Pediatric Posttransplant Anesthesia: A Summary Review of the Literature With Recommendations for Clinical Practice

Taylor Loykasek, RN, BSN

Premature pediatric patients who previously received a multivisceral organ transplant and subsequently present for nontransplant surgery will offer multiple challenges to the anesthesia practitioner caring for the patient during the operative period. Multivisceral organ transplant is a treatment option for patients with irreversible intestinal and hepatic failure. Physiologic complications of this population include bronchopulmonary dysplasia, reactive airway disease, and delayed gastric motility. Because of prolonged hospitalization and chronic illness, this population frequently is difficult to achieve peripheral venous access. Immunosuppressive medications may result in lymphoproliferation of the airway, increased risk of infection, alterations in organ system function, and the need to ensure continuation of scheduled immunosuppression therapy. The posttransplant pediatric patient has been exposed to prolonged periods of sedation while in the intensive care unit, resulting in pharmacodynamic tolerance to common anesthetic medications. A review of the current literature in the management of this challenging patient population is presented.

Keywords: Immunosuppression, pediatric transplant anesthesia, sedation tolerance.

Management of the multivisceral organ transplant pediatric recipient presenting for nontransplant surgery requires knowledge of the physiologic changes incurred after transplantation, as well as the pharmacologic effects of immunosuppression and long-term sedation. After the initial transplant, these patients may return to the operating room (OR) for a variety of related procedures. Some of these procedures include exploratory laparotomy, contrast computed tomography requiring sedation, or endoscopy. Because of the frequent surgeries and associated long-term intensive care unit (ICU) hospitalization, these patients are prone to many comorbidities. Virtually all organ systems may be affected, and the anesthesiologist should be aware of what to expect when preparing an anesthetic plan.

Physiologic and Pathophysiologic Anesthetic Considerations in the Transplanted Infant

Multivisceral organ transplant of both small intestine and liver is reserved for pediatric patients who are not responsive to medical therapy and conservative surgical options for treatment of intestinal failure. These patients are unable to maintain weight, hydration, and electrolyte homeostasis. Intestinal failure may be caused by short bowel syndrome, mucosal enteropathy, and dysmotility syndromes. Short bowel syndrome may occur secondary to surgical resection to treat necrotizing enterocolitis, intestinal atresia, and midgut volvulus.

Bronchopulmonary dysplasia (BPD) is a common clinical finding in this patient population, frequently occurring in infants born under 30 weeks’ postgestational age. Peripartum risk factors to the premature infant that may lead to the development of BPD include chorioamnionitis and intrauterine growth restriction. Postpartum risk factors to the premature infant that may lead to the development of BPD include infections, oxidative stress due to cellular production of oxygen free radicals, prolonged mechanical ventilation with high inspired oxygen concentration, and corticosteroid administration. The pathogenesis of BPD has been identified as diffuse airway damage, proliferation of smooth muscle cells, neutrophilic inflammation, and fibrosis of the lung parenchyma caused by disruption of the immature lung structures. Chest radiographic findings for BPD include scattered fibrosis of the lung parenchyma and architectural distortion. Symptoms seen in the infant with BPD include wheezing, substantial airflow obstruction during the first 3 years of life, and hyperreactive airways. Although corticosteroid therapy is a risk factor for BPD, corticosteroids are being used to treat infants and toddlers affected with BPD. Corticosteroids are employed in the management of BPD to limit the inflammation of the airways and parenchyma; however, the risk for side effects of corticosteroid therapy is a source of controversy for the routine use of corticosteroid therapy. Inhaled β₂-agonist and anticholinergic therapy are used to treat functional exacerbations of reversible airway obstruction. Diuretic therapy is used for patients with high inspired oxygen concentration requirements or those with associated cardiac failure.
Considerations for the anesthesia practitioner caring for the posttransplant pediatric patient with BPD include airway hyperreactivity, high inspired oxygen requirements, and tracheal stenosis associated with long-term mechanical ventilation. With the pulmonary comorbidities that this patient population frequently has, they are often scheduled for respiratory care/chest physical therapy and pulmonary medications. It is ideal to schedule these treatments before transport to the OR.

There is limited research available for cardiac considerations specific to the pediatric multivisceral transplant population. Tacrolimus immunosuppressive therapy has been shown in the literature to cause rare cases of reversible myocardial hypertrophy after cardiac transplant. Both tacrolimus and cyclosporine therapy have been shown to cause hypertension in pediatric liver transplant recipients, requiring antihypertensive medications for 17% of infants at 1 month after transplant for tacrolimus and 60% of infants 1 month after transplant for cyclosporine. Immunosuppressive drugs such as tacrolimus, cyclosporine, and corticosteroids have been implicated in causing hypertension, diabetes, and hyperlipidemia in the adult transplant population. According to Goh and Warren, adult posttransplant patients presenting for surgery should have extensive cardiovascular testing done, including 12-lead electrocardiography and echocardiography as indicated by the patient’s medical history. Although there is limited research available to define the cardiac complications that may present in the pediatric posttransplant population, the anesthesia practitioner should rely on medical history and physical assessment to guide cardiac testing. A history of tacrolimus or cyclosporine therapy may warrant additional query into the patient’s cardiac status before clearance for moderately or highly invasive surgery.

The multivisceral organ transplant recipient will also have gastrointestinal (GI) considerations for the anesthesia practitioner. The patient may have chronic upper GI bleeding resulting from peptic ulcer disease, gastritis, or cytomegalovirus gastritis. The patient may also have chronic hepatobiliary or pancreatic disease after transplantation, with a higher incidence of long-term total parenteral nutrition lipid therapy. If a gastric tube is already in place before the patient’s arrival in the OR, the tube should be suctioned before induction to reduce gastric volume. Otherwise, a gastric tube may be placed orally and suctioned after induction.

**Intravenous Access and Fluid Therapy**

Venous access can be challenging in the chronically ill pediatric patient who has had frequent intravenous (IV) catheterizations throughout the course of hospitalization. Access that has been placed in the ICU, such as a double-lumen Broviac catheter, may not be sufficient for the OR course if the case is highly invasive and associated with high blood loss and homeostasis disruption requiring multiple infusions. Peripheral intravenous (PIV) access is an acceptable means of venous access in the posttransplant recipient presenting for minor surgery or diagnostic procedures. In the pediatric posttransplant recipient, the readily accessible veins are frequently exhausted. Several techniques are available to assist the anesthesia practitioner in obtaining PIV access. Transillumination is a readily available and inexpensive method to identify peripheral veins. In a study by Goren et al in 2001, vascular access was achieved in pediatric patients (age range, 2 to 32 months) in the emergency department in the first attempt in 39 of 40 patients. Additional options for aiding the anesthesia practitioner in obtaining PIV access include warming the extremities with water-soaked blankets to locally vasodilate the veins and combining nitroglycerine with a eutectic mixture of lidocaine and prilocaine (EMLA) cream, which has positively affected venous dilatation and ease of venous access. Although an option, a nitroglycerine/EMLA cream combination may not be the best choice for the patient who is susceptible to hypotension.

Central venous access is vital in the critically ill patient, serving to provide both a route for long-term infusions of antibiotics and parenteral nutrition as well as reliable venous access. The 3 most common sites of central venous access in critically ill pediatric patients are femoral, subclavian, and internal jugular veins. Karapinar and Cura performed a study comparing central venous access routes in critically ill pediatric patients and the associated complications. All patients were accessed using sterile Seldinger technique in the care of an experienced clinician. The femoral and jugular route had higher first-attempt success rates, 94% and 96.4%, than the subclavian, which had a 87.4% first-pass success rate. Infection control is critical in the posttransplant pediatric patient because of long-term immunosuppression therapy. Central line infection in the pediatric patient is the most common hospital-acquired infection in pediatric ICUs. Some approaches that the anesthesia practitioner can take to prevent catheter-associated bloodstream infections are adequate handwashing before placement of lines and when accessing lines, sterile technique when placing both peripheral and central access catheters, ethanol or chlorhexidine lock caps on catheter hubs, and the use of antibiotic-impregnated catheters and bandages.

On the debate of crystalloid vs colloid therapy in pediatric patients, the posttransplant pediatric patient should have an individualized fluid plan developed by the anesthesia practitioner based on patient physiologic status and the qualities of the solutions available. Albumin is considered the intraoperative gold standard in volume replacement, and is available in the United States as a 5% solution and a 25% solution. The 25% albumin can be expected to replace 3 to 5 times its volume for plasma volume, whereas...
5% albumin will replace plasma volume in a 1:1 ratio. In critically ill pediatric patients, such as those patients returning to the OR shortly after transplant, increased vascular permeability may worsen edema by allowing leak of the administered albumin into the interstitium. Albumin administration to the critically ill pediatric patient is a source of current debate. A study in the United Kingdom on the administration of albumin for fluid resuscitation in critically ill children resulted in a reduction in edema and decreased inspired oxygen requirements compared with children receiving fluid resuscitation by crystalloid solution. Compared with synthetic colloid solution, albumin is associated with fewer anaphylactic reactions and decreased coagulation derangements.

The synthetic colloid products hydroxyethyl starches (HESs) are a more stable polysaccharide than naturally occurring polysaccharides that are not rapidly metabolized by circulating amylases. The HES products are associated with a hypocoagulable state, which is hypothesized to be due to interference with von Willebrand factor, factor VIII, and platelet function. Another downside to HES products is the creation of hyperviscous urine and induction of renal tubular swelling, which may worsen renal function in a critically ill pediatric patient. Because of the range of side effects of the HES products, these products are not frequently used in this patient population in clinical practice. These patients may have existing renal impairment due to immunosuppressive therapy as well as existing disease, which will preclude the use of these products that have the possibility of worsening the renal function.

**Immunosuppression**

Posttransplant patients are placed on immunosuppressive medication regimens that will have varying considerations for the anesthesia practitioner. With the current 5-year survival rate of pediatric patients receiving intestinal transplants at 55%, anesthesia practitioners can be expected to increasingly provide preoperative, perioperative, and postoperative care to these patients in nontransplant operations and procedures. The more common immunosuppressive agents that will be seen include cyclosporine, tacrolimus, corticosteroids, monoclonal antibodies, and azathioprine. The preoperative assessment by the anesthesia practitioner in consideration of the side effects of immunosuppressive therapy should include function of the grafted organs, rejection status, infection, and function of organs that may be targeted by immunosuppressive therapy.

Patients receiving tacrolimus or cyclosporine immunosuppressive therapy should have a focused airway assessment performed, or in the event of emergent intubation, the anticipation of a possible difficult airway. Tacrolimus and cyclosporine therapy have been known to cause posttransplant lymphoproliferative disease, with a prevalence of up to 4% in the pediatric posttransplant population. This disease is due to Epstein-Barr virus resulting from cytotoxic T-cell suppression by tacrolimus and cyclosporine therapy. Affected tissues include lymph nodes, tonsils, and extranodal organs such as the liver. The risk of posttransplant lymphoproliferative disease to the pediatric patient requiring anesthesia is life-threatening airway obstruction caused by enlargement of the epiglottis and aryepiglottic folds.

Liver assessment of the patient receiving immunosuppression therapy is key in determining an anesthetic plan. Tacrolimus and cyclosporine, 2 of the more common antirejection medications, are known to have effects on liver function. In a study of 38 children receiving tacrolimus therapy, hepatic enzyme levels became slightly elevated in 7.9% of patients and markedly elevated in 7.9%. Of 73 children receiving cyclosporine therapy, 15% experienced slightly elevated hepatic enzyme levels. Hepatotoxicity was low for both groups: cyclosporine at 2.3% and tacrolimus at 0%. When developing an anesthetic plan for this population, the anesthesia practitioner must consider liver function when selecting medications based on metabolic route, as well as considerations for diminished plasma proteins and clot factors.

Tacrolimus and cyclosporine therapy have been implicated in renal compromise as well. Both immunosuppressive therapies cause renal vasoconstriction, which may lead to a dose-related decrease in renal blood flow and glomerular filtration rate. Before anesthesia, the practitioner should evaluate renal function to assess the potential impact on drug selection.

Additional considerations for the anesthetic plan for the immunosuppressed patient include route of intubation, coagulation status if regional anesthesia is to be considered, avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs), and continuation of immunosuppression regimen. Because of immunosuppression, oral endotracheal intubation is the preferred method for intubation, as the nasal passages may pose a risk of infection. If the patient is receiving azathioprine or antithymocyte for immunosuppression and regional anesthesia is planned, the platelet count should be evaluated because thrombocytopenia may occur with either medication. The NSAIDs add to the nephrotoxic effects of cyclosporines, because both drugs alter renal microcirculation. Immunosuppression should be maintained throughout the perioperative period.

**Sedation Pharmacology and Tolerance**

Critically ill pediatric patients requiring mechanical ventilation in the pediatric intensive care unit (PICU) require long-term sedation and analgesia that can have implications on anesthetic pharmacology during the perioperative phase. Pharmacodynamic tolerance is change occurring at the target receptors or distal to the receptor.
Over time this can result in a decrease in efficacy of the drug or an increasing requirement of the dose to achieve the desired effect. The pharmacodynamics of tolerance are a steady-state plasma concentration of the drug with a decreased clinical effect.

Opiates such as fentanyl are frequently administered for sedation during mechanical ventilation for the posttransplant pediatric patient. Pharmacodynamic tolerance to fentanyl has been demonstrated by Arnold et al by the measurement of plasma fentanyl concentrations required to achieve sedation goals on day 1 compared with day 8. Fentanyl infusion requirements were 11.6 ± 6.9 μg/kg/h on day 1, with an increase to 52.5 ± 19.4 μg/kg/h rate on day 8. The mechanism to pharmacodynamic tolerance in the sedated patient in the PICU is poorly understood; however, several mechanisms have been suggested. With discontinuation of opiate medications after long-term infusion, tachycardia and hypertension will result because of decreased agonist activity in the reticular activation system and sympathetic centers. If the patient is receiving opiate by infusion or as-needed IV push, the anesthesia practitioner should continue the therapy on the patient’s transport to the OR and before induction to prevent withdrawal.

Benzodiazepines such as midazolam are often used in the PICU for sedation during mechanical ventilation, as posttransplant, premature infants are often treated for respiratory failure associated with BPD. Within 24 hours of discontinuing a midazolam infusion (infusion rate range, 0.17 to 0.56 mg/kg/h), physical symptoms of withdrawal can be seen, such as tachycardia, hypertension, agitation, hallucination, hyperpyrexia, and GI symptoms. The proposed mechanism for the pharmacodynamic withdrawal of benzodiazepines is a disinhibition of the central nervous system because of the decrease in efficiency with the same concentration of γ-aminobutyric acid (GABA). Benzodiazepine therapy administered in the ICU should be continued during transport to the OR and during the preinduction period to prevent withdrawal symptoms. Au et al and Imray and Hay described case reports of prolonged propofol infusions for sedation during mechanical ventilation of more than 5 days being associated with physical withdrawal symptoms. These symptoms include confusion, generalized tonic-clonic movements, and hallucinations. There is debate that tolerance to propofol develops over repeated procedural sedation in pediatric patients. Deer and Rich published a case report on a 2-year-old male patient who received 19 treatments in which propofol was used as the induction agent, with the 19th treatment requiring a 16 mg/kg induction dose. However, Setlock et al describe a retrospective study in 134 pediatric patients, with a mean of 27 treatments, receiving radiation treatment with propofol as the procedural sedation drug of choice. The population in the study by Setlock et al did not develop a tolerance to propofol regardless of the higher mean number of procedures performed with the drug. The anesthesia practitioners who are providing procedural sedation or general anesthesia with propofol as the induction agent should be aware of the possibility of a higher induction dose of propofol, although not all pediatric patients will exhibit this.

Withdrawal symptoms seen clinically may be confused with other conditions, such as infection, central nervous system insults, hypoxia, or hypercarbia. Central nervous system manifestations of physical withdrawal include seizures, hyperactive deep tendon reflexes, tremors, generalized jitteriness, irritability, hallucination, sneezing, yawning, and hypertonicity. The GI symptoms that the anesthesia practitioner may be presented with include uncoordinated suck and swallow, vomiting, diarrhea, feeding intolerance, and persistent residuals with enteral feedings. Activation of the sympathetic nervous system is frequent, with symptoms including tachycardia, hypertension, and tachypnea. It is important to differentially diagnose the cause of clinical symptoms of withdrawal from other causes of the aforementioned symptoms.

Conclusion
As successful multivisceral organ transplants increase in pediatric patients and as these patients continue to live longer, anesthesia practitioners will increasingly see these patients as acute cases in tertiary care facilities and in community hospitals for minor procedures. Both scenarios seen by the practitioner will present similar challenges, including difficulty in venous access, impaired organ function, the side effects of common immunosuppression drugs, and the need for increased drug dosages to achieve the desired clinical effect. A thorough assessment of the affected organ systems and knowledge of the common pathophysiologic and pharmacologic issues can assist the anesthesia practitioner in developing a successful anesthetic plan for this challenging population.

REFERENCES


**AUTHOR**

Taylor Loykasek, RN, BSN, is a student at Georgetown University Nurse Anesthesia Program, Washington, DC. Email: loykastj@gmail.com

**ACKNOWLEDGMENTS**

The author would like to thank Donna Jasinski, CRNA, PhD, and Denise Tola, CRNA, MSN.