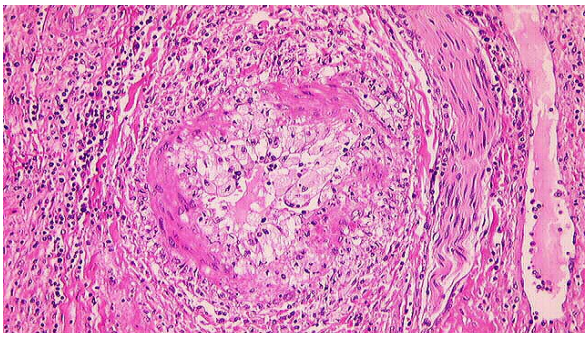
CHRONIC REJECTION

FOAMY ARTERIOPATHY



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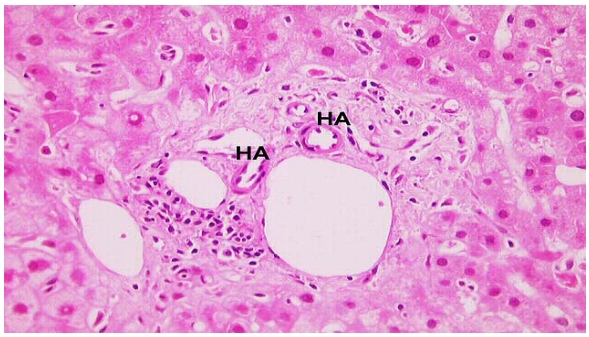

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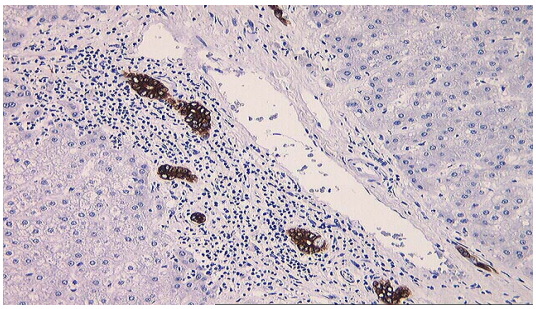
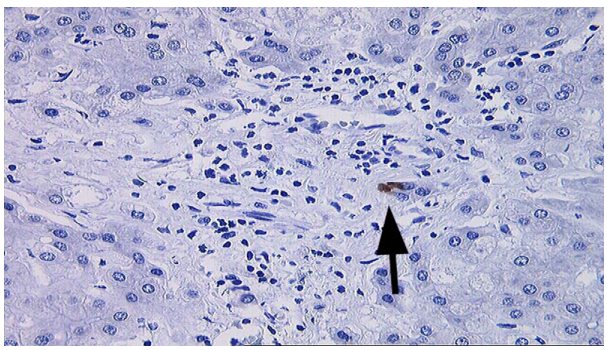


Cytokeratin 19 stains biliary epithelium (CK-19)



Management of CR

- Switch cyclo to TAC in early CR (TB <10)
  - <50% success*
  - Ductular reaction is a positive feature
- Add on mTOR-I or MMF but little data
- Consider infection prophylaxis
- Avoid over-immunosuppression with late cases of liver synthetic dysfunction

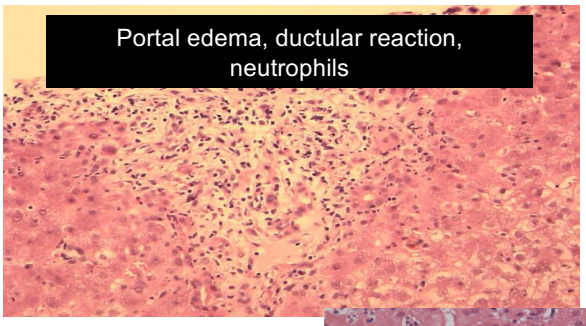
Demetris et al. Transplantation 1992. Roberts et al. Transplantation 1993.
Sher et al. Transplantation 1997 (FK506 US Multicenter study group)

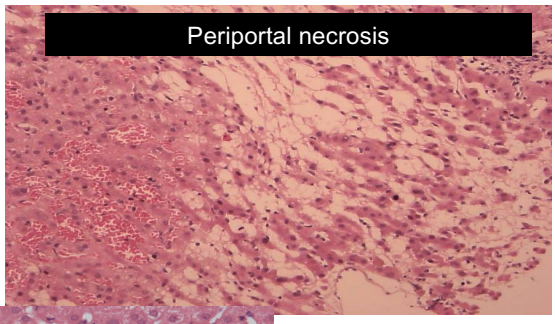
When to Consider AMR?

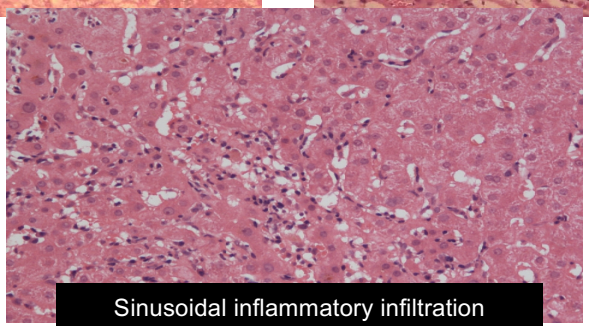
- Refractory rejection (steroid resistant)
- Retransplant patient (sensitized)
- HLA mismatch, positive X-match
- Necrosis/Vascular Injury
- SLK (kidney)
- Unexplained chronic fibrosis or inflammation
- Diagnosis: Histologic findings (next slides), C4d staining in the venules, presence of DSA

Demetris et al. AJT Oct; 16 (10): 2816-2835

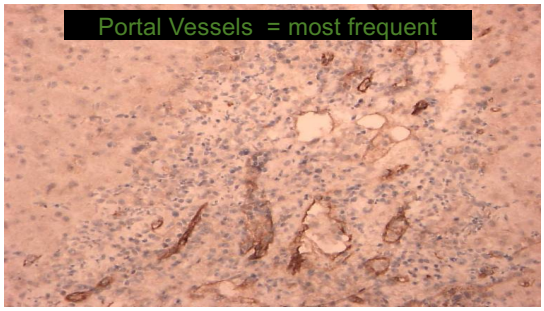
Acute Antibody-Mediated Rejection

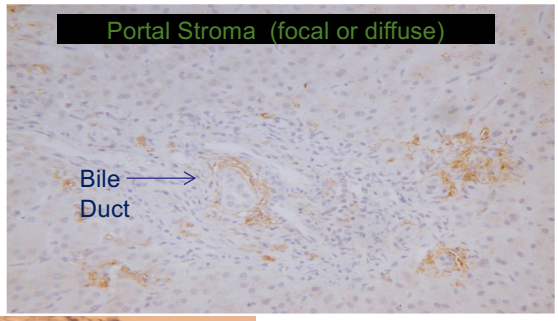


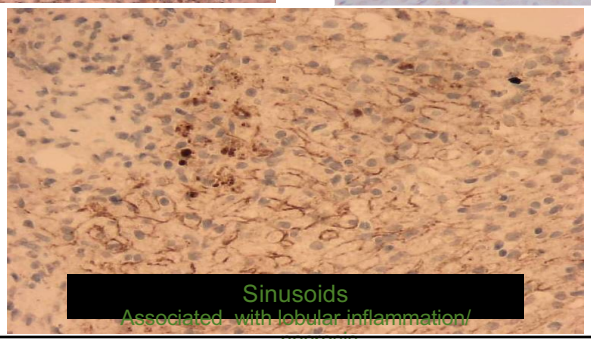




Immunostaining for C4d







Management of AMR

- Borrowed from other organ transplants (kidney) which also do not have data-driven guidelines for therapy
- Antibody binding agent: IVIG
- Antibody removing therapy: Plasmapharesis
- Antibody production inhibitor: Rituximab (anti-CD20), Bortezomib (proteasome inhibitor – inhibits plasma cells)
- Complement inhibition (blocks injury from DSA): Eculizumab

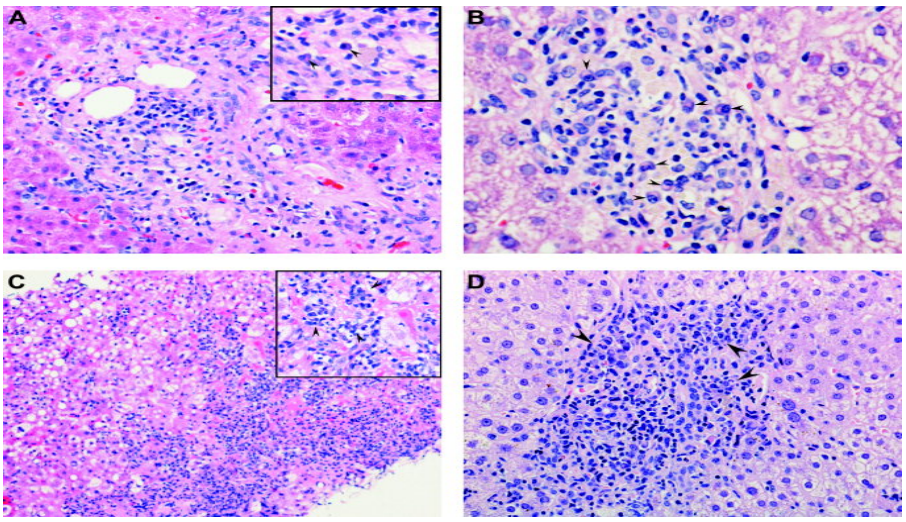
Charlton, Levitsky et al. ILTS consensus statement. Transplantation 2018 May

Variants of Rejection

- Plasma cell hepatitis
  - Early, often with negative autoantibodies (>60%)
  - Centrilobular necrosis associated
  - ? Antibody mediated rejection
- Idiopathic posttransplantation hepatitis
  - 5-15% will have fibrosis progressing to cirrhosis over 10 years
  - Autoantibodies and plasma cells associated with progression
- Late rejection (> 6 months)
  - May be histologically different
  - Lobular activity, interface hepatitis, central perivenulitis (without endothelitis); Can also mimic PCH
  - Possible evolution to CR with hepatocyte dropout in the perivenular regions and loss of inflammation

Fiel et al. Liver Transplantation 2008. Banff Working Group Hepatology 2006

PLASMA CELL HEPATITIS



LT Recipients at Higher Risk for Immune-Mediated Injury

- Autoimmune liver disease
- Previous episodes of rejection/late ACR
- Necessitated minimization of maintenance immunosuppression
  - PTLD
  - Setting of cancer chemotherapy
  - Sepsis
  - Attempt at immunosuppression withdrawal
- Non-adherence (standard deviation of trough levels)
- Presence of donor-specific HLA antibodies
- Presence of certain viral infections, i.e. CMV, HCV

Banff Working Group on Liver Allograft Pathology; Liver Transpl 2012

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Management of Immunosuppression in the High-Risk Patient

- Ongoing regular laboratory testing
- Clinician awareness of ongoing risk
- Patient education to seek medical advice for:
  - viral syndromes
  - illnesses affecting medicinal absorption
  - addition of new medications/herbs
  - change to generic preparation
- Consideration of protocol liver biopsy
- Maintenance corticosteroids in patients with AIH

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GVHD post-LT

- <1% but >80% mortality (sepsis)
- Typically 2-8 weeks post-LT
- Triad of rash, cytopenia, diarrhea… and normal allograft function
- Diagnosis: FISH X-Y chimerism, PBMC donor-recipient chimerism, skin biopsy. GI biopsy rarely needed
- Treatment: high dose steroids, lymphodepletion, ? stop IS (host vs. graft response against donor-reactive cells), stem cell transplant