Anesthesia for Liver Transplantation

Current Practice and Future Directions
U.S. Liver Transplants performed 1988-2002

Deceased Donor

Living Donor

Transplant Year

Transplants
**Survival rates for Liver Transplants Performed 1996-2001 in U.S.**

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Time Post Transplant</th>
<th>Survival Rate</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Primary</td>
<td>1 year</td>
<td>87.1</td>
<td>86.5-87.7</td>
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<tr>
<td>Repeat</td>
<td>1 year</td>
<td>69.3</td>
<td>66.8-71.7</td>
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<tr>
<td>Primary</td>
<td>3 year</td>
<td>79.7</td>
<td>79.0-80.4</td>
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<tr>
<td>Repeat</td>
<td>3 year</td>
<td>59.8</td>
<td>57.4-62.1</td>
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# Survival rates for Liver Transplants Performed 1996-2001

<table>
<thead>
<tr>
<th>Listing Status</th>
<th>Time Post Transplant</th>
<th>Survival Rate</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>1</td>
<td>1 year</td>
<td>76</td>
<td>73.9-78</td>
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<tr>
<td>2A</td>
<td>1 year</td>
<td>80.3</td>
<td>78.9-81.7</td>
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<tr>
<td>2B</td>
<td>1 year</td>
<td>88.1</td>
<td>87.4-88.8</td>
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<tr>
<td>3</td>
<td>1 year</td>
<td>91.6</td>
<td>90.2-93</td>
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<tr>
<td>1</td>
<td>3 year</td>
<td>69</td>
<td>67.2-70.8</td>
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<tr>
<td>2A</td>
<td>3 year</td>
<td>70.5</td>
<td>68.4-72.6</td>
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<tr>
<td>2B</td>
<td>3 year</td>
<td>79.7</td>
<td>78.6-80.8</td>
</tr>
<tr>
<td>3</td>
<td>3 year</td>
<td>83.8</td>
<td>82.7-84.8</td>
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</table>
The rapid growth of the wait list
Organ Allocation: Model for End-Stage Liver Disease

(MELD) score, adapted February 27, 2002

• Replaces the former status 2A, 2B and 3 that depended on part on the Child-Turcotte-Pugh score

• Status 1 reserved for acute fulminant hepatitis remains in place

• Waiting time eliminated as criterion for organ allocation

• MELD Score: starts at 10 and is capped at 40

• Special circumstances referred to regional review board to assure transplantation within 3 months (hepatopulmonary syndrome, oxalosis)
MELD SCORE

0.957*\log_{e}(\text{creatinine}) + 0.378*\log_{e}(\text{bilirubin}) + 1.12\log_{e}(\text{INR}) + 0.6543*10
Liver Transplantation

- Almost routine procedure
- Average blood transfusion 5 U PRBC
- Short post operative ICU stay
- One year survival > 90%
Typical Liver Transplant Candidate

- End stage liver disease
- Portal hypertension
- Gastro intestinal bleeding in Hx
- Ascites
- Encephalopathy
- Coagulopathy
- Electrolyte abnormalities (hypoglycemia, lactic acidosis, hypoproteinemia, hyperammonemia, hyponatremia, hypokalemia)
Liver disease and its effect on other organ systems

- Hepatorenal Failure
- Hepatopulmonary Syndrome
- Cerebral Edema
- Hyperdynamic Circulation
- Multifactorial Coagulopathy
- Kwashiorkor Malnutrition.
Hepatorenal Syndrome

• Initially reduced urinary sodium excretion
• More advanced stage severe impairment in the ability to excrete free water: dilutional hyponatremia etc (serum sodium level < 130 mEq/L)
• Final stage: renal vasoconstriction resulting in a low glomerular filtration rate (GFR)
Symptoms HRS

- Arterial hypotension
- Intense sodium retention
- Dilutional hyponatremia
- Extremely high levels of renin, norepinephrine, and antidiuretic hormone
Treatment HRS

- Liver transplantation is the ideal treatment
- Immediately after transplantation, a further impairment in renal function may be observed, and more than one third of the patients require hemodialysis.
- Liver plus renal transplant
- Sometimes dialysis during surgery to keep Potassium levels normal
Hepatopulmonary Syndrome

• Caused by pulmonary vascular dilatation
• Arterial hypoxemia
  – PaO2 < 70 mm Hg (10 kpa) on room air
  – or AaO2 gradient > 20 mm Hg
• Oxygenation is often worse in the standing position or with exercise


**Intracranial Hypertension**

- Cerebral edema, leading to intracranial hypertension, occurs in approximately 50% to 80% of patients with fulminant hepatic failure.
- It is a leading cause of death in acute fulminant hepatic failure.
- Far less commonly, intracranial hypertension may complicate the course of hepatic encephalopathy in end-stage chronic liver disease.
Intracranial Hypertension Treatment

- The goals of management are to maintain ICP below 20 mm Hg and CPP above 50 mm Hg.
- Maintenance of the MAP of at least 60 mm Hg
- Prevention and treatment of volume overload
- upper body elevated 10° to 20°
- hyperventilation
- Mannitol if ICP > 20 mm Hg for more than 5 min
Hyperdynamic Circulation

- Increased plasma volume and cardiac output
- Reduced peripheral vascular resistance, and arterial blood pressure within normal limits
- Arteriolar vasodilation responsible for this hyperdynamic circulation occurs in the splanchnic circulation
- Intense vasoconstriction in nonsplanchnic arterial vascular territories, including the kidneys, brain, muscle, and spleen
Coagulopathy

- Liver has a central role in hemostasis by producing not only coagulation factors, but also coagulation inhibitors, fibrinolytic proteins, and their inhibitors.
- All forms of coagulopathy: hypo as well as hyper
Coagulopathy

- Vitamin K Deficiency-Related Coagulopathy
- Decreased Hepatic Synthesis of Coagulation Factors
- Platelets:
  - Thrombocytopenia (sequestration of platelets in the spleen)
  - Dysfunction
- Excessive Fibrinolytic Activity
- DIC
Malnutrition

- Liver regulates protein and energy metabolism
- Loss of muscle mass and fat stores
- However, 10-30% of liver failure patients are obese
Porto-Pulmonary Hypertension

• mean pulmonary artery pressure $\geq 25$ mm Hg
• increased pulmonary vascular resistance of $>120$ dyn·s/cm$^5$
• pulmonary capillary wedged pressure of $<15$ mm Hg
• endothelin 1 levels are increased
• Incidence in patients with refractory ascites is high (15%)
• Right heart cath is most reliable method for diagnosis
A Right Atrial Pressure > 14mmHG is predictive for Pulmonary Hypertension


Figure 3  Positive and negative predictive values of right atrial pressure (RAP) for the presence of pulmonary hypertension in cirrhosis with refractory ascites in patients with and without portopulmonary hypertension (PPHTN).
Mortality Risk
(Krowka et al: Liver Transpl 2000;6:443-450.)

- Moderate pulmonary hypertension (MPAP < 35 mm Hg) poses no remarkable risk for transplant
- MPAP 35-50 mm Hg: 50% intra and postoperative mortality
- MPAP > 50 mmHg: mortality 100%. Recent data show that this may not be true (Starkel et al: Liver Transpl. 2002;8:382-8.
- ? Prostacycline or pulmonary vasodilator therapy
ARDS

- ARDS complicating liver failure has a 100% mortality
- Reluctance to transplant these very-high-risk patients
- However, in absence of sepsis or pneumonia successful outcome has been reported (Doyle et al: Transplantation. 1993;55:292-6)
Preoperative conditions that make the patient critically ill

• Organ dysfunction as a result of liver disease
  – ESRD
  – Increased intracranial pressure associated with acute fulminant failure
  – Stage 3 to 4 encephalopathy with increased intracranial pressure
  – Portopulmonary hypertension, i.e. more than moderate pulmonary hypertension
  – ARDS as a result of ESLD
Preoperative conditions that make the patient critically ill

- Diseases not related to liver disease
  - Coronary Artery Disease
  - Obstructive Cardiomyopathy,
  - Valvular Disease
  - Severe obstructive pulmonary disease
  - Severe restrictive pulmonary disease
**Coronary Artery Disease**

- Important impact on perioperative morbidity and mortality
- Dobutamine stress echocardiography is a poor predictor of major cardiac events. (Williams et al. Transplantation, 2001)
  - Study in 61 patients with cardiac risk factors who underwent liver transplantation, DSE was normal in 25, nondiagnostic in 34 because of inadequate heart rate response, and abnormal in two patients.
  - Major perioperative cardiac events occurred in eight patients, all with normal or nondiagnostic DSE studies.
  - Negative predictive value 86%

Use Coronary angiography in high risk patients
Intra-operative conditions that make the patient critically ill

- Sudden massive blood loss
- Intractable hypotension
- Intraoperative pulmonary edema
- Intraoperative pulmonary thromboembolism
- Severe hyperkalemia
Sudden massive blood loss

- Quickly leads to hypovolemia, low cardiac output, and hypotension.
- If uncorrected, this results in tissue hypoperfusion and ultimately a fatal outcome.
**Treatment Sudden Massive Blood Loss**

- Massive transfusion to normalize volume status
- Appropriate correction of acid-base state and ionized calcium concentrations are imperative
- Avoid over treatment with sodium bicarbonate because this can result in a large increase in sodium concentration and central pontine myelinolysis.
- Consider Tromethamine, instead of or in addition to sodium bicarbonate, because it does not contain sodium.
- Appropriate metabolic control requires frequent analysis of blood samples
- Correct coagulopathy
**Intractable Hypotension (1)**

- Patients with severe liver disease usually have a hyperdynamic circulation, with mild hypotension despite a significant increase in cardiac output caused by a significantly lower systemic vascular resistance and mild tachycardia.
- The cause of the low systemic vascular resistance is unclear, but abnormal prostaglandin and/or endothelin metabolism has a role.
Intractable Hypotension (2)

• Intraoperatively, hypotension may be the result of:
  – further reduction in systemic vascular resistance
  – a reduction in cardiac output
    • low preload (reduced venous return or hypovolemia)
      – placement of vascular clamps on major vessels (portal vein, inferior vena cava)
      – hemorrhage, third-space losses, and continued ascites production that are insufficiently corrected.
    • impaired cardiac performance
      – low ionized calcium concentrations in the plasma, a result of chelation of calcium by citrate present in blood products
      – Acidosis
Intractable Hypotension (3)

• Some patients with severe liver disease already have reduced myocardial contractility before the start of the liver transplant procedure, called cirrhotic cardiomyopathy.

• There is now sufficient evidence that factors as a decreased number of beta receptors, alterations in myocardial plasma membrane properties, and accumulation of myocardial depressant substances can affect cardiac function in these patients.

• However, cardiac dysfunction usually is masked by a reduction in afterload.
Intractable Hypotension (4)
Reperfusion of the graft:

- May be associated with significant hemodynamic instability, manifested by hypotension, bradycardia, and even sinus arrest.
- Factors such as hyperkalemia, acidosis, sudden hypothermia, and release of vasoactive substances from the grafted liver may all have a role in this postreperfusion syndrome.
- Occurs in 8-30%
Treatment Intraoperative Hypotension: Determined by the Cause

• invasive monitoring, including determination of cardiac output and filling pressures, is imperative
• filling pressures frequently are inaccurate in determining the volume status of the patient
• transesophageal echocardiography (TEE) may provide more useful information.
Treatment Intraoperative Hypotension

- normalization and optimization of the volume status
- If cardiac output remains low despite optimal volume status, inotropic agents have to be infused (e.g., dopamine, dobutamine, low-dose epinephrine)
- If blood pressure remains low despite improvement or normalization of cardiac output, inotropic agents with vasoconstrictive properties have to be added (e.g., greater doses of epinephrine, phenylephrine, vasopressin)
Pulmonary Edema

• Cardiogenic:
  – after graft reperfusion, in which there can be volume overload, and certainly when venovenous bypass is not used

• Non-cardiogenic:
  – Incidence is 0.73%, which is higher than incidence of transfusion related acute lung injury in other larger blood loss surgeries (0.075%-0.12%)
  – exact cause of the noncardiogenic pulmonary edema is unknown but probably combination of transfusion related acute lung injury together with reperfusion injury; Increased permeability pulmonary edema
  – Occurs after reperfusion
  – Resolves within 6 hours
Pulmonary edema
Treatment

• positive end-expiratory pressure and keeping the patient mildly hypovolemic while maintaining cardiac output with inotropic agents
Intraoperative Pulmonary Embolism

- Both thromboembolism and air embolism can occur
- If a significant part of the pulmonary vasculature is obstructed, this will lead to right ventricular failure, low cardiac output, and severe hemodynamic instability
- Usually immediately after graft reperfusion:
  - excessive activation of the coagulation system??
Intraoperative Pulmonary Embolism Treatment

- Vigorous CPR to break up the clot
- Support of right ventricular function by using inotropic agents.
Severe Hyperkalemia (1)

• Main cause seems to be massive transfusion, especially in the presence of renal failure or anuria
  – Stored red blood cells release potassium; therefore, the remaining plasma in the transfusion bag contains large amounts of potassium.
  – Red blood cells will take up this released potassium once transfused into a recipient and metabolically active
  – However, packed cells that are reaching their expiration may contain unviable red blood cells that will not become metabolically active again after transfusion.
Severe Hyperkalemia (2)

- Hyperkalemia may become critical at the moment of reperfusion when there is a sudden but short-lived increase in plasma potassium concentration because the grafted liver releases potassium on reperfusion, even after flushing the organ before the portal anastomosis is started.

- Severe hyperkalemia can result in cardiac conduction abnormalities and arrhythmias, potentially resulting in cardiac arrest.
Treatment Hyperkalemia

• Treatment of severe hyperkalemia includes calcium chloride, sodium bicarbonate, and epinephrine

• Prevention includes insulin-glucose administration and washing of packed red blood cells.
Piggy back and Conventional Technique
**Veno - Venous Bypass**

- When complete cross clamping of the vena cava is not tolerated
- To decompress Portal Hypertension and diminish bleeding
- Heparin coated tubing
- Maintain flows > 2L/min
- Does not prevent reperfusion syndrome
- Does not prevent renal function deterioration
- Complications:
  - Emboli, vascular damage, heat loss
In some patients, a temporary portacaval shunt can be performed prior to the heptectomy in the piggy-back technique in order to decrease blood loss and bowel congestion.
The effect of liver disease on the clearance of administered Anesthetics: The importance of the hepatic extraction ratio
Hepatic Clearance: importance of perfusion

- Hepatic blood clearance = $Q \times E$
- If hepatic extraction ratio is 1, elimination is only limited by liver blood flow: clearance is perfusion rate limited
- If hepatic extraction ratio is low, changes in blood flow do not affect clearance very much. Clearance is dependent on liver enzyme activity: Capacity Dependent Elimination
Hepatic Clearance:

- If hepatic extraction ratio is relatively low then enzyme activity is the rate limiting step. Drug clearance is being altered by liver disease.
- If hepatic extraction ratio is high, there is so much hepatocellular activity that modest changes in enzyme activity cause little or no change in clearance. All drug is extracted anyway. Drug clearance is not altered by liver disease.
## Extraction Ratio’s

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<thead>
<tr>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
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<tbody>
<tr>
<td>Propofol</td>
<td>Alfentanil</td>
<td>Thiopental</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Midazolam</td>
<td>Diazepam</td>
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<tr>
<td>Fentanyl</td>
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<td>Lorazepam</td>
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<td>Sufentanil</td>
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<td>Demerol</td>
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<tr>
<td>Ketamine</td>
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Anesthesia Plan

• Rapid Sequence Induction with Cricoid Pressure: Thiopental or etomidate and succinylcholine
• Maintenance with high dose fentanyl, midazolam, low dose isoflurane and vecuronium or pancuronium
• Larger bore IV access: at least two 9 French Catheters
• One or two rapid infusion systems (500 ml/min)
Vasopressors

- Dopamine, epinephrine, neosyneprhrine
- Vasopressin
Monitoring

• R Femoral arterial line plus R radial arterial line if redo transplant
• Pulmonary artery catheter via R internal jugular vein
• Transesophageal echocardiography
Transesophageal Echocardiography (TEE)

- Initially used reluctantly due to potential for damage to esophageal varices and bleeding, but this seems to be an unusual complication
- Provides additional information regarding preload and contractility
- Helps in diagnosis and management of emboli
- Helps in the management of cardiac disease, related or unrelated to hepatic disease
- Allows for the evaluation of major vessels such as anastomosis of upper vena cava
Figure 1. Transesophageal echocardiogram showing a large thrombus in the RA, attached to the tricuspid valve in patient 1. (RV, right ventricle; RA, right atrium.)
Living donor Liver Transplants
Living donor Liver Transplant in adult patients

• Is still an evolving procedure
• Donor suffers significant morbidity and mortality is ~ 0.3%
• Recipient mortality is higher in patients with advanced liver disease
• Biliary complications remain a major problem
• Results probably equivalent to deceased donor transplants
• Will be the major growth area in this field
LIVER REGENERATION FOLLOWING LDLT

n=31

Marcos et al: Transplantation, vol.69(7), April 2000, 1375-79
Cardiac output, SVR and Heart Rate increase significantly immediately after removal of the right lobe

<table>
<thead>
<tr>
<th>Table 2. Hemodynamic Characteristics of Donors</th>
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<tbody>
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<td>Hemoglobin (g/dL)</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Prehepatectomy</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Posthepatectomy</td>
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<td></td>
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</table>

NOTE. Values expressed as mean ± SD, median (range).
Abbreviations: HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; SVR, systemic vascular resistance; CVP, central venous pressure.
*Significantly different between the two groups, $P < .05$.
†Determined at the moment of marker injection.
‡Determined by CO divided by HR.

Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.
Pediatric Transplants

- 623 pediatric liver transplant in USA in 2001
- 167 in children < 1 year
- 8 in neonates
Transplantation in neonates presents unique medical and technical challenges

- **Neonates**
  - Patient survival 57%
  - Graft survival 38%

- **Infants 3-12 month**
  - Patient survival 82.1%
  - Graft survival 72.8%

- **Children 1-5 yrs**
  - Patient survival 84.1%
  - Graft survival 72.8%

- **Children > 6 yrs**
  - Patient survival 91%
  - Graft survival 82%