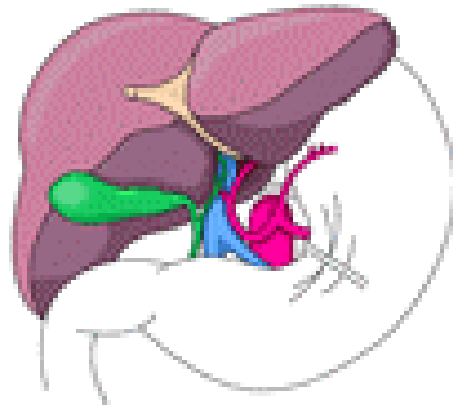


LIVER ROTATION MANUAL



Welcome to the Liver Transplant rotation. UCLA is one of the largest liver transplant services in the country, performing in excess of 200 liver transplants per year. We transplant both adult and pediatric patients, with recipients <18 years of age accounting for about 21% of our patients.(1) Although the vast majority of our transplant organs are cadaveric, UCLA maintains a living donor liver transplantation (LDLT) program for both adult-to-adult and adult-to-child donations. Additionally, the small bowel transplantation program operates under the purview of the liver transplantation program. Small bowel transplantation is frequently paired with liver transplantation because chronic TPN can result in cirrhosis.

Of the adult patients that we transplant, the largest group (37%) presents with Hepatitis C cirrhosis. In the pediatric population, the largest diagnostic group is biliary atresia (47%). One-year patient survival for primary transplant is 81% for adults and 82% for children.(1)

This handout contains a suggested set-up, a description of the surgical procedure, and discusses the attendant anesthetic considerations for liver transplantation. There are additional sections covering some of the procedures that are common on, but unique to, this service.

The pharmacy provides a compartmented red box for each case that contains drugs not on the anesthetic cart, but that we frequently find necessary. We share this box with the OR nurses, who will usually take what they need (contrast, antibiotics, etc.) and then give us the box.

Contents of the red box

Unasyn 3 gm. (1)
7.5% Sodium bicarbonate 50 cc (2)
10% Calcium chloride 10 cc (10)
25% Mannitol 50 cc (2)
Amicar 5 gm/20 cc (4)
Tranexamic acid 1 gm/10 cc (1)
Hydrocortisone 500 mg/5 cc (2)
Insulin 100U/cc (1)

Set up

One blood pump w/ fluid warmer
One syringe pump w/carrier fluid for infusions

Drawn up

Induction agent

Neuromuscular blocker

Narcotics (high-dose pack from pharmacy)

1% Lidocaine

Sodium bicarbonate

Calcium chloride

Epinephrine 10 mcg and 100 mcg/cc concentrations

Phenylephrine 100 mcg/cc

Atropine

Available/stocked

Heparinized lab syringes (8)

Appropriate collection tubes for lab tests: blue and purple-topped tubes

2-3 Syringe pumps

3 Blood component administration sets (filtered)

Needleless- system adapters

Pre-op evaluation

The current philosophy of organ allocation for liver transplantation gives priority to the sickest patients. This is determined by a continuous, lab-result-based index called the Model for End-Stage Liver Disease (MELD) score.(2) Although there are some exceptions made, notably in the case of hepatocellular carcinoma, this allows stratification of patients based on fairly objective criteria. MELD was developed by the Mayo Clinic as a means to predict short-term (3 month) survival of end-stage liver disease patients undergoing TIPS (trans-jugular, intra-hepatic, porto-systemic shunt) procedures(2). It is calculated as:

$$0.957 \ln(\text{creatinine mg/dl}) + 0.378 \ln(\text{bilirubin mg/dl}) + 1.12 \ln(\text{INR})$$

Although not perfect – the MELD score can be transiently increased by acute events such as SBP, bleeding, etc., and may be artificially elevated by intrinsic renal disease - it has since been validated as a predictor of 3-month survival in patients with chronic liver disease of various etiologies and severity(3). It has also been shown to predict post-transplant mortality.(4)

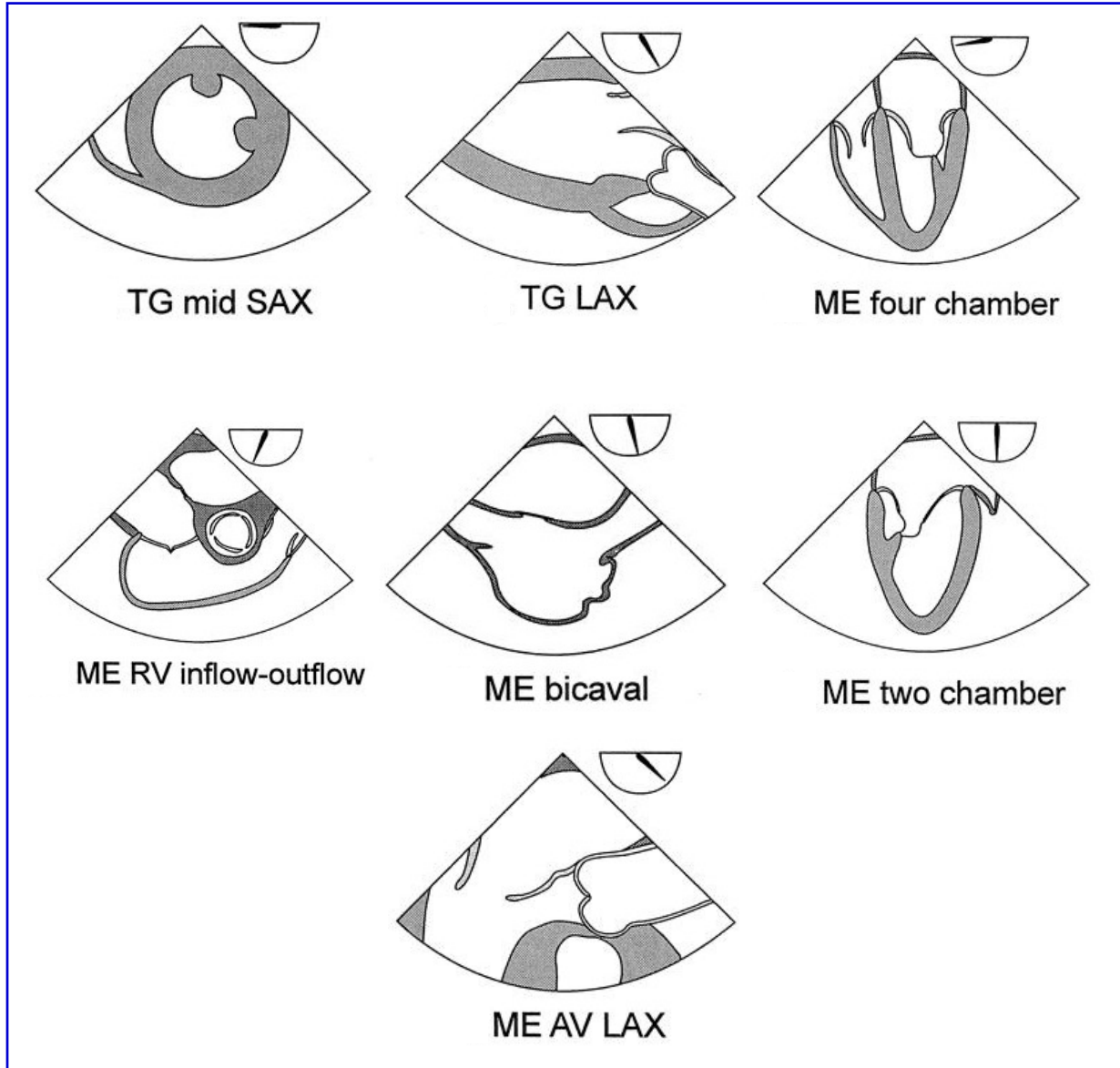
Determining the MELD score at which transplantation becomes worthwhile because it increases the patient's expected lifespan is relatively straightforward. One year mortality post-transplant exceeds mortality on the waiting list for patients with MELD scores < 15.(5)

Determining which patients are too sick for transplant is less clear and more controversial. Need for poly-pressor/inotrope therapy, high FiO₂ (>60%), evidence of severe neurologic pathology, and sepsis with concomitant SIRS and/or DIC, are indications that the patient is a poor transplant candidate and consideration be given to removing him/her from the waiting list.

The pre-operative condition of our recipients varies widely. Some come from home, called when an organ becomes available. Some are in the ICU, ventilated, on renal replacement therapy and pressors. There are some co-morbidities which should be highlighted if present because they dictate a change in management. These include evidence for ↑ ICP, cardiac disease, hepatopulmonary syndrome, and pulmonary hypertension. In some cases, notably with pulmonary hypertension, they may overshadow the underlying liver disease for risk of peri-operative complications.

Standard access includes a cordis for Swan-Ganz catheter placement, and adequate venous access for the rapid infuser. This may be done by placing two 9 Fr cordises or by placing a single 12 Fr MAC. At least one (and sometimes two) arterial line (s) is/are also placed. The TEE is used frequently. Placement of it should follow NGT positioning, as the reverse order makes NGT passage difficult. We do place the TEE in patients with known esophageal and gastric varices. However, consideration must be given to the risks vs. benefits, especially in those patients who have undergone recent therapy for variceal bleeding. Additionally, care must be taken not to manipulate the probe in and out of the transgastric view with the probe anteflexed. See Fig.1 for views that are particularly useful in our patients, and a suggested order of obtaining them.

Figure 1



From ASE/SCA Guidelines for Performing a Comprehensive Intraoperative Multiplane Transesophageal Echocardiography Examination, Anesth Anal 1999,89:870-84

Starting the case

For a number of reasons, all patients are considered to have full stomachs and are induced and intubated using cricoid pressure. Invasive monitoring is generally not placed prior to induction. Patients who are seriously ill usually come to the OR from the ICU with monitors already in place.

Once the patient is asleep he is maintained on some combination of narcotics and isoflurane. Nitrous oxide is avoided both because of its effect on the bowels and because of the possibility of air embolism associated with veno-venous by-pass and reperfusion of the graft.(6,7,8) Patients with acute liver disease and advanced coma should be anesthetized without cerebral vasodilators (see discussion of fulminant hepatic failure under “Special Considerations”).

Veno-venous bypass (VVB) is used in some of our adult cases, both to decompress the splanchnic circulation and to compensate for caval cross-clamp. Unless the patient has had previous manipulation of the vessels (e.g. peritoneovenous shunt or Hickman catheter placement) cutdowns for VVB in the patient undergoing a primary liver transplant are usually done over the left axillary and left iliac veins. This means that the left subclavian and the left upper extremity are not available for venous access. If the patient is re-transplanted soon after the primary transplant (within a couple of weeks), the cutdown sites are frequently re-used. Otherwise, in later re-dos, the cutdown sites are reversed to the right side.

The blood bank should be called as early as possible to order blood products. The standard set-up for adult patients is 10 U each of FFP and PRBCs. A decision to keep ahead a certain number of units (usually 5 or 10) on either product may be made or revised at any time. Platelets and cryoprecipitate are not automatically set up for each case and are ordered as needed. Please note that platelets and cryoprecipitate should not be placed in the rapid infuser because they will form clot.

Patient warming measures should be instituted as early as possible. All fluids should be warmed and the breathing circuit humidified. The nurses usually place the lower-body warming blanket and connect and turn on the Bair Hugger. However, you should check to see that this is done. The temperature control should be turned on high. If bypass is not used, the upper body Bair Hugger may be used as well.

If VVB is employed, an in-line heater may be used to efficiently gain lost ground on the temperature. For pediatric patients and adults done without bypass, trying to warm up a cold

patient is particularly tedious and best to be avoided by early attention to temperature maintenance. Prior to line placement is not too early, since a patient can easily lose 2 to 3 degrees during a difficult establishment of monitoring lines.

Labs should be drawn when the arterial line is established, and in the hourly range thereafter. They may be drawn more frequently if there is clinical instability e.g. with large blood replacement, post-reperfusion, or with metabolic/electrolyte instability such as in fulminant hepatic failure or renal failure.

A well-placed and working NG tube is a must. The fear of initiating variceal bleeding is largely unfounded(9) and is in any case overshadowed by the need to keep the stomach decompressed for surgical exposure. The tube should be suctioned frequently, but not constantly, to avoid traumatizing already fragile gastric mucosa. Significant GI bleeding requires active lavage to prevent clot formation that interferes with drainage, and may even necessitate switching from and NG to an Ewald tube. If GI bleeding begins during bypass or on cross-clamp, it will generally improve after reperfusion. Consideration should be given to calling a GI consultant for significant bleeding that starts before the anhepatic phase, or that continues into the neohepatic phase. Nasal and pharyngeal bleeds are common with NG placement and are not trivial in this patient population. This mandates careful technique, lubrication, and vasoconstriction. Care should also be given to the method of NG tube fixation, avoiding tight taping against the alae, as this may lead to ulceration over time.

Unless you are furiously trying to keep up with blood replacement in a difficult dissection, the preanhepatic phase is a “housekeeping” period. The goals are to: 1) optimize the patient’s hemodynamic/volume status, 2) find and correct (if necessary) electrolyte and metabolic abnormalities, and 3) find and correct hemostatic abnormalities. This is your opportunity to “spiff” your patient.

Significant electrolyte abnormalities occur frequently in end-stage liver disease. They may present as a consequence of underlying disease and previous therapy, or they may appear as a result of blood and fluid therapy intra-operatively. The electrolytes that most commonly get our attention are Na⁺, K⁺, Ca⁺⁺, and Mg⁺⁺.

Sodium

The hallmark effect of cirrhosis on renal function is avid salt and water retention. Cirrhotics have elevated levels of aldosterone and ADH, both of which lead to hyponatremia. This, coupled

with the fact that many of these patients are on diuretics but not fluid restriction, can easily set the stage for severe hyponatremia.

Particularly in the setting of liver disease, large acute increases in serum sodium are associated with central pontine myelinolysis, a devastating neurologic complication.(10,11) Correction of serum sodium should ideally be made before surgery using the most reasonably conservative means. If this is not possible, limitation of the perioperative increase in sodium is important. Although the data is far from satisfying, a 1989 study of liver transplant patients suggests an allowable increase of up to 16 meq/L over an 8-day perioperative period.(12) FFP is an obligate source of sodium via sodium citrate, and is probably our biggest source of exogenous sodium. However, one may choose to avoid NS in IVs, using LR, Plasmalyte, or ½ NS instead. Furthermore, “salt-poor” 25% albumin may be used instead of 5% albumin, and THAM, a non-sodium buffer, instead of sodium bicarbonate, to treat acidosis. One may mix one’s own 5% albumin by adding one 50 cc bottle of 25% albumin to 200 cc of any diluent one chooses.

Potassium

The combination of gastrointestinal losses, poor nutrition, and diuretics are the most common causes of hypokalemia in the cirrhotic patient. Less common causes include hyperaldosteronism and renal tubular acidosis (particularly in autoimmune disease). Although this is rarely a problem in adults, it not infrequently needs to be addressed in the pediatric population.(13) In general, the tendency is to avoid repletion until after reperfusion. Then it may be done as an infusion at 0.3 meq/kg/hr.

Conversely, hyperkalemia is not uncommon in the adult population and rarely seen in children. Banked blood is the main source of exogenous K+ intra-op, and it is most often in the setting of massive blood loss and replacement that we encounter trouble with hyperkalemia in kids. There is currently a Blood Bank protocol to reduce the K+ load in PRBC units for pediatric patients in whom massive blood loss is anticipated. This is done by centrifuging off plasma and re-suspending the cells in NS.

Hyperkalemia in the adult population is most commonly encountered in the patient with hepatorenal syndrome (HRS). While it is not a given in every patient with HRS, problems with hyperkalemia should always be anticipated because most therapeutic options take time. These are:

Insulin/glucose

Diuresis

Sodium bicarbonate/calcium chloride

Dialysis/CVVH

Of these, only $\text{HCO}_3^-/\text{CaCl}_2$ is useful in the acute setting (e.g. EKG abnormalities on reperfusion) along with an increase in ventilation. The most commonly used modalities are diuresis, insulin/glucose therapy, and dialysis. Insulin/glucose may be given in a ratio of 2 gm glucose per unit of insulin. This is roughly the 10U insulin/one 50 cc amp D50 dose with which you are familiar. Setting up dialysis requires obtaining access (done by the surgeons) and paging the renal fellow on call. It will be no less than 1 hour before the dialysis nurse arrives, so dialysis should be considered sooner rather than later.

Calcium

The ailing liver is unable to adequately metabolize the citrate anticoagulant present in banked blood products. Because citrate binds calcium, expect to administer supplemental calcium. This may be done by infusion, bolus, or both. Products with the largest amounts of citrate are FFP and platelets, so calcium replacement moves in tandem with their administration. As a general rule of thumb, count of giving at least 3 gm. of CaCl_2 for every 10U of FFP administered.

Magnesium

Magnesium has received an increasing amount of attention, particularly in the settings of acute myocardial ischemia and critical care. Liver transplant patients have several reasons for hypomagnesemia including nutritional deficiency, diuretic-induced loss, and GI losses.

Mg^{++} is an obligate co-factor in all enzymatic reactions involving ATP. However, like potassium, the vast majority of it is sequestered in tissue. Thus although low plasma levels are indicative of Mg^{++} deficiency, normal levels are no guarantee of adequate body stores.

Cardiac manifestations appear as EKG waveform abnormalities and dysrhythmias. The EKG may show prolonged PR and QT intervals, a widened QRS, or U waves. Ventricular dysrhythmias are more common than atrial dysrhythmias, and digoxin toxicity is potentiated by magnesium deficiency.

Whether Mg^{++} levels drop to clinically significant levels during OLTx is controversial. The assumption is that Mg^{++} binds to citrate in the same fashion as Ca^{++} , and there is reason to worry. Studies measuring serial Mg^{++} levels during OLTx have yielded mixed

results.(14,15,16) Nonetheless, low baseline Mg⁺⁺ levels should be treated. Furthermore, dysrhythmias due to hypomagnesemia tend to be resistant to conventional therapy. The empiric use of Mg⁺⁺ in this setting should be considered. In an emergency situation, a dose of MgSO₄ 2gm IV (16 meq) over 5 minutes may be given. A repeat dose may be given in 10 minutes if no clinical effect is observed.

Renal protection

Effective protection of the kidneys in liver transplantation is an area of controversy. Renal function is frequently compromised preoperatively in patients, most often due to hepato-renal syndrome (HRS). Potential further intra-operative insults include hemodynamic instability with prolonged hypotension, and caval cross-clamp. Although the pathophysiology of HRS is different from that of aortic cross-clamp or CPB, common pharmacologic protective strategies such as PGE₁(17), dopamine(18), and mannitol(19) have similarly failed to show benefit. Fenoldopam, a selective DA-1 agonist, has its proponents despite a paucity of literature(20). VVB has also failed to modify post-operative renal impairment, although it continues to be useful in maintaining hemodynamic stability during caval cross-clamp.(21,22)

Recently, an interesting approach has been to treat the pre-existing HRS. Current thinking is that HRS is the end-product of splanchnic vasodilation in response to portal hypertension.(23) Splanchnic vasodilation results in arterial underfilling and hypotension despite total body volume overload. The renal response to this state of affairs is renal vasoconstriction and the activation of the renin-angiotensin-aldosterone system. Instead of trying to reverse the renal vasoconstriction with renal vasodilators (old thinking), recent therapy targets the splanchnic vasodilation. Studies using splanchnic vasoconstrictors such as terlipressin (IM) and vasopressin have shown improvement in renal function in HRS.(24,25)

Anti-fibrinolytics

There are two classes of anti-fibrinolytic drugs in clinical use for liver transplantation. These are the lysine analogues (epsilon-aminocaproic acid and tranexamic acid), and a non-specific, but somewhat selective, serine protease inhibitor (aprotinin).

Lysine analogues compete with fibrin and fibrinogen for the lysine-binding sites on plasminogen, blocking its enzymatic activity on its usual substrate (fig.2). Aprotinin is a direct inhibitor of plasmin, among other serine protease enzymes such as kallikrein and activated Protein C. Because of its broad spectrum of activity, it is also associated with inhibition of the contact activation pathway (with prolongation of the PTT), inhibition of platelet PAR1 activation (preventing thrombin-modulated platelet aggregation)(26), and attenuation of the inflammatory response(27). This last property may be responsible for the observed decrease in vasoactive drugs needed with reperfusion in liver transplantation(28,29).

It should always be kept in mind that hemostasis is a matter of balance between the forces that promote clot and those that limit clot, and that liver disease affects both sides of the balance. Although most of our patients do clinically exhibit a bleeding diathesis, abnormal conventional coagulation studies (PT, PTT, fibrinogen, platelet count), which test only the pro-coagulant system, are no guarantee of this because

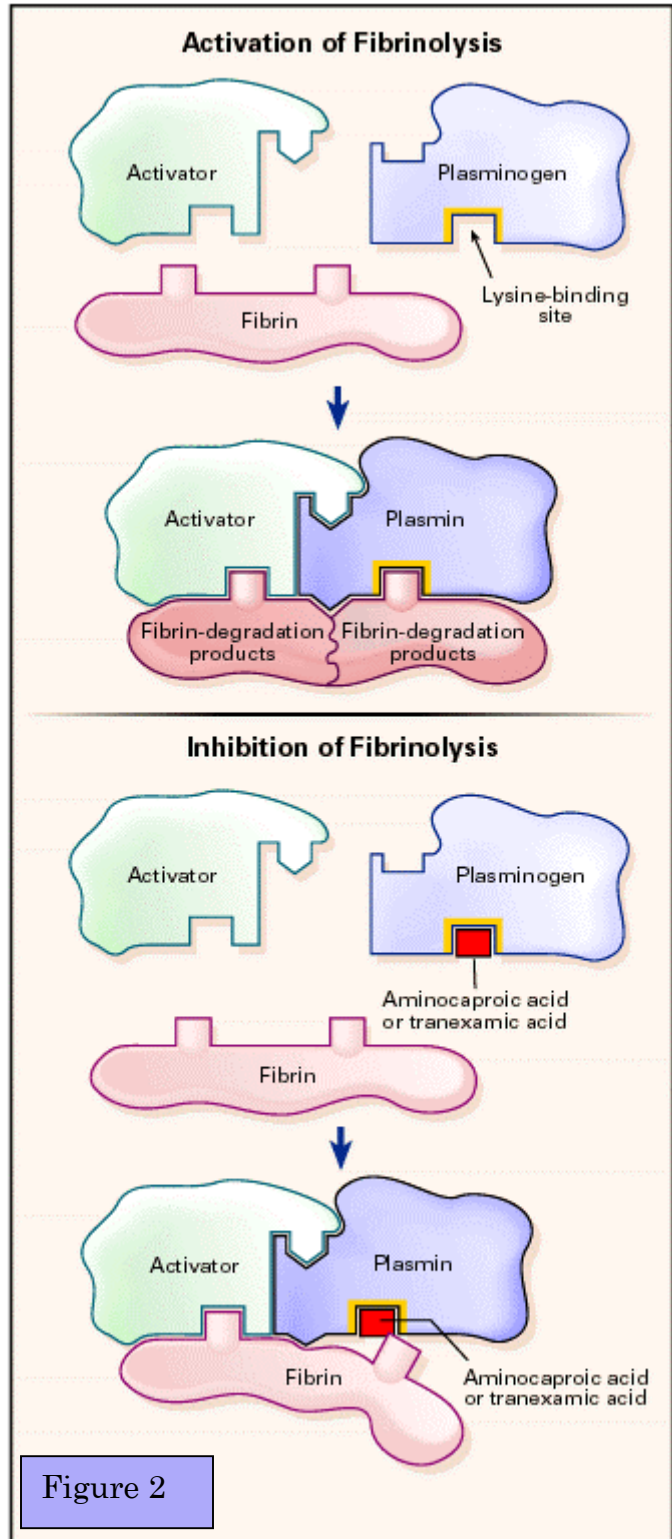


Figure 2

Mannucci, PM, Hemostatic Drugs, NEJM, Vol 339;4:245.

they give no indication of the function of the anti-coagulant system. Thus, although our patients usually exhibit a bleeding diathesis, a more profound defect in anticoagulant forces than in procoagulant forces could produce a thrombotic diathesis.

Anti-fibrinolytic use in liver transplantation is intended to tip the balance back toward coagulation in a setting recognized for pathological activation of the fibrinolytic system. Anti-fibrinolytic drugs have not been associated with an increased incidence of thrombosis in liver transplantation in general. There are, however, several case reports of pulmonary embolus in association with their intraoperative administration.(6,30,31) Because they affect hemostatic balance, there are some contra-indications to their use. These include: Budd-Chiari syndrome, history of thrombosis, documented hypercoagulable syndrome (e.g. Factor V Leiden abnormality, anti-phospholipid Abs, Protein C or S deficiency, etc.), DIC, and tumor.

The use of anti-fibrinolytic drugs in liver transplantation is controversial. There is no consensus on which drug, what dose, when, or how long is best(32,33). Because of two catastrophic, intraoperative embolic events in the setting of aprotinin administration, the UCLA surgical team almost never uses aprotinin, and then only as a rescue drug. This means that we only use the lysine analogues, with varying preferences of drug and dose among attendings.

Anhepatic phase

Cross clamp of the caval and portal circulations decreases venous return by 50%(34). In non-cirrhotic patients without underlying cardiac disease, adaptation to the sudden decrease in preload is accomplished by increases in serum vasopressin and catecholamines(35). Whether the increase in catecholamine levels is a by-product of decreased hepatic metabolism from hepatic vascular exclusion, or the result of increased secretion is unclear. However, it is clear that the increase in vasopressin levels is due to an increase in secretion, as there is no hepatic clearance of vasopressin.

The reliance on vasopressin and catecholamine (particularly norepinephrine) response to compensate for hepatic vascular exclusion (HVE) may present a problem for the ESLD patient whose sympathetic system is already in overdrive and who suffers from autonomic dysfunction(36,37). Furthermore, it has been postulated that like patients in vasodilated septic shock(38), ESLD patients with a similar hemodynamic picture may also suffer from vasopressin

deficiency. Thus, they may be unable to muster the necessary hormonal responses to caval cross-clamp.

Another possible contributor to intolerance of caval clamp is underlying cardiomyopathy. Although many patients with ESLD have supra-normal ejection fractions and cardiac outputs, this is due to their extraordinarily low PVR. When stressed, their cardiac dysfunction becomes apparent. Cirrhotic cardiomyopathy is characterized by the following features: attenuated contractile response to exercise (systolic dysfunction)(39), prolonged QT interval(40), left atrial and/or ventricular hypertrophy(41), and diastolic dysfunction.(41,42) Thus it can easily be seen how a maneuver that decreases pre-load and requires peripheral vasoconstriction (increase in afterload) as an adaptive response could unmask cirrhotic cardiomyopathy.

In the absence of VVB, most adult patients will require some intervention to maintain acceptable hemodynamic parameters. This includes volume, pressor, and/or inotrope therapy, guided by the PAC or TEE. Current indications for VVB at UCLA are somewhat flexible and are more often technical than medical. VVB can be helpful in patients with significant cardiac disease, FHF, and pulmonary hypertension by limiting volume loading to tolerate cross-clamp, and minimizing fluid shifts associated with clamping and unclamping. However, studies suggest that the use of low-dose vasopressor agents may achieve the same purpose without untoward sequelae.(43,44)

Many centers will perform a test clamp of the IVC to determine whether the patient will tolerate hepatectomy without VVB. Commonly used indications for VVB include a decrease of >50% in cardiac output or and MAP<60 mm despite adequate pre-clamp volume. There is evidence, however, that even patients who initially “flunk” a caval test clamp may tolerate caval clamp with volume and inotrope/pressor therapy, and without an increase in perioperative morbidity or mortality.(43,45)

VVB is not an entirely benign procedure. In addition to the time cost of establishing axillary and iliac access, there are the usual risks of bleeding and infection, and the not-so-usual risks of venous air embolism, brachial plexus injury, and post-operative venous thrombosis and lymphocele.(46) Additionally, despite adequate flow (>1L/min), we have occasionally had clot formation within the bypass system.

Establishment of VVB involves drainage of the (usually) left iliac and portal venous blood with return to the left axillary vein. Up to 40% of the cardiac output may be returned to the

central circulation this way.(47) Hemodynamic stability may be expected with a VVB flow of at least 25% of the cardiac output.(47) (Our perfusionist, Dmitri, usually runs flows in the range of 2L/min.)

This is a relatively quiet time. Unless there is GI bleeding, there is usually no significant blood loss after the recipient hepatectomy. The supra-hepatic IVC anastomosis is done first, followed by the infra-hepatic IVC. During the infra-hepatic anastomosis, the donor liver is flushed of its preservative from the portal vein and out the closing infra-hepatic caval anastomosis. A comment about venting the donor organ is inserted here because the decision to vent should be made before completion of the infra-hepatic caval anastomosis. Although studies do not support routine venting (i.e. flushing 300-500 cc of blood from the recipient's portal circulation through the donor liver and out the infra-hepatic cava), a study done at UCLA identified a subset of hyperkalemic patients who did seem to benefit from it.(48) Over time, this has been expanded to include marginal donor organs and/or unstable recipients.

The beginning of portal anastomosis is a good time to send off a set of labs. These results should be back just before reperfusion and allow you to gauge how much buffer and calcium you would like to give before reperfusion.

In order to do the portal anastomosis, the recipient vein is clamped and is no longer part of the VVB circuit. This results in a fall in bypass flow to 10%-25% of C.O.(47) and, often, hypotension requiring volume and/or pressor support.

In anticipation of reperfusion the patient should be placed on 100% O₂, and the inhalational agent decreased. Prophylactic bicarb and calcium may be administered, according to the attending's particular practice.

Reperfusion of the patient's liver begins with release of the supra-hepatic caval clamp, followed by the infra-hepatic caval, and portal clamps. Release of the supra-hepatic caval clamp has little hemodynamic consequence. Release of the infra-hepatic caval clamp restores venous return. One should see an increase in filling and peripheral pressures. There may be a small drop in temperature, perhaps 0.5⁰ C. Release of the portal clamp results in the most profound changes. Temperature will drop another 1.5⁰ C acutely, then recover about 0.5⁰ C of that fairly quickly as the graft liver warms up. Immediate hemodynamic changes include an increase in cardiac output, PAP, and PCWP, and a decrease in SVR and MAP. About 30% of patients will exhibit "post-reperfusion syndrome" (PRS), defined as a >30% decrease in MAP within 5

minutes of reperfusion and lasting at least 1 minute.(49) Although cardiac dysfunction may sometimes contribute to PRS(6), the most common culprit is a profound decrease in SVR.(50)

It has been our long-standing belief, on the basis of anecdotal evidence, that PRS has a strong correlation with the quality of the donor organ. Moreover, we believe that the quality of reperfusion portends graft function in the neohepatic phase. Several studies have already examined the relationship between donor organ quality and the incidence of initial poor function (IPF) or primary non-function (PNF). Donor factors such as cold ischemia time, donor age, percentage of steatosis, days of ICU hospitalization, hypernatremia, and non-heartbeating procurement have all been associated with an increase in IPF and/or PNF(51-55). However, the relationship of these factors to hemodynamic stability during reperfusion, and graft function in the immediate post-reperfusion period is less established. Other than one study which implicated donor age >50 as being associated with an increased incidence of PRS(56) there has been nothing published. At UCLA, Dr. Neelakanta has unpublished data which demonstrates an association between “super-extended criteria” donors (donors having at least 3 of the generally accepted extended-donor criteria) and a greater incidence of hyperkalemia, and hemodynamic perturbation requiring pharmacologic intervention, on reperfusion. An abstract presented at the 2006 ILTS meeting in Milan suggests a correlation between severity of PRS and subsequent graft function. In this study from the University of Pittsburgh, patients who experienced significant PRS also had greater overall FFP and RBC transfusion requirements (although it is not known whether this is also true for the neohepatic phase in particular), a greater incidence of persistent fibrinolysis, and a greater incidence of re-transplantation (again, time course is unclear).(57)

Our surgical colleagues have also noted that grafts and recipients must be appropriately “matched” to maintain good patient outcomes. Specifically, it has been observed that grafts which accrue more than two risk factors portending poor function are associated with a significant increase in 1-year mortality.(58) Moreover, both graft survival and patient survival drop steeply when extended-criteria grafts are combined with higher MELD (>20) recipients. (59,60)

Hypotension associated with PRS usually responds well to phenylephrine. Many end-stage liver disease patients are somewhat resistant to pressors, probably because of already high circulating levels of catechols and vasodilator substances. You should be prepared to use

increased doses based on hemodynamic response, or consider using other drugs such as epinephrine, norepinephrine, or vasopressin. Dysrhythmias (especially ventricular) should be treated aggressively as they may deteriorate. Furthermore, maintaining an effective stroke volume is critical in redistribution of acid, potassium, and cold blood away from the heart. Although PRS is described as lasting 5-15 minutes, it may sometimes last considerably longer, requiring pressor support for more than an hour.

Neohepatic phase

Unless PRS is a continued problem (suggesting graft dysfunction), the main issue of the neohepatic phase is hemostasis. Increased TPA(61), hypothermia, dilution of clotting factors(62), and release of heparin bound to the donor liver(62) all contribute.

As part of the transplant protocol, you need to remember to give the patient a 1-gram bolus of hydrocortisone post-reperfusion. This dose is included in the red pharmacy box.

Although the hepatic artery may sometimes be anastomosed prior to reperfusion, this is usually done post-reperfusion. This decision is made by the surgeon, usually on the basis of technical considerations. Anastomosis and reperfusion of the hepatic artery is without hemodynamic consequence unless it is necessary to patch it to the aorta, requiring full or partial aortic cross-clamp.

If a calcium infusion was utilized, it should be discontinued post-reperfusion. The ability to maintain a normal serum ionized calcium level without supplement is considered evidence of citrate metabolism and good graft function. Other evidence includes clearance of acid with correction of the base deficit and a return toward normothermia from the metabolic activity of the new liver. The surgeons will generally note the feel of the new liver (soft is good, hard is bad), the color and uniformity of that color, and the production of bile.

The biliary drainage procedure is the most common source of post-op surgical complications. Drainage is either done by end-to-end anastomosis of the recipient and donor common bile duct (choledocholedochostomy) or by Roux-en-Y choledochojejunostomy. The latter is used for patients with abnormal extrahepatic bile ducts (biliary atresia, sclerosing cholangitis), a particularly small donor bile duct, or a situation where there are multiple donor bile ducts to implant.

Completion of the biliary anastomosis is a good time to start titrating in narcotic for post-op pain relief. Our drug of choice is morphine because its metabolism is well-maintained even in liver disease.(63,64) A good target dose is 0.5 mg/kg, if the patient tolerates it.

Patients are transported with resuscitation drugs, muscle relaxant, stand-by ETT, and laryngoscope. Most of us continue only vasoactive infusions on transport. The cardiac output set-up (syringe, tubing, and fluid) and the mask included with the ambu bag should be turned over to the ICU nurses and RT.

Special considerations

Chronic active hepatitis B – the serologic marker of CAHB is HBSAg positivity. We give 10,000 U HBIg (32 cc in the current formulation) IV to these patients during the anhepatic phase to prevent recurrence in the graft. You may notice that the insert for HBIg cautions against giving it IV. Ignore this. However, do keep in mind that IV HBIg may precipitate profound drops in SVR and blood pressure. It should be given slowly – on a pump or 2-3 cc at a time.

There is additionally a subset of HBSAg-, HBcAb+ donors who have active HBV capable of recurring in the donor liver.(65) These donors are infected with an HBV containing a pre-core mutation that does not show HBSAg seropositivity. Recipients of these grafts also receive HBIg as described above.

Fulminant hepatic failure

The most common cause of fulminant hepatic failure (FHF) in this country is acetaminophen toxicity.(66) The hallmark of FHF is encephalopathy and evidence of significant hepatic dysfunction (usually INR >1.5), which develops within 26 weeks after the onset of illness, classically in a patient with no history of ongoing liver disease.

This encephalopathy is different from the encephalopathy of chronic liver disease because it is associated with vasogenic and cytotoxic damage in the CNS. There is loss of integrity of the blood-brain barrier, leading to cerebral edema with increased intracranial pressure (ICP) and eventual herniation. The incidence of cerebral edema, while almost nil on Stage 1 and 2 encephalopathy, rises to 25%-35% in Stage 3 coma, and to 65%+ in Stage 4.(67) Patients in Stage 3 or 4 coma are frequently followed with serial head CT scans. Occasionally, an ICP monitor will be placed.

Management of ↑ ICP includes muscle relaxation and osmotherapy with mannitol to keep serum osmolality at 310 mosm in those patients with adequate renal function. Intubation for airway protection often becomes necessary in patients with Stage 3 or greater encephalopathy. Because cerebral blood flow varies widely in FHF patients, it is difficult to make a recommendation on hyperventilation. Although it can reduce the intracranial blood volume if autoregulation is still intact, it may also reduce perfusion in the face of cytotoxic cerebral edema. In a position paper published in 2005(67), the American Association for the Study of Liver Diseases (AASLD) could ascribe no benefit to prophylactic hyperventilation in FHF patients. As such, it was recommended that it be used only temporarily in the setting of impending herniation, and not as part of routine management. Steroids are of no benefit.(68) Drugs that decrease both cerebral blood flow and O₂ consumption such as thiopental are also useful, and may be used either as a bolus for peaks in ICP or as an infusion. A thiopental infusion may be started with a bolus of 3-5 mg/kg followed by 1-5 mg/kg/hr. Modest hypothermia to 33 –34⁰ C has also been suggested to be beneficial.(69)

Inhalational agents and other cerebral vasodilators should be avoided. A study by Lidofsky et.al, on ICP monitoring in FHF suggests that treatment of systemic hypertension by adrenergic blockade (they used esmolol or labetalol) may be preferable to direct vasodilators such as nitroprusside.(70)

DIC is not uncommon in FHF. The decision to use antifibrinolytic therapy should be made with care.

Pediatric patients

Indications for liver transplantation in the pediatric population differ significantly from those in adults. Whereas the leading indication for transplantation in adults is post-necrotic cirrhosis, the most common pediatric indication is biliary atresia(71). Other common indications are progressive intrahepatic chloestasis syndromes (Alagille's, Caroli's, and Byler's diseases), metabolic syndromes, and FHF.

In recognition of the differences in transplant indications and the increased scarcity of suitable graft organs for pediatric patients, a separate model for predicting 90-day mortality in this population was developed. This is the Pediatric End-stage Liver Disease (PELD) model.(71) It differs from the adult model (MELD) in that it does not include any measurement of renal

function, but does consider age, growth failure, and serum albumin, in addition to bilirubin and INR. Similarly to the adult model, a minimum PELD score that defined a 1-year survival benefit from transplantation was identified (PELD = 17), but a score that defined futility of transplantation was not.(72)

Pediatric patients differ in a number of ways from adult patients:

Access/monitoring – we do not place Swan-Ganz catheters in these patients. Central monitoring is via a CVP placed by the anesthesiologist or by a Hickman catheter placed by the surgeon at the beginning of the case. Otherwise, we establish at least one, and preferably two additional volume lines, and an arterial line. Femoral and foot arterial lines are not desirable because the aorta is often cross-clamped for hepatic artery anastomosis

Hepatic artery thrombosis (HAT)-Because the incidence of HAT is about 10% in pediatric patients (more than twice that of adults), precautions are taken to prevent this catastrophic occurrence. This is particularly true of the very small child less than 15 kg.Our practice is to:

Keep the hematocrit in the mid-20's (hemodilution), and

Not give procoagulants unless there is a significant bleeding problem (the surgeons will discuss this with us). These include FFP, platelets, cryprecipitate, and especially, antifibrinolytics. The surgeons tolerate an INR in the 2-3 range post-op, so don't jump to treat abnormal values less than that.

VVB is not used. To prevent clot formation, patients need to be at least 20 kg. and be able to provide a bypass flow of at least 1L/min in order to be placed on bypass. In practice, even most older children and adolescents tolerate caval cross-clamp quite well. It is essential to have these patients full prior to cross-clamp and then to allow them to run fairly dry during the anhepatic stage to avoid fluid overload on reperfusion. We aim for a CVP of about 10 mm Hg prior to clamp.

LIVING DONOR AND SPLIT LIVER TRANSPLANTATION

UNOS data on liver transplantation shows a consistent increase in the numbers of patients on the waiting list for transplant. Unfortunately, this is not matched by a commensurate increase in donor organs. An increasing number of patients die each year without having been transplanted. Additionally, in the past there was an under-supply of cadaveric pediatric donors. At one time,

the percentage of pediatric patients (<10 yr.) who died awaiting their transplant was roughly twice that of adults.

The lack of pediatric donors in particular prompted a series of creative solutions. Initially, the pediatric organ pool was enlarged by taking what was available, i.e. an adult liver, and transplanting an appropriately sized portion of that organ. The remainder was discarded. While this immediately improved the situation for pediatric recipients, it did nothing for the global organ shortage. One donor organ was still being used for one recipient. Although reduced-size organ transplantation may still be used in an emergency situation, this technique has largely been abandoned in favor of other options.

One of those options is living donor liver transplantation (LDLTx). In this procedure, a portion (segments 2 and 3, also called the left lateral segment) of a donor adult's liver is transplanted into a pediatric recipient. This technique was pioneered largely in those countries that do not recognize the concept of brain death, and therefore cannot harvest organs from heart-beating patients. It has since been expanded to accommodate adult recipients, using the right hepatic lobe. The obvious drawback is that this procedure puts an otherwise healthy person at risk for complications, including death.⁽⁷³⁾ A prospective study of living donors from Beaujon Hospital in France supports the belief that while left lateral segmentectomies are not without morbidity, right hepatectomy is associated with a greater incidence both of overall complications, and particularly of serious complications (i.e. potentially life-threatening and requiring medical intervention or re-admission to the ICU)⁽⁷⁴⁾. In order to minimize anesthesia complications, we tend to limit invasive procedures in our living liver donors. These include epidural, central venous line, and arterial line placement. Several studies (including one from UCLA) support the use of peripheral venous pressures (PVP) as a proxy for CVP.^(75,76,77) Additionally, the surgeon's painstaking dissection results in significantly less blood loss than a standard hepatectomy. This, together with the generally healthy state of the donor, makes allogeneic transfusion largely unnecessary.

Another technique that was introduced was split-liver transplantation. Using this technique, both a left lateral segment and an extended right lobe (tri-segment) are generated for transplantation by dividing the liver on the back bench after harvest ("ex-vivo"). Although initial survival results were abysmal and the technique largely abandoned for a period of time, there was a major development that brought this procedure back into favor. The techniques

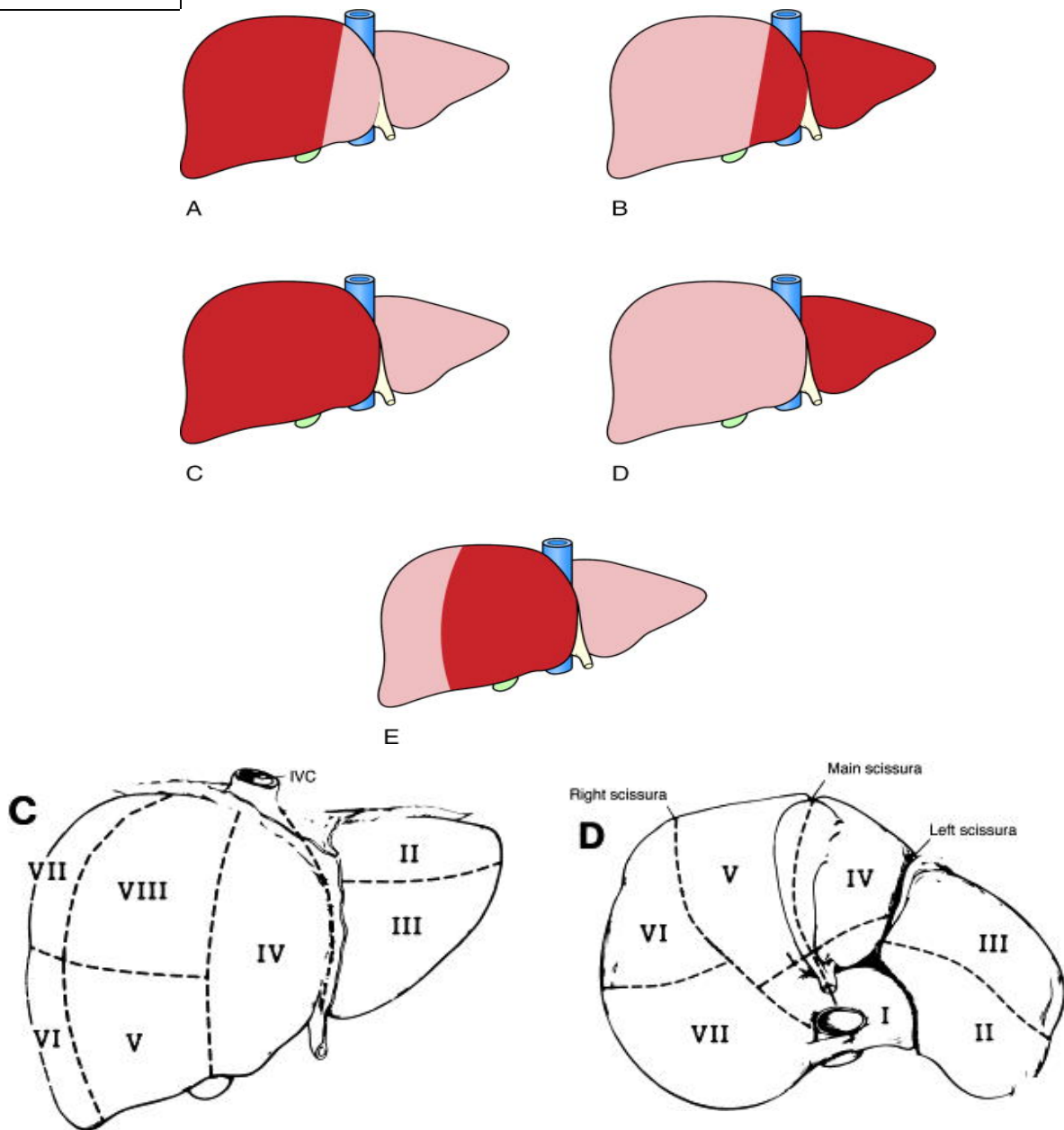
learned from performing LDLTx were applied to cadaveric donors so that the splitting of the liver was done in a heart-beating donor (“in-situ”) rather than on the back bench. In addition to reducing organ ischemia time and eliminating back bench manipulation, it allowed the donor’s clotting factors to seal the raw surface of the cut graft, reducing post-reperfusion bleeding.

The anastomotic connections for the right-side cadaveric graft are generally identical to those for a standard orthotopic liver transplant ; 1) supra-hepatic cava, 2) infra-hepatic cava, 3) portal vein, and 4) hepatic artery. However, the left lateral segment and all living donor grafts are sewn in “piggyback” fashion. This requires dissection of the liver off the recipient’s IVC, which is left intact. The piggyback procedure then requires only 3 vascular anastomoses: 1) hepatic veins (to IVC), 2) portal vein, and 3) hepatic artery.

HEPATIC RESECTION

The liver transplant service performs hepatic resections most often for metastatic tumor, but also for lesions such as primary liver tumors, hemangiomas, and cysts. To discuss hepatic resection, it is first helpful to review the anatomy of the liver. The liver has a dual blood supply, with inflow from the portal vein and hepatic artery, and drainage via the hepatic veins (right, middle, and left) into the IVC. The American description of hepatic anatomy uses surface landmarks to define the right, left, caudate, and quadrate lobes, but these divisions do not correlate with vascular supply or biliary drainage. Couinaud’s description of hepatic anatomy divides the liver into 8 segments on the basis of vascular supply, and is the preferred system for surgical discussion (fig.3).

Figure 3



The commonly performed major hepatic resections are indicated by the shaded areas. **A**, Right hepatectomy or right hepatic lobectomy (segments V-VIII). **B**, Left hepatectomy or left hepatic lobectomy (segments II-IV). **C**, Extended right hepatectomy, extended right hepatic lobectomy, or right trisegmentectomy (segments IV-VIII). **D**, Left lateral segmentectomy or left lobectomy (segments II-III). **E**, Extended left hepatectomy, extended left lobectomy, or left trisegmentectomy (segments II, III, IV, V, VIII). (From Blumgart LH, Jarnagin W, Fong Y: *Liver resection for benign disease and for liver and biliary tumors*. In Blumgart LH, Fong Y [eds]: *Surgery of the Liver and Biliary Tract*. London, WB Saunders, 2000, pp 1639–1714.)

Hepatic resections can be broadly separated into 3 categories:

Anatomic – margins determined by segmental anatomy

Enucleation – excision of well-defined, non-invasive lesions

Non-anatomic – margins defined by the lesion

Unsurprisingly, non-anatomic resections have the most potential for blood loss.

Figure 4 gives both a visual illustration of, and a segmental anatomic description of, commonly performed surgical resections.

Selection criteria

In patients who have no underlying hepatic disease, extent of resection is limited either by total hepatic involvement (i.e. lesions throughout the left and right lobes) or by non-hepatic disease. In patients with intrinsic liver disease, determining acceptable extent of resection is more complex, and is concerned with predicting residual function and regenerative capacity. As a general rule of thumb, Child's A patients may undergo a major resection, such as a lobectomy (although probably not a tri-segmentectomy), and Child's B patients may undergo a minor resection, such as a segmentectomy. Child's C patients are poor candidates for resection and should be given non-surgical therapy.

Key to reducing operative morbidity and mortality are minimizing operating time and blood loss. Operating time is not within the anesthesiologist's control, but we can help limit blood loss and allogeneic transfusion.

Two techniques available to us are: maintenance of a low CVP to reduce blood loss, and isovolemic hemodilution to reduce allogeneic transfusion. Multiple studies have shown a correlation between caval pressure and blood loss/transfusion requirements during hepatic resection. (78,79) Specific recommendations are for a CVP < 5mmHg as long as the patient maintains a urine output > 25 cc/hr and a BPs > 90 mmHg.(78) Using these guidelines the investigative groups have reported no post-operative renal failure attributable to the anesthetic technique.(80,81)

For a variety of reasons, it is desirable to avoid allogeneic transfusion. Those patients for whom transfusion is anticipated because expected blood loss approximates or exceeds allowable blood loss, may be candidates for isovolemic hemodilution. This is a simple technique that requires only a few supplies:

Scale (in the substerile room for OR 20)

500 cc bottle CPD-A (OR pharmacy)

Blood collection bags (blood bank, perfusionist's supply room next to OR 22, sometimes Anesthesia lab)

Short male-male connector (Anesthesia lab)

A target hematocrit for transfusion is identified for the patient. The anesthesiologist decides, based on the allowable blood loss, the volume of blood to be removed from the patient and replaced with acellular fluid. Sixty cc of CPD-A is added to each blood collection bag used, and 500 cc of blood per collection bag is removed via a large-bore venous access. Bags are labeled and numbered in order of collection. They may be stored at room temperature for up to 8 hours, and so can be kept in the OR with the patient. Blood is re-infused when the target transfusion hematocrit is reached or when major blood loss has finished i.e. after the liver has been divided. Infusion is done in reverse order of collection (hence the reason for numbering) so that the bag with the highest hematocrit and concentration of procoagulants gets infused last.

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