# Dental Sedation and General Anesthesia Considerations for Patients Posthepatic Transplantation

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Hepatic compromise poses significant impacts upon the care of patients undergoing routine dental treatment. When sedation or general anesthesia is planned for dental treatment or oral and maxillofacial surgery, an understanding of basic liver function and clinical evaluation can assist in adapting treatment modifications for patients with limited function due to previous disease and resultant organ transplantation efforts. Beginning with a basic overview of hepatic physiology, this review will outline the specific functions of digestion, metabolism, synthesis, and detoxification involving the liver. Specific clinical considerations will be reviewed regarding comorbidities that develop prior to and after liver transplantation that often impact a patient's suitability for ambulatory and office-based care. Lastly, choices in both local anesthetics, sedative medications, general anesthetics, and postoperative analgesics utilized in dental treatment will be discussed.

**Key Words:** Orthotopic liver transplant; Anesthesia considerations; Dental considerations; Liver failure; Hepatic; Immunosuppression.

The prevalence of individuals with significant hepatic compromise or corrected hepatic function presenting for dental treatment in office-based settings is increasing. Often, these patients require considerations for anxiety and pain control, and sometimes, focused preoperative evaluation is required when advanced forms of sedation or general anesthesia are planned. When compared with the general population, patients who have received orthotopic liver transplant (OLT) are more likely to have an increased frequency of hypertension, metabolic syndrome, diabetes, obesity, dyslipidemia, or malignancy. In particular, cardiovascular disease greatly affects the long-term prognosis of OLT.

## OVERVIEW OF HEPATIC PHYSIOLOGY

The liver is largely responsible for metabolic homeostasis. The critical functions of the liver include: (1) digestion and bile production; (2) metabolism and glucose homeostasis; (3) synthesis of cholesterol, urea, hormones, and proteins; and (4) detoxification of urea, bilirubin, and other potential toxins.[1]

### Digestion

The liver helps regulate digestion through the production of bile. Bile is produced at a rate of approximately 0.25 to 1 L per day in adults. Bile, composed mostly of cholesterol, is important for the digestion of dietary fats, converting them into fatty acids via bile salts. Bile is produced by hepatocytes and stored in the gallbladder where it is secreted into the duodenum. Its secretion helps eliminate excess dietary cholesterol by utilizing mixed micelles formed by organic biliary solutes, eventually forming feces. Bile salts further emulsify dietary fats, fat-soluble vitamins (A, D, E, and K), and lipophilic drugs. Bile salts also regulate the water movement from hepatocytes into bile and water absorption through the small bowel.[1]

### Metabolism

Bilirubin is a byproduct of the breakdown of red blood cells, particularly hemoglobin, and exists as either unconjugated or conjugated bilirubin. Unconjugated bilirubin is not water

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soluble, instead binding to serum albumin to facilitate its intravascular transport to the liver. This unconjugated bilirubin (UCB) complex protects the tissues from the potentially toxic effects of bilirubin. UCB enters the liver where it undergoes the addition of glucuronic acid facilitated by the enzyme glucuronyl transferase. This process creates conjugated bilirubin, a water-soluble molecule that can then be eliminated by the body primarily via the gastrointestinal tract. Once entering the colon, bilirubin is deconjugated by intestinal bacteria to a group of compounds known as urobilinogens. These urobilinogens are further oxidized and reabsorbed into the enterohepatic circulation and secreted into bile, with some entering the urine.[1]

The liver is also vital for protein metabolism, catabolism of proteins into energy or storage forms, protein synthesis, and the management of excess amino acids and nitrogen waste. Excess amino acids not used in peripheral tissues are brought to the liver, where they are oxidized for energy in lieu of carbohydrates or lipids or converted into glucose, ketone bodies, or fats. When amino acids are catabolized for energy production throughout the body, ammonia, glutamine, glutamate, and aspartate are produced. These products are processed by the liver, where the waste nitrogen is converted to urea through the urea cycle and excreted in urine.

Lipolysis, the degradation of triglycerides by hydrolysis into free fatty acids and glycerol in adipose cells, returns fatty acids to the liver where they are metabolized. Conversely, fatty acids undergo esterification with glycerol to form triglycerides for storage in adipose tissue or B-oxidation to yield energy in the form of ATP and ketone bodies. The fasting state favors oxidation and lipolysis, while the fed state favors esterification and lipogenesis.[1]

The liver is also responsible for the metabolism of the fat-soluble vitamins A, D, E, and K. It is also the site for the storage of vitamin A, the activation of vitamin D (25-hydroxylation), and the posttranslational gamma-carboxylation of vitamin K. The uptake, storage, and metabolism of many water-soluble vitamins, including thiamine, riboflavin, vitamin B6, vitamin B12, folate, biotin, and pantothenic acid occur in the liver. It converts some of these vitamins into active coenzymes, turning them into storable metabolites or returning them to the enterohepatic circulation. In addition, the reticuloendothelial system of the liver clears activated coagulation factors, activated complexes of the coagulation and fibrinolytic cascade, and the end products of fibrin degradation.[1]

The liver assists with glucose homeostasis through glycogenesis, glycogenolysis, and gluconeogenesis. The liver breaks down stored glucose (glycogen) to provide glucose to the systemic circulation via glycogenolysis. Some enteric carbohydrates that circulate systemically are converted to glycogen for storage by glycogenesis, while excess carbohydrates are mostly converted to fatty acids and stored in adipose tissue. After prolonged fasting (eg, 48 hours), hepatic glycogen stores are depleted, and the liver shifts from glycogenolysis to gluconeogenesis. Amino acids (mainly alanine) from muscle breakdown serve as the substrate for hepatic gluconeogenesis. During a prolonged fast, fatty acids from adipose breakdown are also beta-oxidized in the liver, releasing ketone bodies.[2]

## Synthesis

Cholesterol is an integral part of the cell membrane and is a foundation of many steroid hormones. Approximately 50% of cholesterol in the body is produced in the liver. Biosynthesis involves the conversion of acetyl CoA to acetoacetyl-CoA3 and HMG-CoA (a target of the "statin" drugs). Once packaged together, the cholesterol is released into circulation as a very low-density lipoprotein. Degradation of the triglyceride portion of the package results in the formation of low-density lipoproteins which are delivered to peripheral tissues. High-density lipoproteins are responsible for transporting excess cholesterol from the peripheral tissues back to the liver.[1]

The urea cycle occurs within the hepatocytes and involves the conversion of toxic ammonia into urea. Ammonia is the result of protein catabolism and is a byproduct of gut flora. Ammonia is also an end product of glutamine breakdown, formed in muscles by the binding of ammonia to glutamate. Conversion of ammonia to urea occurs in 5 stems and uses 6 different enzymes. Once urea is created, it is released into the bloodstream and transported to the kidneys where it is ultimately excreted in the urine.[1]

The liver is also responsible for the synthesis of many prohormones and hormones. Activation of vitamin D, insulin-like growth factor 1, and deiodination of T4 to T3 occurs in the liver and allows for their proper functions. Synthesis of prohormone angiotensinogen is imperative for the renin-angiotensin-aldosterone system. Hormone-carrying globulins such as corticosteroid-binding globulin and thyroxine-binding globulin are also synthesized in the liver. While it is an important part of the hormone synthesis process, the liver is also responsible for degradation of circulating hormones like T3 (thyroid hormone), glucagon-like peptide 1, progesterone, and androgens.[1]

Clinically relevant to dental procedures and surgery is the role of the liver in producing proteins for coagulation. The liver is responsible for all plasma protein synthesis except gamma globulins. Major clotting factors are synthesized here including fibrinogen, prothrombin, factors V, VII, VIII, IX, XI, XII, and XIII, proteins C and S, and antithrombin. Most notably, albumin is made in the liver and is the main serum-binding protein in the body.[1] Albumin is the most prevalent protein found in blood and is responsible for maintaining oncotic pressures and transporting steroids and fatty acids.

## Detoxification

Many foreign chemicals not incorporated into cellular metabolism are referred to as xenobiotics and can be drugs

or toxins. The liver detoxifies xenobiotics and endogenous toxins (eg, peroxides and reactive aldehydes) via phase I and phase II metabolic pathways. Phase I reactions, through oxidation, reduction, and/or hydrolysis, increase the polarity and water solubility of molecular compounds, which allows for easier excretion. Phase I enzymatic reactions often involve hepatic cytochrome P450 oxidases. Phase II transferase reactions couple the parent compound with a conjugate molecule, creating a less toxic or less active byproduct.[2] Phase II reactions occur via glucuronidation, acetylation, methylation, and/or conjugation. Ultimately, xenobiotics and other endogenous toxins are inactivated, detoxified, and prepared for elimination.

## Assessing Liver Function

The liver is a complex organ system with a multitude of critical responsibilities as previously discussed. The preoperative assessment of a patient's liver function is key when managing patients with hepatic dysfunction. A liver function test or hepatic panel includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), conjugated and unconjugated bilirubin, prothrombin time (PT), international normalized ratio (INR), lactate dehydrogenase (LD), total protein (TP), globulin, and albumin. High serum levels of these enzymes occur mostly in cases of acute hepatitis or mechanical damage to the liver.[3] Table 1 displays various hepatic diseases and their associated changes in lab values.

An important metabolic enzyme for hepatocyte metabolic processes, such as the Krebs cycle and glycolysis, is LD which is increased in cases of hepatitis or hepatocytic injury.[3] The reticuloendothelial system of the liver metabolizes hemoglobin into bilirubin to be transported into the bile ductules. GGT, an enzyme found in the liver, kidneys, and pancreas, and ALP are 2 important enzymes for the canalicular system. If an obstruction of the flow of conjugated bilirubin occurs, there will be an increase in serum GGT and AP.[3] GGT is much more sensitive to an obstruction than AP, AST, or ALT, and an increase in GGT can be useful in detecting obstructive jaundice cholangitis and cholecystitis. GGT can also be utilized as an additional marker for secondary hepatic metastasis and prostatic cancer in males.[4]

Seeing as the liver is the site for the synthesis of over 90% of the proteins in the body including albumin, decreases in the serum levels of total protein and albumin may represent liver pathology in which at least 80% of liver tissue may be nonfunctional, as in severe cirrhosis and fulminant hepatic failure.[3] The liver is also the site for the metabolism of ammonia, the end-product of amino acid transamination and deamination, so serum ammonia levels can rise with more than 80% of hepatic tissue damage.

The model for end stage liver disease (MELD) is a tool used to estimate a patient's potential to survive over a 3-month

**Table 1.** Hepatic Diseases and Associated Liver Function Test Values

| *Differential diagnosis* | *AST* | *ALT* | *LD* | *ALP* | *TP* | *Albumin* | *Bilirubin* | *Ammonia* |
|---|---|---|---|---|---|---|---|---|
| Normal value | 5–30 IU/L | 4–36 IU/L | 50–150 IU/L | 30–120 IU/L | 60–80 g/L | 35–50 g/L | 2–17 µmol/L | 15–45 µg/dL |
| Hepatitis | High | High | High | High | High | Normal | High | Normal |
| Cirrhosis | Normal | Normal | Normal | Normal/slightly high | Low | Low | High | High |
| Biliary obstruction | Normal | Normal | Normal | High | Normal | Normal | High | Normal |
| Space-occupying lesion | Normal/high | Normal/high | High | High | Normal | Normal | Normal/high | Normal |
| Passive congestion | Slightly high | Slightly high | Slightly high | Normal/slightly high | Normal | Normal | Normal/slightly high | Normal |
| Fulminant failure | Very high | High | High | High | Low | Low | High | High |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LD, lactate dehydrogenase; TP, total protein.

**Table 2.** Model for End Stage Liver Disease (MELD) Score[5]

| *MELD score* | *Mortality at 3 months* |
|---|---|
| >40 | 71.3% |
| 30–39 | 52.6% |
| 20–29 | 19.6% |
| 10–19 | 6.0% |
| <9 | 1.9% |

period,[5] and it evaluates serum bilirubin, serum creatinine, and international normalized ratio (INR; Table 2). The MELD score ranges from 6 to 40 with higher numbers being more likely to receive an organ transplant. The Child-Pugh scoring system is typically used to assess the severity of chronic liver disease, specifically cirrhosis.[6] Patients are accessed in 5 areas of disease, including total bilirubin, serum albumin, prothrombin time or INR, ascites, and hepatic encephalopathy, and are scored from 1 to 3, with 3 being the most severe (Table 3).[6] Based upon the number of cumulative points, patients are categorized as Child-Pugh A, B, or C, which corresponds to their 1- and 2-year survival rates (Table 4).[6] Ascites is the accumulation of fluid between the 2 layers of the peritoneum because of portal hypertension and vasodilation from exposure to increased levels of circulating nitric oxide. Accumulation of fluid denotes a shift from compensated to decompensated cirrhosis.

## LIVER TRANSPLANT

Liver transplantation is a widely accepted treatment for end-stage liver disease. Common pathologies that may require liver transplantation include congenital biliary atresia, biliary hypoplasia, metabolic disorders, and acute liver failure. Orthotopic liver transplant (OLT) is defined as removal of the liver with irreversible end-stage liver disease and replacement with a liver allograft from a recently deceased donor. The other 2 types of hepatic transplantation include living donor and split donor transplants. In the living donor transplant, the donor would donate either their right or left hepatic lobe. The recipient's lobe should quickly grow, often increasing to approximately 85% of a full liver's size within a week. A split transplant involves parsing out the liver of a deceased donor, with the larger lobe being donated to an adult recipient and the smaller lobe to a pediatric recipient.

**Table 4.** Interpretation Child-Pugh Score

| | *Class A* | *Class B* | *Class C* |
|---|---|---|---|
| Total points | 5–6 | 7–9 | 10–15 |
| 1-year survival | 100% | 80% | 45% |
| 2-year survival | 85% | 60% | 35% |

Several medications are utilized in the management of liver transplantation to prevent or reduce graft rejection. Patients commonly develop T-cell mediated rejection within 6 weeks of transplantation that requires immediate immunosuppression. Calcineurin inhibitors, like cyclosporin and tacrolimus, decrease the risk of graft rejection significantly and improve survivability with rejection risks as low as 5% in adult patients. However, rejection rates can approach 16% in the pediatric population.[7] Other immunosuppressants, such as azathioprine and mycophenolate, are usually used with steroids to aid in reducing rejection of grafts as well.[8] Monoclonal antibody therapies, such as intravenous (IV) muromonab-Cd3, are generally utilized for pediatric patients with liver transplants.[9]

## Cardiovascular Changes

One of the major collateral organ systems affected by OLT is the cardiovascular system. Cardiovascular disease can include ischemic heart disease, heart failure, or thromboembolism. The incidence of cardiovascular disease in patients following OLT is 1.1% to 23% in the first month, 1.1% to 50% for months 1 to 6, and 0% to 32% after 6 months following transplantation.[10] The 10-year probability of OLT patients having cardiovascular disease is approximately 11%.[10] Some other the risks include intraoperative cardiac events, preoperative heart disease, elevated integrated MELD score, previous stroke, postoperative sepsis, left ventricular hypertrophy, and moderate to severe tricuspid regurgitation.[10]

Hypertension is an uncommon diagnosis in patients prior to OLT. However, in approximately 70% of cases, post-transplant hypertension occurs due to reversal of chronic systemic vasodilation, sympathetic stimulation from immunosuppressive medications such as tacrolimus, and anti-inflammatory mineralocorticoid augmentation.[10,11] These changes can lead to metabolic dysfunction which may contribute to the development of acute coronary syndrome (ACS)

**Table 3.** Child-Pugh Score

| *Factor* | *1 Point* | *2 Points* | *3 Points* |
|---|---|---|---|
| Total bilirubin, μmol/L | <34 | 34–50 | >50 |
| Serum albumin, g/L | >35 | 28–35 | <28 |
| PT/INR | <1.7 | 1.71–2.30 | >2.30 |
| Ascites | None | Mild | Moderate to severe |
| Hepatic encephalopathy | None | Grade I–II | Grade III–IV (or refractory) |

Abbreviations: INR, international normalized ratio; PT, prothrombin time.

or congestive heart failure (CHF). Heart failure can develop after liver transplantation due to preoperative impaired cardiac contractile function, termed cirrhotic cardiomyopathy.[11,12] The appearance of normal cardiac function prior to transplant may be misleading as increased cardiac output may be compensatory due to longstanding systemic vasodilation. Transplantation usually prompts reversal of the pretransplant hyperdynamic state.[11] Other cardiac changes can also include new-onset atrial fibrillation which can further increase the risk of hemodynamic and thrombotic shifts.[11] If a patient with an OLT has signs of cardiac involvement, they should be adequately evaluated prior to any dental or oral surgical procedures relative to cardiac output, rhythm disturbances, coagulation, and tolerance to activity.

### Renal Changes

Chronic kidney disease (CKD) is commonly encountered in patients needing OLT and can improve after transplantation, although the risk for chronic renal failure at 5 years can approach 18% to 22%.[11] Common preoperative renal diseases include hepatorenal syndrome and hypovolemia-induced prerenal azotemia (ie, increased serum levels of nitrogenous waste products due to low kidney perfusion).[11] There are 2 categories of renal damage. The first occurs early, is usually reversible, and is related to vasoconstriction of the afferent arteriole to glomeruli with a resultant reduction of the glomerular filtration rate. The second category is irreversible and occurs through hyaline degradation of the renal arterioles causing glomerulosclerosis.[12]

Risk factors for renal disease after OLT include dose-dependent calcineurin inhibitors (tacrolimus and cyclosporin), advanced age, diabetes mellitus, hypertension, malignancy, high body mass index, and weekly dialysis prior to transplantation.[11,12] Prevention of post-transplant CKD is based primarily on management of conditions such as hypertension or diabetes. The utilization of angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs) can mitigate the nephrotoxic effects of the calcineurin inhibitors.

### Metabolic Changes

Patients who have undergone OLT are at higher risk for developing metabolic syndrome when compared with the general population as it affects roughly 43% to 58% of transplant recipients. Metabolic syndrome is a grouping of factors that increase risk for diabetes, stroke, and cardiovascular disease. These risks include insulin resistance and increased inflammatory markers that promote the development of diabetes mellitus and the formation of atherosclerotic plaques. Generally accepted criteria for metabolic syndrome include impaired glucose tolerance (fasting glucose $\geq$ 100 mg/dL), abdominal obesity with a waist circumference over 102 cm in men or 88 cm in women, hypertriglyceridemia (serum triglycerides $\geq$ 150 mg/dL), low high-density lipoprotein (HDL) levels (HDL $<$ 40 mg/dL in men or $<$ 50 mg/dL in women), and hypertension greater than or equal to 130/85 mm Hg.[10,12] Patients with type 2 diabetes mellitus prior to transplantation are at a 6-fold higher risk for developing metabolic syndrome after transplant.[12]

Immunosuppressive medications play a primary role in the post-OLT recipient's metabolic derangement. Corticosteroids are administered early and can induce pancreatic beta cells to increase insulin resistance.[10,12] Calcineurin inhibitors (eg, tacrolimus and cyclosporin) affect the development of diabetes mellitus by damaging the islet cells and increasing the potential for developing hypertension.[10,12] Organ transplant rejection prophylactic medications, such as sirolimus and other (mTOR) inhibitors, may contribute to dyslipidemia.[12] Dyslipidemia occurs in 45% to 71% of liver transplant recipients.[10,12] Risk mitigation is achieved by minimizing the effective immunosuppressive doses and encouraging an active and healthy lifestyle. The development of metabolic syndrome in transplant recipients increases the risk of developing graft steatosis, which in turn increases the chances of recurring or developing nonalcoholic fatty liver disease.[10]

Weight gain after OLT is anticipated in the first year as many patients had experienced malnutrition, weight loss, and sarcopenia prior to transplantation. The occurrence of obesity at 2 years approaches 22% and 38% at 3 years.[10] A body mass index (BMI) greater than 30 kg/m$^2$ at 1 year post OLT is associated with a 2-fold higher risk of long-term, all-cause mortality.[10] Risk factors for developing new-onset obesity include the following: male gender, alcoholic liver disease, and hepatocellular carcinoma at the time of OLT.[10] Diet, exercise, and pharmacological interventions (eg, glucagon-like peptide-1 agonists) are the mainstay of obesity management. Bariatric surgery can be considered, but there is a higher risk of mortality compared with the general population.

The incidence of new-onset type 2 diabetes mellitus after OLT is approximately 15% to 25%, and its development can greatly impact graft function and overall quality of life.[10] Risk factors for development include: new onset hyperglycemia ($<$30 days), prolonged cold ischemia time ($>$9 hours), older male recipient ($>$50 years), elevated BMI ($>$25 kg/m$^2$), hepatitis C, prolonged posttransplant ICU stay ($>$15 days), cytomegalovirus infection, and corticosteroid- and sirolimus-based immunosuppression.[10] Tacrolimus inhibits insulin in a dose-dependent manner and therefore is less of a risk.[10]

## DENTAL SEDATION AND ANESTHESIA CONSIDERATIONS

Since the 1-year survival rate for OLT is greater than 90%, there is a growing likelihood that these patients may require

dental or oral surgery procedures requiring sedation or general anesthesia. An exhaustive preoperative evaluation should be performed for patients with a history of OLT undergoing a procedure with or without sedation and/or general anesthesia. There are numerous medical conditions that will require close evaluation, collaborative consultation, and possible optimization. Multiple medications may interfere with hepatic cytochrome P450 3A4 isoenzymes and modifications to drug selection and dosing must be considered.

## Preoperative Evaluation

Prior to undergoing a more than minimally invasive dental procedure, it is prudent to evaluate for graft function and hepatic functional trends. Laboratory studies that evaluate liver function should be considered including serial prothrombin times, serum bilirubin, albumin, and liver enzymes such as ALT and AST.[13] If available, recent transplant team notes and sedation/anesthesia records should be evaluated to assess for airway management, hemodynamic stability, graft function, immunosuppressive medications (or recent changes), hospitalizations for rejection, steroid therapies, or any other signs of graft failure.[11] As the liver is involved in the metabolism of many drugs, there is potential for variation in drug volume distribution, excretion, and bioavailability.

## General Anesthesia

General anesthesia can be safely performed in patients who have undergone liver transplantation. The recipient liver will recover the capacity for drug metabolism after reperfusion. However, reduced levels of serum albumin (ie, hypoalbuminemia) can take several weeks to reach normal levels, potentially increasing the free fraction and bioavailability of circulating sedatives, anesthesia adjuncts, anesthetics, and other medications with strong affinities to serum proteins.[11] Inhalational and IV anesthetics have proven to be safe and do not affect graft function.[11,14] However, despite the route of administration, the increased free and serum-bound drug availability require the same attention. Benzodiazepines, although extensively metabolized by CYP450, can be administered safely; however, they may have prolonged effects dependent upon serum albumin levels or liver and renal status. The use of nitrous oxide can be seen as controversial as has been implicated in bone marrow suppression and immunosuppression via methionine synthetase, although contemporary and convincing evidence is lacking.[11] Succinylcholine can be utilized and would allow for more rapid intubating conditions as immunosuppressed patients can be more susceptible to aspiration pneumonia.[11] Stress dose steroids are usually not indicated for OLT patients undergoing general anesthesia for routine dental or noncomplex oral surgery procedures unless substantial chronic steroids are utilized for immunosuppression and major invasiveness of the surgical course is anticipated.[14]

## Dental Treatment Considerations for Patients Post-OLT

Oral manifestations of immunosuppressive agents that are commonly used in organ transplant include a high prevalence of caries, delayed dental development, enamel hypoplasia, green-stained dentition from high serum bilirubin, gingival bleeding, and gingival enlargement.[15,16] For pediatric patients managed with cyclosporin, drug-induced gingival overgrowth changes are seen in the first 2 to 6 months of administration and diminish around 12 months.[15] Due to the likely enlarged gingiva and potential risk for medical complexities, it is imperative to stress proper oral hygiene and have more frequent recall visits for those unable to properly manage themselves. Treatment of the gingival enlargement itself usually involves interventions of medical, nonsurgical, surgical, or combined approaches. As the medical treatment can involve antibiotics, liver function tests may be required.

As mentioned earlier with the liver being involved in the vitamin K-dependent pathways, preparation of the patient for any oral surgical procedure may require a blood panel prior to scheduling. The possibility for vitamin K injections to prepare patients for procedures as well as potential IV or oral tranexamic acid may be necessary. Chairside considerations including tranexamic rinses, extended postoperative observations times, and informed consent for postoperative hospital stays may be necessary. Although antibiotic prophylaxis is not indicated for liver recipients, those taking immunosuppressants may require antibiotics to aid in healing and prevent infection because of their immunosuppressive medications. In OLT patients where significant oral bleeding is expected or if the patient is susceptible to prolonged bleeding, it is important to have local measures, such as topical clotting agents, sutures, and the ability to apply pressure for an extended time planned and established prior to the procedure.

Antibiotic prophylaxis is generally not indicated for liver transplant recipients as a singular factor. Immunosuppressive medications certainly increase the risk of an opportunistic infection among susceptible patients. Monoclonal antibody therapy can also increase the recurrence of viral hepatitis and other viral infections such as Epstein-Barr, cytomegalovirus, herpes simplex, and viral lymphoproliferative disorders.[17] As previously mentioned, chronic steroid use to augment immunosuppression can significantly alter the hypothalamic-pituitary-adrenal (HPA) axis, thereby requiring steroid augmentation prior to potentially significant surgical stress.

Dyslipidemia is a common diagnosis encountered in OLT patients. Many patients will be taking a “statin,” or HMGCoA-reductase inhibitor, which is likely to be metabolized via cytochrome P450 3A4 (CYP3A4) enzymatic pathways. This

interaction can be greatly affected by the use of local anesthetics, such as lidocaine, and should be evaluated prior to administration for possible drug-drug interactions leading to toxicity.[18] An emphasis upon minimizing medications to the lowest effective dose and close consultation with the patient's hepatologist and primary care physician are recommended for dosing and medication choice.

Finally, when considering postoperative analgesics, the hepatotoxic potential of acetaminophen must be weighed against other available opioid and nonopioid alternatives and combinations in patients with liver dysfunction. Acetaminophen is long known to cause hepatocyte damage via accumulation of N-acetyl p-benzoquinone imine (NAPQI) in patients with alcoholic cirrhosis, yet short-term therapeutic dosing does not lead to significant decreases in liver function or accumulation of NAPQI in nonalcoholic cirrhosis. Generally, acetaminophen is avoided in patients with compromised liver function, yet with posttransplant patients, hepatic function may be restored to normal or near-normal levels to tolerate therapeutic dosing. Both morphine and hydromorphone undergo significant hepatic extraction ratio and therefore exhibit increased bioavailability in patients with liver dysfunction, so fentanyl remains a fairly predictable opioid analgesic choice.[19] Nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered with careful consideration for significant comorbidities associated with liver dysfunction and OLT, namely hypertension and CKD.[20] Calcineurin inhibitors are also nephrotoxic, and NSAID administration can further exacerbate ailing renal function. For occasions where moderate to severe postoperative pain is anticipated, oral opioid analgesics and opioid/acetaminophen combinations may be of value contingent upon posttransplant hepatic function. While some studies state that analgesic requirements are generally lowered posttransplant compared with pretransplant, coordinated evaluation and consultation with the care team should involve assessing current renal function and other possible interactions.[21] Opioid analgesic selection can also be guided by the patient's current hepatic function, as certain opioids rely on metabolic pathways that could be impaired. Oxycodone, for example, undergoes metabolism via cytochrome P450 isoenzymes rather than through glucuronidation as is the case for other opioids such as codeine, morphine, and hydromorphone.[22] Long-acting intraoral local anesthetics and liposomal bupivacaine formulations remain viable analgesic choices for patients with liver transplantation as well.[23]

## CONCLUSION

Recipients of an OLT are likely to have a greater incidence of cardiovascular disease, reduction of renal function, and increased risk of metabolic syndrome compared with the general population. Cardiovascular disease greatly affects the long-term prognosis of OLT, and de novo hypertension may develop posttransplant due to shifts in portal flow. Renal function can largely be spared by aggressive control of hypertension and diabetes mellitus in the immediate pre- and posttransplant period. Metabolic syndrome is commonly encountered after OLT due to immunosuppressive medications such as corticosteroids and calcineurin inhibitors. As the long-term success rates for liver transplants continue to climb, there is a high likelihood that these recipients will require dental or oral surgical treatment under sedation or general anesthesia. Communication with the patient's transplant team and consultant physicians is critical to ensure proper medication administration, infection management, and potential medication interactions.

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## CONTINUING EDUCATION QUESTIONS – DENTAL SEDATION AND GENERAL ANESTHESIA CONSIDERATIONS FOR PATIENTS POSTHEPATIC TRANSPLANTATION

This continuing education (CE) program is designed for dentists who desire to advance their understanding of pain and anxiety control in clinical practice. After reading the designated article, the participant should be able to evaluate and use the information appropriately in providing patient care.

The American Dental Society of Anesthesiology (ADSA) is accredited by the American Dental Association and Academy of General Dentistry to sponsor CE for dentists and will award CE credit for each article completed. You must answer 3 of the 4 questions correctly to receive credit.

Submit your answers online at www.adsahome.org. Click on "On Demand CE."

CE questions must be completed within 3 months and prior to the next issue.

1) The liver is responsible for which of the following metabolic processes?

   a. Clearance of activated coagulation factors
   b. Elimination of urea from the bloodstream
   c. Hypothalamic-Pituitary-Adrenal (HPA) axis regulation
   d. Reticulocyte formation

2) Which of the following liver function tests is specific for hepatic function for glycolysis?

   a. Alanine aminotransferase (ALT) levels
   b. Aspartate aminotransferase (AST) levels
   c. Lactate dehydrogenase (LD) levels
   d. Serum albumin levels

3) Which of the following posttransplant conditions occurs from a reversal of long-standing systemic vasodilation or anti-inflammatory steroid augmentation?

   a. Diabetes mellitus type 1
   b. Encephalopathy
   c. Hypertension
   d. Pancreatitis

4) Which of the following postoperative analgesics should be carefully considered for patients on calcineurin inhibitors when kidney function is compromised?

   a. Intravenous fentanyl
   b. Liposomal bupivacaine
   c. Low-dose oral acetaminophen
   d. Therapeutic dosing of ibuprofen