Liver / Intestine Transplantation Protocol

Recipient

<table>
<thead>
<tr>
<th>Transplant Team</th>
<th>Pager</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greg DEMBO</td>
<td>995-2181</td>
<td><a href="mailto:gdembo@u.washington.edu">gdembo@u.washington.edu</a></td>
</tr>
<tr>
<td>Ken MARTAY</td>
<td>680-0592</td>
<td><a href="mailto:kmartay@u.washington.edu">kmartay@u.washington.edu</a></td>
</tr>
<tr>
<td>Youri VATER</td>
<td>991-8596</td>
<td><a href="mailto:yvater@u.washington.edu">yvater@u.washington.edu</a></td>
</tr>
<tr>
<td>Alex VITIN</td>
<td>540-3202</td>
<td><a href="mailto:vitin@u.washington.edu">vitin@u.washington.edu</a></td>
</tr>
</tbody>
</table>

Intestine Transplantation (Recipient) CPT Code: 44135 (cadaver)
44136 (living)

Liver Transplantation (Recipient) CPT Code: 47135

This protocol is intended as a guideline only and may need modification according to the patient's condition, surgical protocol, and clinical studies in progress. Please check with the attending transplant anesthesiologist. For OR setup, please consult the laminated photo guidebook in OR-13 too.

General Information

In patients with intestinal failure (= inability maintain a sufficient nutritional, electrolyte and fluid balance for more than 1 month without TPN) secondary to Crohn’s disease, superior mesenteric artery or vein thrombosis, trauma etc, and end-stage liver disease, a combined liver/intestine transplantation is the only remedy. Because of long-term TPN infusions central venous access may be complicated by central vein thrombosis.

The patient will usually arrive in the holding area with an iv-line in situ. Please check the proper function of this line. Other lines can be placed in the OR under sterile conditions after induction of anesthesia. Sterility in transplant patients is paramount because infection is the main cause of postoperative death after solid organ transplantation in the immune-suppressed patient!
**OR set-up**

- Transplant anesthesia cart
- Orange liver transplant medication box

- Standard pre-filled syringe kit
  - Hydromorphone, 2 mg, 3 vials
  - Cisatracurium, 20 mg, 5 vials
  - Fentanyl, 1000 µg, 2 vials

- Calcium Chloride, 1000 mg, 10 ml syringe(s)
- Epinephrine, 10 µg/ml, 10 ml syringe
- Epinephrine, 100 µg/ml, 10 ml syringe
- Methylene Blue, 2 ampoules (do not open until required)
- NaHCO₃, 50 mmol, 50 ml syringe(s)
- Phenylephrine, 100 µg/ml, 10 ml syringe

- 2 Alaris 4-infusion-pumps + tubing
- 2 Alaris syringe pumps + tubing

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- Infusion solutions for Alaris infusion pumps:

<table>
<thead>
<tr>
<th>Infusion solution</th>
<th>Baseline infusion rate</th>
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<tr>
<td>Aminocaproic Acid, 3x20 ml vials.</td>
<td>Do not prepare infusion without consulting your Attending!</td>
</tr>
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<td>NACL, 1000 ml</td>
<td>50 ml/hour (carrier fluid)</td>
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</table>

  **For infusion dilute 5g in 250ml NACL bags = 20mg/ml solution**
  - Loading dose: 5 g over 1 hour, followed by
  - Maintenance dose: 1 g / hour until end of surgery

**Inotrope Infusions**

<table>
<thead>
<tr>
<th>Name</th>
<th>Solution</th>
<th>Baseline Infusion Rate Setting</th>
<th>Minimum – Maximum dose (µg/kg/min)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>400 mg in 250 ml D5W</td>
<td>3.0 µg/kg/min</td>
<td>1.0 – 20.0*</td>
<td>Infuse throughout surgery</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>5 mg in 250 ml D5W</td>
<td>0.01 µg/kg/min</td>
<td>0.05 – 0.5*</td>
<td>Infuse if required</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>50 mg in 250 ml D5W</td>
<td>0.1 µg/kg/min</td>
<td>0.1 – 1.0*</td>
<td>Infuse if required</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>50 mg in 250 ml D5W</td>
<td>0.1 µg/kg/min</td>
<td>0.05 – 1.0*</td>
<td>Infuse if required</td>
</tr>
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</table>

* clinical situations may require deviations from the recommended minimum – maximum doses!
Liver/Intestine Transplantation Protocol - Recipient

- **Infusion solutions for Alaris syringe pumps:**
  
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<td>Cisatracurium, 40 mg, 20 ml syringe</td>
<td>0.8 – 1.0 µg/kg/min</td>
</tr>
<tr>
<td>Fentanyl, 1000 µg, 20 ml syringe</td>
<td>1.0 – 5.0 µg/kg/hr</td>
</tr>
</tbody>
</table>

- **Blood products:** 1000 ml 5% Albumin in OR; 10 units packed cells, 10 units unthawed FFP, 2 units unthawed Cryoprecipitate should be available in house for the patient.
- **Plasmalyte** is the preferred crystalloid i.v.-solution. The failing liver is inefficient in metabolizing lactate.
- **Mannitol 20%,** 1000 ml (see protocol for details).

### Preoperative patient management in the holding area

The patient preparation for a liver transplantation requires about 2 hours. When the patient has arrived in the holding area check for signs of encephalopathy: decreased alertness, poor concentration, drowsiness, lethargy, sleepiness, degree of rousability.

If the patient shows no signs of encephalopathy, give **Midazolam, 2 mg, i.v.**, to lower anxiety, and apply oxygen by nasal prongs or mask, and a pulse oximeter. Start antibiotics to give the patient an additional cover for the insertion of lines in the holding area and in the OR.

The patient may arrive in the holding area with the following medication:

- **Thymoglobulin (ATG), 1.5 mg/kg, iv;** start infusion in OR 1 hour after steroid premedications given. Infuse over 12 hours.
- **Acetaminophen, 650 mg, po/pring** (if not already given on the floor)
- **Diphenhydramine, 50 mg, iv** (if not already given on the floor)
- **Methylprednisolone, 1000 mg, iv** (if not already given on the floor). Ask surgeon for right timing.
- **Ampicillin/sulbactam, 3gm (or other antibiotic);** start infusion in holding area
- **Fluconazole 400mg iv**
- **Hepatitis-B Immune Globulin, 10,000 units, iv**: Patients with Hepatitis-B positive HB surface antigen) may receive Hepatitis-B immune globulin. Spike the bottle first after the surgeon has inspected the patients internal organs and decided to go ahead with the liver transplant. Start infusion when patient is anhepatic, and infuse over 4-6 hours.

<table>
<thead>
<tr>
<th>Basiliximab</th>
<th>Hepatitis-B immune globulin</th>
<th>Methylprednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Immune suppressant</td>
<td>Antibodies</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity to drug</td>
<td>Hypersensitivity to immune globulins</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Dyspnea</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Dysuria</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>
Insert under sterile conditions 1 or 2 arterial lines (preferably right and/or left radial artery). If two arterial lines, one line is for monitoring, and one for blood sampling.

**Preoperative patient management in OR**

Patients for combined liver / intestinal transplants are usually on long-term TPN so that nil-by-mouth time shouldn’t be an issue. Patients with liver failure often have ascites which can increase abdominal pressure, so that induction of anesthesia should be performed with (modified) rapid sequence induction and with cricoid pressure.

After the patient is asleep insert:

- 1 Triple-Cordis line + PA catheter preferably into the right internal jugular vein. Use SonoSite because patients on long-term TPN infusions may have developed venous thrombosis!

After all lines have been placed, connect:

- the Belmont infusor to the 9 Fr port of the Triple-Cordis line
- the hotline to the 12 G port of the Triple Cordis line
- the infusion pumps to the PA-line
- Check proper position of the Swan-Ganz catheter through chest-x-ray!

Draw baseline arterial blood gas sample (blood gas syringe) and ThrombElastoGraph (TEG) blood sample (blue topped vial & lavender topped vial).

- Insertion of naso-gastric tube. Apply vasoconstrictive nasal spray (in orange transplant box) to nose before naso-gastric tube is inserted!
- TEE machine in OR for patient assessment

**Intraoperative patient management**

**Removal of the recipient's liver and intestine (dissection stage)**

Removal of the recipient’s liver and intestine can take many hours.

**Anhepatic stage**

During the anhepatic phase of the operation the patient, the diseased liver will be removed. Shortly before test clamping optimize the patient’s preload, and check laboratory data.

- **Hepatitis-B Immunoglobulin, 10,000 units, iv**: If the recipient has Hepatitis-B (+ primary hepatocellular carcinoma) he/she may receive Hepatitis-B immunoglobulin. Spike the bottle first after the surgeon has inspected the patients internal organs and decided to go ahead with the liver transplant. Start infusion when patient is anhepatic, and infuse over 4-6 hours.

**Recirculation stage**

About 15-20 minutes prior to recirculation of the liver / intestine graft, infuse Mannitol 20%, 1g/kg bolus (rate: ~ 50 ml/hr), and correct pH, base excess with bicarbonate, calcium, and hyperventilate. At the moment of recirculation of the liver graft, start infusion of Mannitol 20%, 1g/kg over 1-hour duration. After recirculation of the liver graft there may be a period of hemodynamic instability, due to circulating oxygen free radicals and the release and accumulation of cytokines (**reperfusion injury**; MAP < 30% of baseline MAP for 1-5 minutes after reperfusion; **reperfusion syndrome**; MAP < 30% of baseline MAP for > 5 minutes after reperfusion). Support patient with vasoactive agents (preferred drug: **Dopamine**), if
necessary. Aim for CVP = 12-14 mmHg because too little fluid load can impair the intestinal graft’s perfusion, while fluid overload may cause mucosal edema in the intestinal graft that can impede the grafts anastomoses. If Mannitol alone will not prevent fluid overload, give Furosemide boluses. Check blood gases and TEG as required and correct acidosis and coagulopathy.

**Postoperative patient management**

After surgery has finished, the patient usually stays intubated and ventilated, and will be directly transferred to ICU.

**Insulin infusion protocol**

Start insulin infusion according to algorithm to keep serum glucose levels 70-100 mg/dl. If despite insulin infusion, serum glucose levels are > 300 mg/dl, give additional insulin boluses until serum glucose levels are 200 mg/dl or less.

**Insulin infusion**: 100 ml NACL with Humulin (regular human insulin), 100 units ->

\[
\text{Concentration of solution} : 1 \text{ unit / ml}
\]

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dl)</th>
<th>Insulin Infusion Rate (units/hr)</th>
<th>IV-Infusion Rate (ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>70 – 109</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>110 – 119</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>120 – 149</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>150 – 179</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>180 – 209</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>210 – 239</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>240 – 269</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>270 – 299</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>300 – 329</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>330 – 559</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>&gt; 360</td>
<td>12.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>
Protocol
for high intracranial pressure (ICP) management
in patients with fulminant hepatic failure

CPP = MAP – ICP

CPP = Cerebral Perfusion Pressure
MAP = Mean Arterial Pressure
ICP = Intracranial Pressure

Airway:
- Deep induction and paralysis, good mask ventilation, avoid cough during laryngoscopy.
- Keep neck straight and avoid pressure on jugular veins.
- Head in 15-30° elevation, but avoid excessive head elevation (up to 60°) in hypotensive patients because this may cause reduction in cardiac index and increase in cerebral perfusion pressure due to decreased drainage of CSF from foramen magnum.
- Secure endotracheal tube with tape, and avoid tourniquet around the patient’s neck.
- Patients with hepatic coma grade 3+4 should be intubated in ICU.

Breathing:
- Tidal volume 8-10 cc/kg, avoid high inspiratory pressures, use CMV mode.
- Avoid PEEP (increases intracranial pressure through decreasing intracerebral venous return).
- Always check for bilateral breath sounds, avoid one lung ventilation.
- Avoid hypoxia and hypercapnia. High PaCO₂ and low PaO₂ increase cerebral blood flow.
- Maintain moderate hyperventilation (PaCO₂ = 30-35 mmHg). Low PaCO₂ (alkalosis) produces arteriolar constriction, hypoperfusion and cerebral ischemia.
- Quick transition from low PaCO₂ to normal PaCO₂ may increase cerebral blood flow and cause cerebral edema postoperatively.

Circulation:
- Maintain mean arterial pressure (MAP) >70 mmHg and cerebral perfusion pressure (CPP) > 50 mmHg.
- Keep oxygen carrying capacity high (CaO₂ = Hb x 1.34 x SaO₂ + 0.0031 x PaO₂).
- Balanced fluid management, treat coagulopathy, and maintain colloid osmotic pressure.
- Control blood glucose level. Hyperglycemia is a contributing factor to neurological damage in the presence of cerebral ischemia.
Liver/Intestine Transplantation Protocol – Recipient

Anesthesia:

- Proceed cautiously with venous access through right internal jugular vein, because head rotation as well as hematoma and venous occlusion through large-bore catheter may cause intracranial pressure elevation. Subclavian venous access may be an alternative. Discuss with surgeons!
- For placement of ventriculostomy or CSF lumbar drainage – check coagulation status and discuss with surgeons!

- Use induction agents that reduce intracranial pressure: thiopental (3-5 mg/kg), propofol (2-4 mg/kg), etomidate (0.3 mg/kg), lidocaine (1.5 mg/kg) and assist ventilation to reduce PaCO₂.
- Avoid awake intubation if the airway doesn’t appear difficult.
- Non-depolarizing muscle relaxants are preferable, because fasciculations may increase intracranial pressure. However, if use of a depolarizing muscle relaxant is indicated, pretreat with non-depolarizing muscle relaxant to avoid fasciculations.
- Intubation outside the OR should be done under anesthesia.
- Maintenance of anesthesia: thiopental (1-4 mg/kg/hr) or propofol (4 mg/kg/hr), and opioid (Fentanyl 2-5 µg/kg/hr) infusion titrated according to blood pressure: reduces intracranial pressure and seizure activity.
- Patients with end-stage liver disease and fulminant hepatic failure have low SVR. Use barbiturates carefully in order to avoid hypotension.
- Etomidate (0.3 mg/kg) is a good agent for induction. Continuous infusion resulting in a high total dose may cause adrenal suppression that should be treated by steroids.
- Avoid isoflurane because it raises intracranial pressure and provides little cerebral protection.
- Mannitol may help to prevent ischemic brain injury through reduction of intracranial pressure. Dosage of mannitol: 0.25-2.0 g/kg. The higher the dosage the quicker the onset of action. Lower dosages are effective as well and have less side effects (severe hyperosmolarity, hemolysis, rhabdomyosis, renal failure, rebound increased intracranial pressure). Mannitol 0.25 mg/kg is recommended as initial dose. Control serum osmolarity. Mannitol is indicated if osmolarity < 310 mosm/l.
- Loop diuretic furosemide 0.5-1.0 mg/kg.
- Steroids (decadron) 1mg/kg/day in divided dose (only for patients with vasogenic edema surrounding tumors, abscesses, and organized hematomas).
- Hyperthermia is a common complication in patients with increased intracranial pressure. Intermittent use of cisatracurium 0.2mg/kg/dose may aid in decreasing body temperature. Antipyretics and cooling blankets are contraindicated because they may cause shivering in unparalyzed patients which could potentially worsen hyperthermia.

ICP:

- Intracranial pressure monitoring allows rapid therapeutic response to cerebral edema and elevated intracranial pressures (ICP).
- The ICP should be maintained at < 20 mmHg.
- ICP > 40 mmHg is associated with poor neurological outcome post liver transplantation
- Keep cerebral perfusion pressure (CPP) > 50 mmHg to avoid cerebral ischemia.
- A cerebral perfusion pressure < 40 mmHg lasting for more than two hours is a contraindication for an urgent liver transplantation. Discuss with surgeons!
- Graft reperfusion can cause profound vasodilation accompanied by severe increase in intracranial pressure: maintain cerebral perfusion pressure (CPP) > 50 mmHg with inotrops, hyperventilation, mannitol, thiopental / propofol, lidocain infusion, head up position and CSF drainage (if ventriculostomy or lumbar drain are present).
- Cerebral edema is the leading cause of death in patients with fulminant hepatic failure that occurs in 75% of patients with stage-4 hepatic encephalopathy.
- Traditional clinical signs of elevated intracranial pressure – bradycardia, hypertension, rigidity, abnormal papillary reflexes – are unreliable in patients with fulminant hepatic failure!
Liver/Intestine Transplantation Protocol

Recipient

FLOW CHART

OR set-up

___ Transplant anesthesia cart in OR
___ Orange liver transplant medication box in OR

___ Cisatracurium, 20 mg, 5 vials
___ Fentanyl, 1000 µg, 2 vials
___ Standard OR-syringe kit

___ Calcium Chloride, 1000 mg, 10 ml syringe(s) prepared
___ Epinephrine, 10 µg/ml, 10 ml syringe prepared
___ Epinephrine, 100 µg/ml, 10 ml syringe prepared
___ Methylene Blue, 2 ampules (do not open until required)
___ NaHCO₃, 50 mmol, 50 ml syringe(s) prepared
___ Phenylephrine, 100 µg/ml, 10 ml syringe prepared

___ 2 Alaris 4-infusion-pumps + tubing
___ 2 Alaris syringe pumps + tubing

• Intracranial pressure monitoring options are: epidural catheter, subdural bolt, parenchymal monitors, and intraventricular catheters.
• In patients with fulminant hepatic failure, epidural transducers may be the safest way for intracerebral pressure monitoring.
**OR set-up, cont.**

**Infusion solutions for Alaris infusion pumps:**

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<tbody>
<tr>
<td>Aminocaproic Acid, 3x20 ml vials</td>
<td></td>
</tr>
<tr>
<td>Spike only if liver transplant is confirmed to go ahead! For infusion dilute 5g in 250ml NACL bags = 20mg/ml solution</td>
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</tr>
<tr>
<td>Loading dose: 5 g over 1 hour, followed by Maintenance dose: 1 g / hour until end of surgery</td>
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<tr>
<td>NACL, 1000 ml</td>
<td>50 ml/hour</td>
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<tr>
<td>Mannitol 20%, 1000 ml</td>
<td>(carrier fluid)</td>
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**Inotrope Infusions**

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**Infusion solutions for Protégé 3010 infusion pumps:**

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**Blood products:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 ml 5% Albumin in OR</td>
<td></td>
</tr>
<tr>
<td>10 units packed cells in house</td>
<td></td>
</tr>
<tr>
<td>10 units unthawed FFP in house</td>
<td></td>
</tr>
</tbody>
</table>
2 units unthawed Cryoprecipitate in house

**Preoperative patient management in the holding area**

- Ampicillin/sulbactam, 3gm (or other antibiotic); start infusion in holding area!
- Fluconazole 400mg iv
- Midazolam, 2 mg, iv, given
- 1 or 2 arterial lines (preferably right and/or left radial artery) inserted

**Preoperative patient management in OR**

After the patient has been put to sleep:

- Triple-Cordis line + PA catheter in preferably right internal jugular vein inserted. Use Site Rite because patients on long-term TPN infusions may have developed venous thrombosis.
- Check proper position of the Swan-Ganz catheter through chest-x-ray!

After all lines have been placed:

- Belmont infusor connected to 9 Fr port of the Triple-Cordis line
- Hotline connected to the 12 G port of the Triple Cordis line
- Infusion pumps connected to the PA-line
- Methylprednisolone, 1000 mg, i.v., given after induction of anesthesia (if not already given on the floor)
- Baseline arterial blood gas sample (blood gas syringe) and
- ThromboElastoGraph (TEG) blood sample (blue topped vial & lavender topped vial) taken, accompanying forms completed (see laminated sample forms in OR) and all sent to lab.

**Intraoperative patient management**

- 5 blue topped vials labeled
- 5 lavender topped vials labeled
- 5 ThromboElastoGraph (TEG) forms prepared (see laminated sample forms in OR-13)
- 5 blood gas forms prepared (see laminated sample forms in OR-13)
- Hepatitis-B Immunoglobulin, 10,000 units, iv: Spike the bottle first after the surgeon has inspected the patients internal organs and decided to go ahead with the liver transplant. Start infusion when patient is anhepatic and infuse over 4-6 hours.