

Liver Transplantation

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Disclosures

- Consultant for Wolters-Kluwer

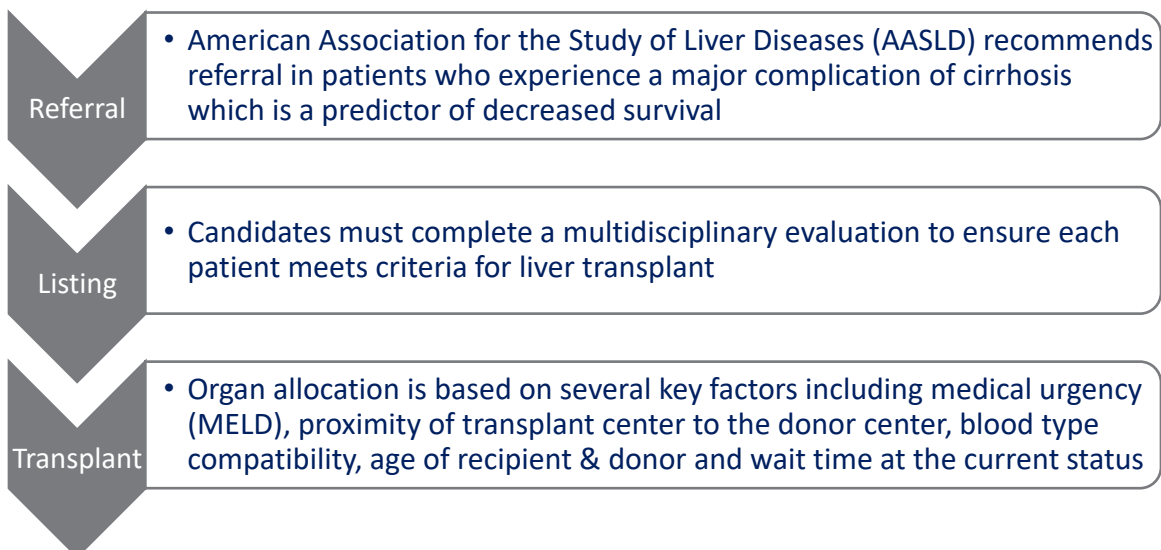


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Learning Objectives

- Describe diagnoses that may lead to referral for liver transplantation.
- Identify indications and contraindications for liver transplantation.
- Create a medication regimen for a liver transplant recipient taking into account immunologic risks and comorbid conditions.
- Summarize the presentation and management of common immunologic and non-immunologic complications after liver transplantation.
- Evaluate potential causes of medication non-adherence after liver transplantation.

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Martin P, DiMartini A, Feng S, et al. Hepatology 2014;59(3):1144-1165.

<https://optn.transplant.hrsa.gov/patients/by-organ/liver/questions-and-answers-about-liver-allocation/>. Accessed in April 2022.

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Who should be evaluated for liver transplant?

- Severe acute liver disease or end stage liver disease (ESLD)
 - Exhaustion of medical therapies
 - Occurrence of an index complication
 - Ascites, hepatic encephalopathy, or variceal hemorrhage
 - Hepatocellular dysfunction with a MELD score ≥ 15

Martin P, DiMartini A, Feng S, et al. Hepatology 2014;59(3):1144-1165.

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Multidisciplinary Evaluation Process

- Initial considerations
 - Major comorbid conditions
 - Ongoing, uncontrolled psychosocial concerns
 - Any immediate contraindications
 - Active extrahepatic malignancy
 - Active and uncontrolled infection outside of the hepatobiliary system
 - Active substance abuse
 - Technical and/or anatomical barriers
 - Brain death

Formal Evaluation to Assess Candidacy for LT

Financial screening

Medical evaluation: general health screening

- | | |
|----------------------|---------------------|
| • Laboratory testing | • Hepatology |
| • Hepatic imaging | • Cardiac clearance |

Transplant surgery evaluation

Anesthesia evaluation

Ancillary support services

- | | |
|-------------------------|---------------|
| • Psychiatry/psychology | • Social work |
| • Financial counseling | • Nutrition |
| • Infectious diseases | • Pharmacy |

Martin P, DiMartini A, Feng S, et al. Hepatology 2014;59(3):1144-1165.
 O'Leary JG, Lepe R, Davis GL. Gastroenterology 2008;134(6):1764-1776.

Adapted from O'Leary JG, Lepe R, Davis GL. Gastroenterology 2008;134(6):1764-1776.

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Prognostic Models



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Acute Liver Failure

- Challenging to predict which patients will require LT
 - MELD score has not improved accuracy of prediction
- King's College Criteria remains the best predictive tool
- Liver support systems limited to use within clinical trials
- Urgent LT remains standard of care

Lee WM, Larson AM, Stravitz RT. Hepatology 2011;1-22. Lee WM, Stravitz RT, Larson AM. Hepatology 2012;55(3):965-967.
Lee WM, et al. Gastroenterology 2009;137(3):856-864. Larson A, et al. Hepatology 2005;42(6):1364-1372.

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King's College Criteria for Acute Liver Failure

Acetaminophen-Induced ALF

Strongly consider LT listing if: arterial lactate >3.5 mmol/L after early fluid resuscitation

List for LT if: pH <7.3 OR arterial lactate >3 mmol/L after adequate fluid resuscitation

List for LT if all 3 occur within a 24 hour period: presence of grade 3 or 4 hepatic encephalopathy, INR >6.5 and Creatinine >3.4 mg/dL

Non-Acetaminophen-Induced ALF

List for LT if: INR >6.5 and encephalopathy present (irrespective of grade) OR

Any 3 of following (encephalopathy present; irrespective of grade):

- | | |
|--|-----------------------------|
| • Age <10 or >40 years | • Jaundice for >7 days |
| • INR ≥3.5 | • Serum bilirubin ≥17 mg/dL |
| • Unfavorable etiology such as Wilson Disease, idiosyncratic drug reaction or seronegative hepatitis | |

Adapted from AASLD Position Paper: The Management of Acute Liver Failure: Update 2011

Lee WM, Larson AM, Stravitz RT. Hepatology 2011;1-22. Lee WM, Stravitz RT, Larson AM. Hepatology 2012;55(3):965-967.

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Child-Turcotte-Pugh (CTP) Score

- Child-Turcotte (1964)
 - Classification system to assess prognosis of cirrhotic patients
 - Incorporated 5 parameters: serum albumin, serum bilirubin, ascites, encephalopathy and nutritional status
 - Attributed to one of three risk stages (A, B or C)
- Pugh (1972)
 - Modified the classification by replacing nutritional status with prothrombin time

Ruf A, et al. Ann Hepatol 2022;27(1):100535.

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Model for End-Stage Liver Disease (MELD)

- MELD calculation uses bilirubin, INR, serum creatinine & sodium
 - In 2016, calculation was modified to include serum sodium
 - Assigns a score to each liver transplant candidate
 - Scores range from 6 to 40
 - Scores correspond to 90-day survival of 90% to 7%, respectively
- MELD scores are used to rank candidates on the waitlist in terms of short-term mortality

Piotrowski D, et al. Clin Exp Hepatol 2018;4(4):240-246. Said A, et al. J Hepatol 2004;40(6):897-903.

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Question 1: DM is a 23 year old female who is transferred to your transplant center for management of acute liver failure and liver transplant evaluation. Upon arrival, she is intubated in the setting of altered mental status and unable to communicate with the transplant team. The paramedics note DM has no significant past medical history. Per your institution's protocol, an acetaminophen level is drawn and the result is elevated at 326 mcg/mL. Which of the following prognostic models is most appropriate to assess acute liver failure and determine need for a liver transplantation?

- A. Child-Turcotte-Pugh Score
- B. King's College Criteria
- C. Milan Criteria
- D. Model for End-Stage Liver Disease

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- A. Child-Turcotte-Pugh Score
- B. King's College Criteria**
- C. Milan Criteria
- D. Model for End-Stage Liver Disease

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Indications for Liver Transplantation

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Indications for Liver Transplant

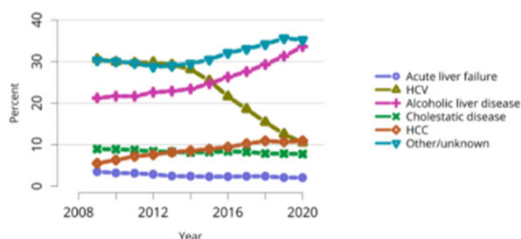
- Complications of cirrhosis
 - Ascites
 - Chronic GI blood loss due to portal hypertensive gastropathy
 - Encephalopathy
 - Liver cancer
 - Refractory variceal hemorrhage
 - Synthetic dysfunction
- Systemic complication of chronic liver disease
 - Hepatopulmonary syndrome
 - Portopulmonary hypertension
- Liver-based metabolic conditions with systemic manifestations
 - Alpha-1-antitrypsin deficiency
 - Familial amyloidosis
 - Glycogen storage disease
 - Hemochromatosis
 - Primary oxaluria
 - Wilson's disease
- Acute Liver Failure
- Primary graft non-function
- Hepatic artery thrombosis

Martin P, DiMartini A, Feng S, et al. Hepatology 2014;59(3):1144-1165. O'Leary JG, Lepe R, Davis GL. Gastroenterology 2008;134(6):1764-1776.

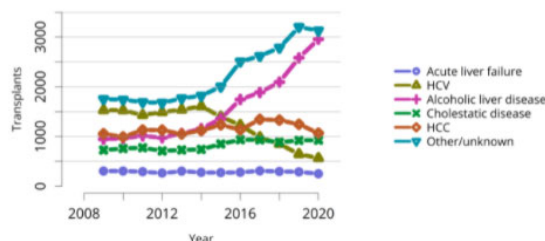
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2020 OPTN/SRTR Annual Data Report

Adults waiting for liver transplant by diagnosis



Liver transplants by diagnosis



https://srtr.transplant.hrsa.gov/annual_reports/2020/Liver.aspx. Accessed April 2022.

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Causes of Cirrhosis leading to ESLD

- Alcohol-related liver disease
- Autoimmune hepatitis (AIH)
- Hepatic malignancies
 - Hepatocellular carcinoma (HCC)
 - Cholangiocarcinoma (CCA)
- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Viral hepatitis
 - Hepatitis B (HBV)
 - Hepatitis C (HCV)
- Metabolic conditions
 - Alpha-1-antitrypsin deficiency
 - Familial amyloidosis
 - Glycogen storage disease
 - Hemochromatosis
 - Non-alcoholic steatohepatitis (NASH)
 - Primary hyperoxaluria
 - Wilson's disease
- Vascular disorders of the liver

O'Leary JG, Lepe R, Davis GL. Gastroenterology 2008;134(6):1764-1776.

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Hepatocellular Carcinoma (HCC)

- Diagnosis
 - Imaging studies using contrast-enhanced CT or MRI
- Management & LT considerations
 - Decrease progression of disease
 - Bridging or downstaging therapies
- Transplant outcomes
 - Tumors within Milan criteria
 - Low risk of HCC recurrence (15%)
 - Five-year survival is > 70%

Milan criteria

- Solitary tumor (diameter < 5 cm) OR
- Up to 3 tumor nodules (each < 3 cm)
- No vascular invasion or extra hepatic metastasis

UCSF criteria

- Solitary tumor (diameter < 6.5 cm) OR
- 3 or fewer tumor nodules with the largest lesion being < 4.5 cm or a total tumor diameter < 8 cm without vascular invasion

Heimbach JK, et al. Hepatology 2018;67(1):358-380. Abdelfattah MR, et al. Eur J Gastroenterol Hepatol 2018;30(4):398-403.

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Causes of Acute Liver Failure

- Acetaminophen hepatotoxicity
- Acute alcoholic hepatitis
- Acute fatty liver of pregnancy/hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome
- Acute ischemic injury
- Autoimmune hepatitis (AIH)
- Budd-Chiari syndrome
- Drug induced liver injury (DILI)
- Malignant infiltration
- Mushroom poisoning
- Unknown etiology
- Viral hepatitis
- Wilson's disease

Lee WM, Larson AM, Stravitz RT. Hepatology 2011;1-22. Lee WM, Stravitz RT, Larson AM. Hepatology 2012;55(3):965-967.
 Lee WM, et al. Gastroenterology 2009;137(3):856-864. Larson A, et al. Hepatology 2005;42(6):1364-1372.

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Management of Acute Liver Failure

- Diagnosis: acute insult and encephalopathic
 - Prompt laboratory testing is essential
- Minimize risk of intracranial hemorrhage (ICH)
 - Serum ammonia concentrations and serum sodium
 - Role of hypertonic saline and mannitol
- Optimizing mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) to preserve neurologic function
- Evaluation of INR and potential bleeding risk

Lee WM, Larson AM, Stravitz RT. Hepatology 2011;1-22.
 Lee WM, Stravitz RT, Larson AM. Hepatology 2012;55(3):965-967.
 Lee WM, et al. Gastroenterology 2009;137(3):856-864.
 Larson A, et al. Hepatology 2005;42(6):1364-1372.

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Acetaminophen (APAP) Hepatotoxicity

- Ingestion exceeding 10 g/day
 - Results in very high AST/ALT levels often > 3500 IU/L
- Check APAP level on presentation
 - Rumack-Matthew nomogram
- Consider activated charcoal if ingestion occurred within 4 hours
- Antidote: N-acetylcysteine (NAC)
 - Oral & intravenous (IV) regimens are available
- NAC Dosing Regimens
 - Oral or nasogastric tube:
 - 140 mg/kg followed by 70 mg/kg every 4 hours x 17 doses
 - IV administration:
 - Loading dose: 150 mg/kg in 5% dextrose over 15 minutes
 - Maintenance dose: 50 mg/kg given over 4 hours followed by 100 mg/kg over 16 hours

Lee WM, Larson AM, Stravitz RT. Hepatology 2011;1-22.

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Question 2: You are the transplant pharmacist participating in evaluation clinic for liver transplant candidates. Which of the following candidates would be the best for your center to consider listing at this time?

- A. 42 year old female with ESLD secondary to alcohol-related liver disease. She reports no complications associated with her liver disease at this time and her MELD score is 12. Her sister is present and agrees to be her caregiver.
- B. 78 year old male with ESLD secondary to HCV and HCC. His MELD score is 20. His tumor is outside of Milan Criteria. He presents to clinic alone and is unable to identify a caregiver at this time.
- C. 60 year old female with ESLD secondary to AIH c/b HE and variceal bleed (both are treated and well controlled). Her MELD score is 15. Her urine toxicology is positive for alcohol and she informs the team she is actively drinking in the setting of known liver disease.
- D. 52 year old male with ESLD secondary to NASH c/b ascites and HE. His MELD score is 32. His wife is present and agrees to be his caregiver.

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- D. **52 year old male with ESLD secondary to NASH c/b ascites and HE. His MELD score is 32. His wife is present and agrees to be his caregiver.**

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Question 3: AS is a 45 year old male referred to your transplant center for liver transplant evaluation. His PMH is significant for ESLD secondary to alcohol related liver disease, polysubstance abuse, hypertension and depression. AS attends the multidisciplinary evaluation clinic with his designated caregiver and completes all required testing. Which of the following would be a contraindication to listing for liver transplant at this time?

- A. History of depression, controlled on medication
- B. History of high blood pressure, uncontrolled on medication
- C. History of polysubstance abuse with a positive cocaine toxicology result at the time of evaluation
- D. History of alcohol related liver disease with his last drink two years ago

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Liver Allocation & Donor Considerations

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Organ Allocation

- 2020 OPTN policy change resulting in implementation of a new distribution system focusing on medical urgency and distance between donor & recipient centers
- All deceased donor liver allografts are first offered to:
 - Most urgent candidates (Status 1A and 1B) at transplant hospitals within a radius of 500 nautical miles of the donor hospital
 - Following the above offers, adult liver donors will be offered to candidates at hospitals within distances of 150, 250 and 500 nautical miles of the donor hospital by medical urgency
- Status 1A: highest priority allocation for candidates ≥ 18 years of age
 - Life expectancy less than 7 days, anhepatic, primary non-function, hepatic artery thrombosis (HAT), or acute decompensated Wilson's disease
- Status 1B: highest priority allocation for pediatric candidates < 18 years of age

Organ procurement and transplantation network (OPTN) policies. Accessed April 3, 2022.

Policy and system changes effective January 11, 2016, adding serum sodium to MELD calculation-UNOS. Accessed on November 30, 2019.

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MELD Score Exceptions

- Standardized MELD score exceptions for a specific diagnoses
 - Cholangiocarcinoma (CCA)
 - Cystic Fibrosis
 - Familial amyloid polyneuropathy
 - Hepatic artery thrombosis (HAT)
 - Hepatopulmonary syndrome (HPS)
 - Metabolic disease
 - Portopulmonary hypertension
 - Primary hyperoxaluria
 - Hepatocellular carcinoma (HCC)
- If the candidate does not meet requirements for a specific diagnosis, then an individualized request may be submitted to the National Liver Review Board
 - Candidate's transplant center must provide requested MELD score and supporting information for this request

Organ procurement and transplantation network (OPTN) policies. Accessed April 3, 2022.

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Types of Donor Allografts

- Deceased donor grafts
 - Liver only grafts
 - Simultaneous liver-kidney grafts
 - Simultaneous liver-intestine grafts
 - Other less common combinations:
 - Simultaneous liver-heart
 - Simultaneous liver-lung
- Living donor grafts (partial grafts)
 - Right lobe without middle hepatic vein (MHV)
 - Laparoscopically assisted right lobe hepatectomy without MHV
 - Right lobe with MHV
 - Left lobe
 - Left lateral segment
 - Right posterior sector graft

Miller CM, et al. Transplantation 2016;100(6):1238-1243.

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ABO-Incompatible Liver Transplants

- Limited to use in emergent situations
- UNOS registry data analysis
 - Graft survival was significantly worse in ABO-incompatible LT compared to ABO-compatible LT
 - Characteristics linked to increased risk of graft loss in ABO-incompatible LT
 - Life support, repeat transplant, split grafts, and HCC

Stewart ZA, Locke JE, Montgomery RA, et al. Liver Transpl 2009;15(8):883-893.

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Hepatitis B Core Antibody Positive Allografts

Lab Test	Result	Interpretation
HBsAg HBcAb HBsAb	negative negative negative	Susceptible
HBsAg HBcAb HBsAb	negative positive positive	Resolved HBV infection
HBsAg HBcAb HBsAb	negative negative positive	Immunized
HBsAg HBcAb HBsAb	positive positive negative	Active HBV infection (usually chronic) • If HBcAb IgM present, may be represent an acute infection
HBsAg HBcAb HBsAb	negative positive negative	Multiple possibilities: • Distant resolved infection • False positive

Adapted from Seem DL. Am J Transplant 2013;13(8):1953-1962.

- HBsAg-negative recipients who receive a HBcAb-positive allograft should receive long-term antiviral therapy to suppress viral replication

- Lamivudine
- Entecavir
- Tenofovir disoproxil fumarate
- Tenofovir alafenamide

Abbreviation Key:

- HBsAg = Hepatitis B surface antigen
- HBcAb = Hepatitis B core antibody
- HBsAb = Hepatitis B surface antibody

Te H, et al. Clin Transplant 2019;33:e13514.

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Hepatitis C Infected Allografts

HCV Antibody	HCV NAT	Interpretation
Negative	Negative	No infection
Positive	Negative	No active infection Prior exposure with spontaneous clearance Prior exposure with successful treatment False positive antibody test
Negative	Positive	Acute infection in antibody window period False positive NAT test
Positive	Positive	Active infection (acute or chronic)

Adapted from Levitsky J. Am J Transplant 2017;17(11):2790-2802.

- For HCV-negative recipients receiving a HCV-infected graft, AASLD recommends:
 - Early HCV treatment with a pangenotypic direct-acting antiviral (DAA) regimen
 - When recipient is clinically stable, within 2 weeks of transplant (preferably within first week)

<https://www.hcvguidelines.org/unique-populations/organs-from-hcv-viremic-donors>. Accessed April 2022.

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Treatment of HCV-Uninfected Recipients of Liver Grafts from HCV-Viremic Donors

Genotype	Recommended Treatment Regimen	Duration
1-6	Daily fixed-dose combination of glecaprevir /pibrentasvir (Mavyret®)	12 weeks
1-6	Daily fixed-dose combination of sofosbuvir*/velpatasvir (Epclusa®)	12 weeks

*Amiodarone and sofosbuvir containing DAAs are not recommended for coadministration

Adapted from <https://www.hcvguidelines.org/unique-populations/organs-from-hcv-viremic-donors>. Accessed April 2022.
<https://www.hep-druginteractions.org/checker>. Accessed April 2022.

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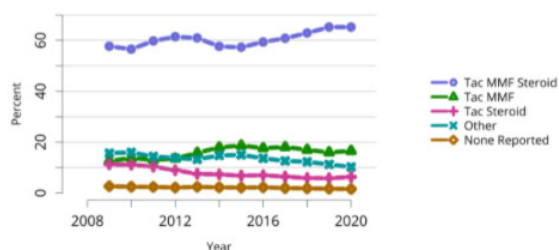
Medication Regimens for Liver Transplant Recipients

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Immunosuppression Strategies in LT

- Induction therapy was not administered in the majority (72%) of adult liver transplant recipients
- Approximately 60% of LT recipients are maintained on a triple drug regimen
 - Tacrolimus, mycophenolate and steroid
- Dual maintenance regimen are less common
 - Tacrolimus and mycophenolate (< 20%)
 - Tacrolimus and steroid (< 10%)

OPTN/SRTR 2020 Annual Data Report



https://srtr.transplant.hrsa.gov/annual_reports/2020/Liver.aspx. Accessed April 2022.

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Selection & Adjustment of Immunosuppression

- Patient specific considerations
 - Indication of LT
 - Comorbidities
 - Medication Toxicities
 - History of or risk for:
 - Rejection
 - Prior transplant
 - Cancer
 - Infections
 - Pregnancy planning
- Lack of universally accepted immunosuppression regimen
- No comprehensive test to assess overall level of immunosuppression
 - Utilize multiple variables to evaluate
 - Therapeutic drug monitoring
- Medication related adverse effects
- Potential drug-drug interaction

Lucey MR, et al. Liver Transpl 2013;19(1):3-26.

Charlton M, et al. Transplantation 2018;102(5):727-743.

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Medication Regimens

- Immunosuppression
 - Triple drug regimen: tacrolimus, mycophenolate mofetil & prednisone
- Anti-infection prophylaxis
 - Fungal: nystatin, clotrimazole, fluconazole or an echinocandin
 - Cytomegalovirus (CMV):
 - Moderate or high risk: valganciclovir
 - Herpes simplex virus (HSV): acyclovir or valacyclovir
 - Pneumocystis jiroveci pneumonia (PJP): sulfamethoxazole-trimethoprim
- Other routine therapies
 - Venous thromboembolism (VTE) prophylaxis
 - Antiplatelet therapy with aspirin
 - Stress ulcer prophylaxis with proton pump inhibitor
 - Decrease cholesterol content of bile using ursodiol

Lucey MR, et al. Liver Transpl 2013;19(1):3-26.
 Shay R, et al. Transplant Proc 2013;45:330-334.

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Question 4: TK is 58 year old Caucasian male with ESLD secondary to alcohol-related cirrhosis. His PMH is significant for HTN, T2DM, obesity, and seizures. He is referred to the multidisciplinary clinic to be evaluated as a liver transplant candidate. You complete a medication history with TK in clinic. Which of the following medications presents a pharmacologic risk for TK as a potential liver transplant recipient?

- A. Phenytoin
- B. Amlodipine
- C. Metformin
- D. Hydralazine

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Question 4: TK is 58 year old Caucasian male with ESLD secondary to alcohol-related cirrhosis. His PMH is significant for HTN, T2DM, obesity, and seizures. He is referred to the multidisciplinary clinic to be evaluated as a liver transplant candidate. You complete a medication history with TK in clinic. Which of the following medications presents a pharmacologic risk for TK as a potential liver transplant recipient?

- A. Phenytoin
- B. Amlodipine
- C. Metformin
- D. Hydralazine

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Evaluating Allograft Function in Liver Transplant Recipients

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Evaluating Liver Allograft Function

- Laboratory testing
 - Liver function tests
 - INR
 - CMV polymerase chain reaction
 - Viral hepatitis work-up (depending on symptoms and patient history)
- Imaging/Procedures
 - Ultrasound of the liver
 - Endoscopic retrograde cholangiopancreatography (ERCP)
 - Magnetic resonance cholangiopancreatography (MRCP)
 - Liver biopsy

Lucey MR, et al. Liver Transpl 2013;19(1):3-26.
 Singh S, et al. Mayo Clin Proc. 2012;87(8):779-790.

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Common Causes of Liver Allograft Dysfunction

Allograft rejection (acute or chronic)
Cytomegalovirus infection or reactivation
Recurrence of primary liver disease <ul style="list-style-type: none"> • Hepatitis C • Hepatitis B • Autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis) • Return to alcohol use • Hepatocellular cancer • Nonalcoholic steatohepatitis
Vascular complications (hepatic artery thrombosis or stenosis, venous outflow impairment)
Biliary complications (bile leak, biliary strictures, stones/cast)
Drug-induced liver injury
Sepsis or systemic infection
Development of new unrelated liver disease in allograft

Adapted from Singh S, et al. Mayo Clin Proc. 2012;87(8):779-790.

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Immunologic Complications After Liver Transplant



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T Cell-Mediated Rejection (TCMR)

Grading Criteria	
Indeterminate	<ul style="list-style-type: none"> • Portal and/or perivenular inflammatory infiltrates related to alloreaction • Insufficient tissue damage for diagnosis of mild acute rejection
Mild	<ul style="list-style-type: none"> • Rejection-type infiltrate involving minority of the triads • Mostly confined to portal spaces • Confluent necrosis/hepatocyte dropout absent
Moderate	<ul style="list-style-type: none"> • Rejection-type infiltrate involving most or all portal tracts • Confluent necrosis/hepatocyte dropout limited to minority of perivenular areas
Severe	<ul style="list-style-type: none"> • Moderate plus spillover into periportal areas and/or moderate-severe perivenular inflammation extending into the hepatic parenchyma • Perivenular hepatocyte necrosis involving a majority of perivenular areas
Quantitative Scoring (Rejection Activity Index [RAI])	
Scoring ranges in value from 1 to 3 for each of the following: portal inflammation, bile duct inflammation damage and venous endothelial inflammation	

Adapted from Demetris AJ, et al. Am J Transplant 2016;16:2816-2835.

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Treatment of TCMR

- First line for mild to moderate TCMR:
 - Methylprednisolone 500-1000 mg IV daily x 3 days
 - Modifications to the maintenance regimen
- For severe, persistent or refractory TCMR:
 - Repeat methylprednisolone pulse
 - Consider antibody therapies (antithymocyte globulin or alemtuzumab)
 - Additional modifications to the maintenance regimen

Demetris AJ, et al. Am J Transplant 2016;16:2816-2835.

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Antibody-Mediated Rejection (AMR)

Criteria for Diagnosis of Acute AMR in Liver Allografts

Definitive for acute/active AMR (must have all four):

1. Histopathological pattern of injury
2. Positive serum DSA
3. Diffuse (C4d score = 3) microvascular C4d deposition
4. Reasonable exclusion of other insults

Suspicious for AMR (must have both):

1. DSA is positive
2. Non-zero h-score with: C4d score + h-score of 3 or 4

Indeterminant for AMR (must have 1+2 and 3 or 4):

1. C4d score + h-score is ≥ 2
2. DSA not available, equivocal or negative
3. C4d staining not available, equivocal or negative
4. Co-existing insult might be contributing to the injury

Criteria for Chronic Active AMR in Liver Allografts

Probable chronic active AMR (must have all four):

1. Histopathological pattern of injury including both
 - a. Unexplained or at least mild mononuclear portal and/or perivenular inflammation
 - b. At least moderate portal/periportal, sinusoidal and/or perivenular fibrosis
2. Recent circulating HLA DSA in serum samples
3. At least focal C4d-positive (>10% portal tract microvascular endothelial)
4. Reasonable exclusion of other insults that might cause a similar pattern of injury

Possible chronic active AMR:

1. As above, but C4d staining is minimal or absent

Demetris AJ, et al. Am J Transplant 2016;16:2816-2835.

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Treatment of AMR

- Mild Acute AMR:
 - Standard TCMR treatment with steroid pulse
- Moderate to Severe AMR:
 - Plasmapheresis and IVIg +/- B cell-directed therapy
- Chronic AMR:
 - No published studies to date
 - Adherence to tacrolimus based regimen important for prevention

Demetris AJ, et al. Am J Transplant 2016;16:2816-2835.

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Immunologic Related Disease Recurrence after LT

- | | |
|--|---|
| <ul style="list-style-type: none"> • Autoimmune hepatitis <ul style="list-style-type: none"> – Occurs in approximately 30% – Incidence ↑ with time post-LT and after discontinuation of steroids | <ul style="list-style-type: none"> • Primary biliary cirrhosis (PBC) <ul style="list-style-type: none"> – Occurs in 20-30% over 10 years – Median time is 3 to 6 years • Primary sclerosing cholangitis (PSC) <ul style="list-style-type: none"> – Occurs in 20-25% after 5-10 years – No recommended medical therapy |
|--|---|

Lucey MR. Liver Transpl 2013;19(1):3-26. Lindor KD. Hepatology 2019;69(1):394-419.
 Manns MP. Hepatology 2010;51(6):2193-2213. Chapman R. Hepatology 2010;51(2):660-678.

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Non-immunologic Post-Transplant Complications



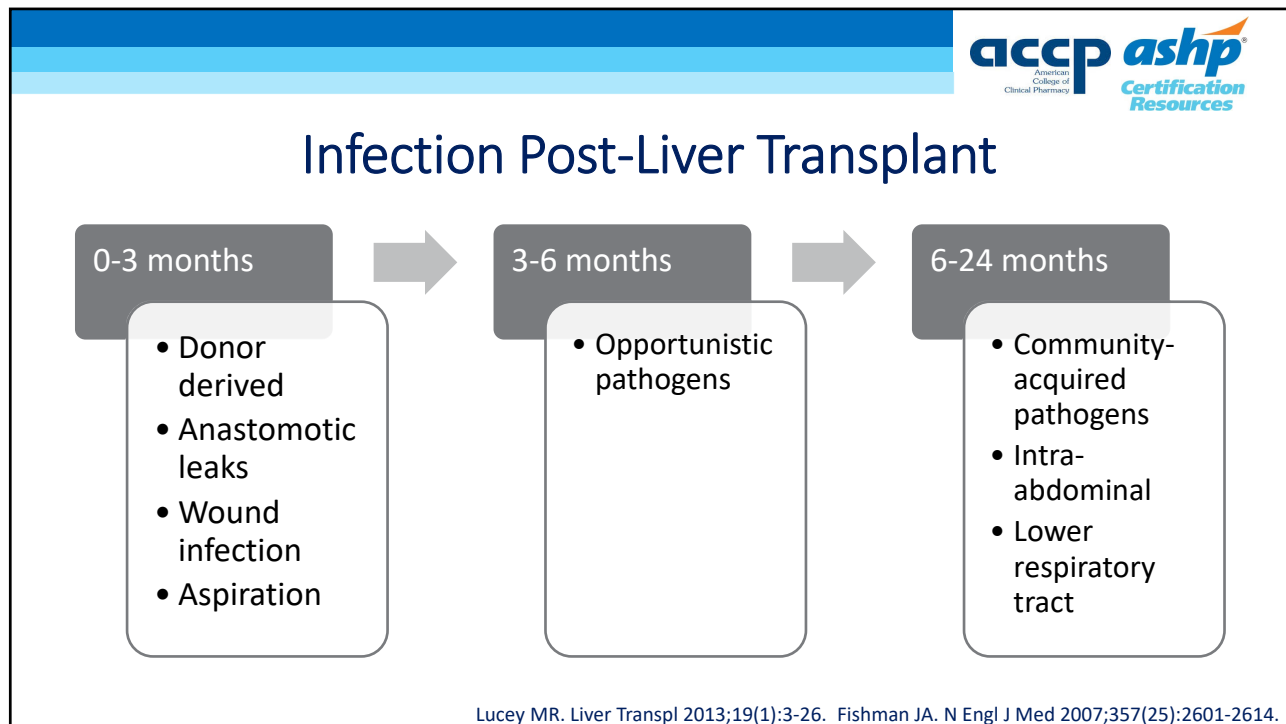
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Surgical Complications



- Vascular complications
 - Hepatic artery
 - Stenosis, thrombosis, pseudoaneurysm or steal phenomenon
 - Stenosis: may be higher risk with donation after cardiac death (DCD) grafts
 - Hepatic artery thrombosis (HAT)
 - Portal vein thrombosis
 - Relatively rare in adults; more common in partial grafts
 - Percutaneous endovascular interventions have become primary treatment
 - Vena cava
 - Hepatic venous outflow obstruction is rare
- Biliary complications
 - Bile leaks, biliary strictures, stones/cast
 - Potential interventions: surgical, percutaneous, or endoscopic
 - Significant morbidity

Patel P. Curr Opin Organ Transplant 2019;24(2):138-147.

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Cytomegalovirus (CMV)

- Associated with significant morbidity & mortality in LT recipients
- Diverse clinical manifestations
 - Most common include viremia, bone marrow suppression and involvement of the GI tract and liver
- Risk factors include CMV seropositive donor organ, use of anti-lymphocyte antibodies, rejection and coinfection with other immunomodulating viruses, bacteria or fungi

Lucey MR. Liver Transpl 2013;19(1):3-26.

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Drug Induced Liver Injury (DILI)

- Associated with prescription drugs, OTC medications and herbal supplements
 - Rarely cause dose-related toxicity
- Idiosyncratic drug hepatotoxicity usually occurs in the first 6 months
 - Chronic medications used for 1-2 years are unlikely to cause damage
- No specific antidotes
- Any possible offending agent should be discontinued

Some Drugs Which May Cause Idiosyncratic Liver Injury

Isoniazid	Dapsone	Gemtuzumab
Sulfasalazine	Etodolac	Terbinafine
Phenytoin	Didanosine	Methyldopa
Statins	Efavirenz	Diclofenac
Propylthiouracil	Carbamazepine	Labetalol
Ciprofloxacin	Pyrazinamide	Tolcapone
Disulfiram	Isoflurane	Allopurinol
Cocaine	Itraconazole	Ketoconazole
Valproic acid	Nicotinic acid	Abacavir
Amiodarone	Imipramine	Doxycycline

Adapted from Lee WM, Larson AM, Stravitz RT. Hepatology 2011;1-22.

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Disease Recurrence after LT

- Nonalcoholic steatohepatitis (NASH)
 - Histological evidence of NAFLD is common
- Alcohol-related liver disease
 - Wide variation in reported rates of return to drinking after LT (10-90%)
 - Approximately 20% of patients return to harmful consumption
- Viral hepatitis
 - HBV: infrequent with antiviral therapy
 - HCV: 100% recurrence if untreated prior to LT; direct acting antivirals (DAA) allow for SVR post-LT
- Hepatocellular carcinoma (HCC)
 - Within Milan: 10%
 - Outside Milan: 40-60%

Lucey MR. Liver Transpl 2013;19(1):3-26. Te H, et al. Clin Transplant 2019;33:e13514. Chalasani N. Hepatology 2018;67(1):328-357. Heimbach JK, et al. Hepatology 2018;67(1):358-380. Abdelfattah MR, et al. Eur J Gastroenterol Hepatol 2018;30(4):398-403.

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Question 5: TJ is 58 year old black male who received a DDLT last night for ESLD secondary to DILI likely caused by doxycycline. Due to his emergent need for LT, you learn from reviewing his medical record, that TJ received a PHS increased risk donor who was ABO-incompatible. This morning he was found to have a bile leak on imaging. Which of the following is an immunologic risk for TJ following liver transplant?

- A. Drug induced liver injury (DILI)
- B. PHS increased risk donor
- C. ABO-incompatible donor
- D. Bile leak

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- B. PHS increased risk donor
- C. **ABO-incompatible donor**
- D. Bile leak

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Additional Post-Transplant Considerations



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Impact of Comorbidities

Impact of Immunosuppression on Metabolic Syndrome				
	HTN	Obesity	Diabetes mellitus	Hyperlipidemia
CNI	++	+	++	+
MMF, AZA	-	-	-	-
Corticosteroids	+	+	+++	+
mTOR inhibitors	+	-	-	++

- Kidney Disease
 - Etiology of renal impairment in LT recipients is multifactorial
 - Reduction or withdrawal of CNIs may be considered

Prevalence of cardiovascular risk factors and chronic kidney disease after the first year post-LT

- Systemic hypertension (40-85%)
- Obesity (24-64%)
- Diabetes mellitus (10-64%)
- Dyslipidemia (40-66%)
- Metabolic syndrome (50-60%)
 - Any 3 of the 4 risk factors listed above
- Chronic kidney disease (30-80%)
 - Stage 3-4, estimated glomerular filtration rate = 15 to <60 mL/minute/1.73 m²
- End stage kidney disease (5-8%)

Adapted from Charlton M, et al. Transplantation 2018;102(5):727-743. Adapted from Lucey MR, et al. Liver Transpl 2013;19(1):3-26.

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Impact of Malignancy

- Surveillance
 - HCC: routine imaging is recommended, but intervals between testing and overall duration has not been established
 - Institution specific protocols
 - PSC/inflammatory bowel disease: annual screening colonoscopy with biopsies
 - Annual consultation and assessment by dermatologist
- Immunosuppression considerations
 - High levels of immunosuppression may be linked to increased rates of HCC recurrence
 - Specifically, calcineurin inhibitors (CNI) & corticosteroids
 - Potential benefit of converting to mTOR inhibitor, but data is inconclusive

Lucey MR, et al. Liver Transpl 2013;19(1):3-26.

Charlton M, et al. Transplantation 2018;102(5):727-743.

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Common Barriers to Adherence after Transplant

Age	Overall health and wellness
Gender	Physical function
Ethnicity	Cognitive status
Education level	Side effects of medications
Income and financial constraints	Cost of medications
Insurance status	Cultural conditions
Lack of psychosocial support	Distance to transplant center
History of mood or anxiety disorders	Follow-up visits conflict with daily activities

Doyle IC. Am J Health-System Pharm 2016;73(12):909-920.

Serper M. Transpl Int 2018;31(8):870-879. Moayed MS. Int J Org Transplant Med 2019;10(3):115-126.

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Strategies & Interventions to Reduce Non-adherence

- Medication education to patients & caregivers
 - Using various tools to help patients understand complex regimens
 - Web- and app-based medication lists, pillboxes, handwritten lists, color coding and numbering systems
 - Best practice: self-assessment checklist or competency
 - Ongoing, continuous med education throughout transplant phases
- Guidance on medication refills, access and delivery options

Doyle IC. Am J Health-System Pharm 2016;73(12):909-920. Serper M. Transpl Int 2018;31(8):870-879.

Klein A. Transplantation 2009;87(6):839-847. Moayed MS. Int J Org Transplant Med 2019;10(3):115-126.

Neuberger JM. Transplantation 2017;101(4S):S1-S56. Maldonado AQ. Am J Health-System Pharm 2013;70(10):900-904.

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Question 6: You are participating in the pre-liver transplant evaluation clinic and assessing each potential LT candidate for pharmacologic and non-pharmacologic risks for LT. NP is 52 year old Asian female with ESLD secondary to HBV cirrhosis and HCC. Her PMH is significant for HTN, T2DM, and anxiety. She verbalizes that she has a good understanding of her current medications and using a pillbox at home to help organize her medications. She notes that she has been seeing a therapist to help manage her anxiety as it has become worse in the knowledge of her chronic liver disease. She is accompanied by several family members during the visit who plan to provide her with support throughout her transplant journey. Which characteristic about NP is a risk factor for non-adherence?

- A. Age
- B. Gender
- C. History of anxiety
- D. Lack of psychosocial support

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- A. Age
- B. Gender
- C. History of anxiety**
- D. Lack of psychosocial support

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Key Takeaways

- Appropriate assessment of patients with liver disease for LT requires a thorough multidisciplinary team approach
- Acceptable indications for LT include both for acute and chronic liver diseases
- Immunosuppression regimens vary based on patient-specific risk factors, comorbidities or other special considerations
- Immunologic complications can be acute or chronic, cellular or antibody mediated as well as related to disease recurrence
- Non-immunologic complications can vary widely and require careful management
- Adherence is important for graft and patient survival

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Liver Transplantation

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