Anesthesia for Transplantation

✓ 2026 Edition

Gaurav P. Patel
Susan A. Smith
Editors

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Preface

Transplant anesthesiology represents one of the most challenging and rewarding subspecialties in modern anesthetic practice. The complexity of managing patients with end-stage organ failure, the physiologic derangements that accompany organ transplantation, and the critical timing required for successful outcomes demand a unique combination of knowledge, skill, and clinical judgment. This textbook emerges from the recognition that comprehensive, focused guidance in this rapidly evolving field is essential for anesthesiologists who care for transplant patients.

Over the past several decades, advances in immunosuppression, surgical techniques, organ preservation, and perioperative care have transformed transplantation from an experimental procedure to standard treatment for end-stage organ disease. These developments have significantly improved patient outcomes, yet they have also increased the complexity of anesthetic management. Today's transplant anesthesiologist must possess deep understanding of the pathophysiology of organ failure across multiple systems, familiarity with evolving surgical approaches, expertise in hemodynamic management during complex physiologic transitions, and knowledge of how to optimize conditions for successful graft function.

This textbook provides essential guidance for the recognition and management of unique challenges encountered in the field. Structured to address each major organ system, the book covers preoperative assessment and optimization of patients with end-stage organ disease; intraoperative management strategies for liver, kidney, heart, lung, intestines, and pancreas transplantation; the physiologic changes that occur during organ reperfusion and the immediate post-transplant period; postoperative care and common complications; and special considerations including pediatric transplantation, living donor procedures, and multiorgan transplants.

Each chapter addresses the pathophysiology of organ failure, specific anesthetic considerations, monitoring strategies, common complications and their management, and evidence-based approaches informed by current guidelines and expert consensus. These recommendations draw upon established protocols from major transplant centers, published literature, and the collective experience of leading experts in the field.

The importance of this work extends beyond technical anesthetic management. Transplant anesthesiologists serve as integral members of multidisciplinary teams, working closely with surgeons, hepatologists, cardiologists, pulmonologists, nephrologists, intensive care specialists, among others. Success in this field requires

not only anesthetic expertise but also the ability to collaborate effectively, communicate clearly under pressure, and make rapid decisions in dynamic clinical situations.

It is our hope that this textbook will serve as both a comprehensive reference and a practical guide for anesthesiologists at all career stages—from residents and fellows beginning their training in transplant anesthesia to experienced physicians seeking to refine their approach to these complex cases. We encourage readers to apply this knowledge thoughtfully, always placing patient safety and optimal outcomes at the center of clinical decision-making.

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This book represents the culmination of years of clinical work and reflects the collective expertise and support of many individuals, to whom we are deeply grateful.

We extend our sincere gratitude to all the contributing authors whose expertise and dedication made this textbook possible. Your willingness to share your knowledge, your commitment to excellence in transplant anesthesiology, and your thoughtful contributions have been invaluable to this project.

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We are profoundly grateful to the residents, fellows, anesthetists, and faculty anesthesiologists in Emory's Department of Anesthesiology. Your daily dedication to patient care, pursuit of clinical excellence, and commitment to education continue to inspire us. The questions you ask, the cases you present, and the insights you share have enriched our understanding and shaped the content of this book.

We also extend our sincere thanks to the leadership at Emory School of Medicine and the Department of Anesthesiology for their encouragement and support of this academic endeavor. Your commitment to advancing the field of anesthesiology and fostering an environment of scholarship and innovation made this work possible.

Finally, we acknowledge the transplant patients and their families, whose courage and trust in our care motivate us to continually advance our knowledge and refine our practice. It is our privilege to serve you.

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Introduction to Transplant Anesthesia

1

Susan A. Smith, Cinnamon L. Sullivan, and Gaurav P. Patel

Overview

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Organ transplantation represents one of the most remarkable achievements in modern medicine. Behind every successful transplantation lies the critical work of a multidisciplinary team, within which the transplant anesthesiologist plays a pivotal role. This chapter serves as an introduction to the specialized field of transplant anesthesiology, highlighting its significance, unique challenges, and the essential role of the transplant anesthesiologist in optimizing patient outcomes.

While subsequent chapters will explore the specific considerations for individual organ transplantations in detail, this introduction aims to establish the importance of specialized anesthetic care in the transplantation process. The evolution of transplant anesthesiology as a subspecialty mirrors the advancement of transplantation medicine itself, reflecting the increasing complexity of procedures and the growing recognition of perioperative management as a determinant of graft and patient survival.

The Unique Landscape of Transplant Anesthesiology

Transplant anesthesiology stands apart from other anesthetic subspecialties due to several distinctive characteristics. First and foremost is the complex physiological process navigated during these procedures. Patients presenting for transplantation typically suffer from end-stage organ dysfunction, which creates profound systemic effects that complicate anesthetic management [1, 8]. The anesthesiologist must possess a thorough understanding of the pathophysiology of organ failure and its implications for perioperative care [14, 16].

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Additionally, transplant procedures introduce unique logistical and timing challenges rarely encountered in other surgical specialties. The unpredictable availability of donor organs often necessitates surgery at any hour, with minimal advance notice [26, 37]. This demands that transplant anesthesiologists maintain constant readiness and the ability to rapidly formulate anesthetic plans for highly complex patients. The time-sensitive nature of organ preservation further compresses the preoperative evaluation window, requiring quick yet thorough assessment skills [21, 26].

In addition, the anesthesiologist must optimize recipient conditions to support the new organ while also preserving the integrity and function of the transplanted organ [8, 30]. This dual focus distinguishes transplant anesthesiology and demands specialized knowledge and skills that transcend traditional anesthetic practice [19, 29].

The Critical Role of Transplant Anesthesiologists

Preoperative Evaluation and Optimization

The transplant anesthesiologist's role begins before the patient arrives in the operating room. As key members of transplant selection committees, anesthesiologists contribute vital perspectives on perioperative risk assessment and potential optimization strategies [32, 33]. Their evaluation extends beyond standard preoperative assessments to include specialized considerations such as:

- Impact of end-stage organ disease on other organ systems [16, 25].
- Cardiovascular risk stratification, optimization, and ability to tolerate hemodynamic stresses of transplantation [20, 32].
- Pulmonary optimization and pulmonary complications of organ failure and implications for ventilation strategies [22, 33].
- Coagulation abnormalities associated with organ dysfunction [4, 15].
- Evaluation of frailty and consideration for prehabilitation [34].
- Metabolic derangements requiring perioperative correction [14, 35, 36].
- Immunosuppression status and infection risk [31, 33].

The transplant anesthesiologist's preoperative involvement may span months or years as patients await suitable donor organs. During this time, they contribute to ongoing risk assessment and patient optimization, often serving as consultants to help maintain transplant candidacy despite progressive organ dysfunction [20, 37].

When a donor organ becomes available, the preoperative assessment must be quickly updated, focusing on interval changes in the recipient's condition and any acute issues that might impact transplant success [26, 37]. This rapid yet comprehensive evaluation requires significant clinical judgment and efficiency [19].

Intraoperative Management
The intraoperative phase represents the most visible aspect of transplant anesthesiology. During surgery, the anesthesiologist must balance multiple competing priorities:

1. *Hemodynamic Management*: Maintaining adequate organ perfusion while adapting to physiologic changes during various phases of transplantation [5, 7, 26]. This may include managing large-volume fluid shifts, significant blood loss, reperfusion phenomena, and post-implantation graft function [12, 21, 27].
2. *Preservation of Residual Organ Function*: Protecting remaining functional capacity of compromised organs through careful selection of anesthetic agents, ventilation strategies, and hemodynamic targets [1, 8, 19].
3. *Coagulation Management*: Navigating the complex coagulopathies associated with end-stage organ disease, massive transfusion, and reperfusion, often requiring point-of-care testing and individualized component therapy [4, 6, 12, 15].
4. *Metabolic Homeostasis*: Addressing acid-base disturbances, electrolyte abnormalities, glucose derangements, and temperature management, particularly during the reperfusion phase [2, 10, 35, 36].
5. *Immunomodulation*: Coordinating the administration of immunosuppressive induction therapy within the context of anesthetic management [19, 31].

These challenges require not only technical expertise but also situational awareness and communication skills. The transplant anesthesiologist must anticipate potential complications before they manifest and coordinate responses with surgical colleagues [18, 19].

Postoperative Care and Transition
Transplant anesthesiologists often remain involved in long-term follow-up, particularly when recipients require subsequent procedures or develop complications related to immunosuppression or chronic rejection [9, 12, 25].

Evolution of Transplant Anesthesiology

The history of transplant anesthesiology parallels the broader trajectory of transplantation medicine. From the early historical kidney transplants to the complex multi-organ procedures today, anesthetic management has evolved significantly [23, 31]. Early transplant anesthetics focused primarily on basic physiologic support, with limited monitoring capabilities and pharmacological options.

As transplantation expanded to include liver, heart, lung, and composite tissue procedures, anesthetic techniques grew increasingly sophisticated [1, 19, 29]. The introduction of advanced monitoring, specialized pharmacologic agents, and improved understanding of transplant physiology changed the field. Particularly significant has been the development of organ-specific protection strategies and the recognition of reperfusion injury as a critical determinant of outcome [8, 12, 30].

Modern transplant anesthesiology incorporates advanced technologies such as transesophageal echocardiography, thromboelastography, continuous cardiac output monitoring, and advanced ventilation strategies [4, 7, 15]. These tools, combined with enhanced pharmacologic options and preservation techniques, have contributed to steadily improving outcomes despite increasingly complex recipient populations [14, 18].

The subspecialty continues to evolve, with current research focusing on areas such as machine perfusion of donor organs, xenotransplantation considerations, and personalized immunomodulation strategies [11, 14, 31]. Transplant anesthesiologists are at the forefront of these innovations, contributing both expertise and research insights [18, 19].

Organizational and Educational Framework

The recognition of transplant anesthesiology as a distinct subspecialty has led to the development of formal fellowship training programs and specialized practice groups [26, 27]. Major transplant centers typically maintain dedicated teams of anesthesiologists with specialized training and experience in transplantation. These teams work collaboratively with surgeons, intensivists, coordinators, and other specialists to provide comprehensive transplant care [19, 26].

Professional societies such as the Society for the Advancement of Transplant Anesthesia (SATA) and the Liver Transplantation Section of the International Liver Transplantation Society (ILTS) provide organizational frameworks for education, research, and practice standards [3, 19]. Fellowship programs now offer structured training in the specific knowledge domains required for transplant anesthesiology.

These educational pathways reflect the growing recognition that transplant anesthesiology requires specialized knowledge beyond that provided in general anesthesiology training [19, 26, 27].

Current Challenges and Future Directions

Despite remarkable progress, transplant anesthesiology faces significant challenges. The persistent organ shortage has led to expanded donor criteria, resulting in more marginal organs being utilized [11, 14]. This trend requires transplant anesthesiologists to develop new strategies for optimizing outcomes with a higher number of Extended Criteria Grafts, including machine perfusion technologies and novel pharmacological approaches [11, 21].

Additionally, the increasing age and comorbidities of transplant recipients require more sophisticated risk assessment and perioperative management [16, 20, 25]. Transplant anesthesiologists must balance the desire to provide transplantations against the risks of adverse outcomes in increasingly complex and sicker patients [12, 14, 20].

Ethical Considerations in Transplant Anesthesiology

Transplantation medicine inherently involves complex ethical considerations, and anesthesiologists encounter these dilemmas throughout their practice [12, 19]. Issues such as organ allocation, management of living donors, determination of futility, and resource utilization all intersect with anesthetic practice [11, 24].

Transplant anesthesiologists often participate in difficult decisions regarding candidate selection, balancing medical suitability against the ethical imperative to provide life-saving therapy [19, 30]. They may also be involved in living donor procedures, where they must prioritize the safety and welfare of healthy individuals undergoing surgery for the benefit of others [11, 26].

Conclusion

Transplant anesthesiology represents a specialized field requiring unique knowledge, skills, and perspective [18, 27]. The transplant anesthesiologist serves not only as a perioperative physician but as an integral member of the transplant team throughout the patient journey [19, 22, 26]. Their expertise influences decisions from candidate selection through long-term follow-up, with a significant impact on graft and patient outcomes [11, 12, 17].

The challenges of transplant anesthesiology—physiological complexity, logistical demands, and technical difficulty—are balanced by the reward of participating in truly important care [1, 8, 27].

As transplantation medicine continues to advance, the role of specialized anesthesia care will only grow in importance [17, 19]. The expertise of transplant anesthesiologists will remain essential to navigating the increasingly complex landscape of organ replacement therapy and maximizing the benefit derived from each precious donor organ [12, 26].

The chapters that follow will explore the specific considerations for individual organ transplantation procedures. Each type of transplantation presents unique challenges and considerations, yet all share the common theme of requiring specialized anesthetic expertise to optimize outcomes [1, 18, 27].

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Preoperative Evaluation for Liver and Kidney Transplantation

2

Kathleen Yu and Susan A. Smith

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The decision to proceed with transplantation requires careful weighing of operative risks against anticipated survival benefit and improvement in quality of life. The preoperative evaluation assesses the severity of primary organ failure, the presence and extent of dysfunction in other organ systems, and comorbid conditions that may influence the perioperative management and posttransplant outcomes. This multidisciplinary process includes a detailed history and physical examination, laboratory and diagnostic testing, and consultation with specialists in cardiology, pulmonology, infectious diseases, behavioral health, and other fields. Because waiting times for donor organs are often prolonged, a candidate's clinical status may change substantially between initial listing and the time of transplantation. A final preoperative assessment, performed in the hours before surgery, is therefore essential to identify interval disease progression or development of new comorbidities, anticipate perioperative risk, and create an individualized anesthetic and perioperative management plan. This chapter presents an organ-based framework for the preoperative evaluation of candidates for kidney and liver transplantation, with a focus on considerations that inform perioperative care.

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Kidney Transplantation

Pathophysiology of End-Stage Renal Disease

End-stage renal disease represents the most advanced stage of chronic kidney disease and is characterized by irreversible loss of kidney function, defined by an estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73 m^2 or the requirement for renal replacement therapy, including dialysis or kidney transplantation [205]. The most common etiologies include diabetes mellitus, hypertension, glomerular diseases, cystic kidney diseases, and interstitial nephritis [93]. Identification of the underlying cause is important because it informs the risk of disease recurrence after transplantation and helps anticipate systemic manifestations related to the primary disease process. As kidney function declines, patients may develop volume overload, resistant hypertension, anemia, metabolic acidosis, electrolyte abnormalities (including hyperkalemia, hyponatremia, hypocalcemia, and hyperphosphatemia), chronic kidney disease–mineral and bone disorder, protein-energy malnutrition, and uremic symptoms [205]. Because end-stage renal disease affects multiple organ systems, a structured preoperative evaluation is essential to identify comorbid conditions that influence perioperative risk and to optimize modifiable factors before surgery.

Preoperative Evaluation

Cardiovascular

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease, accounting for approximately half of deaths among patients receiving dialysis and one-third of deaths after kidney transplantation [25, 91]. The primary objective of preoperative cardiac evaluation is to identify active cardiac conditions, including unstable coronary syndromes, decompensated heart failure, severe valvular disease, and clinically significant arrhythmias that may require treatment before transplantation or preclude candidacy [37]. The evaluation also provides an opportunity to optimize cardiovascular risk factors to reduce perioperative and posttransplant complications.

All kidney transplant candidates should undergo a cardiovascular assessment that includes a comprehensive history and physical examination, a resting 12-lead electrocardiogram, and transthoracic echocardiography [37, 40]. Common echocardiographic findings in this population include left ventricular hypertrophy, systolic and diastolic dysfunction, valvular calcification, pericardial effusion, and features consistent with uremic cardiomyopathy [91]. Cardiology consultation is indicated for patients with symptomatic cardiovascular disease, echocardiographic findings suggestive of significant coronary artery disease, including regional wall motion abnormalities or left ventricular ejection fraction less than 40%, clinically significant valvular disease, or pulmonary hypertension [40].

The role of noninvasive stress testing in asymptomatic kidney transplant candidates remains controversial. The most recent American Heart Association and American College of Cardiology guidance supports the selective use of stress echocardiography or myocardial perfusion imaging in asymptomatic candidates with multiple cardiovascular risk factors, including advanced age, smoking, diabetes mellitus, cerebrovascular disease, peripheral artery disease, or dialysis duration longer than 1 year [40]. Routine noninvasive stress testing in asymptomatic candidates without high-risk features is generally discouraged, as it has not been shown to improve posttransplant outcomes [37, 40]. Commonly used testing modalities, such as dobutamine stress echocardiography, nuclear perfusion imaging, and coronary computed tomography angiography, have important limitations in patients with advanced kidney disease. Coronary computed tomography angiography has high sensitivity but limited specificity due to extensive vascular calcification related to mineral metabolism and the weak correlation between coronary calcium burden and inducible ischemia [39, 55]. Contrast exposure and overestimation of disease severity may lead to unnecessary invasive testing and delays in transplantation [55].

Coronary angiography remains the definitive method for assessing coronary anatomy and ischemic burden in candidates with abnormal noninvasive testing or known coronary artery disease [40]. Decisions regarding revascularization should be individualized based on symptom burden, left ventricular function, procedural risk, and the ability to tolerate and adhere to dual antiplatelet therapy [37, 40]. Randomized trial data in patients with advanced chronic kidney disease and stable ischemic heart disease have not demonstrated reductions in mortality or nonfatal myocardial infarction with coronary angiography and revascularization in addition to optimal medical therapy, compared with optimal medical therapy alone [20, 82]. Revascularization is therefore generally reserved for patients with high-risk coronary anatomy, such as significant left main coronary disease, severely reduced left ventricular systolic function with ejection fraction less than 30%, refractory angina despite guideline-directed medical therapy, or other features conferring critical ischemic risk [40, 82]. After percutaneous coronary intervention, kidney transplantation should be deferred until completion of the required course of dual antiplatelet therapy [127, 144].

Because waiting times for deceased donor organs are often prolonged, practices related to surveillance for coronary artery disease after waitlisting vary widely among transplant centers. Some programs perform periodic reassessments every 1–2 years based on perceived cardiovascular risk, while others repeat testing only when new symptoms develop or comorbid conditions progress [40]. The optimal surveillance strategy remains uncertain. Ongoing clinical trials are evaluating whether foregoing routine repeat screening in asymptomatic waitlisted patients is noninferior to periodic screening and may help inform future, more evidence-based surveillance recommendations [237].

Arrhythmia assessment is an integral component of preoperative cardiac evaluation. Atrial fibrillation is the most common arrhythmia in patients receiving dialysis and is associated with increased risks of stroke, heart failure, and mortality [72, 234, 241]. In patients with atrial fibrillation, ventricular rate should be adequately

controlled, and a perioperative anticoagulation strategy should be established [213]. Among older recipients, atrial fibrillation has been associated with increased early posttransplant mortality [123]. Other clinically significant arrhythmias, including ventricular tachyarrhythmias, high-grade atrioventricular block, or newly identified conduction abnormalities, may increase the risk of sudden cardiac death and warrant further evaluation, including consideration of cardiac implantable electronic devices when indicated [193, 223]. Perioperative management of cardiac devices should follow institutional protocols. Because kidney transplantation is typically performed below the umbilicus, clinically significant electromagnetic interference is uncommon, and routine device reprogramming is usually unnecessary [213]. Preoperatively, clinicians should confirm the device type, manufacturer, indication, pacing dependence, response to magnet application, and battery status [213]. A coordinated perioperative plan involving electrophysiology, anesthesia, and surgery is essential, with continuous monitoring and availability of backup pacing and defibrillation capabilities [213].

Valvular heart disease is also common in end-stage renal disease, with progressive calcification of the aortic and mitral valves often leading to clinically significant stenosis or regurgitation [141]. Transthoracic echocardiography should be performed when patients are euvolemic, ideally after dialysis at dry weight with adequate blood pressure control, to accurately assess lesion severity [141]. Decisions regarding the timing of valvular intervention relative to transplantation should be individualized in collaboration with cardiology, taking into account symptom burden, lesion severity, and surgical risk. Intervention is indicated for symptomatic severe valvular disease and may be considered in selected asymptomatic patients with severe regurgitant lesions, severe aortic stenosis, or rapidly progressive disease [141]. Annual echocardiographic surveillance is recommended for patients with known moderate or severe valvular disease [37, 141].

Pulmonary

Pulmonary abnormalities are prevalent in end-stage renal disease and reflect the effects of volume overload, uremia, and disordered mineral metabolism. Fluid retention and increased pulmonary vascular permeability may lead to pleural effusions and pulmonary edema, reducing gas exchange and respiratory reserve [189]. Additional manifestations include uremic pleuritis, pulmonary fibrosis, metastatic pulmonary calcification, and respiratory muscle weakness [189]. Pulmonary hypertension is frequently encountered, with reported prevalence as high as 80% [53]. Its pathogenesis is multifactorial and includes chronic left-sided volume overload, high-output states related to arteriovenous fistulas, chronic anemia, endothelial dysfunction, and pulmonary vascular calcification in the setting of abnormal calcium–phosphate homeostasis [53]. Obstructive sleep apnea affects an estimated 50–60% of patients with advanced chronic kidney disease [3]. Recurrent hypoxemia and hypercapnia can promote pulmonary vasoconstriction and may exacerbate pulmonary hypertension [76]. Clinically significant pulmonary hypertension is associated with right- and left-sided heart failure, chronic respiratory failure, and increased mortality, underscoring the importance of careful pulmonary assessment during transplant evaluation [183].

The primary goals of preoperative pulmonary evaluation are to establish baseline respiratory status and to estimate the risk of postoperative pulmonary complications. Initial screening should include pulse oximetry and chest radiography [37]. Chest computed tomography is recommended for candidates with chronic obstructive pulmonary disease or substantial smoking history (30 pack-years or greater) to better characterize parenchymal lung disease and assess malignancy risk [37]. Pulmonary function testing should be obtained in patients with reduced functional capacity, significant respiratory symptoms, or known pulmonary disease [37]. Severe obstructive or restrictive abnormalities on spirometry may indicate prohibitive perioperative risk and should prompt specialist evaluation to determine transplant suitability [37].

Assessment for sleep-disordered breathing and pulmonary hypertension is an important component of pulmonary evaluation. Candidates with symptoms or risk factors for obstructive sleep apnea should undergo polysomnography, with initiation of continuous positive airway pressure therapy when obstructive sleep apnea is confirmed [76]. Asymptomatic candidates who have been receiving dialysis for at least 2 years or who have risk factors for pulmonary hypertension, including portal hypertension, connective tissue disease, congenital heart disease, or chronic obstructive pulmonary disease, should undergo screening with transthoracic echocardiography [37]. Transthoracic echocardiography is also indicated in symptomatic patients to assess right ventricular size and function and to estimate pulmonary artery pressures [37]. Candidates with an estimated pulmonary systolic pressure greater than 45 mm Hg should be evaluated by a cardiologist [37]. When echocardiographic findings suggest clinically significant pulmonary hypertension, when the diagnosis remains uncertain, or when findings are expected to influence candidacy or perioperative management, right heart catheterization should be considered to confirm the diagnosis and define pulmonary vascular resistance and filling pressures [53]. Patients who require pulmonary hypertension-directed therapy should be managed collaboratively with cardiology or pulmonology specialists, with optimization of treatment and volume status before transplantation. Because some pulmonary hypertension therapies interact with calcineurin inhibitors and other immunosuppressants, close postoperative monitoring for drug–drug interactions and therapeutic efficacy is warranted [189].

Tobacco use should be addressed in all candidates through counseling and structured cessation support. Kidney Disease: Improving Global Outcomes guidelines recommend smoking cessation at least 1 month before waitlisting but do not mandate exclusion of candidates who continue to smoke [37]. Ongoing tobacco use, however, is associated with inferior posttransplant outcomes compared with cessation [59]. In the setting of limited organ availability, some transplant programs incorporate active smoking into candidacy decisions and may defer transplantation until smoking cessation is achieved.

Hematologic

Patients with end-stage renal disease have a complex hemostatic profile characterized by concurrent risks of bleeding and thrombosis [50, 69]. Bleeding tendency is largely attributable to uremia-induced platelet dysfunction, in which accumulation

of uremic toxins impairs platelet adhesion and aggregation and disrupts primary hemostasis [101]. Clinically, this dysfunction may present as mucocutaneous bleeding, oozing from vascular access sites, or gastrointestinal bleeding [101]. Anemia is nearly universal in this population and further contributes to bleeding risk by reducing platelet–endothelial interactions and impairing oxygen delivery [67]. The etiology of anemia is multifactorial and includes inadequate erythropoietin production by peritubular interstitial cells, inflammation-mediated iron sequestration and impaired absorption, dialysis-related blood loss, occult gastrointestinal bleeding, frequent phlebotomy, micronutrient deficiencies, and shortened red blood cell survival [67, 156].

Despite heightened bleeding risk, patients with end-stage renal disease are also predisposed to thrombosis. Circulating procoagulant factors, including fibrinogen, factors VII and VIII, von Willebrand factor, homocysteine, prothrombin fragments, and D-dimer, are often elevated because of increased hepatic synthesis and reduced renal clearance [35]. Concurrent depletion of endogenous anticoagulants such as antithrombin III, together with impaired fibrinolysis due to reduced plasminogen levels and increased plasmin–antiplasmin complexes, further shifts the hemostatic balance toward thrombosis [226]. Use of erythropoiesis-stimulating agents may additionally increase thrombotic risk by increasing blood viscosity and promoting platelet activation [132]. A history of venous thromboembolism, particularly recurrent or unprovoked events, warrants careful review of prior episodes and current anticoagulation, and consideration of hematology consultation. Testing for inherited or acquired thrombophilia may be appropriate in selected cases, but many assays have limited reliability in end-stage renal disease, and results should be interpreted cautiously [236].

Given these competing risks, a structured hematologic evaluation is essential. Initial assessment should include a complete blood count with differential and reticulocyte count to assess anemia severity and marrow response [147]. Iron studies, including ferritin and transferrin saturation, are needed to evaluate iron stores and guide supplementation. Measurement of vitamin B12 and folate levels is recommended to identify reversible nutritional deficiencies [147]. In patients receiving erythropoiesis-stimulating agents, recent hemoglobin trends and dosing history should be reviewed [147]. Standard coagulation tests, including prothrombin time, activated partial thromboplastin time, and fibrinogen concentration, may identify overt coagulopathies but do not assess uremic platelet dysfunction, making a detailed bleeding history a critical component of risk stratification [147]. In selected high-risk patients, platelet function testing or viscoelastic studies, including thromboelastography or rotational thromboelastometry, may provide additional information, although their role in end-stage renal disease has not been validated and availability varies across centers [175].

Preoperative management should balance bleeding and thrombosis risk and focus on the correction of reversible abnormalities. Anemia should be managed stepwise by addressing iron, vitamin B12, and folate deficiencies. Intravenous iron is preferred over oral formulations in the setting of chronic inflammation or functional iron deficiency [147]. Erythropoiesis-stimulating agents should be used

judiciously to maintain hemoglobin level in the range of 10–12 g/dL, as overcorrection is associated with increased thrombotic risk [147, 148]. Red blood cell transfusion should be reserved for symptomatic or refractory anemia because of the risks of volume overload and human leukocyte antigen alloimmunization [211]. In patients with uremic platelet dysfunction, dialysis within 24 h of transplantation may reduce circulating uremic toxins and improve hemostasis [154]. Desmopressin may be administered before surgical incision to transiently enhance platelet function through the release of von Willebrand factor and factor VIII; however, evidence demonstrating a reduction in bleeding in this setting is limited [196]. Cryoprecipitate or antifibrinolytic therapy may be considered for refractory bleeding [196].

Many kidney transplant candidates receive chronic anticoagulant or antiplatelet therapy for atrial fibrillation, venous thromboembolism, coronary artery disease, or dialysis access patency. The need for antithrombotic therapy should not preclude transplant candidacy [37]. At the time of donor organ offer, antiplatelet agents should be withheld and anticoagulation reversed when feasible, recognizing that complete drug clearance is often not possible [35]. Observational data suggest that, with appropriate perioperative management, rates of reoperation and transfusion are not increased among recipients receiving antithrombotic therapy [61]. Direct-acting oral anticoagulants require caution. Kidney Disease: Improving Global Outcomes guidelines recommend avoiding transplantation while a patient is actively receiving a direct-acting oral anticoagulant unless the program has perioperative expertise and access to reversal agents [37]. When these resources are unavailable, candidates should be transitioned to a vitamin K antagonist before waitlisting, in consultation with hematology [37]. For patients receiving vitamin K antagonists, perioperative management should be individualized based on thrombotic and bleeding risk, including consideration of prothrombin complex concentrate for rapid reversal when transplantation is imminent [37]. In patients with prior heparin-induced thrombocytopenia, perioperative anticoagulation should use non-heparin agents [37]. Overall, antithrombotic management requires multidisciplinary coordination to optimize intraoperative safety.

Endocrine

Endocrine and metabolic disorders are common in patients with end-stage renal disease and have important implications for candidacy and perioperative risk. Diabetes mellitus is the leading cause of end-stage renal disease and the most frequent indication for renal replacement therapy worldwide [51, 217]. Chronic hyperglycemia leads to progressive glomerular injury, resulting in proteinuria, hypertension, and irreversible loss of kidney function [9]. Many candidates also have microvascular and macrovascular complications, including retinopathy, neuropathy, and autonomic dysfunction, and an increased burden of coronary, peripheral, and cerebrovascular disease [9]. Pretransplant evaluation should assess glycemic control using hemoglobin A1c and fasting plasma glucose, review insulin and noninsulin treatments, document duration of diabetes, and evaluate for end-organ complications [37]. Adequate glycemic control reduces the risk of perioperative infections, wound complications, and cardiovascular events, and a hemoglobin

A1c target of 7.0% is generally recommended [51]. Glycemic targets should be individualized to reduce hypoglycemia risk, particularly in frail patients and in those with poor nutritional status.

Thyroid dysfunction is more prevalent in patients with end-stage renal disease than in the general population [178]. Hypothyroidism is associated with fatigue, fluid retention, depression, cognitive impairment, and adverse cardiovascular outcomes. Hyperthyroidism, although less common than hypothyroidism in advanced kidney disease, may precipitate tachyarrhythmias, high-output heart failure, and, in severe cases, thyroid storm [153]. Thyroid function testing, including measurement of thyroid-stimulating hormone and free thyroxine, should be performed in candidates with symptoms suggestive of thyroid disease or with a known thyroid disorder, and abnormalities should be treated before transplantation [178].

Metabolic syndrome is defined by the presence of at least three of the following features: central obesity, insulin resistance, hypertension, hypertriglyceridemia, and low high-density lipoprotein cholesterol [214, 240]. Obesity increases operative complexity and is associated with higher rates of wound complications and delayed graft function [43]. Dyslipidemia is common in patients with advanced kidney disease and often persists or worsens after transplantation because of the metabolic effects of immunosuppressive therapy [43]. Preoperative management should emphasize weight reduction, blood pressure control, and lipid-lowering therapy to reduce cardiovascular risk [37]. Many transplant programs apply an upper body mass index threshold, commonly 35–40 kg/m^2, to start transplant evaluation because of the increased risk of perioperative complications and graft loss in patients with severe obesity [34, 170].

Chronic kidney disease–mineral and bone disorder reflects disrupted calcium, phosphate, parathyroid hormone, and vitamin D homeostasis [161]. Reduced renal phosphate excretion and impaired vitamin D activation promote hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism, contributing to renal osteodystrophy, increased fracture risk, vascular and soft tissue calcification, and increased cardiovascular morbidity [161]. Evaluation should include measurement of serum calcium, phosphorus, parathyroid hormone, and alkaline phosphatase. Routine monitoring is recommended beginning at chronic kidney disease stage 3a [102]. Management includes dietary phosphate restriction and use of phosphate binders, vitamin D analogs, and calcimimetic agents [37, 102]. In patients with severe hyperparathyroidism refractory to medical therapy, parathyroidectomy should be considered before transplantation to reduce the risk of persistent hyperparathyroidism and to improve graft and patient outcomes [14, 33].

Gastrointestinal

Patients with end-stage renal disease have an increased risk of peptic ulcer disease and ulcer-related bleeding compared to the general population, and peptic ulcer disease remains the most common gastrointestinal complication after transplantation [48, 167]. Contributing factors include uremia-related mucosal injury, altered gastric acid secretion, and chronic exposure to corticosteroids or nonsteroidal

anti-inflammatory drugs [224]. Symptomatic patients should undergo testing for *Helicobacter pylori* infection and esophagogastroduodenoscopy [37]. Kidney transplantation should be deferred in the presence of active peptic ulcer disease until healing is confirmed on endoscopy [37]. Routine endoscopic screening for peptic ulcer disease, diverticular disease, or gallstones is not recommended in asymptomatic candidates [37, 58].

Because immunosuppression increases the risk of viral reactivation and progression of liver disease, all candidates should undergo screening for chronic viral hepatitis [37]. Evaluation includes testing for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C virus antibody, with confirmatory nucleic acid testing when serologies are positive [66, 94, 103]. Transplantation should be delayed in candidates with acute hepatitis until hepatic function has stabilized [37]. Candidates with cirrhosis require hepatology consultation to assess disease severity and cirrhosis-related complications [37]. Isolated kidney transplantation may be appropriate in patients with compensated cirrhosis, whereas decompensated liver disease warrants evaluation for simultaneous liver–kidney transplantation [37, 56, 155].

Patients with end-stage renal disease also have an elevated risk of colorectal cancer, which may increase further after transplantation because of chronic immunosuppression [6, 16, 160]. Colorectal cancer screening should follow age- and risk-based guidelines established for the general population, with earlier initiation or more frequent surveillance in candidates with a personal or family history of colorectal cancer or inflammatory bowel disease [37]. Lesions suspicious for advanced adenoma or carcinoma should be definitively treated before transplantation [37].

Gastrointestinal bleeding contributes to iron deficiency and anemia in this population [150]. Risk factors include uremic platelet dysfunction, use of antithrombotic agents, heparin exposure during dialysis, gastrointestinal angiodysplasia, and peptic ulcer disease [150, 188]. Peptic ulcer disease is the predominant cause of upper gastrointestinal bleeding, while angioectasias are the leading cause of lower gastrointestinal bleeding [100]. Evaluation is indicated when iron deficiency persists despite supplementation, anemia is disproportionate to dialysis-related losses, or previously stable hemoglobin levels decrease abruptly [188]. Esophagogastroduodenoscopy and colonoscopy are first-line diagnostic studies [188]. Management includes endoscopic treatment of identified lesions, eradication of *Helicobacter pylori* infection when present, optimization of dialysis, and correction of iron deficiency with intravenous iron therapy [37].

Other gastrointestinal conditions may affect transplant candidacy and perioperative management. Transplantation should be deferred after acute pancreatitis until complete clinical resolution, typically after a minimum of 3 months without recurrence [37]. Chronic pancreatitis with exocrine insufficiency should be treated with pancreatic enzyme replacement therapy [37]. Symptomatic cholelithiasis should be managed with cholecystectomy prior to transplantation to reduce the risk of post-transplant biliary complications [37]. Routine prophylactic cholecystectomy in asymptomatic patients has not demonstrated a clear benefit, but cholecystectomy

may be considered in selected high-risk individuals, such as those with a history of gallstone pancreatitis [37]. Inflammatory bowel disease is not a contraindication to transplantation, but transplantation should be performed during clinical remission, as active disease increases postoperative risk and may complicate immunosuppressive management [37, 78]. Gastroparesis, particularly in patients with diabetes mellitus, can impair nutritional intake and increase aspiration risk [191, 207]. Symptoms such as nausea, early satiety, or vomiting should prompt evaluation and inform anesthetic and nutritional planning.

Sarcopenia and frailty are widespread in patients with end-stage renal disease and are important predictors of transplant outcomes [105]. Sarcopenia, defined by reduced skeletal muscle mass and strength, is associated with increased risks of graft failure and mortality [62, 70, 206]. Frailty reflects diminished physiologic reserve across multiple domains, including mobility, strength, nutrition, and cognition, and is associated with delayed graft function, reduced tolerance of immunosuppression, early hospital readmission, and increased posttransplant mortality [70, 71, 145, 146]. Although no single screening tool has been universally adopted, frailty assessment should be incorporated into the transplant evaluation to support risk stratification and perioperative planning [130]. Candidates identified as frail or sarcopenic may benefit from comprehensive geriatric assessment and often require prolonged rehabilitation and delayed return to independent ambulation [152, 173]. Early identification allows for implementation of targeted prehabilitation strategies that may partially reverse frailty [110]. Prehabilitation should include progressive resistance and aerobic exercise, balance and gait training, and nutritional optimization with adequate protein and caloric intake [200]. Correction of vitamin D deficiency, anemia, and iron deficiency may further improve exercise tolerance and facilitate participation in rehabilitation [200]. Perioperative care should emphasize early mobilization, adequate nutrition, and multimodal analgesia with minimization of systemic opioid exposure [130].

Neurologic

Preoperative neurologic evaluation should focus on cognitive function, prior cerebrovascular events, peripheral and autonomic neuropathy, and other neurologic disorders that may affect perioperative management, adherence to immunosuppressive therapy, or posttransplant recovery. Cognitive impairment may involve deficits in attention, memory, language, or executive function and can compromise informed consent, medication adherence, and self-care [95]. When cognitive impairment is suspected, screening with validated tools such as the Mini-Mental State Examination or Montreal Cognitive Assessment is recommended [95]. Abnormal screening results should prompt further evaluation but do not, in isolation, preclude transplantation [37]. Decisions regarding transplant candidacy should consider severity and stability of impairment, availability of caregiver support, and anticipated benefit from transplantation [37].

Uremic encephalopathy is a potentially reversible neurologic syndrome resulting from the accumulation of uremic toxins, electrolyte disturbances, and impaired blood–brain barrier function [184]. Clinical manifestations include fluctuating

mental status, impaired attention and memory, sleep–wake disturbances, tremors or asterixis, and, in severe cases, seizures or coma [197]. Episodes may be precipitated by infection or inadequate dialysis and often improve with optimization of renal replacement therapy [197]. Diagnosis is clinical and requires exclusion of alternative causes of encephalopathy. Blood urea nitrogen concentrations correlate poorly with symptom severity, and neuroimaging is often nonspecific [184].

End-stage renal disease is associated with an increased risk of ischemic and hemorrhagic stroke and transient ischemic attack, reflecting the combined effects of traditional vascular risk factors and dialysis-related mechanisms, such as endothelial injury, vascular calcification, and dialysis-associated cerebral hypoperfusion [104, 120, 142]. Neuroimaging may reveal white matter disease, silent cerebral infarction, or cerebral microbleeds [104, 120]. Patients with a history of stroke or transient ischemic attack require careful neurologic assessment. Current guidelines recommend deferring kidney transplantation for at least 6 months after stroke and at least 3 months after transient ischemic attack to allow for neurologic stabilization and reassessment of functional status [37]. Routine carotid ultrasonography is not recommended in asymptomatic candidates without focal neurologic findings or carotid bruits [37, 185].

Peripheral and autonomic neuropathies result from uremia, diabetes, nutritional deficiencies, and dialysis-related factors [15]. Peripheral neuropathy typically presents as a distal, symmetric sensorimotor process and may range from mild sensory loss to painful paresthesia, muscle cramps, gait instability, and weakness [15]. These symptoms can potentially limit mobility and rehabilitation after transplantation. Evaluation should document symptom burden, distribution and severity of deficits, history of falls, and use of neuropathic pain medications. Autonomic dysfunction may manifest as orthostatic hypotension, impaired heart rate variability, disordered thermoregulation, and gastrointestinal dysmotility [192]. Autonomic neuropathy increases susceptibility to intraoperative hypotension and exaggerated blood pressure fluctuations during anesthetic induction and surgery, and should prompt close hemodynamic monitoring and vasoactive support when indicated [192].

Selective neurologic screening is appropriate in specific high-risk populations. Patients with autosomal dominant polycystic kidney disease have an increased risk of intracranial aneurysm [28]. Screening with magnetic resonance angiography or computed tomography angiography is recommended for candidates with a personal history or a first-degree family history of subarachnoid hemorrhage [37]. Screening may also be considered in candidates with a prior intracranial aneurysm or new, concerning neurologic symptoms. When an intracranial aneurysm is identified, management should be determined in consultation with neurology and neurosurgery, taking into account aneurysm size and location, rupture history, and procedural risk [28]. These findings may influence transplant timing, the need for pretransplant intervention, and perioperative blood pressure goals.

Many neurologic complications improve following successful kidney transplantation. Observational data demonstrate a reduced risk of subsequent cerebrovascular events among transplant recipients compared with candidates who remain on the

waiting list [126]. Peripheral neuropathy may stabilize or improve, particularly when uremia is a contributing factor [26, 27, 85]. Mild cognitive impairment or stable neuropathies do not preclude transplantation. In contrast, progressive neurodegenerative disorders, such as advanced dementia, remain contraindications because of the risk of nonadherence and limited survival benefits [37].

Infectious Disease

Patients with end-stage renal disease have increased susceptibility to infection as a result of uremia-associated impairment of innate and adaptive immune responses, leading to diminished host defense and reduced vaccine effectiveness [99]. Additional contributors to infection risk include the presence of indwelling dialysis catheters, shared medical equipment, and frequent exposure to healthcare settings. Patients receiving dialysis are at risk for catheter-associated bloodstream infections and peritonitis [17]. Given this heightened baseline risk and the need for life-long immunosuppression after transplantation, infectious disease evaluation is essential to identify active infections, detect latent infections with potential for reactivation, and guide vaccination, prophylaxis, and posttransplant surveillance strategies.

Evaluation should begin with a detailed clinical history that includes prior infections, antimicrobial exposures, occupational and environmental exposures, travel to endemic regions, and behavioral risk factors [37, 66]. Standard laboratory screening includes serologic testing for human immunodeficiency virus types 1 and 2, human T lymphotropic virus types 1 and 2, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, herpes simplex virus, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody, and syphilis [37, 66, 103]. Screening for latent tuberculosis infection should be performed using either purified protein derivative skin testing, with consideration of anergy in immunocompromised patients, or an interferon gamma release assay [37, 66]. Testing for regionally endemic pathogens, including *Strongyloides stercoralis*, *Trypanosoma cruzi*, and *Coccidioides* species, should be guided by epidemiologic risk and exposure history [37, 125].

Immunization status should be reviewed and updated before transplantation, as vaccine responses are more robust when vaccines are administered several months before initiation of immunosuppression. Inactivated vaccines are safe in this population and should be administered in accordance with national recommendations [37, 49]. Candidates should receive an annual inactivated influenza vaccination, pneumococcal polysaccharide vaccination if not administered within the previous 5 years, and hepatitis A and hepatitis B vaccination if seronegative [37, 49]. Tetanus, diphtheria, and pertussis vaccination should be updated if not administered within the preceding 10 years. Human papillomavirus vaccination is recommended regardless of age [37, 49].

Live attenuated vaccines, including measles, mumps, and rubella and varicella, may be administered to seronegative candidates who are not significantly immunocompromised, provided vaccination occurs at least 4 weeks before transplantation [37, 49]. Live vaccines are contraindicated after transplantation because of the risk of uncontrolled replication of vaccine-derived viral strains in the setting of immunosuppression [49].

Contraindications to Transplantation

Referral for kidney transplant evaluation is typically guided by clinical judgment rather than rigidly applied criteria. Nephrologists integrate patient-specific factors with transplant center policies, professional societies, and their own clinical experience. National survey data demonstrate substantial variability in how these criteria are interpreted and applied, especially with respect to psychosocial factors, leading to differences in referral practices across clinicians and care settings [232]. Contraindications to transplantation are best understood as absolute or relative, depending on whether transplantation is unlikely to provide benefit or poses unacceptable risk, or whether risks may be mitigated through treatment, time, and further management.

Absolute contraindications are conditions in which transplantation is unlikely to confer meaningful improvement in survival or quality of life or would expose the patient to unacceptably high risk. These include active, untreated infection and active malignancy, with the exception of certain indolent or low-grade cancers for which immunosuppression is unlikely to worsen outcomes [37]. Transplantation is also contraindicated in patients with severe, irreversible cardiac or pulmonary disease that prevents safe surgery, decompensated cirrhosis when combined liver–kidney transplantation is not planned, and progressive central neurodegenerative disorders [37]. Some systemic conditions represent absolute contraindications unless treated and in sustained remission, including uncontrolled plasma cell dyscrasias and systemic amyloidosis with significant extrarenal involvement [37]. Transplantation should not proceed in the setting of severe ongoing nonadherence, uncontrolled substance use disorder, or unstable psychiatric illness, as these factors may compromise decision-making and posttransplant safety [37].

Relative contraindications are conditions that increase perioperative or posttransplant risk but may improve with intervention or time. A recent stroke or transient ischemic attack warrants a delay of transplantation to allow for neurologic recovery and reassessment of functional status [37]. Symptomatic cardiovascular or peripheral arterial disease requires diagnostic evaluation and appropriate treatment before proceeding with transplantation [37]. Severe hyperparathyroidism should be medically or surgically treated before transplantation. Severe obesity, frailty, and poorly controlled diabetes may justify deferral while these risk factors are optimized [37]. Although Kidney Disease: Improving Global Outcomes and European Renal Best Practice guidelines emphasize that advanced age alone is not a contraindication, transplantation in recipients older than 80 years is performed infrequently, in part because of higher rates of infectious complications, immunosuppression-related malignancy, and early posttransplant mortality, most often attributable to cardiovascular disease [2, 37, 162]. Active gastrointestinal disease or acute hepatitis should be treated and stabilized before transplantation [37]. Many malignancies require disease-specific waiting periods after completion of therapy to better define recurrence risk [37]. Psychosocial concerns should be approached as modifiable barriers and addressed through counseling and support services rather than automatic exclusion [37]. In these cases, transplantation should proceed once modifiable risks have been addressed and the anticipated benefit outweighs the residual risk.

Liver Transplantation

Introduction and Organ Allocation

End-stage liver disease represents the terminal phase of hepatic injury and is characterized by irreversible loss of hepatic synthetic, metabolic, and detoxification function [79]. Liver transplantation is the definitive therapy and can extend life expectancy while improving quality of life [79]. Liver transplantation may be indicated in acute liver failure, acute-on-chronic liver failure, and decompensated cirrhosis [57]. Although these syndromes differ in etiology, acuity, and short-term prognosis, they are all associated with high mortality [57]. Accurate characterization of the underlying liver failure syndrome informs the urgency of evaluation, perioperative risk stratification, and transplant candidacy.

Acute liver failure is defined by the rapid development of severe liver damage, coagulopathy, and hepatic encephalopathy in patients without known preexisting liver disease or cirrhosis [201]. Common etiologies include acetaminophen toxicity, drug-induced liver injury, viral hepatitis, autoimmune hepatitis, pregnancy-related liver diseases, including hemolysis, elevated liver enzymes, and low platelet count syndrome and acute fatty liver of pregnancy, Wilson disease, mushroom poisoning, Budd–Chiari syndrome, ischemic liver injury, and malignant hepatic infiltration [201]. Acute liver failure is further classified by the rate of progression. Hyperacute liver failure occurs within 0–6 days of initial insult, acute liver failure occurs 7–21 days, and subacute liver failure occurs more than 21 days later [201]. Etiology and rate of progression are important determinants of prognosis and guide management decisions, particularly with respect to transplant referral. Given the high morbidity and mortality associated with acute liver failure, early referral to a liver transplant center is essential [201].

Acute-on-chronic liver failure and decompensated cirrhosis occur in patients with established chronic liver disease, generally defined by hepatic injury persisting for more than 6 months. Patients with cirrhosis often experience a prolonged asymptomatic, compensated phase before progression to decompensation with clinically overt complications such as ascites, gastrointestinal bleeding, hepatic encephalopathy, and hepatorenal syndrome [12]. Acute-on-chronic liver failure represents a severe form of decompensation precipitated by a superimposed insult, leading to systemic inflammation, extrahepatic organ failure, and high 3-month mortality in the absence of definitive therapy [18]. Common precipitating events include bacterial or viral infection, drug-induced liver injury, alcohol-associated hepatitis, gastrointestinal bleeding, portal or hepatic vein thrombosis, and hepatic ischemia [18]. In patients with cirrhosis, the development of these sentinel events, which signal a substantial worsening of prognosis, should prompt referral for liver transplantation evaluation [57].

Because donor organs are limited, liver transplantation relies on allocation systems that prioritize candidates according to medical urgency. Several scoring systems have been developed to estimate disease severity and short-term mortality. The Child–Turcotte–Pugh score incorporates serum bilirubin, serum albumin,

international normalized ratio, ascites, and hepatic encephalopathy [60]. Although historically important, this score is limited by subjectivity in grading clinical variables and by the exclusion of renal function, which is a major determinant of outcomes in advanced cirrhosis [60]. To address these limitations, the Model for End-Stage Liver Disease (MELD) score was developed using objective laboratory values, specifically serum bilirubin, serum creatinine, and the international normalized ratio, to estimate 90-day mortality [136]. This model was adopted in 2002 by the United Network for Organ Sharing as the basis for liver allocation in the United States [60].

Subsequent refinements incorporated serum sodium to better capture circulatory dysfunction and advanced portal hypertension. The MELD-Na score, implemented in 2016, improved the prediction of waitlist mortality, particularly among patients with refractory ascites and hepatorenal syndrome [96, 198]. Persistent limitations, including underestimation of mortality in certain patient populations, led to the development of MELD 3.0 [109]. This updated model incorporates serum albumin and female sex, recalibrates existing variables, and introduces interaction terms to better reflect nonlinear relationships among predictors [109]. MELD 3.0 was adopted in 2023 by the Organ Procurement and Transplantation Network as the standard liver allocation model in the United States [113].

In liver transplantation evaluation, MELD-based systems to prioritize candidates with higher medical urgency are complemented by a comprehensive assessment of physiologic reserve and comorbid disease. This evaluation includes a detailed assessment of cardiovascular, pulmonary, renal, neurologic, hematologic, and metabolic function, as well as infection risk and malignancy surveillance [57]. Psychosocial factors, including history of medication adherence, substance use, mental health conditions, social support, and ability to comply with complex post-transplant care, are also critical determinants of transplant eligibility and long-term outcomes [57].

Final transplant candidacy is determined by a multidisciplinary selection committee that typically includes hepatologists, transplant surgeons, anesthesiologists, intensivists, psychiatrists or psychologists, social workers, and transplant coordinators. The committee integrates measures of disease severity, surgical complexity, physiologic reserve, comorbid disease burden, and psychosocial readiness to generate a composite risk assessment. Based on this assessment, the committee may recommend listing, deferral pending further evaluation or optimization, or denial when contraindications or nonmodifiable high-risk features are present.

Once a patient is approved for transplantation and an organ offer is accepted, attention shifts to immediate perioperative readiness. Anesthesiologists perform a final preoperative assessment within hours of surgery, reassessing cardiopulmonary and neurologic function, volume status, laboratory trends, and the extent of extrahepatic organ dysfunction. This evaluation provides a final opportunity to identify interval disease progression, anticipate intraoperative challenges, and refine the anesthetic plan. The remainder of this chapter reviews the core elements of this preoperative evaluation.

Preoperative Evaluation

Cardiovascular

Cardiovascular disease is a leading cause of morbidity and mortality after liver transplantation [40]. Cardiac complications account for approximately half of rehospitalizations within the first 30 and 90 days after transplantation, and coronary heart disease is the most common cause of late posttransplant cardiac events [21]. Cardiovascular risk is particularly high among patients with metabolic dysfunction–associated steatotic liver disease or steatohepatitis-related cirrhosis, who frequently have comorbid diabetes mellitus, hypertension, hyperlipidemia, and obesity, along with a higher prevalence of preexisting coronary and structural heart disease [42]. Pretransplant cardiac risk is exacerbated by significant hemodynamic stress, blood loss, electrolyte disturbances, and systemic inflammation that occur during transplantation, and this increased risk persists after transplantation in the setting of chronic immunosuppression [21]. Accurate cardiac risk assessment is challenging because the circulatory and neurohormonal adaptations of advanced cirrhosis alter baseline hemodynamics and reduce the reliability of standard diagnostic testing [21]. Preoperative cardiovascular evaluation, therefore, requires a comprehensive approach that integrates clinical judgment with imaging, functional assessment, and selective invasive testing to stratify risk while minimizing unnecessary procedures.

Advanced cirrhosis is associated with profound alterations in cardiovascular physiology that complicate cardiac evaluation. Reduced systemic vascular resistance and elevated resting cardiac output may mask myocardial ischemia or ventricular dysfunction [87]. Impaired chronotropic responsiveness further limits the sensitivity of noninvasive stress testing [87]. Cirrhotic cardiomyopathy, which is present in up to half of patients with end-stage liver disease, is characterized by impaired contractile and chronotropic reserve, diastolic dysfunction, and electrophysiologic abnormalities such as prolongation of the corrected QT interval [230]. Because systolic function is often preserved at rest, myocardial dysfunction may become evident only during periods of physiologic stress [230]. Dobutamine stress echocardiography can help in identifying cirrhotic cardiomyopathy, with attention to left ventricular systolic and diastolic dysfunction, global longitudinal strain, and chamber enlargement, blunted contractile response to stress, and right ventricular dysfunction [87]. Liver transplant is the only definitive treatment, and patients with cirrhosis are at increased risk of perioperative heart failure and postoperative mortality [230].

Myocardial ischemia often presents atypically in liver transplant candidates [11, 218]. Symptoms such as dyspnea, reduced exercise tolerance, and fatigue may be attributed to anemia, ascites, sarcopenia, deconditioning, hepatopulmonary syndrome, or other complications of advanced liver disease rather than to cardiac pathology [124]. As a result, clinically significant coronary or myocardial disease may remain unrecognized before surgery. The physiologic stress of transplantation, including large intravascular volume shifts, hemorrhage, venous clamping, reperfusion, metabolic disturbances, and systemic inflammation, places substantial strain on the myocardium and can unmask previously compensated disease

intraoperatively or in the early postoperative period [218]. These factors limit the reliability of conventional perioperative cardiac risk indices and highlight the need for a transplant-specific approach to cardiovascular assessment [218].

Current guidelines recommend that all liver transplant candidates undergo a standardized baseline cardiovascular evaluation, followed by risk-stratified advanced testing when indicated. Assessment begins with a comprehensive history and physical examination focused on symptoms of ischemia, heart failure, arrhythmia, and exercise intolerance, as well as identification of traditional risk factors such as diabetes mellitus, hypertension, dyslipidemia, tobacco use, and family history of coronary disease [40]. A 12-lead electrocardiogram should be obtained to assess for arrhythmias, conduction abnormalities, evidence of prior myocardial infarction, and prolongation of the corrected QT interval [40]. Resting transthoracic echocardiography is essential to assess left and right ventricular systolic function, diastolic function, chamber dimensions, myocardial strain, valvular abnormalities, and estimated pulmonary artery pressures [40]. Particular attention should be given to right ventricular size and function, as the abrupt changes in preload and afterload during reperfusion may precipitate right ventricular failure. Evaluation of diastolic function is also important given the high prevalence of diastolic dysfunction in cirrhotic cardiomyopathy [222]. An agitated saline contrast study should be performed to assess for intracardiac or intrapulmonary shunting [40].

Further testing is guided by cardiovascular risk stratification. Patients considered low risk, including individuals younger than 40 years with preserved functional capacity, no traditional cardiovascular risk factors, no prior transplantation, and normal baseline cardiac studies, generally do not require additional cardiac evaluation [40]. Candidates at intermediate risk should undergo noninvasive stress testing [40]. Pharmacologic stress echocardiography and myocardial perfusion imaging are commonly used; however, both modalities have reduced sensitivity and negative predictive values in patients with cirrhosis, who frequently cannot achieve target heart rates. In addition, higher resting myocardial blood flow and relatively reduced stress-induced flow reduce the diagnostic accuracy of myocardial perfusion imaging in this population [1, 40].

Candidates at high cardiovascular risk, including those older than 60 years, those with multiple traditional risk factors, established coronary artery disease, reduced left ventricular ejection fraction, regional wall motion abnormalities, or abnormal stress testing, should undergo anatomic coronary assessment, with coronary computed tomography angiography recommended as the preferred initial modality [40]. This technique has a high negative predictive value for excluding clinically significant obstructive coronary disease and allows assessment of stenosis severity and overall plaque [114, 133]. However, coronary computed tomography angiography has limitations. The study requires intravenous iodinated contrast, heart rate control, breath holding, and supine positioning, which may be difficult in patients with ascites, orthopnea, or limited mobility [21]. Extensive coronary calcification may reduce interpretability, and the modality is contraindicated in patients with severe contrast allergy, atrial fibrillation, or intolerance to beta-adrenergic blockade [40]. When coronary computed tomography angiography is not feasible, is

nondiagnostic, or identifies high-risk anatomy requiring further clarification, invasive coronary angiography remains the gold standard and is central to decisions regarding revascularization and transplant candidacy [40].

Decisions regarding coronary revascularization in liver transplant candidates require multidisciplinary discussion involving cardiology, hepatology, transplant surgery, anesthesiology, and critical care, with careful consideration of the cardiovascular benefit, bleeding risk, and potential for delaying transplantation. Although routine revascularization in asymptomatic patients has not been shown to improve outcomes, identification of significant coronary stenosis may influence transplant candidacy, operative planning, and perioperative management [40]. High-grade lesions may warrant intervention before transplantation given the significant hemodynamic stress of surgery, recognizing that revascularization necessitates a period of dual antiplatelet therapy to maintain stent patency [40]. Patients with multivessel coronary disease that is not amenable to revascularization and who have a substantial burden of jeopardized myocardium should generally be declined for transplantation because of prohibitive perioperative risk [40]. Selected candidates with complex three-vessel disease may be considered for combined coronary artery bypass grafting and liver transplantation at experienced centers [40].

Coronary revascularization should be undertaken only in patients who are otherwise appropriate candidates for liver transplantation, as the procedure carries significant risk in decompensated cirrhosis and may delay transplantation [21]. While earlier guidelines favored bare metal stents to allow for a short course of dual antiplatelet therapy, newer-generation drug-eluting stents are associated with lower rates of stent thrombosis and restenosis and, in the general population, allow for shorter durations of dual antiplatelet therapy, typically 3–6 months and, in selected patients at high bleeding risk, as little as 1 month [40]. Data on the optimal duration of dual antiplatelet therapy in liver transplant candidates remain limited [40]. Stent selection and the timing of transplantation must be individualized, accounting for coronary anatomy, urgency of transplantation as reflected by the Model for End-Stage Liver Disease score, and the competing risks of stent thrombosis and bleeding [40].

Functional status and frailty are strong predictors of waitlist mortality, posttransplant mortality, hospitalization risk, and length of stay [118]. In cirrhosis, frailty is characterized by sarcopenia, immobility, reduced energy expenditure, and malnutrition and is exacerbated by liver-specific factors such as chronic inflammation, impaired protein synthesis, anorexia, early satiety from ascites, and hepatic encephalopathy [118]. Age-related decline and non-hepatic comorbidities further compound vulnerability and may not improve after transplantation [118]. The Liver Frailty Index provides an objective assessment of physical frailty in patients with cirrhosis using grip strength, chair stands, and balance testing [115]. Incorporation of this index into clinician assessment significantly improves the prediction of waitlist mortality compared with subjective clinician assessment alone [116]. Importantly, longitudinal changes in frailty predict waitlist mortality independent of baseline frailty and liver disease severity [117].

Functional capacity can be assessed using patient-reported and performance-based measures. The Duke Activity Status Index is a 12-item questionnaire that estimates peak metabolic equivalents and correlates with measured oxygen uptake [83]. Lower scores, reflecting reduced functional capacity, are associated with increased mortality before and after liver transplantation [233]. The 6-minute walk test provides a complementary assessment of aerobic capacity, with walking distances less than 250 m associated with increased mortality risk [36]. Cardiopulmonary exercise testing remains the gold standard for evaluating aerobic fitness and cardiovascular reserve, allowing direct measurement of oxygen uptake and identification of the primary cause of exercise intolerance [213]. Cardiopulmonary reserve, as reflected by the anaerobic threshold, has strong predictive value for 90-day post-transplant survival and duration of critical care stay [169]. Because elements of frailty and functional impairment are potentially modifiable, standardized assessments should inform the intensity and focus of nutritional and physical therapy in candidates waiting for liver transplantation [118].

Cardiovascular risk may evolve during prolonged waitlist periods. Cardiovascular assessment should be repeated at least annually in waitlisted candidates and should include, at a minimum, an updated clinical evaluation, electrocardiography, and resting transthoracic echocardiography [40]. Candidates with known coronary artery disease, prior revascularization, metabolic dysfunction–associated steatohepatitis, or diabetes mellitus may require more intensive surveillance with stress testing or anatomic coronary imaging [40].

In addition to coronary disease, candidates should be evaluated for portopulmonary hypertension, a form of pulmonary hypertension that develops in the setting of portal hypertension [140]. Pulmonary vascular remodeling results from a combination of increased shear stress due to the hyperdynamic circulation, imbalance between vasodilatory and vasoconstrictive mediators related to portosystemic shunting, and systemic inflammation [92, 235]. These mechanisms promote pulmonary vasoconstriction, elevated pulmonary arterial pressures, and increased right ventricular afterload. Portopulmonary hypertension affects approximately 5–8.5% of liver transplant candidates and is associated with high perioperative morbidity and mortality [235]. Importantly, the presence and severity of portopulmonary hypertension do not correlate reliably with the severity of liver dysfunction or portal hypertension, and affected patients may be asymptomatic or have nonspecific symptoms [235].

Screening with transthoracic echocardiography is recommended for all transplant candidates to estimate pulmonary artery pressures and assess right ventricular structure and function [235]. Because elevated estimated pulmonary pressures on echocardiography may reflect volume overload rather than intrinsic pulmonary vascular disease, right heart catheterization remains the gold standard for diagnosing and classifying portopulmonary hypertension [235]. Catheterization should be performed in patients with an estimated right ventricular systolic pressure greater than 45 mm Hg or with echocardiography findings suggestive of elevated pulmonary pressures, such as pulmonary artery dilation, right atrial enlargement, or diastolic dysfunction [92, 140]. Diagnostic criteria include a mean pulmonary artery pressure

of at least 20 mmHg, pulmonary vascular resistance of at least 160 (2 WU), and pulmonary capillary wedge pressure of 15 mmHg or less, after excluding alternative causes of pulmonary hypertension [235].

All candidates with portopulmonary hypertension should be evaluated by a pulmonary hypertension or cardiology specialist for initiation and titration of vasodilator therapy [140]. Commonly used agents include prostacyclin agonists, endothelin receptor antagonists, phosphodiesterase inhibitors, and guanylate cyclase stimulators [92]. Liver transplantation may be considered in carefully selected candidates who experience a sustained hemodynamic response to medical therapy, defined by a reduction of mean pulmonary artery pressure to 35 mmHg or less and pulmonary vascular resistance to less than 400 dyn·s/cm^5 (5 WU) [140]. With early diagnosis, multidisciplinary management, and use of vasodilator therapy as a bridge to transplant, appropriately selected candidates have achieved excellent long-term survival after liver transplantation [106, 121, 194].

Pulmonary

Pulmonary complications are a major source of perioperative morbidity and mortality in liver transplantation [106, 121, 194]. The most clinically consequential pulmonary manifestations of advanced portal hypertension include hepatopulmonary syndrome, hepatic hydrothorax, and spontaneous bacterial empyema. These conditions reflect advanced hepatic dysfunction, altered pulmonary vascular physiology, and impaired host defenses and have important implications for transplant eligibility, perioperative management, and postoperative outcomes [159]. In selected circumstances, such as severe hypoxemia due to hepatopulmonary syndrome, candidates may qualify for MELD exception points to expedite transplantation [75].

Hepatopulmonary syndrome is defined by the triad of chronic liver disease or portal hypertension, arterial hypoxemia, and intrapulmonary vascular dilations [239]. The syndrome affects approximately 5–32% of liver transplant candidates and is attributed to increased circulating and local concentrations of vasodilatory mediators, including nitric oxide, carbon monoxide, and vascular endothelial growth factor, which promote diffuse dilation of pulmonary precapillary and capillary vessels [239]. These vascular abnormalities lead to ventilation–perfusion mismatch and functional right-to-left intrapulmonary shunting, producing a spectrum ranging from asymptomatic hypoxemia to progressive dyspnea [239]. Orthodeoxia, defined as a decrease in arterial oxygen tension when moving from the supine to the upright position, and platypnea, defined as dyspnea that worsens when upright, are characteristic clinical features [180]. Physical examination may reveal digital clubbing, cyanosis, and spider angiomas [180].

Screening for hepatopulmonary syndrome begins with seated pulse oximetry while the patient breathes room air [239]. An oxygen saturation of 96% or less should prompt arterial blood gas analysis in the sitting position to directly measure the arterial oxygen tension and calculate the alveolar–arterial oxygen gradient [239]. Diagnostic criteria include an arterial oxygen tension less than 80 mmHg or an elevated alveolar–arterial gradient greater than 15 mmHg in younger patients and greater than 20 mmHg in older patients, in the absence of an alternative explanation

for impaired gas exchange [239]. Confirmation of intrapulmonary shunting is obtained using contrast-enhanced transthoracic echocardiography with agitated saline [180]. Appearance of microbubbles in the left atrium between the third and sixth cardiac cycles after right atrial opacification supports intrapulmonary shunting, whereas earlier appearance suggests intracardiac shunting [180]. In selected candidates, particularly those with coexisting parenchymal lung disease or equivocal echocardiographic findings, technetium-99 m–labeled macroaggregated albumin scintigraphy may be used to quantify the degree of right-to-left shunting [239]. In this study, radiolabeled particles bypass dilated pulmonary capillaries and accumulate in systemic organs, most commonly the brain, allowing estimation of the shunt fraction [239]. While less sensitive and more invasive than contrast-enhanced transthoracic echocardiography, scintigraphy may be particularly useful when echocardiographic findings are inconclusive or technically limited [203]. Liver transplantation remains the only effective treatment for hepatopulmonary syndrome [239]. Although severe hypoxemia increases perioperative risk, transplantation is typically followed by improvement in oxygenation and favorable long-term survival, supporting listing in appropriately selected patients [140].

Hepatic hydrothorax is defined as a pleural effusion in a patient with portal hypertension and cirrhosis in the absence of primary cardiac or pulmonary disease [111]. The condition occurs in approximately 5–10% of patients with advanced liver disease and most commonly involves the right hemithorax, although left-sided or bilateral effusions may occur [111]. Pathogenesis reflects a combination of sodium and water retention and transdiaphragmatic movement of ascitic fluid through diaphragmatic defects into the pleural space [86]. Clinical presentation varies with the volume and rate of pleural fluid accumulation and the presence of coexisting cardiopulmonary disease [111]. Patients may develop hypoxemia, dyspnea, cough, or, in severe cases, respiratory failure [111]. Preoperative management should prioritize symptom control and exclusion of pleural space infection. Initial therapy consists of dietary sodium restriction and diuretic treatment [111]. When medical therapy is inadequate, therapeutic thoracentesis may be required to relieve respiratory symptoms [86]. Hepatic hydrothorax is considered refractory when symptoms cannot be controlled with medical therapy alone, when two or more therapeutic thoracenteses are required, or when diuretic treatment is limited by adverse effects or intolerance [86]. Liver transplantation is the definitive treatment. Interim management strategies may include serial thoracentesis, pleurodesis, or surgical repair of diaphragmatic defects in selected cases [86].

A serious infectious complication of hepatic hydrothorax is spontaneous bacterial empyema, defined as infection of a preexisting pleural effusion in the absence of concurrent pneumonia [22]. The condition is most commonly caused by enteric organisms, including *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa*, and *Enterococcus* species, and reflects the immune dysfunction associated with cirrhosis [177]. Diagnosis is established by pleural fluid analysis demonstrating a polymorphonuclear leukocyte count greater than 250 cells/mm^3 with a positive bacterial culture, or greater than 500 cells/mm^3 with a negative culture, in the absence of radiographic evidence of pneumonia [22]. Management consists of early

empiric antibiotic therapy, typically with a third-generation cephalosporin, with subsequent tailoring based on culture results and clinical response [177]. Chest tube drainage should be reserved for patients with pus or loculated effusions [177]. Development of spontaneous bacterial empyema is associated with poor prognosis and indicates advanced hepatic decompensation [177].

Pretransplant pulmonary evaluation begins with a detailed history and physical examination aimed at identifying liver-related pulmonary complications and coexisting respiratory disease [203]. History should assess exertional dyspnea, orthopnea, platypnea, cough, wheezing, hemoptysis, and chest discomfort [159]. Risk factors for intrinsic lung disease, including tobacco use, occupational or environmental exposures, prior thoracic surgery, and known pulmonary disorders, should be reviewed [159]. Physical examination should evaluate for digital clubbing, cyanosis, peripheral edema, and signs of volume overload [159]. Lung auscultation should assess for wheezing, crackles, diminished breath sounds, or abnormalities that may suggest obstructive lung disease, interstitial lung disease, pleural effusion, or consolidation. Cardiovascular examination should be integrated into the pulmonary assessment, as right ventricular dysfunction and elevated pulmonary pressures may contribute to respiratory symptoms [203].

Screening should include pulse oximetry to screen for hypoxemia. Arterial blood gas analysis provides further evaluation of oxygenation and ventilation and allows for calculation of the alveolar–arterial oxygen gradient [140]. An arterial oxygen tension below 80 mmHg or an elevated alveolar–arterial gradient greater than 15–20 mmHg should prompt evaluation for hepatopulmonary syndrome [140]. Chest radiography should be obtained to assess lung parenchyma, pleural spaces, cardiac silhouette, and pulmonary vascular markings [159]. Functional capacity can be assessed using the 6-minute walk test, which reflects exercise tolerance and cardiopulmonary reserve [159]. Reduced walking distance is associated with increased hospitalization risk, poorer quality of life, and higher mortality among liver transplant candidates [45].

High-resolution chest computed tomography should be obtained when clinical or radiographic findings raise concern for interstitial lung disease, bronchiectasis, pulmonary nodules, or complex pleural pathology [159]. Pulmonary function testing is routinely incorporated into liver transplant evaluation [140]. In end-stage liver disease, pulmonary function tests frequently demonstrate a restrictive pattern attributable to ascites, hepatic hydrothorax, diaphragmatic elevation, sarcopenia, and other systemic effects of hepatic failure rather than intrinsic parenchymal lung disease [107]. Although pretransplant pulmonary function parameters do not reliably predict posttransplant mortality, measures such as diffusing capacity for carbon monoxide, total lung capacity, and residual volume have been associated with duration of mechanical ventilation and length of hospital stay after transplantation [107]. Severe obstructive or restrictive ventilatory defects may constitute contraindications to liver transplantation, particularly when they reflect irreversible pulmonary disease. In candidates with hepatic hydrothorax, the etiology of the pleural effusion should be confirmed with imaging and, when indicated, diagnostic thoracentesis to exclude alternative causes [203].

Hematologic

Hematologic abnormalities are nearly universal in patients with end-stage liver disease and reflect profound disruption of hemostasis [215]. Cirrhosis is characterized by parallel reductions in procoagulant and anticoagulant factors, resulting in a fragile, rebalanced hemostatic state that may shift toward bleeding or thrombosis in response to stress [215]. Thrombocytopenia, coagulopathy, anemia, and thrombotic complications are common manifestations of this altered hemostatic profile and have important implications for perioperative bleeding risk, transfusion requirements, and intraoperative management.

Thrombocytopenia affects up to three-quarters of liver transplant candidates and arises from several well-established mechanisms [221]. Reduced hepatic production of thrombopoietin impairs megakaryocyte maturation and platelet production in the bone marrow [221]. Portal hypertension leads to splenic congestion and hypersplenism, resulting in sequestration and accelerated clearance of circulating platelets [221]. Bone marrow suppression further exacerbates thrombocytopenia, particularly in patients with chronic alcohol use, hepatitis C infection, iron overload, or exposure to myelotoxic medications such as antivirals or chemotherapeutic agents [221]. Immune-mediated platelet destruction may also occur in association with autoimmune liver disease or chronic viral hepatitis [221]. Although platelet count is frequently used as a surrogate marker of bleeding risk, its predictive value is limited except in cases of severe thrombocytopenia, typically defined as a platelet count less than 50,000 cells/L. Compensatory increases in von Willebrand factor and reduced activity of ADAMTS13 often preserve primary hemostasis despite moderate thrombocytopenia [195]. In patients with severe thrombocytopenia, short-term use of thrombopoietin receptor agonists or platelet transfusion may be considered, with careful monitoring for thrombotic complications such as portal vein thrombosis [195].

Coagulation abnormalities in end-stage liver disease result from impaired hepatic synthesis of procoagulant factors, including fibrinogen and factors II, V, VII, IX, X, and XI, as well as anticoagulant proteins protein C, protein S, and antithrombin [215]. These parallel deficiencies produce a rebalanced but unstable equilibrium that may shift toward bleeding or thrombosis in the setting of infection, renal dysfunction, systemic inflammation, or surgical stress [215]. Standard coagulation assays, including prothrombin time expressed as the international normalized ratio, primarily reflect reduced procoagulant factor activity and do not account for concurrent changes in anticoagulant pathways or fibrinolysis [215]. As a result, these tests frequently overestimate bleeding risk and correlate poorly with perioperative hemorrhage or transfusion requirements [158]. Additional contributors to hemostatic instability include low fibrinogen concentrations, platelet dysfunction, and hyperfibrinolysis [176]. At the same time, many patients demonstrate a prothrombotic tendency driven by elevated levels of von Willebrand factor and factor VIII and impaired clearance of activated clotting factors, increasing the risk of portal vein thrombosis and venous thromboembolism [176]. These features highlight the dynamic nature of coagulation abnormalities in cirrhosis and the limitations of conventional laboratory testing for perioperative risk stratification.

Anemia in advanced liver disease is multifactorial. Anemia of chronic disease is the most common etiology and is mediated by inflammation-driven upregulation of hepcidin, which reduces intestinal iron absorption and restricts iron release from macrophage stores [131]. Nutritional deficiencies of iron, vitamin B12, and folate are common due to poor dietary intake, malabsorption, and impaired hepatic storage [131]. Chronic gastrointestinal blood loss from esophageal or gastric varices and portal hypertensive gastropathy further contributes to iron deficiency [73]. Additional contributors include bone marrow suppression related to chronic alcohol use or viral hepatitis, renal dysfunction with reduced erythropoietin production, and immune-mediated hemolysis [131]. In advanced cirrhosis, spur cell hemolytic anemia may develop and is associated with a particularly poor prognosis [219].

Preoperative hematologic evaluation includes a complete blood count to assess hemoglobin concentration, leukocyte count, and platelet levels, along with coagulation studies including prothrombin time/international normalized ratio, activated partial thromboplastin time, and fibrinogen concentration [165]. Blood typing and antibody screening are essential to facilitate timely access to blood products. Candidates with a positive antibody screen should be discussed early with the blood bank to ensure availability of compatible products. Although not routinely used in the preoperative phase, viscoelastic testing with thromboelastography or rotational thromboelastometry plays an increasingly important role in intraoperative management [81]. These assays provide real-time assessment of clot formation, strength, and fibrinolysis, integrating platelet, fibrinogen, and coagulation factor activity to guide targeted transfusion strategies that reduce blood product utilization without increasing mortality [81, 231].

An increasing number of liver transplant candidates receive chronic antiplatelet or anticoagulant therapy for indications such as atrial fibrillation, venous thromboembolism, or portal vein thrombosis, reflecting aging and growing medical complexity of the transplant population [149]. Cirrhosis itself confers an elevated risk of both venous thromboembolism and atrial fibrillation, underscoring the need for individualized antithrombotic decision-making [8, 84]. Antithrombotic therapy should not preclude transplant candidacy but requires careful perioperative planning [149]. At the time of donor organ offer, antiplatelet and anticoagulation agents should be withheld and anticoagulation reversed when feasible, recognizing that the urgency of transplantation often limits complete drug clearance [149]. Vitamin K antagonists and low-molecular-weight heparin have traditionally been used in cirrhosis but are limited by altered pharmacokinetics, difficulty interpreting the international normalized ratio, and variable anticoagulant effect [215]. Although direct-acting oral anticoagulants have not been extensively studied in advanced liver disease, emerging observational data suggest comparable or lower bleeding risk relative to vitamin K antagonists in carefully selected patients [158]. Nonetheless, these agents require caution, as hepatic dysfunction may unpredictably alter drug exposure in the absence of reliable laboratory monitoring [149]. When urgent transplantation is anticipated, the availability of appropriate reversal strategies should be assessed in advance, including the use of specific reversal agents [165]. In patients receiving vitamin K antagonists, vitamin K should be administered early to support

the generation of vitamin K-dependent factors [149]. Prothrombin complex concentrate may be considered for rapid reversal when transplantation is imminent [165]. Overall, management of antithrombotic therapy in liver transplant candidates requires close multidisciplinary coordination to balance bleeding and thrombotic risks.

Endocrine

The liver plays an essential role in endocrine regulation through the synthesis, activation, metabolism, and clearance of multiple hormones and hormone-binding proteins [135]. In advanced liver disease, progressive hepatic dysfunction and portal hypertension disrupt these processes, resulting in a broad range of endocrine abnormalities. Common disturbances include impaired glucose regulation, alterations in hypothalamic–pituitary–adrenal and thyroid axis function, hypogonadism, and disorders of bone and mineral metabolism. [135]. These abnormalities influence metabolic control, hemodynamic stability, infection risk, and wound healing [135]. A focused endocrine evaluation is an essential component of the preoperative assessment of liver transplant candidates, with particular attention to glucose regulation, adrenal and thyroid function, and bone health.

Impaired glucose regulation is a common consequence of advanced liver disease and reflects the liver's central role in glucose homeostasis. Liver transplant candidates may experience fasting hypoglycemia, postprandial hyperglycemia, or a combination of both, a pattern often described as hepatogenous diabetes [112]. These abnormalities arise from impaired hepatic gluconeogenesis, reduced glycogen storage capacity, altered insulin clearance, and peripheral insulin resistance and are exacerbated by malnutrition, systemic inflammation, and concurrent renal dysfunction [112]. Hyperglycemia and diabetes mellitus are prevalent in this population and are associated with increased risks of infection, cardiovascular disease, impaired wound healing, and adverse posttransplant outcomes [31]. Contemporary management emphasizes individualized glycemic targets based on overall frailty and hypoglycemia risk rather than reliance on strict hemoglobin A1c thresholds [31].

Hypoglycemia is also common in advanced cirrhosis, particularly among patients with limited nutritional reserve or renal dysfunction [77]. Recognition may be delayed because symptoms such as fatigue, confusion, and altered mental status overlap with symptoms of hepatic encephalopathy and other complications of liver failure [199]. The preoperative endocrine evaluation should therefore assess glycemic patterns, hypoglycemia risk, and diabetes-related end-organ complications to guide an individualized perioperative glucose management strategy. The goal is to prevent sustained hyperglycemia, which has been associated with increased posttransplant mortality, while also avoiding hypoglycemia to reduce neurologic injury and perioperative complications [10].

Adrenal insufficiency reflects impaired regulation of the hypothalamic–pituitary–adrenal axis [64]. Proposed mechanisms include intrinsic defects in adrenal steroid synthesis, chronic adrenal hypoperfusion related to splanchnic vasodilation and reduced effective circulating volume, and cytokine-mediated inhibition of hypothalamic and pituitary hormone secretion [227]. Both absolute adrenal

insufficiency, defined by inadequate cortisol production, and relative adrenal insufficiency, defined by an insufficient cortisol response to physiologic stress despite apparently normal baseline levels, may contribute to circulatory instability, hyponatremia, and adverse perioperative outcomes [227]. Evaluation should be considered in patients with decompensated cirrhosis who develop persistent or unexplained hypotension, severe hyponatremia with serum sodium levels less than 125 mEq/L, or unexplained abdominal pain or fatigue [227]. Assessment of adrenal function in cirrhosis is challenging, and a low threshold for diagnosis of relative adrenal insufficiency is appropriate in the setting of hemodynamic instability [227]. Initial testing typically includes measurement of an early morning total serum cortisol level [227]. In patients with intermediate cortisol values or critical illness, a standard-dose adrenocorticotropic hormone stimulation test may be performed, although interpretation is limited by reduced cortisol-binding proteins and altered cortisol kinetics in cirrhosis [64]. Identification of adrenal insufficiency is essential to anticipate and prevent refractory hypotension and guide perioperative administration of stress-dose steroids.

Thyroid dysfunction reflects the liver's essential role in thyroid hormone activation, transport, and metabolism [164]. The liver is a major site of peripheral conversion of thyroxine to triiodothyronine and synthesizes thyroid hormone–binding proteins [139]. In cirrhosis, reduced deiodinase activity and impaired binding protein synthesis lead to decreased circulating triiodothyronine and thyroxine levels, often with normal or suppressed thyroid-stimulating hormone concentrations. This pattern is consistent with nonthyroidal illness syndrome and correlates more closely with the severity of hepatic dysfunction than with intrinsic thyroid disease [139]. Primary thyroid disease should nonetheless be considered during transplant evaluation, as thyroid abnormalities occur across a range of liver diseases, including chronic hepatitis C infection, hepatocellular carcinoma, and cholangiocarcinoma [164]. Autoimmune thyroid disease and hypothyroidism are particularly prevalent in patients with hepatitis C virus infection and in those with autoimmune liver disorders such as primary biliary cholangitis and autoimmune hepatitis [135, 164]. Clinically significant hypothyroidism may exacerbate metabolic dysfunction and, in severe cases, mimic features of hepatic decompensation, including hyperammonemia and ascites [164]. Hyperthyroidism, although less common, may contribute to hepatic injury through hormone-mediated toxicity or secondary cardiac effects [174]. Thyroid function testing is therefore routinely incorporated into the pretransplant evaluation, with measurement of thyroid-stimulating hormone and free thyroxine as initial studies.

Metabolic bone disease is a well-recognized complication of end-stage liver disease. Osteoporosis and, less commonly, osteomalacia affect up to 50% of patients with cirrhosis [134]. Hepatic osteodystrophy reflects an imbalance between bone resorption and bone formation. Increased osteoclast activity is driven in part by chronic systemic inflammation and elevated proinflammatory cytokines, while bone formation is impaired by reduced osteoblast proliferation and activity [44]. Additional contributory factors include decreased circulating insulin-like growth factor 1 levels, deficiencies of vitamin D and vitamin K related to malabsorption

and impaired hepatic metabolism, chronic cholestasis, physical inactivity, hypogonadism, and altered hepatic synthesis of proteins involved in calcium and phosphate homeostasis [44, 140]. These abnormalities lead to reduced bone mineral density and increase the risk of spontaneous or low-trauma fractures, which are associated with significant morbidity and increased mortality [134]. Given the prevalence and potential complications of hepatic osteodystrophy, assessment of bone mineral density with dual-energy X-ray absorptiometry is recommended at the time of transplant listing, with repeat evaluation every 2–3 years for patients who remain on the waiting list [140].

Gastrointestinal

Gastrointestinal complications are common in end-stage liver disease and contribute to perioperative morbidity and mortality. Gastrointestinal complications arise primarily from portal hypertension, impaired hepatic synthetic and metabolic function, and chronic systemic inflammation. A structured preoperative gastrointestinal evaluation is essential to identify high-risk conditions and guide perioperative planning.

Metabolic dysfunction–associated steatotic liver disease has emerged as one of the leading indications for liver transplantation, reflecting the increasing prevalence of obesity, insulin resistance, type 2 diabetes mellitus, hypertension, and metabolic syndrome [47, 238]. Metabolic dysfunction–associated steatohepatitis represents the inflammatory and fibrotic subtype within this disease spectrum and carries a high risk of progression to cirrhosis and hepatocellular carcinoma [208]. In the United States, steatohepatitis now accounts for a substantial proportion of transplant listings and is the most common indication among women and among patients undergoing transplantation for hepatocellular carcinoma [238]. Metabolic syndrome is defined by central obesity, insulin resistance or diabetes mellitus, hypertension, hypertriglyceridemia, and low high-density lipoprotein cholesterol. It is associated with increased cardiovascular events, infectious complications, and impaired wound healing [225]. These risks may be further amplified after transplantation by immunosuppressive therapies that promote insulin resistance, dyslipidemia, and hypertension [38]. Current guidelines recommend a comprehensive metabolic assessment for all transplant candidates, with particular attention to those with steatotic liver disease [63]. Preoperative evaluation should include cardiovascular risk stratification and laboratory screening for glycemic and lipid abnormalities, with multidisciplinary interventions aimed at optimization before surgery [47]. Most transplant teams consider a body mass index greater than 40 kg/m^2 to represent a contraindication to liver transplantation [63, 208].

Patients with end-stage liver disease are at high risk for upper gastrointestinal bleeding due to esophageal varices, gastric varices, and portal hypertensive gastropathy [52]. Esophageal varices are present in up to 60% of patients with compensated cirrhosis and up to 85% of those with decompensated disease [54]. Gastric varices are identified in up to 16% of potential transplant candidates, and portal hypertensive gastropathy is present in nearly half [52]. The risk of hemorrhage increases with larger variceal size, the presence of red wale signs, and more advanced

liver dysfunction [54]. Variceal bleeding occurs in approximately one-third of patients with cirrhosis and is associated with significant morbidity and mortality [52]. Upper endoscopy is recommended for all patients with cirrhosis to screen for varices and guide prophylaxis [97]. Patients at high risk for bleeding should receive nonselective beta-adrenergic blockade and/or endoscopic variceal ligation [97]. In compensated cirrhosis, surveillance endoscopy is typically performed every 1–3 years depending on disease severity and risk factors, or at the time of clinical decompensation [88]. Following an episode of variceal hemorrhage, endoscopic variceal ligation should be repeated every 2–6 weeks until eradication, with subsequent surveillance endoscopy at 3–6 months and then every 6–12 months indefinitely [88]. Available evidence does not support routine upper endoscopy solely to assess bleeding risk before transesophageal echocardiography, as this procedure has not been shown to significantly increase the risk of variceal hemorrhage [97]. The severity of variceal disease serves as a marker of portal hypertension and may influence intraoperative transfusion requirements [88].

Ascites is the most common initial decompensating event in cirrhosis [24]. Cirrhotic ascites accounts for over 85% of all cases of ascites and results from portal hypertension-mediated splanchnic vasodilation, leading to reduced effective circulating volume, arterial hypotension, and a hyperdynamic circulatory state [157]. These changes activate the renin–angiotensin–aldosterone system, the sympathetic nervous system, and antidiuretic hormone release, promoting renal sodium and water retention [157]. Reduced plasma oncotic pressure from hypoalbuminemia and increased hydrostatic pressure from portal hypertension facilitate the accumulation of fluid within the peritoneal cavity [157]. Evaluation of ascites should include a focused history and physical examination, abdominal Doppler ultrasonography, laboratory assessment of hepatic and renal markers, and diagnostic paracentesis [24]. Paracentesis should be performed in all hospitalized patients with cirrhosis and ascites, even in the absence of overt infection, given the high prevalence of spontaneous bacterial peritonitis [24]. Ascitic fluid analysis should include cell count with differential, albumin concentration, bacterial cultures, and Gram stain [157]. Spontaneous bacterial peritonitis is diagnosed when the ascitic neutrophil count exceeds 250 cells/mm^3 in the absence of secondary peritonitis [157]. Ascites with a low serum–ascites albumin gradient or features suggesting non–portal hypertensive etiologies warrants further evaluation, including cytology, amylase, or mycobacterial studies [157]. Active infection is a contraindication to transplantation and must be fully treated before surgery [140]. Refractory ascites is managed with serial large-volume paracentesis and albumin replacement [157]. Tense ascites may impair ventilation and contribute to intraoperative hemodynamic instability if not adequately controlled preoperatively [163].

Malnutrition, sarcopenia, and frailty are highly prevalent in end-stage liver disease and are determinants of transplant-related outcomes. Malnutrition affects an estimated 50–90% of patients with decompensated cirrhosis, although recognition may be challenging because of ascites and peripheral edema [41]. Sarcopenia, defined by progressive loss of skeletal muscle mass and strength, is common among transplant candidates and is independently associated with increased waitlist

mortality, postoperative complications, and prolonged hospitalization [119]. Its pathogenesis reflects hypermetabolism, chronic systemic inflammation, ammonia toxicity, hormonal disturbances, and impaired protein synthesis [119]. Frailty, characterized by diminished physiologic reserve and reduced functional capacity, affects approximately 25–35% of transplant candidates and frequently coexists with sarcopenia [119]. Together, these conditions increase susceptibility to infection, delay postoperative recovery, and limit functional rehabilitation after transplantation [119].

Poor nutritional status in cirrhosis is multifactorial. Reduced oral intake results from anorexia, early satiety due to ascites, gastrointestinal symptoms, dietary restrictions, and frequent fasting for procedures [209]. Altered gut barrier function, cholestasis, bacterial overgrowth, and portosystemic shunting impair nutrient absorption [209]. Deficiencies of fat-soluble vitamins A, D, E, and K, as well as trace elements such as zinc and selenium, are common [41]. Thiamine deficiency is an important concern in alcohol-associated liver disease, where it may precipitate Wernicke encephalopathy [41].

Pretransplant assessment of nutritional and functional status should include a focused dietary history, evaluation of unintentional weight loss, and examination for muscle and fat wasting [119]. The Subjective Global Assessment integrates these elements and is a validated and reproducible tool associated with hospitalization, quality of life, and mortality in cirrhosis [166]. Objective assessment of sarcopenia using cross-sectional imaging at the level of the third lumbar vertebra provides prognostic information, as reduced skeletal muscle mass correlates with increased mortality [166]. Functional reserve should be assessed using validated instruments such as the Liver Frailty Index, Karnofsky Performance Status Scale, or 6-minute walk test [119]. Current guidelines from major liver societies recommend routine incorporation of objective nutrition and frailty assessments into the multidisciplinary transplant evaluation [119, 140, 166].

Nutritional status and functional reserve have direct implications for anesthetic and perioperative management. Sarcopenia and frailty are associated with impaired respiratory mechanics, altered drug pharmacokinetics, reduced cardiovascular reserve, increased postoperative pulmonary complications, prolonged mechanical ventilation, and extended intensive care unit stays [190, 210]. These associations underscore the importance of prehabilitation strategies, including targeted nutritional support, resistance training, and physical therapy, to reduce perioperative risk and enhance posttransplant recovery [172, 210].

Renal

Renal dysfunction in advanced liver disease reflects a complex interaction of portal hypertension–related circulatory changes, systemic vasodilation, neurohormonal activation, inflammatory stress, and coexisting intrinsic kidney disease [74, 90]. Since the adoption of the MELD-based allocation system, an increasing proportion of transplant candidates present with renal impairment at the time of transplantation [74, 90]. A comprehensive preoperative renal evaluation is essential to distinguish potentially reversible kidney dysfunction from intrinsic or chronic renal disease, to

define the severity and chronicity of injury, and to estimate the likelihood of renal recovery after liver transplantation. This assessment informs perioperative fluid and electrolyte management and plays a role in determining candidacy for combined liver–kidney transplantation.

Hyponatremia is the most common electrolyte abnormality in advanced liver disease [204]. Systemic vasodilation leads to a reduction in effective circulatory volume, activating compensatory neurohumoral pathways including the renin–angiotensin–aldosterone system, sympathetic nervous system, and antidiuretic hormone release [7, 204]. These responses promote sodium and water retention, while impaired renal free water excretion further lowers serum sodium concentration [204]. Hyponatremia is an independent predictor of mortality before and after liver transplantation and is incorporated into the MELD-Na and MELD 3.0 [108, 109, 186]. No absolute serum sodium threshold precludes transplantation; however, levels below 120 mEq/L are associated with increased perioperative risk. Clinically, hyponatremia may cause neurologic symptoms ranging from mild cognitive slowing and confusion to seizures and coma and may precipitate hepatic encephalopathy [7]. Management depends on the underlying volume status. Hypovolemic hyponatremia is treated by restoring effective circulating volume and discontinuing precipitating factors such as diuretics, while hypervolemic hyponatremia is managed with fluid restriction, careful diuretic adjustment, and selective use of vasopressin receptor antagonists, with close monitoring to prevent overly rapid correction and osmotic demyelination [7].

Hepatorenal syndrome is a severe form of kidney dysfunction that occurs in advanced liver disease with ascites in the setting of profound circulatory derangement [168]. The acute form, termed hepatorenal syndrome-acute kidney injury, is defined by an increase in serum creatinine of at least 0.3 mg/dl within 48 h or an increase of at least 50% from baseline within the preceding 7 days, and/or urine output of 0.5 mL/kg or less for at least 6 h that does not respond to adequate volume resuscitation for at least 48 h, in the absence of structural kidney injury [151]. Episodes are frequently precipitated by infection, especially spontaneous bacterial peritonitis, gastrointestinal bleeding, or large-volume paracentesis without adequate albumin replacement [13, 151]. The chronic form, referred to as hepatorenal syndrome-chronic kidney disease, typically follows a more indolent course and is defined by kidney dysfunction persisting for greater than 90 days [151]. Hepatorenal syndrome arises from severe splanchnic vasodilation and reduced effective arterial blood volume, leading to marked neurohormonal activation, renal vasoconstriction, impaired renal perfusion, and disordered sodium and water handling in the absence of intrinsic kidney disease [13, 151]. Diagnosis is clinical and requires exclusion of structural kidney injury, which is supported by bland urine sediment, normal renal ultrasonography, and absence of nephrotoxic exposures [202]. Standard treatment consists of vasoconstrictor therapy, typically terlipressin, administered in combination with concentrated albumin solutions [151]. Despite advances in medical therapy, prognosis remains poor without liver transplantation, with a median survival of less than 2 weeks for the acute form and approximately 6 months for the chronic form [202].

In addition to hepatorenal syndrome, other causes of acute kidney injury must be considered during pretransplant evaluation. Prerenal acute kidney injury occurs in the setting of absolute or relative intravascular volume depletion due to gastrointestinal bleeding, excessive diuresis, diarrhea, or large-volume paracentesis without adequate albumin replacement and typically improves with volume resuscitation and correction of the underlying insult [90]. Acute tubular necrosis is an intrinsic form of kidney injury that may develop after sustained renal hypoperfusion, sepsis, or exposure to nephrotoxic agents [187]. In contrast to hepatorenal syndrome, acute tubular necrosis is characterized by structural tubular injury and is suggested by granular casts on urine microscopy, elevated urinary sodium or urea concentrations, and limited response to intravascular volume expansion [187]. Distinguishing acute tubular necrosis from hepatorenal syndrome remains challenging and requires consideration of clinical context, urine studies, renal imaging, and response to therapy [187]. Less commonly, intrinsic glomerular diseases may cause acute kidney injury, particularly in association with chronic viral hepatitis or autoimmune liver disease [90]. These conditions should be suspected in the presence of hematuria, proteinuria, or active urinary sediment. Renal biopsy remains the gold standard for assessing structural kidney disease [74]. Transjugular biopsy and percutaneous biopsy have both been used, but coagulopathy, portal hypertension, and ascites increase procedural risk regardless of the approach [74, 90].

The primary objective of preoperative renal evaluation is to determine the severity, chronicity, and reversibility of kidney dysfunction. Evaluation should begin with a detailed clinical history focused on risk factors for intrinsic renal disease, including diabetes mellitus, hypertension, recurrent or prolonged episodes of acute kidney injury, exposure to nephrotoxic agents, and episodes of severe hemodynamic instability [140]. The temporal relationship between renal dysfunction and hepatic decompensation is also informative. Acute kidney injury coinciding with worsening portal hypertension or ascites suggests potentially reversible functional injury, while renal dysfunction that predates liver disease or persists despite hemodynamic optimization raises concern for intrinsic kidney disease. Physical examination should assess intravascular volume status, evidence of fluid overload, and signs of advanced portal hypertension [151]. Laboratory evaluation includes serial measurements of serum creatinine and blood urea nitrogen concentrations and urinalysis to assess proteinuria, hematuria, and urinary sediment [140]. Serum creatinine frequently underestimates true glomerular filtration rate in cirrhosis because of reduced muscle mass, impaired hepatic creatine synthesis, and expanded volume of distribution, leading to overestimation of renal function when creatinine-based equations are used [68]. Urinary indices such as urinary sodium concentration and fractional excretion of sodium have limited diagnostic utility, particularly in patients receiving diuretics. [68]. Urinary proteinuria may be misleading due to low serum protein levels [68]. Renal ultrasonography is useful to exclude obstructive uropathy and assess kidney size and cortical thickness, which may suggest chronic parenchymal disease [68]. In selected cases, direct measurement of glomerular filtration rate using radionuclide clearance techniques, supervised timed urine collections, or kidney biopsy may be required to clarify prognosis and guide transplant planning [140].

Simultaneous liver–kidney transplantation is reserved for carefully selected candidates with advanced liver disease in whom recovery of kidney function after isolated transplantation is unlikely. Current Organ Procurement and Transplantation Network policy defines eligibility under three scenarios: chronic renal insufficiency with an eGFR less than 60 mL/minute for at least 90 consecutive days and either an eGFR less than 35 mL/minute or dialysis dependence at the time of listing; sustained acute kidney injury, defined by dialysis dependence for at least 6 consecutive weeks or an eGFR below 25 mL/minute; or select metabolic disorders associated with renal failure, including primary hyperoxaluria, atypical hemolytic uremic syndrome, familial non-neuropathic systemic amyloidosis, or methylmalonic aciduria [30]. Because some patients do not initially meet criteria, a safety net allows priority kidney listing for liver transplant recipients who fail to recover renal function or who develop advanced renal dysfunction within 60–365 days after liver transplantation [30]. Although a kidney biopsy is not required under the Organ Procurement and Transplantation Network policy, histopathologic assessment can clarify the chronicity and reversibility of kidney injury and support transplant selection by improving estimates of renal recovery [30, 229].

Neurologic

Neurologic dysfunction in end-stage liver disease reflects the combined effects of hepatic failure, systemic inflammation, altered cerebral perfusion, and metabolic derangements [65]. Neurologic status may further deteriorate during the perioperative period because of hemodynamic instability, blood loss, electrolyte abnormalities, anesthetic exposure, and immunosuppressive therapy [65]. A structured pretransplant neurologic evaluation is essential to establish baseline cognitive and motor function, distinguish reversible from irreversible neurologic injury, and anticipate postoperative complications such as delirium, prolonged mechanical ventilation, and impaired rehabilitation.

Hepatic encephalopathy is the most common and clinically significant neurologic disorder in patients with advanced liver disease and is a focus of the pretransplant neurologic assessment [80]. Hepatic encephalopathy is defined as neurologic dysfunction caused by liver insufficiency or portosystemic shunting and encompasses a spectrum of neuropsychiatric abnormalities ranging from subtle cognitive impairment to coma [80]. Diagnosis is clinical and requires exclusion of alternative causes of altered mental status [80]. To standardize assessment and guide management, hepatic encephalopathy is classified according to four dimensions: underlying etiology, severity of neurologic impairment, temporal pattern, and the presence or absence of precipitating factors [220]. This framework is particularly relevant in transplant candidates, as each dimension has implications for perioperative risk, transplant timing, and postoperative outcomes.

Based on etiology, hepatic encephalopathy is categorized into three types. Type A occurs in acute liver failure and is characterized by rapid neurologic deterioration with a high risk of cerebral edema and intracranial hypertension [220]. This form is associated with astrocyte swelling, impaired cerebral autoregulation, and blood–brain barrier disruption, placing patients at risk for cerebral herniation. Type B

results from portosystemic shunting without intrinsic liver dysfunction, such as in congenital portosystemic shunts or extrahepatic portal vein obstruction [220]. Type C, the most common form encountered in transplant candidates, occurs in cirrhosis and reflects the consequences of hepatic insufficiency, portal hypertension, impaired ammonia clearance, systemic inflammation, and blood–brain barrier dysfunction, typically with a fluctuating but progressively worsening clinical course. [220].

The severity of hepatic encephalopathy exists along a continuum from minimal disease to overt disease. Minimal hepatic encephalopathy is defined by reproducible deficits in attention, psychomotor speed, and executive function detectable on formal neurocognitive testing but not apparent on routine bedside examination [80]. Although clinically subtle, minimal hepatic encephalopathy is associated with impaired quality of life, reduced capacity for complex tasks, and increased risk of progression to overt episodes [181]. Overt hepatic encephalopathy is graded using the West Haven criteria. Grade 1 includes impaired attention, subtle behavioral changes, and sleep–wake cycle disruptions [220]. Grade 2 is characterized by lethargy, behavioral change, and asterixis [220]. Grade 3 reflects severe cerebral dysfunction with marked confusion, disorientation, and somnolence [220]. Grade 4 represents coma with unresponsiveness to verbal or noxious stimuli [220]. Grades 3 and 4 hepatic encephalopathy are associated with increased in-hospital and 30-day mortality among patients with cirrhosis, independent of other extrahepatic organ failures [19]..

The temporal pattern of hepatic encephalopathy is classified as episodic, recurrent, or persistent. Episodic encephalopathy refers to isolated events with return to baseline mental status [220]. Recurrent encephalopathy involves repeated episodes lasting less than 6 [220]. Persistent encephalopathy is characterized by continuous cognitive or behavioral abnormalities with superimposed relapses of overt encephalopathy [220]. Across all patterns, identification of precipitating factors is critical. Common triggers include infection, gastrointestinal bleeding, electrolyte abnormalities, diuretic excess, constipation, and dehydration [220]. Identification and correction of these reversible factors are essential parts of preoperative optimization.

From a pathophysiologic standpoint, hepatic encephalopathy is a multifactorial process involving ammonia toxicity, systemic and neuroinflammation, and blood–brain barrier dysfunction [182]. In chronic liver disease, bacterial translocation and circulating proinflammatory cytokines promote systemic inflammation [182]. Ammonia crosses the blood–brain barrier and accumulates in astrocytes, where conversion to glutamine leads to cellular swelling and oxidative stress [182]. Inflammatory mediators activate microglia and disrupt synaptic signaling [182]. Increased blood–brain barrier permeability amplifies cerebral exposure to inflammatory mediators [182]. These mechanisms explain why infection or inflammatory stress can precipitate encephalopathy even when ammonia concentrations are only modestly elevated.

Hepatic encephalopathy associated with acute liver failure follows a particularly aggressive course. Astrocyte swelling, cytotoxic edema, vasogenic edema, impaired cerebral regulation, and accumulation of ammonia and glutamine contribute to rapid increases in intracranial pressure [32]. Clinical deterioration may progress

quickly from confusion and agitation to seizures, coma, and, in severe cases, brainstem herniation [216]. Neuroimaging may demonstrate diffuse cortical edema and basal ganglia signal abnormalities related to manganese deposition [129]. Electroencephalography may reveal generalized periodic discharges with triphasic morphology [228]. Management requires intensive care monitoring, airway protection when indicated, identification and treatment of alternative causes of altered mental status, correction of precipitating factors, and empiric therapy with nonabsorbable disaccharides and rifaximin [220].

In contrast, hepatic encephalopathy related to cirrhosis or chronic portosystemic shunting follows a more indolent and fluctuating course. Minimal hepatic encephalopathy affects 20–80% of patients with cirrhosis and is frequently underrecognized, despite causing clinically meaningful impairments in attention, psychomotor speed, coordination, and visuospatial function [220]. Overt hepatic encephalopathy develops in a substantial subset of patients and presents with disorientation, lethargy, personality change, and asterixis, with progression to coma in advanced stages [220]. Liver transplantation is the only definitive therapy for refractory hepatic encephalopathy; however, large portosystemic shunts may cause persistent neurologic dysfunction and recurrent encephalopathy even after transplantation and should be identified and considered for embolization when appropriate [220].

Other neurologic syndromes may complicate advanced liver disease and influence transplant candidacy and postoperative recovery. Acquired hepatocerebral degeneration presents with extrapyramidal features, including bradykinesia, rigidity, dystonia, and dysarthria, and reflects chronic basal ganglia injury related to manganese accumulation [228]. Although dopaminergic therapy may offer mild symptomatic relief, liver transplantation is the only effective treatment [65]. Hepatic myelopathy is characterized by slowly progressive spastic paraparesis with preserved sensation [171]. Peripheral neuropathy occurs in up to 90% of patients with cirrhosis, especially those with alcohol-associated liver disease, and typically manifests as a symmetric distal sensorimotor polyneuropathy [228]. Autonomic dysfunction may cause orthostatic hypotension, gastrointestinal dysmotility, urinary symptoms, and thermoregulatory instability [228]. Recognition of these conditions is important because neurologic comorbidities affect functional recovery and rehabilitation after transplantation.

Preoperative evaluation should begin with a focused history and comprehensive neurologic examination. The history should emphasize prior episodes of hepatic encephalopathy, baseline cognitive function, functional status, and known precipitants of neurologic decline [65]. The examination should assess mental status, speech, cranial nerve function, motor and sensory systems, cerebellar function, and reflexes [65]. Adjunctive testing, including laboratory studies, electroencephalography, and neuroimaging, may be used selectively, although practice patterns vary among transplant centers [65].

Evaluation of suspected hepatic encephalopathy should prioritize exclusion of competing diagnoses, as altered mental status in transplant candidates is often multifactorial [220]. Blood ammonia concentrations may support the diagnosis but correlate poorly with clinical severity in chronic liver disease and should not be used in

isolation [220]. A normal ammonia level has a high negative predictive value and should prompt evaluation for alternative causes [122]. Formal neurocognitive testing may be used selectively to establish a baseline for postoperative comparison, ideally using at least two validated instruments [220]. Neuroimaging and electroencephalography should be reserved for patients with atypical, focal, persistent, or progressive neurologic findings [65]. Laboratory evaluation should focus on identifying possible precipitating factors and excluding alternative diagnoses [122]. Early neurology consultation is recommended in complex or refractory cases.

Neurologic evaluation occurs in concert with psychosocial assessment, as psychosocial factors are integral to transplant candidacy and long-term outcomes. Key domains include mental health stability, substance use history, insight into illness, adherence to medical care, and adequacy of social support [140]. Many candidates have a history of substance use disorder. Although the United Network for Organ Sharing does not mandate a fixed period of abstinence, state-level Medicaid policies may impose minimum abstinence requirements before transplantation [143]. Candidates with poor insight or high risk of relapse may therefore be deemed unsuitable for listing [143]. Adequate social support is essential to ensure successful postoperative recovery, adherence to immunosuppression, and engagement with long-term follow-up [140]. Successful transplantation depends on reliable participation in care and sustained adherence to complex medical regimens.

Infectious Disease

End-stage liver disease is associated with cirrhosis-associated immune dysfunction, characterized by concurrent impairment of innate and adaptive immune responses with chronic systemic inflammation [5, 89]. Cirrhosis disrupts the liver's central role in immune homeostasis through injury to the reticuloendothelial system, reduced synthesis of innate immune and pattern-recognition proteins, and impaired bactericidal activity of phagocytic cells [5]. As the disease progresses, ongoing inflammatory signaling from injured hepatocytes and increased translocation of gut-derived pathogens promote persistent systemic inflammation, leading to immune exhaustion and diminished responsiveness to vaccination [5]. Patients with cirrhosis are highly susceptible to infections even before exposure to posttransplant immunosuppression [89]. The preoperative infectious disease evaluation should therefore focus on identifying active infection, detecting latent infections with potential for reactivation, and recognizing features of hepatic decompensation that increase perioperative infectious risk.

Several infections are particularly relevant in liver transplant candidates and require careful attention during preoperative evaluation. Spontaneous bacterial peritonitis is the most common bacterial infection in patients with cirrhosis and ascites and reflects the combined effects of advanced portal hypertension, intestinal barrier dysfunction, and cirrhosis-associated immune impairment [138]. It is defined as an infection of the ascitic fluid diagnosed by paracentesis demonstrating a polymorphonuclear leukocyte count of at least 250/mm^3 in ascitic fluid, with or without positive bacterial culture, in the absence of an identifiable intra-abdominal source of infection [179]. Clinical presentation is often subtle. Patients may present with

worsening encephalopathy, acute kidney injury, hypotension, or nonspecific clinical deterioration rather than fever or abdominal pain [138]. Diagnostic paracentesis should be performed in any patient with ascites who develops an acute change in clinical status [12, 179]. Early initiation of empiric antibiotic therapy improves survival, and adjunctive intravenous albumin reduces the risk of renal failure and mortality in high-risk patients [12]. Spontaneous bacterial empyema represents an infection of a preexisting hepatic hydrothorax and is diagnosed by a positive pleural fluid culture with a neutrophil count greater than 250/mm^3 or, in the absence of a positive culture, a neutrophil count greater than 500/mm^3. Management parallels that of spontaneous bacterial peritonitis [12]. Resolution of infection and clinical stabilization should be confirmed before proceeding with transplantation [140].

Acute bacterial cholangitis is another high-risk infection encountered in patients with underlying cholestatic liver disease. In primary sclerosing cholangitis, chronic biliary inflammation and fibrosis result in multifocal strictures and impaired bile flow, predisposing patients to recurrent ascending infections [29, 98]. Classic features include high fever, abdominal pain, and jaundice, accompanied by elevated inflammatory markers and cholestatic liver enzyme abnormalities [4]. Episodes may occur even in the absence of biliary obstruction, particularly in the presence of dominant strictures or following biliary instrumentation [4]. Recurrent cholangitis reflects advanced biliary disease and limited hepatic reserve [29]. Preoperative assessment should confirm resolution of active infection, adequacy of antimicrobial therapy, and effective biliary drainage when indicated, as ongoing infection increases perioperative risk [140].

Chronic viral hepatitis remains a major indication for liver transplantation worldwide [46]. All candidates should undergo comprehensive screening for hepatitis B virus and hepatitis C virus infection [128]. In patients with chronic hepatitis B infection, pretransplant antiviral therapy with potent nucleoside or nucleotide analogs is essential to achieve viral suppression, as higher viral loads at the time of transplantation are associated with increased risk of graft reinfection and accelerated allograft injury [46]. Antiviral therapy is typically continued through the perioperative period, often in conjunction with short-term hepatitis B immune globulin, followed by long-term posttransplant surveillance [128]. Chronic hepatitis C infection is now highly treatable with direct-acting antiviral agents [46]. Achievement of a sustained virologic response before transplantation may delay disease progression, reduce the need for transplantation in selected patients, and decrease the risk of posttransplant viral recurrence [128]. In contemporary practice, antiviral therapy may be initiated before or after transplantation depending on disease severity, organ availability, and access to treatment, with careful coordination to minimize drug–drug interactions with immunosuppressive regimens [128]. Use of organs from hepatitis C virus–viremic donors for both viremic and nonviremic recipients, followed by posttransplant antiviral therapy, has become increasingly common [23]. With effective antiretroviral therapy, liver transplantation is feasible in carefully selected patients with human immunodeficiency virus infection, generally requiring a CD4 lymphocyte count greater than 100 cells/L and anticipated virologic suppression at the time of transplant [140]. Outcomes are comparable to those of noninfected recipients, except in hepatitis C virus–coinfected patients who have worse

survival, particularly in the setting of low body mass index, older donor age, or combined liver–kidney transplantation [140, 212].

Beyond liver-specific considerations, infectious disease evaluation of liver transplant candidates is otherwise similar to that of other solid organ transplant populations. Assessment should include a detailed history of prior infections, antimicrobial exposures, risk factors for latent infection, vaccination status, travel or residence in endemic regions, occupational exposures, and high-risk behaviors [66]. Standard screening includes serologic testing for human immunodeficiency virus types 1 and 2, human T lymphotropic virus types 1 and 2, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, herpes simplex virus, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody, and syphilis [66]. Screening for latent tuberculosis should be performed using either a tuberculin skin test or an interferon gamma release assay [66, 137]. Testing for regionally endemic pathogens should be guided by epidemiologic exposure risk [137].

Immunization status should be reviewed early in the transplant evaluation process. Inactivated vaccines are safe and should be administered according to national guidelines, as vaccine responses are more robust before transplantation [49]. Live attenuated vaccines may be considered in seronegative candidates who are not significantly immunocompromised when administered well in advance of transplantation but are contraindicated after transplant because of the risk of uncontrolled viral replication [49]. All liver transplant candidates should undergo formal dental evaluation, as untreated oral disease may serve as a source of systemic infection following transplantation [140]. Necessary dental procedures should be completed before transplantation with careful attention to bleeding risk [140].

Contraindications to Transplantation

Contraindications to liver transplantation encompass clinical situations in which transplantation is unlikely to provide meaningful survival or quality-of-life benefit or in which perioperative or posttransplant risk remains unacceptably high despite appropriate optimization. Decisions regarding transplant candidacy are guided by the severity and trajectory of liver disease, anticipated survival without transplantation, the presence and reversibility of extrahepatic organ dysfunction, and transplant center–specific expertise. Professional society guidelines provide an important framework for decision-making but must be applied in the context of the individual patient, as risks initially considered prohibitive may evolve with treatment, stabilization, or time. Contraindications are therefore best categorized as absolute or relative, depending on whether risk factors are irreversible or potentially modifiable, with the goal of selecting candidates who can safely undergo transplantation and achieve meaningful long-term benefit.

Absolute contraindications include conditions associated with prohibitive perioperative risk or poor posttransplant survival. These include uncontrolled systemic infection or sepsis; severe, irreversible cardiac or pulmonary disease that precludes safe anesthesia or major abdominal surgery; and active extrahepatic malignancy because of the high risk of recurrence under immunosuppression [140]. Certain hepatic malignancies are also considered absolute contraindications because of aggressive tumor biology, including hepatocellular carcinoma with extrahepatic or

vascular metastatic spread, intrahepatic cholangiocarcinoma outside of highly selected investigational protocols, and primary hepatic angiosarcoma [140]. Human immunodeficiency virus infection is a contraindication in patients with a CD4 lymphocyte count below 100 cells/L or in whom durable viral suppression is not expected by the time of transplantation [140]. Anatomic abnormalities that preclude successful implantation of a donor liver are also absolute contraindications [140]. Persistent nonadherence to medical care, ongoing alcohol or illicit substance use, and the absence of adequate social support are considered contraindications, as these factors compromise safe intraoperative and early postoperative management, adherence to immunosuppressive therapy, and long-term graft survival [140].

Relative contraindications include conditions that increase perioperative risk or reduce the expected benefit of transplantation but may improve with treatment, stabilization, or reassessment. A MELD score below 15 is generally considered a relative contraindication, as the risks of transplantation in this population often outweigh the anticipated survival benefit [140]. Class 3 obesity, defined as a body mass index of 40 kg/m^2 or greater, is also considered a relative contraindication because of increased surgical complexity and higher rates of perioperative complications [140]. Candidacy may be reconsidered following sustained weight loss and optimization of associated comorbidities. Advanced age alone is not a contraindication to liver transplantation; however, patients older than 70 years with frailty, sarcopenia, or significant comorbid disease require careful multidisciplinary evaluation and targeted pretransplant optimization to ensure acceptable outcomes [140].

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Anesthesia for Renal Transplantation

3

Christopher J Little

Preoperative Evaluation

2026 Edition

Introduction

For kidney transplantation, the preoperative evaluation should identify risk factors and address medical, psychological, and social conditions that affect outcomes. Early referral to a transplant program is recommended to assess candidates for preemptive transplantation. Clinicians should discuss transplantation's risks and benefits with patients to facilitate informed decision-making. Periodic reevaluation is necessary to address new issues impacting transplant suitability after candidates are listed for donation [1].

Cardiac Evaluation

The most important goal is to reduce morbidity and mortality related to cardiovascular disease. The high incidence of coronary disease (CAD) in chronic kidney disease (CKD) patients is a significant challenge. Overall, 50% of deaths in end-stage renal disease (ESRD) patients are due to coronary artery disease, and 36% of post-transplant deaths with a functioning graft are cardiac-related. As of January 14, 2014, nearly 90,000 candidates were on the waiting list. In 2011, 5000 potential recipients died before transplantation [2, 3]. The aging candidate pool, with 62% being ≥50 years old in 2011 compared to 28.7% in 1991, means anesthesiologists must prepare for more complex medical comorbidities [4].

Renal transplant candidates need testing for CAD, usually noninvasively, via nuclear myocardial perfusion studies and dobutamine stress echocardiography. While these tests have good prognostic value, they are imperfect for detecting

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angiographically defined CAD in ESRD patients. The association of CAD with subsequent survival is inconsistent, possibly because plaque instability is more critical for infarction risk than angiographic stenosis [5]. A 2005 survey showed variable reliance on initial cardiac evaluation, American College of Cardiology / American Heart Association (ACC/AHA) criteria, or a combination thereof among transplant centers. Due to inconsistent cardiovascular screening and treatment, the ACC/AHA, American Society of Transplant Surgeons (ASTS), American Society of Transplantation (AST), and National Kidney Foundation (NKF) developed a consensus document in 2012 regarding cardiac disease evaluation and management in kidney and liver transplant candidates [6].

All renal recipients must have a preoperative ECG, with abnormal results requiring further cardiac evaluation. The choice of noninvasive cardiac testing is at the evaluator's discretion. Routine repeated left ventricular function testing after listing is not supported by evidence, according to the 2012 consensus report [6]. Coronary artery bypass graft (CABG) may be reasonable for ESRD patients with significant left main coronary artery stenosis (>50%) or significant stenosis (≥70%) in three major vessels or the proximal left anterior descending artery and one other major vessel, regardless of left ventricular function. CABG is preferred over PCI for improving survival in patients with multivessel CAD and diabetes mellitus [6].

Echocardiography is necessary for suspected valvular disease or congestive heart failure. More frequent monitoring is advised for ESRD patients with moderate aortic stenosis due to their rapid progression [7]. Atrial fibrillation is also prevalent in ESRD patients and increases stroke and mortality risk. Pre-existing atrial fibrillation is associated with poor post-transplant outcomes [8].

Pulmonary hypertension (PH) is prevalent among ESRD patients and is associated with worse patient and transplant outcomes, including increased risk of delayed graft function, inferior graft function, and higher mortality [9]. Patients with signs of moderate or severe PH (pulmonary arterial systolic pressure [PASP] >45 mm Hg) on echocardiography require cardiac catheterization [6, 9]. Confirmed significant pulmonary arterial hypertension (WHO Group 1) without a secondary cause warrants evaluation by a specialist before transplantation.

Hypertension and Diabetes Mellitus

Patients with CKD have a high prevalence of hypertension (85–95%) and/or diabetes mellitus. Hypertension can be a cause or consequence of CKD [10]. Approximately one in three adults with diabetes has CKD [11]. In type 2 diabetics, blood pressure control may be more important than chronic glycemic control. Current recommendations target blood pressure < 130/80 mmHg in hypertensive diabetics. In all people with diabetes with ESRD, the type of diabetes, home monitoring method, and usual metabolic control should be assessed, including antidiabetic therapy. Serum glucose levels and HbA1c help evaluate therapeutic control [12]. When formulating an anesthetic plan, anesthesiologists must consider the common comorbidities of diabetes and ESRD, like gastroparesis, autonomic

neuropathy, cardiovascular disease, and peripheral vascular disease [13]. Diabetic autonomic neuropathy is commonly overlooked and may manifest as resting tachycardia, exercise intolerance, orthostatic hypotension, gastroparesis, and hypoglycemic autonomic failure.

Anemia

Avoiding transfusions is essential due to the risk of sensitization, potentially leading to longer wait times, ineligibility for live donors, increased mortality on the waiting list, or worse post-transplant outcomes. However, pre-transplantation erythropoiesis-stimulating agent hyporesponsiveness may be associated with increased kidney allograft failure and mortality [14].

Coagulation Studies

Renal transplant candidates have an increased prevalence of prothrombotic factors, increasing the risk of early graft loss in thrombophilic patients. All candidates should have routine coagulation studies, with more extensive profiles for those with a history of thrombosis, including recurrent arteriovenous graft/fistula thrombosis. This workup may include screening for activated protein C resistance, factor V and prothrombin gene mutations, anticardiolipin antibody, lupus anticoagulant, proteins C and S, antithrombin III, and homocysteine levels.

Pulmonary Disease

Pulmonary function tests may be needed for patients with known lung disease, symptoms of active lung disease or reactive airway disease, and sleep apnea. Recipients with chronic obstructive lung disease and restrictive lung disease have increased post-transplant infectious complications and mortality. Smokers with evidence of chronic lung disease must quit before transplantation and should be referred to cessation programs.

Obesity

Obesity is a cardiovascular risk factor common before and after transplantation. While the role of pre-transplant obesity is uncertain, post-transplant obesity increases the risk of graft failure and mortality. Nutritional intervention can achieve post-transplant weight loss, but its long-term outcome effect is not established [15].

Airway Evaluation

Airway evaluation is crucial, especially in diabetic kidney transplant recipients, who may require advanced airway equipment for difficult airway management [16]. The cause of increased intubation difficulty in diabetics is unknown, but one factor may be abnormal collagen cross-linking due to chronic hyperglycemia. Long-duration diabetes can stiffen joints from connective tissue glycosylation, potentiated by renal insufficiency. Diabetic patients may develop waxy skin, contractures, and stiff joint syndrome, often affecting the head and neck, particularly the atlantooccipital joint, potentially limiting tracheal visualization during laryngoscopy. Diabetes is also frequently associated with obesity, which is an independent risk for difficult intubation and mask ventilation.

NPO Guidelines and Preoperative Medications

For elective surgery, patients should abstain from solids/foods for 8 h preoperatively. Patients with diabetes may have vagus nerve dysfunction, leading to delayed gastric emptying [12]. Patients with diabetes should be screened for symptoms of early satiety, nausea, or vomiting. High suspicion for delayed gastric emptying should prompt consideration of empiric rapid sequence intubation or further evaluation with gastric ultrasound [17]. Patients taking glucagon-like peptide-1 (GLP-1) agonists, like semaglutide, should be thoroughly screened for delayed gastric emptying before induction of anesthesia.

Patients should generally continue all home medications except angiotensin system inhibitors and oral hypoglycemic drugs. Angiotensin inhibitors taken before surgery are linked to a higher incidence of hypotension during anesthesia induction [18]. Oral hypoglycemic drugs are held 24 h before surgery for short half-life drugs and up to 48 h preoperatively for long-acting ones to avoid reactive hypoglycemia, especially with sulfonylureas and associated toxicities and interactions. Continuing beta-adrenergic blockers perioperatively is recommended for patients already taking them to prevent rebound hypertension and tachycardia. Initiating beta-blockers in beta-blocker-naïve patients the night before or morning of noncardiac surgery is not recommended [6].

Fluid Status and Electrolytes

Immediate preoperative assessment should also include identifying disturbances in acid–base balance and electrolytes and estimating fluid status, ranging from hypovolemic to hypervolemic. Volume status can be estimated by dialysis frequency and the last dialysis treatment. Routine hemodialysis before surgery has generally been avoided, but same-day dialysis is unlikely to affect early graft function and may improve postoperative mortality [19, 20].

Surgical Considerations

Anatomy of the Native Kidneys

Human kidneys are located in the retroperitoneal space between T12 and L3 and are surrounded by perinephric fat. They have a bean-shaped appearance with a medial hilum. There is no significant size difference between the right and left kidneys, and patient characteristics do not predict graft size. Each kidney is covered by a fibrous capsule and renal fascia lying on the psoas muscle. The renal arteries originate from the aorta (L1–L2). The right renal artery is typically longer and passes under the inferior vena cava. Renal veins drain directly into the systemic system. The right renal vein is short due to its proximity to the inferior vena cava. The left renal vein is usually longer, passing anterior to the aorta and receiving tributaries from the adrenal, gonadal, and lumbar veins. Because the left renal vein is longer, the left kidney is generally easier to transplant than the right.

Kidney Procurement

During cadaveric procurement, the kidneys are flushed with preservation fluid via a cannula in the distal aorta, with a clamp above the celiac artery. This fluid is vented through the distal vena cava or right heart until blood is evacuated. Kidneys are commonly removed en bloc with segments of the aorta, vena cava, and long ureters. Adrenal glands or parts thereof are excised with each kidney. The right kidney's vasculature is procured with an aortic cuff on the artery and a segment of vena cava on the vein, which can be used for vein extension. The left kidney includes an aortic cuff on the artery but no vena cava on the vein. In live donor procurement, the renal arteries and veins do not have aortic or vena caval cuffs, the adrenal gland is usually preserved, and the ureter length may be shorter.

Bench Preparation of Renal Allograft

This involves dissecting fat around the kidney, mobilizing vessels, and identifying the ureter, taking care to avoid devascularization. The renal vein is carefully examined. The external iliac vein may be mobilized for short right renal veins, or a vena cava conduit may be created from the divided donor vena cava.

Renal Transplant Operation

The operation begins with an operative timeout confirming patient, procedure, and donor organ details. A curvilinear skin incision in the right iliac fossa exposes the retroperitoneum, avoiding peritoneal violation. The epigastric vessels are initially preserved, and the spermatic cord (round ligament in females) is usually preserved.

Following retractor placement, the external iliac artery and vein are circumferentially dissected with lymphatic ligation. The venous anastomosis (renal to external iliac vein) is usually completed first. The arterial anastomosis (renal artery to external iliac artery) follows, with various techniques for multiple arteries. Diuretics are typically given when releasing the clamps (vein then artery) to reperfuse the graft. Graft perfusion and anastomotic bleeding are assessed and addressed. After reperfusion and hemostasis are achieved, the ureter-to-bladder anastomosis is performed. A three-way catheter is inserted, the bladder is distended with irrigation, incised, and the spatulated ureter is anastomosed to the bladder mucosa; a ureteral stent may be placed at this point. The detrusor muscle is then re-approximated, and the operative field is inspected for hemostasis and graft positioning. A drain may be left, and the abdominal layers are closed.

Immunosuppression Induction

Induction therapy is crucial to reduce the risk of acute rejection by providing rapid and profound immunosuppression. Common induction agents in the USA include the IL-2 receptor antagonist basiliximab (Simulect®), the polyclonal T cell–depleting agent rabbit antithymocyte globulin (Thymoglobulin®), and the monoclonal T cell–depleting agent alemtuzumab (Campath-1H®). The choice of agent is individualized based on recipient and donor risk factors, such as PRA >0%, increased human leukocyte antigen (HLA) mismatches, younger recipient/older donor, African-American ethnicity, donor-specific antibodies, ABO incompatibility, delayed graft function, and cold ischemic time > 24 h.

Rabbit antithymocyte globulin (Thymoglobulin®) is a T cell–depleting agent associated with infusion reactions such as fever and hypotension, cytopenias requiring dose adjustments, and an increased risk of infections and post-transplant lymphoproliferative disorder. Alemtuzumab (Campath-1H®) causes profound and prolonged lymphocyte depletion, leading to a higher risk of opportunistic infections, infusion reactions, and rare autoimmune complications such as thyroiditis or immune thrombocytopenia. In contrast, basiliximab (Simulect®), an IL-2 receptor antagonist, is generally well tolerated with only mild infusion-related symptoms and a low risk of infections or malignancy.

Belatacept (Nulojix) is an immunosuppressant drug that blocks a key costimulation signal (signal 2) needed for full T cell activation. It has been shown to be as effective as cyclosporine for patient and graft survival and may eventually replace calcineurin inhibitors. It is given by IV, starting on days 1, 5, 15, 28, and 56, then switched to every 28 days.

Although it carries a slightly higher risk of rejection, patients on belatacept tend to have a higher glomerular filtration rate (GFR), better graft survival, and fewer new donor-specific antibodies. It also causes fewer metabolic side effects. However, it can cause a serious complication called post-transplant lymphoproliferative disorder in patients who are EBV-negative, so it is only used in EBV-positive patients.

Intraoperative Anesthetic Management

Reliable large-bore peripheral intravenous access is essential as high-volume bleeding is possible. The use of central lines has fallen out of favor in kidney transplantation as the risk of major intraoperative bleeding decreases. A pre-induction fluid status assessment is needed, considering the time since their last dialysis. Mild-to-moderate hyperkalemia (5.0–5.5 mmol/L) in steady-state ESRD may be an adaptive response and not a reason to delay surgery, but higher levels or acute increases must be treated. Gastroparesis is common in ESRD, so these patients should be treated as having a full stomach.

Standard monitors are required. Invasive arterial blood pressure monitoring is standard in patients with significant cardiovascular or lung disease or in patients whose graft locations make noninvasive measurements difficult. Transesophageal echocardiography and pulmonary artery catheters may be indicated for severe left ventricular dysfunction, valvular abnormalities, or pulmonary hypertension, though seldom required, as these patients are not typically transplant candidates.

Pharmacokinetics and Pharmacodynamics

Chronic kidney disease affects drugs beyond those renally excreted, with changes in plasma protein binding impacting hepatic metabolism and distribution. Diminished protein binding increases the free drug fraction. Decreased cardiac output can increase drug distribution to the brain and reduce the redistribution rate, leading to higher concentrations and lower dose requirements. Increased cardiac output, which may be seen in anemic patients with ESRD, has the opposite effect. Propofol dose should be reduced in hypovolemic patients or those with decreased left ventricular (LV) function. Etomidate may be useful for induction in severe cardiac compromise but is linked to increased 30-day mortality [21].

While the evidence for sevoflurane use during renal transplantation is sparse, the current consensus in the medical literature indicates that sevoflurane is not associated with significant nephrotoxicity in patients with chronic kidney disease. A retrospective cohort study by Park et al. found no significant association between sevoflurane anesthesia and postoperative acute kidney injury (AKI) in patients undergoing noncardiac surgery [22]. Similarly, a systematic review and meta-analysis by Sondekoppam et al. concluded that sevoflurane does not increase the risk of postoperative renal impairment compared to other anesthetic agents [23]. Finally, studies looking at using low gas flows with sevoflurane use in patients with stable CKD showed no difference or worsening of kidney function [24, 25]. Isoflurane and desflurane can also be used safely in patients receiving kidney transplantation.

Succinylcholine can be used safely if potassium is <5.5 mEq/L, with a transient potassium increase similar to that of healthy patients [26]. Reduced plasma cholinesterase in renal failure may prolong succinylcholine blockade, but this is likely not a clinically relevant difference. Mivacurium, however, may require dose reduction

due to slower recovery from reduced cholinesterase activity. In patients with ESRD, Rocuronium's clearance is reduced, and its effect may be prolonged. Lower doses (0.3 mg/kg) for short blocks have similar recovery times but more variability in renal failure patients [27, 28]. Similarly, vecuronium's action is longer in renal failure due to decreased clearance and renal excretion [29]. Pancuronium clearance is significantly reduced in renal transplant patients, so shorter-acting relaxants are preferred [30]. Variable recovery times are noted for all muscle relaxants in chronic kidney disease, so quantitative neuromuscular blockade monitoring should be used to confirm adequate reversal before extubation. Neostigmine clearance is reduced in renal failure, but pharmacokinetics at the end of renal transplant surgery are similar to those with normal function. The use of sugammadex for the reversal of rocuronium and vecuronium in patients with ESRD and recent kidney transplants is still relatively new, but what studies have been done so far point toward its safety [31]. The relative uncertainty surrounding the efficacy of sugammadex in patients with ESRD highlights the need for quantitative twitch monitoring to confirm reversal.

Fentanyl pharmacokinetics show significant inter-subject variability in transplant patients, with decreased clearance at higher blood urea nitrogen (BUN) levels [32]. Alfentanil and sufentanil kinetics are generally similar in renal transplant patients and controls, but inter-individual variability may be higher with sufentanil [33]. Morphine is usually avoided in patients with CKD as it is associated with excessive and prolonged effects due to decreased clearance and accumulation of active metabolites (morphine-6-glucuronide), increasing the risk of delayed respiratory depression. Renal transplant normalizes morphine clearance, but other opioids are likely safer until graft function is confirmed. Hydromorphone's metabolite (H3G) can accumulate and cause neuro-excitatory symptoms, so dosing should be titrated carefully. Remifentanil pharmacokinetics are largely unchanged in renal disease, though its metabolite elimination is reduced but unlikely to cause significant opioid effects. Meperidine should be avoided in patients with ESRD because its active metabolite, normeperidine, accumulates in renal failure and may cause seizures. Please see Table 3.1 for a summary of the relevant pharmacologic changes in ESRD patients.

Intravenous Fluid Therapy

Determining the patient's preoperative volume status is vital, with consideration given to the last dialysis and the amount of volume removed during that session. Intraoperative volume expansion improves immediate graft function, increasing graft survival and lowering mortality [34]. Diuretics (furosemide), osmotic agents (mannitol), and sometimes dopamine agonists are used post-reperfusion, but only mannitol with volume expansion has been shown to decrease acute tubular necrosis [35]. Dopamine is not beneficial and may be harmful [36]. Maintaining adequate intravascular volume and careful medication titration are essential, as vasopressors (especially alpha agonists) can interfere with renal perfusion. Isotonic crystalloid solutions are generally used, with colloid considered for necessary volume expansion. Albumin's superiority over crystalloids for perioperative volume expansion is

Table 3.1 Common medications administered during renal transplantation and their changes in patients with end-stage renal disease

Medication	Effect of ESRD	Clinical implication
Neuromuscular blocking agents and reversal agents		
Succinylcholine	Reduced plasma cholinesterase may prolong blockade	Can be used safely if potassium <5.5 mEq/L Prolongation is likely not clinically relevant
Cisatracurium	Recovery unchanged in ESRD	Degraded by Hofmann elimination
Rocuronium	Clearance is reduced. Effect may be prolonged	Consider lower doses for short blocks Use quantitative twitch monitoring
Vecuronium	Action is longer	Consider lower doses for short blocks Use quantitative twitch monitoring
Pancuronium	Clearance is significantly decreased	Avoid if feasible
Neostigmine	Clearance is reduced in renal failure	Use the smallest effective dose Use quantitative twitch monitoring
Sugammadex	Use in ESRD and recent kidney transplant is relatively new	Studies point toward safety Use quantitative twitch monitoring
Opioids		
Fentanyl	Decreased clearance at higher BUN levels	Careful titration and monitoring
Alfentanil	High individual variability	Careful titration and monitoring
Sufentanil	High individual variability	Careful titration and monitoring
Morphine	Excessive and prolonged effects	Generally avoided in patients with advanced CKD and ESRD. Increases the risk of delayed respiratory depression
Hydromorphone	Metabolite (H3G) can accumulate	Careful titration and monitoring Commonly used in patient-controlled analgesia (PCA) postoperatively
Remifentanil	Metabolite elimination is mildly reduced	Metabolite unlikely to cause significant opioid effects
Meperidine	Active metabolite (normeperidine) accumulates	May cause seizures **Should be avoided in patients with ESRD**
Post-transplant interaction		
Verapamil and Diltiazem (non-DHP CCBs)	Interaction with calcineurin inhibitor metabolism	Should be avoided postoperatively

not established. Crystalloid solutions should be the first-line choice for resuscitation and maintenance, but colloid may be needed in severe hypovolemia to maintain graft perfusion.

Postoperative Considerations

Initial Postoperative Assessment

Assessing the likelihood of delayed graft function requires information on the donor's status, including cause of death, age, medical history, and cold/warm ischemia time. A Foley catheter is inserted to monitor urine output and decompress the bladder, and adequate venous and arterial access should be established to monitor hemodynamic status.

Hemodynamic Status

Maintaining stable perioperative hemodynamics with a slightly positive fluid balance and moderately higher blood pressure is crucial for adequate graft perfusion. Replacement fluids should be adjusted based on urine output and insensible losses. Common causes of postoperative hypotension include bleeding, anesthetic effects, inadequate volume resuscitation, myocardial infarction, aggressive ultrafiltration, cytokine release syndrome, and sepsis. Hypotension should be promptly treated with isotonic fluids and blood products if anemia is present to prevent acute tubular necrosis and delayed graft function, which is defined as the need for dialysis within the first week. Persistent hypotension with abdominal pain and dropping hematocrit may indicate intra-abdominal bleeding requiring surgical intervention. Antithymocyte globulin can cause cytokine release syndrome with fever, chills, rash, myalgias, hypotension, and tachycardia, typically during the first or second dose. Treatment involves reducing the infusion rate and premedication with antihistamines, H2-blockers, and glucocorticoids.

Hypertension

Postoperative hypertension is generally treated only when systolic blood pressure is greater than 170 mmHg and/or diastolic blood pressure is greater than 100 mmHg after ruling out pain and nausea. Intravenous options include hydralazine and labetalol, while dihydropyridine calcium channel blockers are preferred oral agents. Non-dihydropyridine calcium channel blockers like verapamil and diltiazem should be avoided due to their interaction with calcineurin inhibitor metabolism. Abrupt cessation of pre-transplant antihypertensives like clonidine and minoxidil should be avoided to prevent rebound hypertension.

Pain Control

Concerns with coagulopathy in ESRD have limited the use of neuraxial blocks for postoperative pain control. Transversus abdominus plane blocks have been used for analgesia, though the evidence for their efficacy in abdominal surgery is debated. The anterior quadratus lumborum block is also a novel block with potential for good analgesia, but more research on its efficacy is required. This leaves patient-controlled analgesia with opioids (typically hydromorphone) as the most common analgesic in the postoperative period. Implementing a multimodal analgesia protocol, including non-opioid adjuncts like gabapentin, acetaminophen, and topical lidocaine, can significantly reduce opioid use and improve pain management.

Postoperative Anemia

Anemia is common due to hemodilution, blood loss, and phlebotomy. A goal hemoglobin level of >9 g/dl is generally maintained, especially in diabetics and patients with coronary artery disease. Transfusions are avoided if possible due to the risk of alloimmunization, and erythropoietin-stimulating agents may be considered for slow graft function after ensuring adequate iron stores.

Leukopenia

Postoperative leukopenia can be caused by thymoglobulin, mycophenolate mofetil, and trimethoprim/sulfamethoxazole.

Postoperative Hyperglycemia

Hyperglycemia in both diabetic and non-diabetic patients is managed with continuous insulin infusion, followed by subcutaneous insulin with basal and short-acting coverage once oral intake resumes. Glucose should be closely monitored in simultaneous kidney–pancreas transplant recipients for pancreatic allograft dysfunction.

Electrolyte Disorders

Post-transplant patients are prone to electrolyte disturbances due to IV fluids, solute diuresis, tubular wasting, and immunosuppressive medications. Common abnormalities include hyperkalemia/hypokalemia, hypophosphatemia, hypercalcemia, hypomagnesemia, and hyponatremia. Frequent laboratory monitoring is essential for early detection and management.

Table 3.2 Causes and management of renal dysfunction after transplant

Category	Causes	Diagnosis/management
Pre-renal	Low blood pressure Poor cardiac output Autonomic dysfunction Volume depletion High tacrolimus levels Renal artery stenosis Medications (ACEI/ARB, NSAIDs)	Treat underlying cause (e.g., fluid for hypotension) Discontinue offending medications
Intrinsic renal	Allograft rejection (cellular or antibody-mediated) Acute tubular necrosis Thrombotic microangiopathy Recurrence of primary disease (e.g., FSGS)	Biopsy for rejection Urine microscopy for acute tubular necrosis (tubular cells, muddy brown casts) Monitor proteinuria for recurrent disease
Post-renal	Benign prostatic hypertrophy Foley catheter clots Extrinsic compression (hematoma, lymphocele, urinoma)	Identify and relieve obstruction

Allograft Dysfunction

An abrupt increase in creatinine necessitates evaluation for pre-renal, intrinsic renal, and post-renal causes. Please see Table 3.2 for a detailed outline of common reasons for renal dysfunction after transplant.

Monitoring of Urine Output and Urine Leak

Robust urine output indicates good graft function. Decreased urine output requires assessment of "plumbing" issues, vascular flow, and renal parenchymal injury. Flushing the Foley catheter and a renal Doppler ultrasound are the initial steps. Nuclear scans like mercaptoacetyltriglycine (MAG3) renal scans or diethylenetriamine pentaacetic acid (DTPA) scans can assess perfusion and identify obstruction or leaks. Urine leaks from the vesicoureteric anastomosis are managed conservatively if a drain and stent are present; otherwise, a nephrostomy tube or surgical repair may be needed.

Monitoring of Drains, Ureteral Stents, and Incision Sites

Drain output should be monitored for volume and the presence of gross blood, which requires immediate notification of the surgeon. Ureteral stents are typically removed cystoscopically after 4–6 weeks. The incision site should be monitored for infection, dehiscence, and drainage, with staples or sutures removed by the second or third week.

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Anesthesia Management in Liver Transplantation

4

Flora Simmons

2026 Edition

Liver Anatomy and Function

As the largest solid organ in the body, the liver has an essential role in protein synthesis, hormone synthesis, hemostasis, metabolism, detoxification, and immune function. The liver makes up 2.5% of total body weight; however, it receives nearly 25% of the body's cardiac output [1]. The liver receives a dual blood supply from the portal vein and hepatic artery. The portal vein provides 75% of blood flow to the liver, although it accounts for 50% of oxygen delivery. While the hepatic artery provides 25% of the liver's blood flow, it accounts for 50% of the liver's oxygen delivery. Blood flow to the liver is regulated by both intrinsic and extrinsic mediators. Intrinsic mediators such as adenosine and carbon dioxide allow the hepatic artery to dilate in response to decreased portal venous flow. This process of autoregulation helps to ensure adequate hepatic blood flow despite fluctuations in the splanchnic circulation. Extrinsic factors from the sympathetic and parasympathetic systems help to regulate blood flow by augmenting smooth muscle relaxation to increase blood flow.

The liver is divided into eight anatomical segments (Fig. 4.1). Each segment has its own dual vascular inflow and outflow, as well as biliary drainage. Functionally, the liver is divided into three zones based on oxygenation and metabolic activity. Zone 1 hepatocytes are closest to the portal triad and receive the most oxygenated blood and nutrients. Zone 1 is primarily involved in oxidative metabolism, including gluconeogenesis, cholesterol synthesis, and oxidation of fatty acids. Zone 3 hepatocytes are adjacent to the central veins and receive significantly less oxygenated blood and nutrients compared to zone 1. Zone 3 hepatocytes play a role in glycolysis, lipogenesis, and the biotransformation of drugs via cytochrome P450

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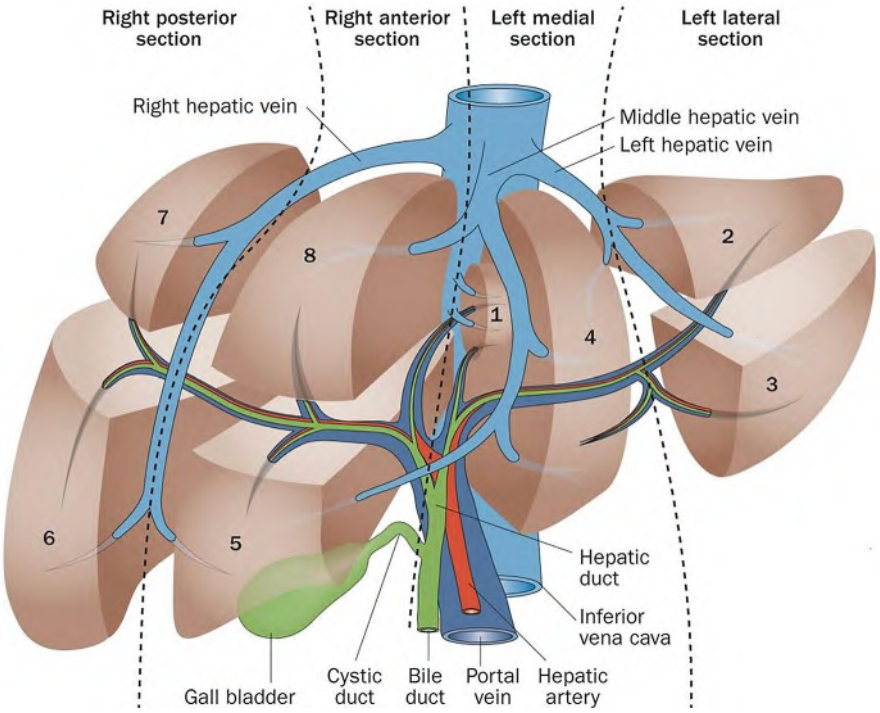

Fig. 4.1 Anatomical segments of the liver. (Siriwardena et al. [2]. Figure 1)

enzymes. Zone 2 is known as the intermediary zone, as its hepatocytes are located between zone 1 and zone 3 and can regenerate after injury or insult to the other zones.

Critical functions of the liver include bile production, metabolism, protein synthesis, hemostasis, and immunity. Bile produced by hepatocytes helps to break down large fat molecules to aid digestion. Bilirubin metabolism occurs via conjugation before entering the bile duct and excretion as bile into the small bowel. Drug metabolism is accomplished mainly by biotransformation, to convert a lipophilic form to a hydrophilic form, to facilitate elimination from the body. The goal of drug metabolism is to make the drug easier to excrete by way of oxidation, reduction, conjugation, or hydrolysis. The liver has a frontline role in immunity by filtering and transforming harmful chemicals and bacteria from the blood. The liver is also responsible for the production of immune factors such as complement components, cytokines, chemokines, and acute phase reactants.

One of the most important roles of the liver is hemostasis. Most coagulation factors, anticoagulants, and proteins involved in fibrinolysis are synthesized in the liver. The liver also produces thrombopoietin, which increases platelet production. End-stage liver disease results in reduced levels of many hemostatic proteins and platelets, due to decreased platelet production or increased platelet turnover. There is a compensatory increase in proteins such as von Willebrand Factor (vWF) and Factor VIII. These concomitant changes in pro-hemostatic and antihemostatic pathways

Table 4.1 Transformation of MELD

	MELD (2002)	MELD-Na (2016)	MELD 3.0 (2023)
Serum bilirubin	✓	✓	✓
Serum creatinine	✓	✓	✓
INR	✓	✓	✓
Serum sodium	–	✓	✓
Dialysis (≥2 times/week)	–	✓	✓
Serum albumin	–	–	✓
Sex	–	–	✓

result in a state of rebalanced hemostasis. This is a tenuous and relatively unstable state that places the patient at risk for bleeding and thrombotic complications.

Liver Disease

Liver disease is now considered the tenth leading cause of death in the United States [3]. According to the Centers for Disease Control (CDC), 4.5 million people are currently living with liver disease. Given its importance in metabolism and other essential homeostatic functions, liver disease can be deleterious to nearly every organ in the body. Liver disease is often categorized by onset as acute liver failure or chronic liver disease. Acute liver failure is defined as rapid and severe liver injury for fewer than 26 weeks. Chronic liver disease is defined as long-term injury to the liver resulting in progressive inflammation and scarring. Acute liver decompensation in patients with known chronic liver disease is considered the syndrome of acute-on-chronic liver failure.

The severity of liver disease is an important predictor of post-transplant mortality and morbidity. The model for end-stage liver disease (MELD) is the most commonly used tool to assess the severity of liver disease. The original MELD score included the following components: international normalized ratio (INR), bilirubin, and creatinine. It was later updated to MELD-Na, which includes the addition of serum sodium and dialysis status (at least twice a week). Over the last 5 years, it has evolved into MELD 3.0, which includes serum albumin and sex, in addition to all components of MELD-Na. MELD 3.0 is now the predominant score used by organ allocation systems to prioritize transplants. Table 4.1 shows the transformation of MELD over time.

Surgical Considerations in Liver Transplantation

Liver transplantation is a complex field that requires the collaboration of a multidisciplinary team. The transplant selection committee comprises transplant surgeons, hepatologists, transplant anesthesiologists, social workers, and transplant

coordinators. The committee must reach consensus to list and transplant patients. The committee's task is to determine whether the patient will tolerate the tremendous stress of liver transplantation surgery and the postoperative recovery. Preoperative optimization is often necessary before listing. For example, a patient with atrial fibrillation may require further rate control or rhythm control before they can be safely transplanted. Evaluation includes a thorough assessment of cardiopulmonary, renal, hematological, and neurological function. Patients are also evaluated for signs of liver decompensation, including ascites, bleeding, hepatic encephalopathy, and kidney injury.

Orthotopic

Orthotopic liver transplantation is the most commonly performed type of liver transplant. Donor organs can be divided into two categories: living or deceased. Deceased donors have a longer ischemia time compared to living donors. Deceased donors can be further classified based on procurement after brain death or after cardiac death. Brain death donation occurs after irreversible loss of brain or brainstem function and requires strict neurological exams to demonstrate the absence of brain function. After being legally declared dead, the body is kept hemodynamically stable before procurement to maintain optimal perfusion of the organs. Donation after cardiac death (DCD) occurs when a donor has suffered devastating brain injury but does not meet formal brain death criteria. These donors are brought to the operating room, and care is withdrawn to allow the donor to expire. When the patient's heart stops beating, the time of death is called, and the organs are recovered.

Improvements in technology have enabled novel advances in organ procurement. Donated livers are traditionally transported via static cold storage in a cooler maintained at 4 °C. This allows a reduction of metabolic requirements, although it is associated with significant ischemia and reperfusion injury. The development of machine perfusion has led to significant advancements using specialized machines to circulate blood through the liver and maintain a physiological environment. Hypothermic machine perfusion (HMP) circulates a cold preservation solution continuously through the liver. Normothermic machine perfusion (NMP) circulates a preservation solution at physiological temperature. Early clinical studies suggest that machine perfusion can enhance liver preservation and improve outcomes after transplantation. Machine perfusion may also reduce the complications associated with accepting marginal or extended criteria organs [4]. See more details in the Organ Procurement chapters.

Living Donors

Living donation liver transplantation (LDLT) was first introduced in children in 1989 and later adopted for adults in 1999. As the demand for liver transplantation continues to increase, living donor liver transplantation has provided organs to

patients who might otherwise die awaiting a deceased donor. In living donor liver transplantation, a living person donates a portion of their healthy liver. This is possible because of the liver's unique regenerative ability. Living donors must be over 18 years old and be in good overall physical and psychological health. Patients can identify their own living donor, such as a close family member, or join matching programs where people who aren't a direct match can find compatible donors.

There are unique perioperative concerns for living donation liver transplant compared to deceased donation. Recipients of living donor liver transplantation have, overall, improved outcomes compared to deceased donation. These recipients have both a higher graft survival at 5 years and a better 5-year survival rate compared to recipients of deceased donors [5]. Surgeons must pay special attention to the donor graft size. The right lobe is often used for live donors due to its larger size. Preoperative screening with imaging is utilized to determine the appropriate graft size based on the recipient's hepatic blood flow. There are significant implications for a graft that is considered too small or too large. A donor graft that is too small can lead to small-for-size syndrome (SFSS), in which the liver graft is unable to meet the recipient's metabolic demands, resulting in hepatic dysfunction. The donor must be left with at least 30% of the liver mass to allow for successful regeneration and the return of normal liver function. Donors generally achieve complete liver regeneration within a year, although they return to baseline function within six months [6].

Anesthetic considerations for the recipient are similar to those for deceased donor liver transplantation. Anesthetic considerations specific to the donor center around pain control and early extubation. Thoracic epidurals or truncal regional nerve blocks are commonly used for postoperative pain control for the donor. There is often a focus on multimodal analgesics to minimize opioid-related side effects in an effort to promote early ambulation. Multimodal agents include ketamine, nonsteroidal anti-inflammatory drugs (NSAIDs), magnesium, gabapentinoids, and dexmedetomidine. The donor is commonly extubated in the operating room and transferred to the intensive care unit for postoperative monitoring. The ERAS Society recommends consideration of early extubation for recipients also, when appropriate [7]. Many recipients are extubated in the operating room prior to arriving to the intensive care unit, although this practice is center-dependent.

Fulminant Patients

Fulminant hepatic failure is characterized by rapid and severe hepatocyte injury leading to a life-threatening syndrome marked by hepatic encephalopathy, elevated transaminases, and severe coagulopathy in patients without pre-existing liver disease. In the United States, the most common cause of fulminant hepatic failure is drug-induced hepatitis due to acetaminophen. Other causes include autoimmune hepatitis, acute fatty liver of pregnancy, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), and hypoxia-induced liver injury. Early diagnosis is crucial in the management of fulminant hepatic failure.

Patients should be admitted to the intensive care unit and evaluated for liver transplantation, which is curative. Management of patients with fulminant hepatic failure can be challenging as the syndrome often results in multi-organ failure. Aside from altered mental status and coagulopathy, patients may develop acute renal failure, hemodynamic instability, and cerebral edema. Cerebral edema is thought to be caused by cytotoxic and vasogenic edema from astrocyte swelling as a downstream effect of the rapid liver injury and hyperammonemia. Early monitoring is paramount and may require measurement of intracranial pressure and cerebral perfusion pressure. Standard treatment measures for intracranial hypertension are applied to the perioperative period. These include hyperventilation and use of osmotic agents such a mannitol or hypertonic saline, when necessary. Innovative approaches to management of fulminant hepatic failure include the use of the molecular adsorbent recirculating system (MARS), an extracorporeal liver support system that aids in the removal of toxins from the blood. Liver support systems play a pivotal role in the management of severe, fulminant hepatic failure, as the etiology is often reversible and the systems can mimic the liver's detoxifying function.

Intraoperative Hemodynamic and Fluid Management

The intraoperative course of liver transplantation is often accompanied by substantial blood loss and hemodynamic instability. A collaborative intraoperative approach with open communication between the surgeon and anesthesiologist is necessary. Hemodynamic monitoring requires standard American Society of Anesthesiologists (ASA) monitors, invasive arterial blood pressure monitoring, and central venous access. Arterial catheterization allows for continuous blood pressure monitoring along with frequent monitoring of electrolytes, glucose, and oxygenation. Rapid blood loss necessitates adequate venous access using large-bore peripheral intravenous catheters (IVs) in addition to central venous access. Central venous pressure can be used as an adjunct to assess volume status and cardiac function. Rapid transfusion devices, such as Belmont® or ThermaCor®, are ideal for the management of extensive blood loss and transfusion. Intraoperative transesophageal echocardiography (TEE) can be used to help assess volume status, contractility, and dynamic cardiac function to optimize the anesthetic management. A recent study found that more than 90% of liver transplant programs utilize TEE in some capacity [8]. Pulmonary artery (PA) catheters have historically been used during liver transplantation, although many centers are moving away from routine placement. PA catheters provide input on cardiac output and can aid in volume assessment. Their use may be considered practical in patients with known cardiac dysfunction. Noninvasive cardiac monitors such as the FloTrac™ can provide an estimate of cardiac output and stroke volume variation using the arterial pressure waveform to assess fluid responsiveness. They can be used as helpful adjuncts for volume assessment.

Fluid Management

There are three distinct phases of liver transplantation: pre-anhepatic (also known as the dissection stage), anhepatic, and neohepatic (also known as the postreperfusion stage). Each stage has its own unique challenges.

The pre-anhepatic phase includes the dissection of the liver and clamping of the portal vein and hepatic artery. Significant fluid shifts from blood loss and ascites removal mark it. Manipulation of the liver and inferior vena cava (IVC) may also lead to rapid hemodynamic changes in preload. There are two surgical techniques for dissection: conventional and piggyback. The conventional surgical technique involves fully cross-clamping and resecting the IVC. The cross-clamping leads to a sudden loss of preload and subsequent hypotension. The piggyback technique uses only a partial IVC clamp followed by anastomosis of the donor's IVC to the recipient's hepatic veins. Therefore, the piggyback technique is more hemodynamically stable, given the preservation of venous return to the heart. When the conventional technique is used, volume loading and vasopressor support must be given to prevent profound hypotension. Volume expansion can be achieved with blood products, albumin, or crystalloids. Lactated Ringer's and other fluids that require metabolism by the liver are avoided. The anesthetic goal during the dissection phase is to maintain hemodynamic stability with fluids and vasopressors, manage coagulopathy, and correct electrolyte abnormalities in preparation for reperfusion.

The anhepatic phase begins with the cessation of blood flow to the native liver and ends at reperfusion of the transplanted liver. Venous return is lower at this stage due to the partial or fully clamped IVC. Some volume resuscitation may be necessary, along with vasopressors and inotropic support. Excessive fluid resuscitation should be avoided during this stage, as gross hypervolemia can lead to congestion of the transplanted liver postreperfusion once the venous return is re-established. While anhepatic, the patient may become increasingly acidotic with increasing lactate and hypocalcemia. This may lead to hyperkalemia and other electrolyte derangements. Hyperkalemia must be aggressively treated before reperfusion. Methods to lower potassium include hyperventilation, diuretics such as furosemide, albuterol, and insulin to move potassium into cells. Calcium is given to stabilize the cardiac membrane. Sodium bicarbonate is controversial but can be used to treat acidosis and shift potassium into cells temporarily. Coagulopathy will progressively worsen throughout the duration of the anhepatic period and may necessitate ongoing blood product transfusion for management.

The neohepatic phase begins with reperfusion of the transplanted liver and continues until the end of the surgery. The IVC is unclamped first, followed by the unclamping of the portal vein. Reperfusion of the portal vein is often characterized by significant hemodynamic instability due to the return of acidotic blood from the portal system and the build-up of vasomediators and potassium. This blood is acidotic and contains a heavy potassium load along with numerous inflammatory and vasodilatory mediators. This results in a significant, although transient, reduction in systemic vascular resistance, cardiac output, and heart rate. Postreperfusion syndrome is defined as a sustained 30% decrease in mean arterial pressure for at least

1 minute during the first 5 minutes after reperfusion. The risk of postreperfusion syndrome increases with prolonged cold ischemic time. Vasopressor support via boluses and infusions is often necessary to treat the hemodynamic instability associated with reperfusion. Once reperfusion is complete and the patient is stable, the hepatic artery is anastomosed and reperfused. Hepatic artery reperfusion is usually not associated with significant hemodynamic changes, but can be associated with disturbances in coagulation.

Intraoperative Adjuncts

Venovenous Bypass

Aside from profound hemodynamic instability, graft reperfusion can also severely compromise other organs and overall metabolic function. There are strategies and adjuncts to help improve hemodynamics and overall outcomes during the intraoperative course. For example, when the conventional surgical technique is used, venovenous bypass (VVB) can be used to maintain greater hemodynamic stability and preload. VVB was developed to mitigate the effects of complete IVC clamping by diverting blood from major vessels below the liver and returning it to a vein above the level of the heart. An extracorporeal circuit and pump are used to divert the blood (Fig. 4.2). VVB also has a beneficial role in reducing blood loss in patients with severe portal hypertension by decompressing varices. VVB has a reported complication rate ranging from 10% to 30% [10]. Complications include air emboli, thromboembolic complications, hematomas, major vessel injury, and brachial plexus injury. Acute Budd–Chiari syndrome is the only absolute contraindication for VVB due to the increased risk of thrombosis and pulmonary embolism.

Continuous Renal Replacement Therapy

Liver transplantation is associated with major fluid shifts, acidosis, and electrolyte abnormalities, each of which can be exacerbated in the setting of renal failure. In fact, reported rates of renal injury after liver transplantation range from 17% to 95% [11]. Risk factors for acute kidney injury during the transplant include full IVC clamp, prolonged anhepatic time, and prolonged hypotension. Continuous renal replacement therapy (CRRT) can be used during the intraoperative course to mitigate these risks. Intraoperative CRRT allows for potassium management, acid–base balance, and, to a lesser extent, intravascular volume adjustments. There is growing evidence for the benefits of intraoperative CRRT, especially in higher MELD patients with renal dysfunction [12]. There are no significant differences in outcomes compared with similar patients who do not receive intraoperative CRRT [13]. More studies are necessary to evaluate CRRT utilization and outcomes in liver transplantation. Hypotension can be an issue if attempts are made to remove excess fluid. Therefore, it is a common strategy to only remove 100 mL or less of fluid per

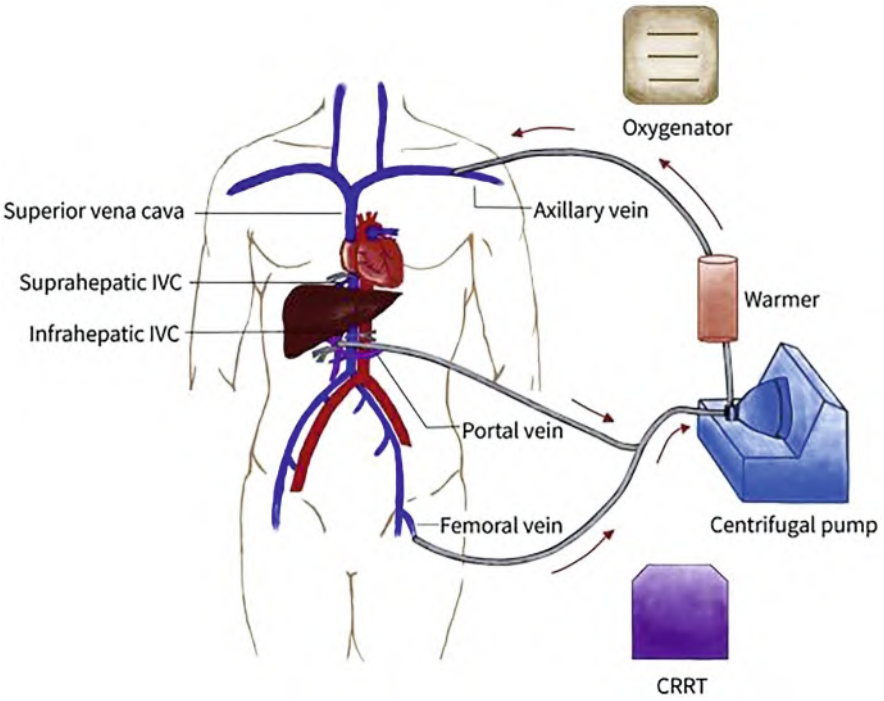

Fig. 4.2 Venovenous bypass system. (Lapisatepun et al. [9]. Figure 1)

hour to prevent hypotension. Thrombosis of dialysis filters is a concern given the likelihood of massive transfusions and decreased anticoagulation use. Finally, hypothermia is frequently seen when using CRRT and occurs due to heat loss from the extracorporeal blood circulation. Pre-emptive steps must be taken to warm the patient prior to initiation of CRRT, and once initiated, multiple warming devices may be necessary. Studies have shown that hypothermia is a risk factor for intraoperative cardiac arrest [14].

Cell Saver

Liver transplantation is associated with massive blood loss and may require massive blood transfusion. Although cell salvage can be used to reduce red blood cell loss from bleeding, recent studies have shown limited clinical benefit [15]. Cell salvage is a technique that collects blood from the surgical field and then filters the blood to remove contaminants before reinfusing it into the patient. This technique has been demonstrated to significantly reduce the need for allogeneic transfusions during hepatic resection surgery [16]. Complications from allogeneic red blood cell transfusions include allergic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), hemolytic reactions, and febrile

nonhemolytic reactions. Cost-effectiveness is considered a drawback to cell salvage. The cost of the salvage machine, equipment, and perfusion staff is weighed against the cost of allogeneic blood and the associated testing and handling fees. In high-risk procedures with significant expected blood loss, the benefit of cell salvage is thought to outweigh the risks and cost. The theoretical risk of cancer dissemination has historically limited the adoption of cell salvage in oncologic surgeries. However, many transplant centers are using cell salvage even in the setting of hepatocellular cancer with no evidence of increased recurrence of disease [17].

Management of Coagulopathy and Blood Products

End-stage liver disease is marked by a status of rebalanced hemostasis, placing the patient at increased risk for both bleeding and thrombosis. This is caused by a reduction in synthesis of most coagulation factors (factors II, V, VI, IX, X, XI, XIII, fibrinogen, prothrombin, and proteins C and S) and the compensatory increase in factor VIII and von Willebrand factor (vWF). Rebalanced hemostasis seen in liver disease is a precarious hemostatic balance that can rapidly tilt toward a hypocoagulable or hypercoagulable status. Several physiologic processes are also rebalanced in end-stage liver disease that can contribute to coagulopathy. Progressive portal hypertension, renal failure, and infection can increase the risk of bleeding. The reduction in protein C level, along with increased production of endothelial factors, can increase the risk of thrombosis. The anesthetic plan must consider this complex pathophysiology in the management and assessment of blood loss.

Conventional coagulation tests, such as prothrombin time (PT) or international normalized ratio (INR), may provide limited insight into the hemostatic profile. These tests measure procoagulant factors but cannot adequately represent the reduction in anticoagulant factors. Thromboelastography (TEG) and thromboelastometry (ROTEM) are considered global tests of hemostasis, reflecting the complex interaction of all components, i.e., red blood cells, plasma, and platelets. These tests use viscoelastic assays to measure the dynamic properties of clot formation, clot strength, and lysis. TEG and ROTEM may better reflect hemostasis in liver disease and provide a more global picture of hemostasis. Other intraoperative tests of importance would include the complete blood count for measurement of hemoglobin and platelets.

Blood transfusions are inherently associated with liver transplantation. Intraoperative bleeding often requires transfusion of red blood cells, fresh frozen plasma (FFP), platelets, and cryoprecipitate. Although transfusion protocols may vary by institution, survey data from anesthesiologists suggest a broad consensus in general practice [18]. Overall, 90% reported an institutional culture of issuing a standardized number of blood products before surgical start, most commonly ten units of red blood cells and ten units of plasma, without platelets or cryoprecipitate [18]. Risk of bleeding also varies based on the institution, but also depends on the severity of liver disease, surgical technique, duration of anhepatic phase, and delays in graft function. During major blood loss, transfusions are guided by

the rate of bleeding, the likelihood of surgical control, and point-of-care testing such as TEG or ROTEM. Nonpharmacological methods are often used by the anesthesiologist and surgeon to manage blood loss. For instance, lowering central venous pressure (CVP) during the dissection phase is one strategy to reduce intraoperative blood loss by lowering hepatic venous pressure. This strategy may not be practical for all patients and may be associated with hemodynamic volatility. Normothermia plays an important role in maintaining hemostasis. Avoiding hypothermia can prevent further platelet dysfunction and reduce subsequent bleeding. The surgeon's use of the piggyback technique can also be a strategy to reduce blood loss.

Antifibrinolytics play a role in reducing blood loss and the need for transfusions during liver transplantation [19]. The most commonly used antifibrinolytics are tranexamic acid and aminocaproic acid, which inhibit fibrinolysis to stabilize clots and reduce bleeding. Routine use of antifibrinolytics is not recommended, given the lack of demonstrated clinical benefit in liver transplantation [20]. The decision to use antifibrinolytics should be based on an individualized strategy that accounts for the patient's overall health, liver severity, and laboratory evidence of fibrinolysis. Factor concentrates are increasingly used despite limited or inconclusive evidence in liver transplantation [21].

Postoperative Care and Complications

Postoperative care of the liver transplant patient requires careful monitoring, ongoing management of coagulopathy, early recognition of graft dysfunction, and management of surgical complications. Coagulopathy may persist beyond the operating room and require ongoing transfusion management in the intensive care unit. Postoperative transfusion strategies steer toward more restrictive practices. Ongoing blood loss with hemodynamic instability may require aggressive resuscitation with blood products. Surgical drain output is monitored hourly and may be used in the decision to return to the operating room for surgical control of bleeding. Post-transplant thrombotic events are not uncommon and can lead to significant morbidity and mortality. Thrombotic events can occur during the early stage or several months after transplantation. Prompt diagnosis is crucial, as thrombosis or stenosis can result in deterioration of the graft and mortality.

Graft Failure

Early graft dysfunction, caused by severe ischemia–reperfusion injury, is associated with a poorly functioning transplanted liver. Although there is no universally accepted definition, it is marked by significantly elevated bilirubin, alanine transaminase (ALT), or aspartate transaminase (AST) levels > 2000 IU/L, and an INR >1.6 within the first seven postoperative days [22]. The severity can vary from

minor, insignificant abnormality to primary graft non-function. Risk factors that can lead to early graft dysfunction include poor quality graft, prolonged ischemic time, and certain operative techniques [23]. Graft dysfunction leads to reduced graft and patient survival. Graft dysfunction may lead to a longer intensive care unit and hospital stay for the recipient. Early identification allows for closer monitoring and a lower threshold for returning for exploratory laparotomy. Milder forms of graft dysfunction may be completely reversible, although the recovery may be extended. Thrombotic complications, including hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT), are serious complications following liver transplantation and are associated with significantly increased mortality. Together, HAT and PVT account for approximately 16% of graft failures [24]. Management of HAT typically involves urgent surgical exploration for revascularization or endovascular intervention with stent placement. Despite these measures, re-transplantation is frequently required, occurring in up to 53% of early HAT cases [24]. Treatment of PVT presents a greater technical challenge, as establishing adequate alternative portal inflow can be difficult. Revascularization is more commonly successful in cases of early PVT compared to late PVT.

Cardiovascular Complications

End-stage liver disease is characterized by baseline systemic vasodilation, which is further exacerbated by anesthetic agents and reperfusion during transplantation. As a result, vasopressors are frequently required for intraoperative hemodynamic management. Reperfusion and the stress of surgery can lead to a temporary reduction in cardiac output. An inotrope such as epinephrine or Dobutamine may be required to treat this low output state. Cirrhotic cardiomyopathy (CCM) may become clinically apparent in the postoperative period, presenting as overt heart failure or significant diastolic dysfunction. Although CCM often remains clinically silent due to its latent presentation, its underlying myocardial and autonomic dysfunction contribute to adverse outcomes, making it an independent predictor of waitlist mortality [25]. Patients with CCM have evidence of at least mild diastolic dysfunction and autonomic dysfunction in the preoperative workup. General heart failure management is sufficient for treatment of CCM. Takotsubo cardiomyopathy, acute stress-induced cardiomyopathy, can also be unveiled during the postoperative period. Takotsubo cardiomyopathy has characteristic regional wall systolic dysfunction in the absence of cardiac enzyme release. It is likely the sympathetic overdrive and increased catecholamines associated with liver transplantation that leads to the development of Takotsubo cardiomyopathy. It can present as florid cardiogenic shock and treatment should involve supporting the hemodynamics with inotropes and vasopressors. Left ventricular function generally recovers within 1–4 weeks [26]. In rare instances, mechanical hemodynamic support with an intra-aortic balloon pump or extracorporeal membrane oxygenation (ECMO) is necessary. In-hospital mortality associated with Takotsubo syndrome following liver transplantation is reported to be approximately 7% [26].

Pulmonary Complications

Many centers extubate liver transplant patients in the operating room, while others wait for extubation to occur in the ICU once the patient is deemed stable with no signs of surgical complications. Immediate extubation in the operating room is associated with a reduced incidence of pulmonary complications, decreased ICU costs, and shorter hospital length of stay [27]. These benefits persist even after adjusting for patient severity and perioperative risk factors. Despite this, liver transplant recipients remain at risk for postoperative pulmonary complications, including atelectasis, pulmonary edema, aspiration, and pneumonia. Pulmonary examination and chest radiograph may reveal evidence of lung collapse, interstitial edema, or pulmonary infiltrates. Pulmonary edema can occur from volume overload, transfusion-related acute lung injury, or re-expansion of a hepatic hydrothorax. Diuresis with Furosemide may be required depending on the cause of pulmonary edema. Pneumonia in this patient profile is not uncommon, and new infiltrates can appear during the postoperative course. Acute lung injury can occur as a complication in fulminant hepatic failure and can lead to acute respiratory distress syndrome (ARDS). Mechanical ventilation strategies generally promote low tidal volumes and low plateau pressures to minimize barotrauma. PEEP levels up to 10–15 cm H_2O generally do not significantly impair hepatic venous outflow [28]. However, higher levels are typically avoided in the immediate post-transplant period due to the potential risk of hepatic congestion and compromise of graft function.

Management of Immunosuppression

Liver transplant outcomes have continued to improve, thanks in part to the modernization of immunosuppressive agents and post-transplant regimens. Immunosuppressive agents act to reduce the risk of graft rejection. Regimens vary by institution; however, there are commonalities regarding the basics of effective use. Most protocols combine multiple agents to maximize different mechanisms of action and minimize side effects. Unlike other organ transplants, human leukocyte antigen (HLA) matching is not required for liver transplantation. Therefore, liver transplant recipients generally require lower immunosuppression than other organ transplant recipients [29]. Induction immunosuppression is typically initiated intraoperatively with high-dose methylprednisolone, administered shortly after graft reperfusion. Maintenance of suppression is often sustained with a calcineurin inhibitor, such as Tacrolimus, alone or with an anti-proliferative agent, such as mycophenolic acid, early in the post-transplantation phase. Antibody induction to inhibit or deplete recipient T cells may be beneficial by reducing the necessary dose of other immunosuppressive agents, along with reducing the incidence of acute rejection. Common T cell–depleting antibodies include antithymocyte globulins, which are also widely used in the management of steroid-resistant rejection. Although immunosuppression plays a significant role in reducing rejection in liver transplant recipients, it can also have a detrimental effect by increasing the risk of

infection, malignancies, nephrotoxicity, neurotoxicity, hyperglycemia, and electrolyte imbalance.

Prevention and Treatment of Rejection

Liver transplant recipients are monitored closely for early and ongoing signs of rejection. Acute cellular rejection, also known as T cell–mediated rejection, results in abnormal liver tests and requires confirmation with a liver biopsy. Induction immunosuppression with methylprednisolone, with or without antithymocyte globulin, is administered to reduce the risk of early graft rejection. The use of antithyomocyte globulin for induction has been associated with a lower incidence of acute cellular rejection [30]. Maintenance therapy is achieved with a calcineurin inhibitor, such as Tacrolimus, in addition to an antiproliferative drug, such as mycophenolate mofetil. Strict medication adherence is imperative, along with frequent monitoring of drug levels and kidney function. Acute cellular rejection is primarily managed with intravenous corticosteroids as first-line therapy, along with optimization of maintenance immunosuppressive drug levels [31]. Approximately 14% of patients demonstrate steroid-resistant rejection, for which treatment with antithymocyte globulin is typically required [31]. With timely and appropriate therapy, acute cellular rejection is often fully reversible and generally does not result in significant long-term impairment of graft function or patient survival.

Chronic rejection of the liver graft is a slow and progressive process that can culminate in graft failure due to damage to hepatic vessels and bile ducts. Its prevalence has declined with the aforementioned improvements in immunosuppressive therapy; however, it still represents an important cause of graft injury. Chronic rejection is thought to be caused by T cell– and antibody-mediated mechanisms. Management of chronic rejection is not well-defined and can be difficult. When identified early, chronic rejection may be partially reversible through optimization or modification of the immunosuppressive regimen. The primary goal of management is to increase overall immunosuppressive blood levels [32]. Patients not already receiving Tacrolimus should be transitioned to a Tacrolimus-based regimen. In those already maintained on Tacrolimus, drug levels should be cautiously increased to achieve therapeutic targets while minimizing toxicity [32]. Although evidence remains limited, adjunctive therapy with mechanistic target of rapamycin (mTOR) inhibitors, such as sirolimus or everolimus, may be considered in patients who fail to respond to escalation of baseline immunosuppression [32].

Long-Term Graft Survival

While short-term graft survival has improved over the last decade, long-term graft survival has been stable. In 2022, graft failure after deceased donor liver transplantation was reportedly 6.3% at 6 months and 7.9% at 1 year [33]. The 3-year graft

Table 4.2 Five years post–liver transplant graft survival rates based on age group

Age	Graft survival at five years
18–34	80.8%
35–49	82.2%
50–64	79.3%
≥65	75%

failure rate was 15.8% in 2022, and the 5-year graft failure rate was 20.7% for those transplanted in 2018 [33].

Graft survival is highly dependent on patient age, race, gender, liver disease etiology, and type of donation. According to the Organ Procurement and Transplantation Network (OPTN), graft survival rates at 5 years post–deceased donor liver transplantation were 75% in patients aged 65 or older, 79.3% in those aged 50–64 years, 82.2% in those aged 35–49 years, and 80.8% in those aged 18–34 years [33]. See Table 4.2. Aside from increasing age, there are other factors associated with lower graft survival, including race, gender, and liver disease etiology. Recipients identifying their race as Black or Other had significantly lower graft survival compared with White, Hispanic, or Asian recipients [33]. Male recipients were more likely to have lower graft survival compared to women. Recipients with hepatocellular cancer (HCC) and MASH (metabolic dysfunction–associated steatohepatitis) diagnoses also had lower graft survival. DCD livers had a 5-year graft survival rate of 75.6% compared to 79.2% for donation after brain death livers [33].

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Anesthesia for Orthotopic Heart Transplantation

5

Gang Chen and Blaine Farmer

2026 Edition

Abbreviations

ACT	activated clotting time
AHA	American Heart Association
AKI	acute kidney injury
AmSECT	American Society of Extracorporeal Technology
ASA	American Society of Anesthesiology
ASE	American Society of Echocardiography
ATHOS-3 trial	Angiotensin II for the Treatment of Vasodilatory Shock trial
CHD	congenital heart disease
CIED(s)	Cardiac Implantable Electronic Device(s)
CKD	chronic kidney disease
CPB	cardiopulmonary bypass
CRT(s)	cardiac resynchronization therapy devices
CT	computed tomography
ECMO	extracorporeal membrane oxygenation support
ePTFE	expanded polytetrafluoroethylene
ESA	erythropoiesis-stimulating agents
FiO2	inspired oxygen fraction
GDMT	guideline-directed medical therapy

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GFR	glomerular filtration rate
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
Hgb	hemoglobin
HIT	heparin-induced thrombocytopenia
HLA	human leukocyte antigen
ICD(s)	implantable cardioverter defibrillator(s)
ISHLT	International Society for Heart and Lung Transplantation
IVIG	intravenous immunoglobulin
LA	Left atrium
LCOS	low cardiac output syndrome
MGP	mechanical graft perfusion system
OHT	orthotropic heart transplant
OPTN	Organ Procurement and Transplantation Network
PAC	pulmonary artery catheter
PGD	primary graft dysfunction
PRA	panel-reactive antibody
PVR	pulmonary vascular resistance
Qp:Qs	pulmonary blood flow to systemic blood flow ratio
RAAS	renin–angiotensin–aldosterone system
RCM	restrictive cardiomyopathy
RHC	right heart catheterization
SCA	Society of Cardiovascular Anesthesiologists
SCA	Society of Thoracic Surgeons (STS)
TEE	transesophageal echocardiogram
TIVA	total intravenous anesthesia
TPG	transpulmonary gradient
TR	tricuspid regurgitation
UNOS	United Network for Organ Sharing
VANCS trial	Vasoplegic Shock after Cardiac Surgery trial
VS	vasoplegic syndrome

Introduction

Christiaan Barnard is credited with performing the first successful human-to-human orthotopic heart transplant (OHT). After several months of planning, Barnard and his cardiology colleague, Velva Schrire, selected Louis Waskansky as the first recipient. At that time, Waskansky was a 53-year-old diabetic who was bedridden because of severe cardiac failure from ischemic cardiomyopathy. Having identified a recipient, the team awaited a donor. That opportunity presented itself on December 2, 1967. Densie Darvall, a 25-year-old woman, was brought to Groote Schuur Hospital after suffering a severe brain injury resulting from a traffic accident. The following day, Waskansky and Darvall were transported to the operating room.

Inside the tenuous 5-h surgery, the donor heart was successfully transplanted into the recipient; however, Barnard initially failed to wean the recipient off

cardiopulmonary bypass (CPB). After shocking the donor heart out of fibrillation, the heart did not beat strongly enough to maintain adequate blood pressure. After a tincture of time, the heart started to gain strength, and on the third attempt, Barnard was finally able to wean the patient off CPB.

Bernard did not inform the hospital administration or the chief of the department until after the surgery. Within hours, the news had spread, and Barnard had focused the world's attention on this medical first in Cape Town, South Africa [1–3]. This groundbreaking medical achievement marked a pivotal moment in cardiac surgery, which had only been practiced for less than a decade at the time [1]. While his first patient's survival was only 18 days, this accomplishment paved the way for significant advancements in surgical techniques, immunosuppressive therapies, and perioperative care for heart transplants.

Since then, heart transplantation has been established as the gold standard for the treatment of patients with end-stage heart failure (HF)—allowing for improved survival rate and quality of life [4]. For patients with end-stage heart failure who have failed guideline-directed therapy and available mechanical support, OHT can significantly improve survival and quality of life. Data from the Organ Procurement and Transplantation Network (OPTN) and the United Network for Organ Sharing (UNOS) demonstrate that the median survival of adult patients with stage D HF without advanced therapies is <2 years [5]. In contrast, the 1-, 3-, and 5-year adult survival rates after OHT are 91.3%, 85.7%, and 80.4%, respectively [6]. As a result of these favorable results, the annual number of heart transplants within the United States continues to climb year over year. In 2022, there were 3668 transplants, marking an 82% increase since 2011 [6].

The cardiothoracic anesthesiologist is a critical member of the multidisciplinary team effort in a heart transplant, and this chapter serves to present the most important and fundamental knowledge required for the care of a recipient. OHT has experienced rapid growth over the past decade, driven by technological advances in mechanical circulatory support and preservation of donor organs, along with the expansion of the donor pool to include donation after circulatory death. While these developments have likely benefited patients and generated enthusiasm in the field, they have also increased the complexity of perioperative management [7, 8]. Thus, there is an increasing need for anesthesiologists to have a comprehensive understanding of the latest knowledge available for managing heart transplant recipients. Furthermore, the novel developments create uncertainty as to optimal management, and much remains to be elucidated in the coming years. Readers of this textbook are therefore encouraged to continue their exploration of the topic to incorporate emerging knowledge in this evolving field.

Listing Considerations

Indications and Contraindications

Generally, a heart transplant is the treatment of last resort for irreversible cardiac pathology that causes significant impairment of daily function, injury and dysfunction of other organs, and significantly shortens lifespan in the absence

of a transplanted heart. The most common indications for heart transplant are chronic advanced heart failure, typically associated with dilated cardiomyopathies, as well as irrecoverable cardiogenic shock and uncontrolled ventricular arrhythmias refractory to medical and device therapies. Less common etiologies encompass restrictive cardiomyopathies (RCMs) such as hypertrophic cardiomyopathy (HCM), complex congenital heart disease (CHD) after surgical palliation has failed, and previous heart transplant recipients with graft failure [8, 9].

Given the associated mortality of untreated end-stage heart disease, there are few absolutely prohibitive contraindications; however, the list of prospective recipients is often far longer than available organs, and so this resource must be carefully allocated. Pre-transplant evaluation focuses on assessing for comorbidities that affect surgical planning, contribute to accelerated graft failure, negatively impact post-transplant quality of life, or lead to premature mortality. Therefore, heart transplant candidacy is carefully determined based on an individualized approach rather than absolute thresholds contraindicating eligibility [8]. Patients seeking a heart transplant must go through an extensive evaluation that may include cancer screening, vetting of a patient's social support network, heart catheterization, CT scans, pulmonary function tests, lab work, as well as PT and nutrition assessments to assess for things like frailty and malnutrition, among other things. A full list of potential contraindications can be seen in Table 5.1.

Table 5.1 Potential contraindications to heart transplant

Age > 70
Obesity (BMI >35 kg/m^2)
Diabetes with poor glycemic control (HgA1c >7.5%) or end-organ damage (neuropathy, nephropathy, or retinopathy)
Severe cerebrovascular or peripheral vascular disease
CKD with GFR < 30 mL/min/1.73 m^2
Biopsy-proven cirrhosis and/or severe liver fibrosis with evidence of portal hypertension
Severe pulmonary dysfunction
Connective tissue disease (e.g., systemic lupus erythematosus, systemic sclerosis, and rheumatoid arthritis) or sarcoidosis[a]
Active illicit drug, tobacco, or alcohol abuse within 6 months
Active mental illness or psychosocial instability
Active or recent malignancy within 5 years[b]
Severe irreversible pulmonary hypertension
Active infections requiring ongoing antibiotic treatment (except for infected durable LVADs)
HIV with opportunistic infections or related malignancy, lack of stable antiretroviral regimen, detectable viral load, and/or low CD4 count
Severe frailty that will preclude adequate post-transplant rehabilitation efforts and is not expected to improve with restoration of cardiac function
High surgical risk resulting from prior cardiac surgery

[a]In heart transplant candidates with connective tissue disease (CTD) that is expected to shorten post-transplant survival, which is associated with severe non-cardiac disease, or that is not controlled with pre-transplant immunosuppression, OHT is not recommended

[b]Wait period differs for stage and type of malignancy

Adult Heart Allocation System

The first heart transplant allocation system was established in 1988 by OPTN and UNOS and initially employed a two-tier approach, categorizing candidates based on the severity of their illness and the duration of their wait on the transplant list. Candidates in Tier 1 were those who required mechanical cardiac support, continuous intubation, and/or intensive care unit (ICU) care, often involving the use of inotropes. Candidates in Tier 2 encompassed all other listed candidates. This system subsequently grew to three tiers in 1998 following the introduction of left ventricular assist devices (LVADs) [10].

The current allocation system was introduced in 2018 to reduce wait list mortality and enhance the sharing of donor organs [7, 10, 11]. Several significant changes were implemented. First, the 1998 system clustered together heterogeneous groups with differing waitlist mortalities. An example of this is that a driveline infection with a predicted waitlist mortality of 4.8% and a patient on veno-arterial extracorporeal membrane oxygenation support (ECMO), with a predicted waitlist mortality of 35.7%, would both be listed as status 1A (high priority) [10]. In contrast, the 2018 system expanded the number of priority groups from 3 to 6 and required specific physiological parameters to be met for status placement. Second, the 2018 allocation system expanded the distance allowed for receiving organs to 500 miles. This modification carries a theoretical concern that organs may have a longer ischemic time. UNOS/OPTN anticipated that this would only affect a small number of patients and a marginal change in post-transplant survival [10]. Lastly, it created status 4 specifically for patients with congenital heart disease, restrictive cardiomyopathy, and hypertrophic cardiomyopathy, as these conditions have relative contraindications to LVADs [10].

As a result of these changes, the overall pre-transplant mortality declined from 15 deaths per 100 patient-years to a plateau of 8.7 deaths per 100 patient-years in 2019 [11]. The prioritization of ECMO and non-dischargeable devices into status 1 and status 2, respectively, has been associated with increased pre-transplant utilization of these technologies. This shift coincided with a reduced use of durable LVAD placement as a bridge to transplant, possibly because of its categorization as status 3 (see Table 5.2) [12]. In essence, these changes incentivized the broader use of temporary

Table 5.2 OPTN/UNOS waitlist statuses and criteria

Status 1	VA-ECMO, non-dischargeable Biventricular Assist Device (BiVAD), MCS with life-threatening arrhythmias
Status 2	IABP, sustained VT or VF, dischargeable BiVAD, TAH, Right Ventricular Assist Device (RVAD), MCS with malfunction, percutaneous MCS
Status 3	Dischargeable LVAD for 30 days, MCS with complication, IV inotrope infusion + hemodynamic monitoring
Status 4	Inotropes without hemodynamic monitoring, stable LVAD, ischemia and intractable angina, CHD, HCM, RCM, retransplantation
Status 5	Combined organ transplants
Status 6	Remaining active candidates

Adapted from OPTN's Criteria requirements in the adult heart allocation policy table https://optn.transplant.hrsa.gov/media/km0bko0h/adult_heart_criteria.pdf

mechanical support devices to enhance a patient's priority for transplantation, even in scenarios where they might not have been utilized under the previous system.

Indications for Combined Transplants

Right heart catheterization (RHC) is routine practice in the preoperative assessment for transplantation. The purpose of this test is twofold: prognostication following heart transplant and evaluation of pulmonary hypertension (Fig. 5.1). An elevated pre-transplant pulmonary vascular resistance ≥2.5 Wood units is associated with increased early post-transplant mortality primarily due to the risk of right ventricular failure [13]. While it is common to encounter findings of group 2 pulmonary hypertension [14], the focus is placed on ruling out structural remodeling of the pulmonary vascular that results in nonresponse to pharmacological pulmonary vasodilators. Potentially prohibitive pulmonary hypertension is defined as pulmonary artery systolic pressure (PASP) ≥ 50 mm Hg and either transpulmonary gradient (TPG) ≥ 15 mm Hg or pulmonary vascular resistance (PVR) ≥ 3 Wood units [8]. In a stepwise fashion, the patient is trialed on vasodilators, continued medical management, and mechanical cardiac support in an attempt to assess improvement in pulmonary pressures. Ultimately, in the event no improvement is noted, the patient may need to be considered for a dual heart–lung transplant.

Pre-transplant evaluation for chronic kidney disease (CKD) aims to determine the presence and severity of intrinsic renal disease, and while it does not preclude consideration, patients with sufficiently low glomerular filtration rate (GFR) are considered for combined heart–kidney transplantation. CKD is relatively common in patients with systolic heart failure and affects an estimated 1 in 4 patients [12]. The main driver for this association is cardiorenal syndrome (CRS), which refers to the reciprocal effects of the heart and kidneys on each other, allowing for failure of

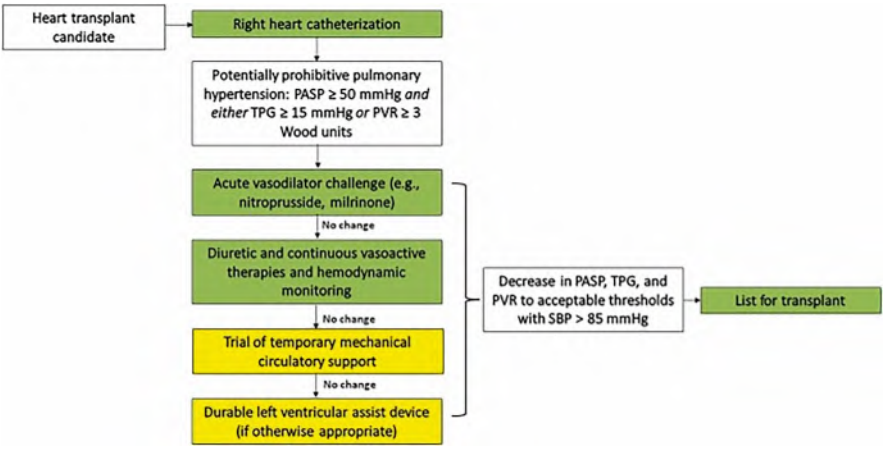

Fig. 5.1 Algorithm for evaluation of pulmonary hypertension in heart transplant candidates. (Reproduced with permission from Peled et al. [8], Elsevier, 2024)

one to cause failure of the other. CRS is classified into five different phenotypes based on primary organ dysfunction and temporal pattern of the disease, with type 2 indicating renal failure arising from heart failure and type 4 indicating heart failure arising from renal failure. Practically, these phenotypes are difficult to elucidate as patients have very similar clinical presentations with overlapping symptoms such as fluid overload, hypertension, and fatigue [15]. Moreover, both phenotypes share common pathophysiological mechanisms, including neurohormonal activation, inflammation, and endothelial dysfunction, making it hard to determine the primary organ of dysfunction [15, 16]. The salient point is the interconnectedness of these two organs and the high likelihood of concomitant renal disease in heart transplant recipients. Whatever the source of renal failure, a glomerular filtration rate (GFR) <45 ml/min/1.73 m^2 should prompt discussions about a combined heart–kidney transplant. Furthermore, patients falling into this category but deemed ineligible for kidney transplantation may also be deemed unsuitable for a heart transplant alone.

Liver injury and disease are other common entities in this patient population, resulting from a combination of ischemia and congestion. In the setting of hepatic dysfunction, additional workup to rule out cirrhosis may be necessary. Abnormal liver function tests on lab work should prompt dedicated liver imaging, usually CT or MRI, with transvenous liver biopsy indicated as the gold standard for determining the presence of cirrhosis and many other liver diseases, as it allows for the collection of tissue and assessment of the gradient between hepatic wedge and free hepatic venous pressures. A normal gradient is defined as ≤5 mmHg and excludes significant portal hypertension. Advanced liver disease and cirrhosis are considered extremely high risk in isolated heart transplant, considering high post-transplant morbidity and mortality [17]. Nevertheless, this patient population can be considered for combined heart–liver transplantation [8].

Preoperative Optimization and Management

Medical Management of Heart Failure

Heart failure is a complex clinical syndrome with signs and symptoms resulting from structural or functional impairment leading to insufficient ventricular filling or emptying of blood. Moreover, this patient cohort is typically diagnosed with advanced heart failure—the most severe stage of heart failure characterized by persistent symptoms, frequent hospitalizations, and potential need for continuous intravenous inotrope therapy (Table 5.3).

In response to reduced cardiac output, neurohormonal systems, including the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, are activated. Prolonged activation of these systems causes vasoconstriction, sodium and water retention, and increased cardiac workload. As such, these systems are targets for medical therapy and form the backbone for guideline-directed medical therapy (GDMT) for treatment of heart failure. The multimodal regimen consists of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin

Table 5.3 Commonly used inotropes and vasopressors

Inotropic agent	Infusion rate (mcg/kg/min)	Effects			
		CO	HR	SVR	PVR
Adrenergic agonists					
Dopamine	5–10	↑	↑	↔	↔
Dobutamine	10–15	↑	↑	↑	↔
PDE3 inhibitor					
Milrinone	0.125–0.75	↑	↑	↓	↓
Vasopressors					
Epinephrine	5–15 mcg/min	↑	↑	↑/↓	↔
	15–20 mcg/min	↑	↑↑	↑↑	↔
Norepinephrine	0.5–30 mcg/min	↔	↑	↑↑	↔

Reproduced with permission from Heidenreich et al. [5], Elsevier, 2022

receptor blockers, angiotensin receptor–neprilysin inhibitors, aldosterone antagonists, sodium–glucose cotransporter 2 inhibitors, and diuretics. Additional therapies once guideline-directed medical therapy has been optimized include ivabradine, vericiguat, digoxin, and polyunsaturated fatty acids [5].

Invasive surgeries and procedures can be beneficial in improving or preventing the progression of heart failure. In patients with heart failure resulting from ischemic cardiomyopathy, the combination of GDMT and surgical revascularization has been demonstrated to have long-term survival benefits and a reduction in hospitalizations for cardiovascular etiologies, including heart failure [18]. These results were unable to be replicated in the REVIVED-BCIS2 trial with percutaneous revascularization [19]. However, one key limitation of the REVIVED-BCIS2 trial is that the patient cohort had a lower Canadian Cardiovascular Society grading score for angina pectoris compared to patients who underwent surgical revascularization in the STITCHES trial. Valvular heart disease is a common cause and a sequela of heart failure. These patients are managed with GDMT and considered for surgical or transcatheter interventions.

As the patient progresses to advanced heart failure (Table 5.4), continuous intravenous inotropes are typically initiated as a bridge to advanced therapies (e.g., transplant, durable mechanical cardiac support) and to palliative therapy for symptom control [5]. To date, there is a lack of robust evidence of benefit to recommend one inotropic agent over another. While the use of these agents allows for symptomatic improvement, there is no survival benefit, and these agents carry risks of arrhythmias and catheter-related infections [5]. In the event that inotropic therapy is insufficient, mechanical circulatory support is the next step in the therapeutic ladder.

Mechanical Circulatory Support

Mechanical circulatory support (MCS) refers to a group of medical devices designed to assist or replace the pumping function of a failing heart. These devices can generally be differentiated primarily by their intended duration of use: temporary MCS and durable MCS. Temporary devices, such as intraaortic balloon pumps (IABPs),

Table 5.4 ESC/AHA definition of advanced heart failure [20]

Severe cardiac dysfunction defined by one or more of the following:
Left ventricular ejection fraction ≤30%.
Isolated RV failure
Non-operable severe valve abnormality or congenital heart disease
LVEF ≥40%, elevated natriuretic peptide levels, and evidence of significant diastolic dysfunction
Severe and persistent symptomatic heart failure corresponding to NYHA class III or IV
Unplanned hospitalization or visits in the past 12 months for episodes of:
Congestive heart failure requiring high-dose intravenous diuretics
Low output requiring inotropes or vasoactive medications
Malignant arrhythmias
Severe impairment of exercise capacity with inability to exercise or low 6-min walk test distance (<300 m) or peak VO_2 (<12–14 mL/kg/min) estimated to be of cardiac origin

Adapted from Heidenreich et al. [5], Elsevier, 2022

temporary ventricular assist devices (tVAD), and veno-arterial extracorporeal membrane oxygenation (VA-ECMO), provide short-term hemodynamic stabilization for days to weeks, typically in acute settings such as cardiogenic shock or post-cardiotomy recovery. These systems are often less invasive compared to durable MCS, but require intensive monitoring and are not designed for extended use. In contrast, durable mechanical support, such as LVADs and total artificial hearts (TAHs), are engineered for long-term implantation—months to years—serving as a bridge to transplant or destination therapy for end-stage heart failure patients that are ineligible for transplant. Durable devices are more complex, require surgical implantation, and are designed for improved patient mobility and outpatient management.

One of the first MCS devices still in use is the intraaortic balloon pump (IABP), which is a pneumatic device that generates counterpulsation to improve coronary perfusion and modestly increase cardiac output by 0.5–1.0 L/min [21]. The term counterpulsation describes balloon inflation in diastole and deflation in early systole that causes retrograde and anterograde blood volume displacement leading to diastolic augmentation and improved coronary perfusion. IABP counterpulsation has to be synchronized with the cardiac cycle. Inappropriate trigger of balloon inflation and deflation leads to timing errors that can reduce the efficacy of the device. Moreover, early device inflation and late deflation can be detrimental and increase myocardial oxygen demand [22]. Contraindications to IABP include moderate-severe aortic insufficiency, aortic dissection or aneurysms, peripheral vascular disease, active bleeding, severe thrombocytopenia, and uncontrolled sepsis [23]. Unfortunately, their use in heart transplants has fallen out of favor, given their minimal improvements to cardiac output, particularly for isolated RV failure. One of the more embarrassing studies for the IABP showed that it was inferior to norepinephrine and barely bested phenylephrine in terms of improving hemodynamics in an animal model [24]. However, it is relatively easy and quick to place, and its improvement in coronary perfusion makes it useful for ischemia-induced ventricular dysfunction where only mild hemodynamic support is needed [24].

Another historical mainstay treatment for acute cardiogenic shock is the temporary ventricular assist devices (tVAD) for the affected ventricle—dubbed LVAD, RVAD, or BiVAD. The tVAD pump is powered by a magnetically levitated centrifugal rotor similar to modern cardiopulmonary bypass circuits, though it lacks a reservoir and can be optionally configured with an oxygenator. It requires central cannulation of the aorta and left atrium or left ventricle for a temporary LVAD, or the pulmonary artery (PA) and right atrium for an RVAD, and so the sternum and chest are necessarily left open at the conclusion of the procedure. tVADs are still commonly used for their ability to produce the highest flow rates and thus more support, but their prolonged use puts the patient at risk for potentially lethal mediastinitis. Figure 5.2 outlines *left* ventricular circulatory support devices, and Fig. 5.3 outlines *right* ventricular circulatory support devices.

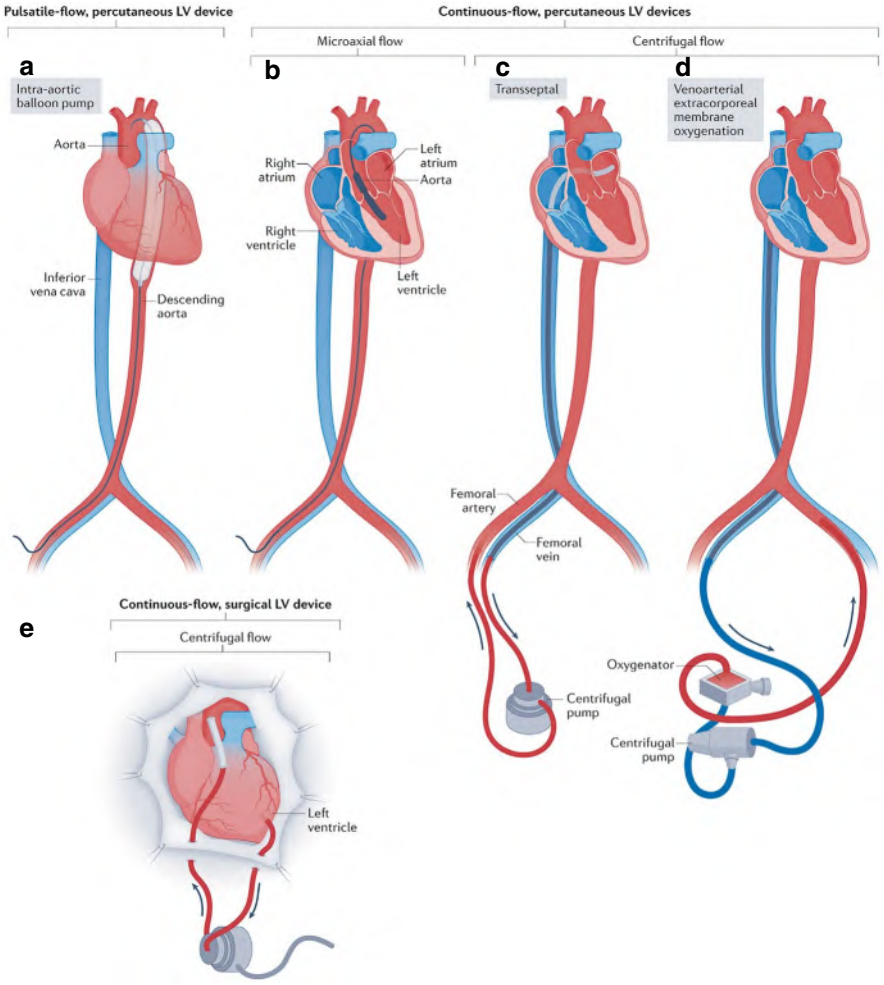

Fig. 5.2 Left ventricular circulatory support devices. (Reproduced with permission from Salter et al. [23], Springer Nature, 2022)

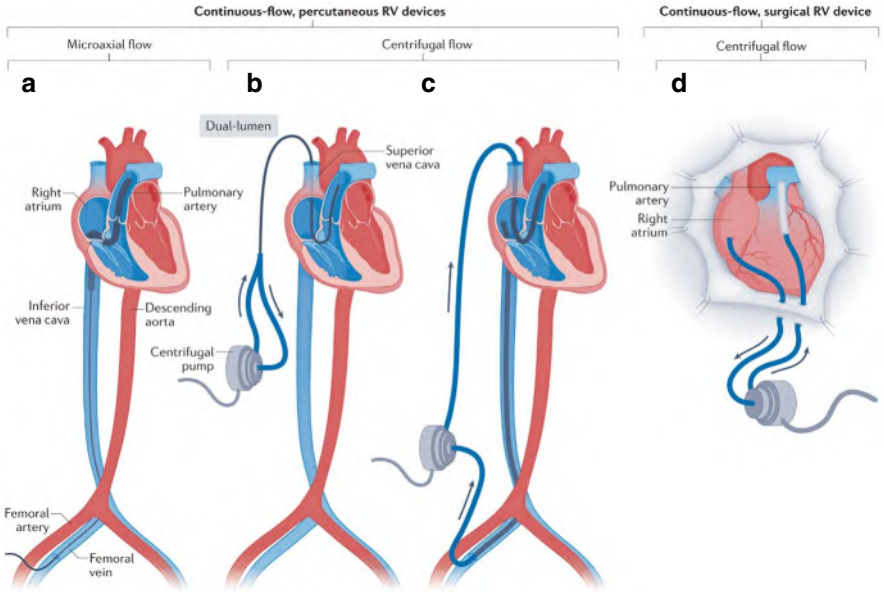

Fig. 5.3 Right ventricular circulatory support devices. (Reproduced with permission from Salter et al. [23], Springer Nature, 2022)

In the subsequent decades since the first use of these tVADs, several percutaneous options have become available that can be placed rapidly and eliminate the need for an open chest but come at the cost of lower flow rates and other complications. Percutaneous devices exist for left and right ventricular support, with a variety of insertion site options, which make them attractive for accommodating unique patient and surgical factors. Current FDA-approved percutaneous support devices include the Impella CP (Abiomed, Danvers, MA, USA), typically inserted via the femoral artery and positioned across the aortic valve under TEE or fluoroscopic guidance. For higher flow requirements, the Impella 5.5 (Abiomed, Danvers, MA, USA) is utilized; however, it requires surgical axillary artery graft access. For right ventricular (RV) support, the Impella RP Flex (Abiomed, Danvers, MA, USA) can be placed via femoral or internal jugular (IJ) access and is positioned across the tricuspid and pulmonic valves. Alternatively, the ProtekDuo (LivaNova, London, England, UK) provides RV support via right IJ insertion and offers the additional benefit of integrated oxygenator support. Finally, the TandemHeart (LivaNova, London, England, UK) functions as a temporary LVAD with oxygenation capabilities, utilizing peripherally inserted cannulas and a drainage catheter placed across the interatrial septum into the left atrium. While these devices vary in cannula size and flow rates, they share common risks such as vascular injury, limb ischemia (arterial), venous obstruction, and hemolysis caused by high-speed internal axial rotors [25]. Recommendation of a particular device is difficult, considering no head-to-head comparisons exist, so selection is typically based on the surgeon experience and case factors.

Lastly, VA-ECMO is another option for MCS that offers high flow rates like tVADs and can be easily and quickly placed through peripherally inserted cannulas while also offering the ability to provide oxygenation on top of hemodynamic support. However, VA-ECMO carries the risk of unpredictable LV unloading, which may predispose to intracardiac blood stasis and clot formation, as well as volume overload that can lead to further myocardial injury [26]. For this reason, it may be combined with an Impella to provide direct drainage of the LV. Table 5.5 provides a comparison of available MCS devices.

Management of Anemia

Preoperative anemia (hemoglobin <12.5 g/dL) is prevalent among cardiac surgery patients due to various factors, including hospital-related interventions, iron deficiency, and concurrent renal dysfunction [28, 29]. It is the single most important determinant of perioperative blood transfusion, which itself is associated with many risks and side effects [30]. Moreover, preoperative anemia is associated with greater odds of adverse outcomes, including death, stroke, and acute kidney injury (AKI) [31–34]. Given these factors, it is imperative to closely monitor and manage preoperative anemia before undergoing OHT.

Preoperative blood product transfusion should be approached with caution in patients who are listed or have the potential to be listed for OHT, as it may lead to allosensitization. If blood transfusion is unavoidable, attempts should be made to minimize the risk of de novo allosensitization by using leukodepleted blood products and single donor or matched thrombocytes [8]. While allosensitization is not a strict contraindication to transplantation, an increasing level of allosensitization in an OHT candidate raises their risk of removal from the waitlist and waitlist mortality [35–37]. Furthermore, sensitization before transplant is associated with reduced postoperative survival, increased risk of rejection, graft loss, and cardiac allograft vasculopathy [35, 37].

Iron and erythropoiesis-stimulating agents (ESA) are potential treatment options for preoperative anemia without the added risk of allosensitization. Iron supplementation has been demonstrated to improve quality of life and reduce the risk of hospitalization in heart failure patients with iron deficiency, either with or without associated anemia [38, 39]. However, the American Heart Association (AHA) advises against the routine use of ESAs for treating anemia in heart failure, as studies have consistently shown that ESAs do not improve quality of life, exercise capacity, mortality, or hospitalization outcomes [5, 38, 40–42]. Instead, ESA increases the overall risk of thromboembolic events [38, 41]. Prophylactic anticoagulation should be considered for deep vein thrombosis (DVT) prevention per manufacturer recommendations (Pfizer, New York). As such, ESA should be used after careful consideration in select OHT candidates with low erythropoietin production in anticipation for surgery.

The Blood Conservation and Hemostasis in Cardiac Surgery survey conducted by Joshi et al. demonstrated that the median transfusion trigger during cardiopulmonary bypass (CPB) was hemoglobin (Hgb) 6–7 g/dL. After weaning from CPB, the

Table 5.5 Mechanical circulatory assist devices

Device	IABP	Impella CP	Impella 5.0 / 5.5	TandemHeart (LA to systemic artery)	VA-ECMO	TandemHeart (RA to AO)	Impella RP
Primary hemodynamic effect	LV volume or pressure unloading	LV volume or pressure unloading	LV volume or pressure unloading	LV volume unloading	Biventricular pressure and volume unloading	RV pressure unloading	RV volume or pressure unloading
Hemodynamic support	Low	Moderate	High	High	High	High	Moderate
Pump mechanism	Pneumatic	Axial flow	Axial flow	Centrifugal	Centrifugal	Centrifugal	Axial flow
Cannula size	7-9Fr	13Fr	22Fr	21Fr inflow; 15–17Fr outflow	18–21Fr inflow; 15–22Fr outflow	21Fr inflow; 15–17Fr outflow	22Fr
Anticoagulation	Very low	Very low	Very low	High	High	High	Very low
Risk of limb ischemia	Very low	Low	Moderate	High	High	High	Low
Risk of hemolysis	Very low	Low	Low	Low	Low	Low	Low

Reproduced with permission from Mandaway and Rao [27]

median transfusion trigger was a higher Hgb target of 7–8 g/dL [43]. German to this discussion is the TRICS III trial findings that transfusion thresholds in cardiac surgery patients at a Hgb of <7.5 were noninferior to Hgb <8.5 g/dL with respect to the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis [44]. While it may be prudent to conserve blood in the setting of OHT and concerns for sensitization, there is no established data to demonstrate that the practiced transfusion threshold of Hgb 6–7 is safe and noninferior to Hgb <7.5.

Allosensitization and Immunosuppression

While blood transfusions are a common cause of allosensitization, other causes include prior transplantation, pregnancy, and human tissue allografts [35, 45]. Patients with LVADs have a higher incidence of allosensitization owing to immunogenicity of the device, leading to aberrant T-cell and B-cell activation, upregulation of cytokines during implantation, and blood product transfusion [35, 45, 46]. Allosensitization is a major barrier to heart transplantation. Allosensitization poses a significant obstacle to heart transplantation, and it is defined by a panel-reactive antibody (PRA) value exceeding 10% [35]. In 2017, UNOS started using calculated PRA (cPRA) for the determination of transplant candidacy. cPRA compares the incompatible HLA antigens to the donor pool [35, 36]. Thus, a transplantation candidate with a cPRA of 80% would be expected to be incompatible with 80% of donors [35]. As such, it comes as no surprise that a candidate with cPRA >80% has a substantial reduction in incidence of OHT, increased removal from waitlist, and increased wait list mortality compared to candidates with cPRA <10% [36].

Desensitization therapy is considered for patients with cPRA >50% in efforts to improve access, reduce wait time, and improve postoperative outcomes [8, 35]. Treatment options include mechanical removal of antibodies (i.e., plasmapheresis) and intravenous immunoglobulin (IVIG) [8, 35]. While plasmapheresis and IVIG are effective at reducing antibodies, they are associated with rebound. Adjuvant therapies, such as rituximab, are used alongside plasmapheresis and IVIG to prevent rebound [8, 47].

At the time of transplantation, immunosuppressants are utilized to prevent allograft rejection. Immunosuppressive regimens fall into three categories: induction, maintenance, and rejection treatment [2]. Induction therapy aims to induce a profound and rapid immunosuppression. This is particularly useful for allosensitized patients and patients with renal impairment, where it allows for the delayed start of nephrotoxic immunosuppressants [2]. There are three general approaches to induction therapy: no induction therapy, non-depletive monoclonal induction using IL-2 receptor antagonists (e.g., basiliximab), and polyclonal induction with antithymocyte globulins (e.g., alemtuzumab) [48]. It is frequently practiced to give basiliximab after coming off bypass given concerns over “wash-out” or loss of the drug

to CPB machinery although a study in pediatric OHT found that basiliximab to be effective whether given pre-CPB or post-CPB [49].

Following transplantation, patients are placed on maintenance immunosuppressive therapy. The current maintenance immunosuppressant therapy for heart transplant patients typically involves a combination of calcineurin inhibitor (e.g., tacrolimus, cyclosporine), cell cycle inhibitor (e.g., mycophenolate mofetil), and corticosteroids [48].

Cardiac Implantable Electronic Devices (CIEDs)

CIEDs include pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy devices (CRTs). An estimated 65–68% of patients possess a CIED prior to transplant as part of guideline-directed medical therapy for prevention of arrhythmias and/or optimization of cardiac output [50, 51]. Overwhelmingly, the data have demonstrated that the utilization of these devices for patients with heart failure with reduced ejection fraction (HFrEF) has resulted in improvements in mortality, functional heart failure classification, and quality of life [52–54]. As such, it comes as no surprise that patients with CIEDs have higher rates of survival to heart transplant and decreased total mortality [55]. The 2022 AHA guideline for management of heart failure recommends these devices for patients after >3 months of goal-directed medical therapy and anticipated survival of >1 year. ICDs are recommended for the primary prevention of sudden cardiac death in patients with left ventricular ejection fraction (LVEF) ≤30%. CRTs are recommended for heart failure patients with heart block, bundle branch block, and/or arrhythmias [5].

CIEDs are often reprogrammed prior to surgery. ICDs and the defibrillator function of CRTs are deactivated to prevent inappropriate defibrillation resulting from misinterpretation of electric activity as arrhythmias. External defibrillation pads are placed as soon as possible thereafter. Pacemaker-dependent patients typically have their devices set to an asynchronous mode to prevent electromagnetic inference and resulting hemodynamically consequential bradycardia. The programmed heart rate is set higher than their baseline to offset the dose dependent reduction of volatile anesthetics on cardiac contractility and output, barring contraindications such as hypertrophic cardiomyopathy and dynamic left ventricular outflow tract obstruction. The definition of pacemaker dependence is complex and marred by the diversity of testing methods. It is generally accepted that pacemaker dependency means "inadequate or absence of intrinsic rhythm potentially resulting in bradycardia-related symptoms" [56].

It is standard practice to remove CIEDs at the time of OHT. While the intracardiac portion can be removed with excision of the native heart, removal of the extracardiac components can be challenging. CIED leads can become adherent or embedded in the vessel walls through which they travel [50]. Retained components are present in 16–42% of patients following their OHT. Complications

associated with CIED removal and retained components include upper extremity deep vein thrombosis, infections, lead migration, and bleeding within the ICD pocket [50, 51].

Management of Anticoagulation and Antiplatelet Medications

Anticoagulants and antiplatelet medications are common in heart transplant recipients and present some challenges given the urgent nature of the procedure. Patients with durable LVADs, temporary MCS, mechanical heart valves, atrial fibrillation, or existing venous thromboembolism require anticoagulation, usually with the vitamin K antagonist warfarin or a direct oral anticoagulant (DOAC) like apixaban, rivaroxaban, or dabigatran. Ischemic cardiomyopathy is also a common indication for heart transplant, and many of these patients are on antiplatelet agents, such as clopidogrel, prasugrel, or ticagrelor, for coronary or peripheral arterial stents. Ideally, all anticoagulant and antiplatelet effects would be reversed prior to transplant, but this could be potentially fatal in many cases, such as in a patient with a durable LVAD. Therefore, a careful risk–benefit analysis of bleeding and thrombosis should take place and involve the patient, surgeon, and cardiologist to determine the most prudent course of action. In patients with less risk, these medications may be stopped and rapidly reversed prior to the procedure, but when the relative risk is less clear, a bridging strategy is usually indicated [57]. If possible, reversal may be delayed until after separation from bypass, but in patients with predicted difficult re-entry into the chest, it may be prudent to do so beforehand. Should the reversal of one of these agents be pursued preoperatively, confirmatory lab testing may be performed but should not delay the procedure.

Correction of anticoagulants and antiplatelet coagulopathy should address the underlying mechanism of the medication and substitute a similar but more rapidly eliminated or easily reversible agent when bridging is indicated. Reversal of warfarin is achieved with vitamin K administration, often intravenously, along with a 4-factor prothrombin complex concentrate (4F-PCC), though fresh frozen plasma (FFP) may also be utilized if 4F-PCC is unavailable or contraindicated due to heparin sensitivity. Additionally, there is concern about an elevated thrombosis risk with the use of 4F-PCC compared to FFP, though it is unclear if this is a result of faster and more complete unmasking of underlying thrombosis risk [58]. FFP administration also carries the risk of significant volume overload in the advanced heart failure patient, so this must also be taken into account when deciding on an appropriate reversal strategy. Dosing of the 4F-PCC or FFP will vary based on patient weight and pre-reversal international normalization ratio (INR), with the goal to bring the INR < 1.5 prior to surgery [59]. In the case of DOACs, some specific reversal agents exist, idarucizumab (Praxbind; Boehringer Ingelheim, Ingelheim, Germany) for dabigatran, and andexanet alfa (Andexxa; AstraZeneca, Cambridge, UK) for apixaban and rivaroxaban; however, availability and cost may be barriers to their use, in which case 4F-PCC may be substituted [60]. Antiplatelet agents have no such antidote, and so rapid reversal is usually achieved with platelet transfusion. In many

cases, an unfractionated heparin infusion is used as the bridging agent of choice for warfarin and DOACs, as it is metabolized rapidly and can be reversed rapidly with protamine if needed. For antiplatelet therapy bridging, cangrelor (The Medicines Company, Parsippany, NJ, USA) is an ultra-rapid acting antiplatelet agent with a half-life of 3–6 min that permits rapid titration and cessation.

Congenital Heart Disease

Advancements in medical, interventional, and surgical management of CHD have significantly improved the survival rates of pediatric patients. Approximately 90% of these patients now have a chance to live into adulthood [8, 61]. As this cohort ages into adulthood, about 12.9% will go on to develop HF, which subsequently becomes the leading cause of death [8, 62]. This number is likely to rise as ongoing advancements extend the life expectancy of this population.

The most common CHDs that require OHT are single ventricle defects, particularly hypoplastic left heart syndrome [63]. The Fontan procedure is a palliative surgery for such patients and others with single ventricle physiology who are not candidates for biventricular repair. This procedure involves the creation of cavopulmonary connections from the superior and inferior vena cava to the right pulmonary artery [64]. As these patients become older, they may exhibit "failed Fontan physiology," which presents as heart failure with elevated systemic venous pressure alongside with extracardiac manifestations that may include protein-losing enteropathy, hepatic dysfunction, renal dysfunction, plastic bronchitis, and lower extremity venous congestion [8, 65].

There are several considerations while caring for a patient with Fontan physiology. Atrial tachyarrhythmias occur in 60% of adult patients with Fontan palliation and are associated with substantial morbidity and mortality [65]. Therefore, external pads should be placed to facilitate prompt cardioversion in case of hemodynamically significant arrhythmias. Mechanical ventilation is a concern because positive pressure increases PVR, resulting in diminished systemic venous return. When on mechanical ventilation, lung volumes should be close to functional residual capacity with minimal positive end expiratory pressure [64]. Cardiovascular goals should be to minimize PVR, promote ventricular contractility, and reduce afterload [64].

It is not uncommon to encounter shunts within this population. It is crucial to monitor their pulmonary blood flow to systemic blood flow ratio (Qp:Qs) prior to removal of the native heart. Qp:Qs goals should be tailored to each patient based on their underlying cardiac lesion, direction of blood flow across the shunt, hemodynamic goals, and systemic oxygenation. Various strategies can be employed to manipulate Qp:Qs. Increasing the inspired oxygen fraction (FiO2) decreases PVR, thereby enhancing pulmonary blood flow and increasing Qp:Qs. Conversely, reducing FiO2 will have the opposite effect [66]. Permissive hypercapnia, which allows higher levels of arterial carbon dioxide, results in an increase in PVR, leading to a decrease in Qp:Qs [61]. Inhaled nitric oxide and

epoprostenol can be used to further reduce PVR and increase Qp:Qs [67, 68]. Positive pressure ventilation also affects PVR proportionally to airway pressures, and excessive pressures can lead to significant reductions in Qp:Qs [69]. However, it is crucial to pay special attention during sternotomy, as chest opening can diminish the impact of positive ventilatory pressure on PVR and result in alterations in Qp:Qs. Lastly, surgical placement of bands or tourniquets around shunts and pulmonary vasculature is an effective way to reduce pulmonary blood flow, thereby decreasing Qp:Qs [70, 71].

Operative Care

Surgical Procedure and Variations

After the anesthesia care team has completed their pre-incision tasks, the patient is turned over to the surgical team. A median sternotomy is performed to access the heart. The aorta, pulmonary artery, superior vena cava, and inferior vena cava are dissected from their adjacent tissue. This process can take substantially longer in patients with a history of prior cardiac or intrathoracic surgery. In order to prevent extended ischemic time for the graft, the recipient may need to go to the operating room well in advance of the donor to ensure adequate time for dissection prior to the organ's arrival. Once the surgical dissection has created sufficient exposure of the heart, CPB with bicaval cannulation is initiated, and the aorta is cross-clamped. Additionally, the inferior vena cava (IVC) and superior vena cava (SVC) will be snared around the venous cannulas to prevent leakage of blood or entrainment of air. If a durable LVAD is present, it is mobilized from the surrounding tissue and prepared for decommissioning [72]. After initiation of cardiopulmonary bypass, the outflow graft is clamped to prevent retrograde flow of blood, the device is turned off, the outflow graft is divided near the ascending aorta, and the device itself is typically removed en bloc with the heart at the time of explant. Additional dissection may need to occur after initiation of CPB due to extensive tissue adhesions and the risk of injuring the heart or great vessels. Once the donor heart arrives and is deemed to be of adequate quality, the diseased heart is removed.

The native heart is excised at the level of the right and left atrioventricular grooves, initially preserving a significant portion of the native atria. On the right side, the excision is performed near the course of the right coronary artery, inferiorly toward the coronary sinus, leaving the atrial cuff attached to the superior vena cava (SVC) and inferior vena cava (IVC). The cuff is later divided and trimmed down as needed to allow connection to the new donor heart. However, not all surgeons retain the cuff [73]. Subsequently, the aorta is divided at the level of the sinotubular junction. The main pulmonary artery is then divided at the level of the pulmonic valve. Next, the left ventricle is excised. On the left side, the excision is conducted through the coronary sinus, which traverses the left atrioventricular groove. This dissection effectively preserves most of the left atrium (LA) while the LA appendage may be excised depending on surgeon preference [72].

There are variations in the order of anastomoses; however, the LA anastomosis is uniformly the first, given that it is the most posterior structure. This can then be followed by delivery of cardioplegia directly to the coronary ostia of the graft and creation of the aortic anastomosis. After the LV is de-aired, the new heart may be reperfused while the other anastomoses are created. The drawback to creating the aortic anastomosis second is the anatomical constraints of completing the back wall of the pulmonary artery (PA) anastomosis, and so some surgeons may choose to do the PA first. Lastly, the surgeon will turn their attention to the right atrium and cava [72].

The biatrial OHT technique was previously introduced by Lower and Shumway in 1960 on canine hearts and continues to be used due to its simplicity [74, 75]. As the name implies, this technique only requires two anastomoses to the atria of the recipient, with the donor RA anastomosed directly to the recipient RA. This is evident after the procedure is complete by the presence of two different P-waves visible on ECG, though only one actually conducts to the atrioventricular (AV) node. However, this technique has been largely supplanted by the bicaval technique, which connects the donor RA to the recipient SVC and IVC separately. This approach does require a marginally longer operation time due to the additional anastomosis but is frequently preferred as it is associated with a lower incidence of atrial arrhythmias and mortality [74, 76]. The techniques are illustrated in Fig. 5.4.

Re-entry Injuries in Redo Sternotomy

It is not uncommon for OHT candidates to have previous sternotomies, particularly in the era of durable LVAD utilization. The incidence of intraoperative injury is estimated to be 7–9% in patients with previous sternotomies [78, 79]. The majority of these injuries occur during re-entry—the period between sternotomy and before cannulation for CPB [78, 79]. Additional risk factors for injury include previous radiotherapy, a greater number of previous sternotomies, and a patient's internal thoracic artery [78–80]. To mitigate these risks, protective strategies include preoperative computed tomography (CT), peripheral cannulation for CPB, and initiation of CPB prior to sternotomy [78–81].

It is also imperative to place defibrillator pads prior to the induction of anesthesia for repeat sternotomies. This is driven by the increased risk of ventricular arrhythmias during the procedure and thick adhesions that may prohibit the use of internal cardiac pads [82]. This risk is accentuated in patients with an internal mammillary artery graft to the coronary vasculature during repeat sternotomy due to the low flow state caused by sternal traction [83].

Considerations for Patients with Durable LVAD

The preparation of a patient with a durable LVAD in anticipation of a heart transplant is a significantly more complex process compared to a patient with a native chest. Like other redo sternotomy patients, a CT scan of the chest and aorta is

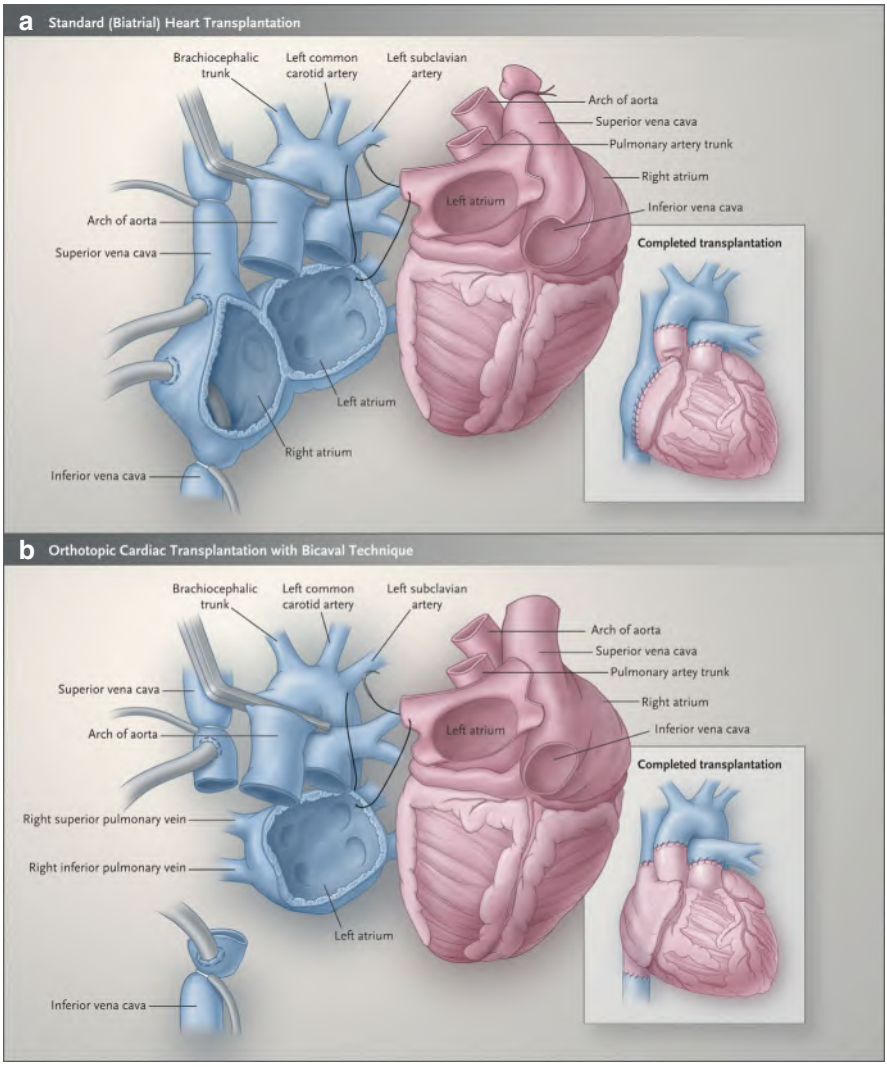

Fig. 5.4 Biatrial and bicaval techniques for orthotopic heart transplantation. (Reproduced with permission from Hunt [77])

helpful in planning [84]. This imaging provides pertinent details such as the proximity of the outflow graft or driveline to the sternum, calcifications in the ascending aorta, and alternative vascular access routes. In patients with drivelines and outflow grafts distant to the sternum, sternotomy can be safely performed without peripheral initiation of cardiopulmonary bypass. The decision for arterial cannulation of the subclavian artery over the femoral artery is often informed by the presence of descending aortic atherosclerosis. During sternotomy, the most severe adhesions are noted to be on the anterior surface of the heart and device components. In the event

of unanticipated bleeding and lack of arterial access, the outflow graft is an option for cannulation in the event of emergencies [84].

A synthetic expanded polytetrafluoroethylene (ePTFE) pericardial membrane may be encountered during reopening because of placement during durable LVAD implantation. There have been several small observation studies that suggest that ePTFE reduces the formation of adhesions [85–87]. However, a study by An et al. demonstrated that during sternal reopening in patients with ePTFE compared to patients without ePTFE, there is no difference in time from incision to initiation of CPB, injuries to mediastinal structures during dissections, or reported intraoperative bleeding [88].

Donor Heart Transportation and Mechanical Graft Perfusion Systems

Ice storage has been the historic standard for preserving and transporting donor organs [89, 90]. Ice storage, or static cold storage (SCS), is limited to 4–6 h of cold ischemic storage, and the effectiveness depends on the solution and its temperature [91]. However, the use of ice subjects the donor hearts to the risk of cold injury through rapid decreases in temperature [90]. Organ preservation using ice also limits its safe total ischemic time, with each 10-min interval associated with a 5% greater risk of primary graft dysfunction (PGD), the most feared complication of heart transplantation that is discussed in greater detail later in this chapter [92]. The presence of PGD carries a 30-day, 1-year, and 5-year mortality of 28.4%, 38.0%, and 45.8%, respectively, compared with 1.9%, 7.1%, and 21.5% for those without PGD [92]. Thereby highlighting the impetus to develop mechanical graft perfusion systems.

There are two categories for mechanical graft perfusion systems (MGP) for heart transplants—normothermic machine perfusion (NMP) and hypothermic machine perfusion (HMP). As their names imply, the difference between the two systems pertains to the temperature at which the heart is maintained, with NMP being maintained close to physiological temperatures and HMP being maintained around 4–10 °C. Once the donor organ is removed from the donor, it is then placed in one of these perfusion systems and perfused using oxygenated blood [93].

There are limited data on the use of these devices. Current studies demonstrate that utilization of MGP leads to a non-statistically significant trend toward improved 30-day mortality compared to cold storage [94, 95]. In many studies, MGP systems are used more frequently for donation after circulatory death (DCD) and for donors that are significantly more distant from the recipient; however, this may be somewhat counterbalanced by the generally healthier recipients that are selected for these grafts. One multicenter study of the Organ Care System (OCS) Heart (TransMedics, Andover, MA, USA), an NMP system, found that over 3225 heart transplants across 56 sites, there was a non-significant difference in 12-month mortality, with 89.9% survival in the OCS group and 92.8% with traditional ice storage. This lack of difference remained robust even after a propensity-matched analysis,

and there was also no difference in rates of PGD or negative outcomes at 12 months, but the authors also point to a significant difference in the distance of the donor, with a median of 667 miles in the OCS group versus 232 miles with ice storage [96]. Similar studies of HMP, XVIVO Heart Assist Transport (XVIVO Group, Gothenburg, Sweden), and the cold static storage system, Paragonix SherpaPak and Cardiac Transport System (SCTS; Paragonix Technologies, Inc., Cambridge, MA, USA), have fared somewhat better in the research, with significantly reduced risk of PGD and at least one post hoc analysis showing a slight benefit to 2-year mortality, though further study is needed to confirm these results and establish their benefit and cost-effectiveness [89, 95, 97]. See Fig. 5.5 for a schematic of the OCS system. See Fig. 5.6 for the SherpaPak system design.

Donation After Circulatory Death

Historically, donation after brain death was the gold standard for cardiac procurement. A shortage of organs and the significant waitlist mortality necessitated the expansion into donated following circulatory death (DCD). The organs from these donors are recovered after elective withdrawal of life support after a predetermined period of circulatory arrest and declaration of death. During this time of circulatory arrest, referred to as the agonal phase, the organs are at risk for ischemia and significant injury. To navigate this risk, the heart is rapidly reanimated using an MGP system and assessed for viability prior to transplantation. An analysis of the UNOS database, covering 2590 heart transplants with 442 DCD donors, found significantly more instances of severe graft dysfunction in the DCD group (9.5%) compared to the

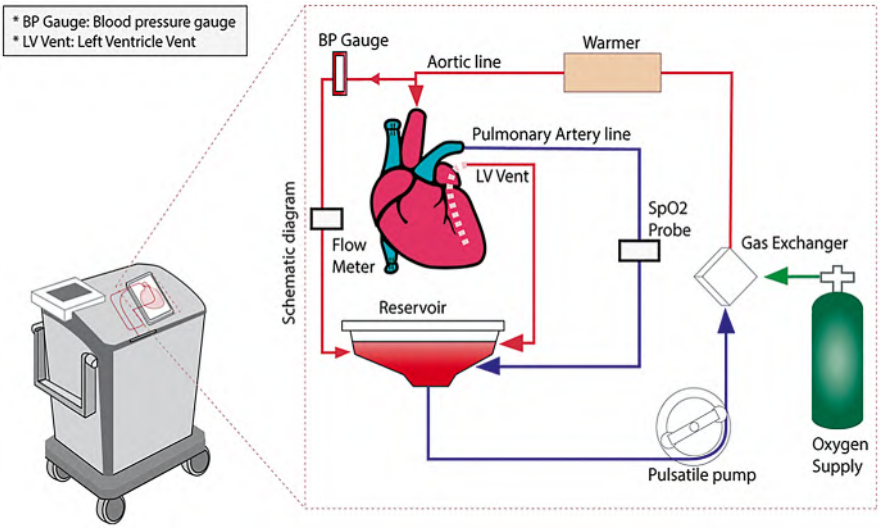

Fig. 5.5 Schematic of the Organ Care System. (Reproduced from Alomari et al. [98], under the Creative Commons license agreement)

Fig. 5.6 Cross-sectional view of the SherpaPak Transport System. (Reproduced from Nasim et al. [99], under the Creative Commons license agreement)

donation after brain death (DBD) controls (5.1%) at 24 h, though the incidence at 72-h was not significantly different (2.3% for DCD vs. 2.9% for DBD) and 30-day mortality was also similar 3.4% for DCD vs. 2.1% for DBD). Receiving a DCD was found to be an independent predictor of graft dysfunction similar to using an undersized graft or ECMO support as a bridge to transplant [100]. However, the transient nature of the graft dysfunction, coupled with the benefit of significantly expanding the donor pool, likely makes DCD a worthwhile pursuit, and further study may allow for better prognostication of graft dysfunction in this subset of donors.

In a more recent variation of this technique, the donor organs may be reperfused in situ prior to harvesting to shorten the ischemic time during the agonal phase. This is performed by cannulating the aorta and right atrium and perfusing the organs with cardiopulmonary bypass or an extracorporeal life support, while intentionally excluding perfusion to the brain via clamping the aortic arch vessels. This is termed normothermic regional perfusion (NRP) and allows for minimal ischemia to the heart during the agonal phase. Initial studies have been very promising, with a multicenter observational study of 157 DCDs utilizing this technique showing a mean withdrawal to reperfusion time of about 27 min and a shorter total cold ischemic time of 144 min vs. 174 min compared to a DBD control group. There were also no differences in MCS requirement (12.8% in NRP vs. 12.7% in DBD) and comparable overall survival over a 5-year follow-up period (HR 0.73, 0.41–1.28 95% CI) [101].

As providers navigate some ethical issues associated with this method of donation, it creates variability in the timing and likelihood of a transplant. In particular, there is no standard waiting period for the passing of the donor, though many hospitals will not wait more than an hour, so a donor that fails to pass in the allotted time will necessarily lead to a lack of an organ for the recipient. For the team caring for the recipient, they must decide how to properly prepare the patient to minimize delays in transplanting the organ while also avoiding situations where a recipient must wait under anesthesia for a prolonged period or undergoes placement of invasive lines for an ultimately canceled procedure. Decisions on appropriate timing should be discussed with the surgical team and consider factors like redo sternotomy, patient stability, and anticipated technical complexity, such as difficult airway or line placement.

Monitors and Lines

Requisite monitors include the standard ASA monitors with additional invasive hemodynamic monitoring that is similar to cardiac surgery in general, with some notable exceptions. Adequate and dependable venous access is also critical to patient safety during OHT given the high propensity for blood product transfusion and vasoactive medication utilization. Best practice dictates that large-bore peripheral intravenous (IV) catheters and arterial catheters be placed prior to induction given the potential for hemodynamic instability during this period. Central venous cannulation is also required both for hemodynamic monitoring, access for pulmonary artery catheters (PAC), and administration of medications that require central access, including many vasopressors, inotropes, and calcium chloride. The use of transesophageal echocardiography is uniform in the absence of contraindications due to the invaluable data it provides about the graft's function after implantation, and its use will be covered more thoroughly in a later section. Precise catheters and insertion locations, along with non-standard monitors, should be individualized to meet patient, surgical, and local needs, but some common configurations and practical considerations are discussed herein.

Arterial catheterization is a vital first step in the preparation for induction and surgery. This procedure is widely performed in a variety of surgical cases, with an estimated 10 million catheter placements annually in the United States and Europe [102]. However, approximately 25% of arterial catheters fail before their intended removal [102], which can lead to serious consequences, particularly in heart transplant (HT) candidates who often experience significant hemodynamic changes during critical portions of the surgery. Several best practices have been shown to significantly reduce catheter failure rates. Ultrasound-guided catheterization has been demonstrated to be superior compared to the landmark technique in terms of failure rate, first pass success, and number of puncture attempts [102–104]. It should be noted that the use of ultrasound is required in patients with durable LVAD because of a lack of pulsatility. Inserting at lower angles (30–45°) minimizes the risk of kinking, a common cause of failure [105]. Using longer catheters with

extended subcutaneous tracts enhances stability, improves waveform quality, and reduces the risk of thrombosis [105]. Selecting an insertion site 4–10 cm proximal to the wrist crease also provides improved overall securement as it is less prone to dislodgement with wrist movement [106]. With regard to the insertion site, the radial artery is the most frequently accessed due to its lower serious complication rate, but the brachial artery may also be considered when radial access is not feasible or has been unsuccessful. In the event of planned axillary artery cannulation, an upper extremity arterial line should be placed on the opposite side to prevent loss of monitoring during temporary axillary artery clamping. A second arterial line may also be placed, typically after induction, to provide backup monitoring, to correlate pressures in patients with significant peripheral arterial disease, and, in the case of a femoral line, to allow for rapid conversion of the catheter to an arterial bypass or ECMO cannula in the event that emergent circulatory support is needed.

For venous access, a central sheath introducer is placed to allow for PAC placement, with additional central venous access and peripheral IVs based on available sites for access, anticipated transfusion needs, and the number of access ports desired. Typically, the introducer is inserted into the right internal jugular (IJ) vein due to the combination of low placement complication and infection risks; however, the left IJ is sometimes preferred to leave the right IJ available if percutaneous RV mechanical support or ECMO is required. However, left IJ placement, particularly with a stiff introducer catheter, is significantly more perilous as the left IJ joins with the brachiocephalic vein at a near 90-degree angle, which increases the likelihood of vascular injury when attempting to navigate the catheter around this turn. Furthermore, the apex of the left lung is also higher than that of the right, and the proximity to the thoracic duct puts both these structures at higher risk of injury. Therefore, these risks should be carefully weighed against the use of other access sites. Additional central venous access can occur through the same vein as the introducer, commonly referred to as a "double stick," which has the advantage of preserving other access sites for temporary dialysis catheters, surgical cannulation, or future central access, but increases the complexity of line placement that requires extra time and expertise to avoid complications.

The use of PAC in cardiac surgery remains a topic of ongoing debate. PAC use allows for measurement of hemodynamic variables that help characterize the etiology of hypotension and evaluation of the response to treatment. However, their benefit has not been fully established in available research, and their use comes with several risks. In patients with left bundle branch blocks, PAC insertion has the potential to cause a concomitant right bundle branch block, which would then result in complete heart block [107, 108]. Similarly, patients with Wolff–Parkinson–White syndrome and Ebstein's anomaly are at heightened risk for developing tachyarrhythmias during PAC placement and use [107, 108]. A PAC should be used with caution in the setting of right-sided mechanical hardware, as it may lead to damage to hardware or the catheter itself [108]. Similarly, the presence of right-sided cardiac masses and vegetations poses additional risk, including bleeding and thromboembolic events [108]. If the PAC is advanced into the PA at the beginning of the case, it is recommended to withdraw it prior to caval snaring on bypass to prevent entrapment or accidental damage to the catheter during cardiectomy. An alternative

approach is to have the surgeon place the tip of the PAC in a safe location and place it back into the pulmonary artery after the donor heart is in place, which also has the benefit of reducing the risk of placement after separation from bypass.

The American Society of Anesthesiology (ASA) released a practice guideline for PAC in 2003. The task force assessed multiple observation studies available at that time with conflicting results regarding hospital mortality and morbidity. As a result, the guideline was unable to come to a consensus regarding the routine utilization of PAC for cardiac surgery [109]. Several new observational studies have been released since the publication of the ASA guideline, which continue to demonstrate mixed results [110–112]. However, in the setting of OHT, the use of PAC can be justifiable as a means for early detection of PGD. Ample evidence has demonstrated that early detection of PGD and initiation of MCS lead to improved outcomes [113, 114].

Induction and Maintenance of Anesthesia

The main objective during induction is to administer the minimum effective dose of sedative to achieve unconsciousness while preserving optimal contractility, SVR, PVR, and preload. Hemodynamic goals are unique to each patient due to their pathology and compensatory mechanisms. In a well-compensated patient, these targets can be informed by their baseline hemodynamic status on arrival for surgery. It is crucial to keep their hemodynamics within close proximity to their baseline during induction and prior to initiation of CPB, as it represents their stable hemostatic state. For patients with low cardiac output, it is sensible to administer a small bolus dose of norepinephrine or epinephrine prior to the induction of anesthesia to assess circulatory time and dose–response. Initiating inotropic and vasopressor infusions prior to induction may be useful in maintaining their hemodynamic stability without need for frequent bolus doses.

As to the ideal choice of induction agent, there is considerable variability in practice with no clear benefit of one method. In a survey of cardiac anesthesiologists, propofol is the most frequently used induction agent for cardiac surgery as a solo agent, 2-drug combination, and 3-drug combination [115]. Propofol was the preferred agent due to perceived ease of use, effectiveness, and rapid onset/offset. Fentanyl was the second most frequently selected induction agent due to its hemodynamic stability, effectiveness, and ease of use. However, etomidate, ketamine, and inhaled volatile anesthetics are also regularly used and successful. So perhaps the most important factors in creating an induction plan are provider experience with a particular agent or method, early treatment of hypotension given long circulatory times in this patient population, and the patience to execute a slow, controlled induction in order to avoid rapid swings in hemodynamics. In any case, particular concerns about patient stability on induction should prompt discussions with the surgical team about the need for surgical presence and preparation, rescue equipment, and involvement of the perfusionist in case emergent initiation of bypass or ECMO is needed.

There have been several studies comparing the use of volatile anesthetics to total intravenous anesthesia (TIVA) as maintenance anesthetic during cardiac surgery. Some studies have found that the use of volatile anesthetics conferred myocardial and cerebral protection, leading to shorter length of ICU stay and reduced mortality [116–119]. There are several mechanisms behind the cell protective properties, including maintaining mitochondrial homeostasis, reduction of reactive oxygen species, and modulation of pathways that promote cell survival [120–122]. In contrast, several other studies refute these findings and demonstrate no benefit in the use of volatile agents over TIVA [115, 123, 124]. Most notable among the recent studies is the MYRAID trial, a pragmatic, randomized, single-blind trial that was conducted at 36 centers in 13 countries, with a total enrollment of 5400 patients undergoing coronary bypass surgery [125]. Patients were randomized to volatile anesthetics or TIVA. There was no reported difference in all-cause mortality at 1 year, rate of myocardial infarction, or duration of ICU stay. In practice, the choice to use a volatile anesthetic or TIVA is frequently informed by geographic and institutional practice. For example, in Europe, it is common practice to use TIVA during CPB due to the European Council directive prohibiting the use of anesthetic vaporizers on CPB machines [115]. In the United States, the use of volatile anesthetics predominates, with isoflurane being the preferred agent of choice. During CPB, the perfusionist administers the bypass anesthetic in the majority of practice settings [115].

Cardiopulmonary Bypass and Anticoagulation

The cardiopulmonary bypass (CPB) machine is used during cardiac surgery to recirculate blood that has been diverted from the heart and lungs to allow a bloodless operative field. Its functions are multifaceted and include gas exchange, circulatory support, temperature regulation, and the ability to contain a reservoir for blood drained from the surgical field. Ventilation can be stopped while on CPB at full support.

Adequate anticoagulation is required prior to the initiation of CPB to prevent consumptive coagulopathy and the formation of microthrombi. The anticoagulation goal for the initiation of CPB is to maintain an activated clotting time (ACT) above 480 s—the gold standard in monitoring anticoagulation for CPB [126]. This threshold is considered a standard of care to ensure adequate anticoagulation while maintaining a margin of safety during CPB. However, ACT values over 400 s are frequently considered therapeutic depending on the type of instrument being used.

The preferred anticoagulant for CPB is unfractionated heparin [126]. Despite the commonly accepted ACT goal, there is no consensus on the accurate calculation of this initial dose of unfractionated heparin. Acceptable options for loading dose include a weight-based dose of 300–400 U/kg or the use of point-of-care tests that determine the whole blood sensitivity to heparin utilizing an associated dose–response.

Individual responsiveness to heparin can vary. The pharmacodynamics of heparin are dependent on the level and function of plasma antithrombin, previously referred to as antithrombin III [126]. Unfortunately, many patients presenting for OHT are often deficient in antithrombin, resulting from continuous heparin infusions or hepatic dysfunction due to congestive hepatopathy [127]. Additional disease states can result in antithrombin deficiency, including hereditary antithrombin deficiency, sepsis, acute disseminated intravascular coagulation, and use of extracorporeal circuits. In patients with hypercoagulability or reduced antithrombin responsiveness, an increased dose of heparin or repletion with recombinant antithrombin is often necessary to achieve a therapeutic ACT. To date, no studies are known to have assessed the minimum level of antithrombin required for anticoagulant activity with heparin.

To further cloud the milieu, unfractionated heparin (UFH) is a mixture of polysaccharide chains with molecular weights ranging from 3000 to 30,000 Daltons, with a mean molecular weight of approximately 15,000 Daltons [128]. This heterogeneity is due to the different lengths and sulfation patterns of the polysaccharide chains, which influence the drug's pharmacodynamics. As a result, only about one third of heparin molecules have anticoagulation activity. The length of heparin molecules influences their clearance from the circulation, with higher-molecular-weight species being cleared more rapidly than lower-molecular-weight species. This results in a differential clearance, which leads to a faster clearance of lower-molecular-weight molecules, thus affecting the relationship between plasma heparin concentration and anticoagulant activity [128].

During CPB, an overestimation of heparin concentration may occur when using the ACT alone. Falsely elevated ACT values can be a result of hypothermia, reduced hemoglobin concentration, hypofibrinogenemia, and pharmacologic agents that are not associated with a concomitant increase in heparin level [126]. While anti-Xa activity is the gold standard for measurement of heparin-related anticoagulant effect, the test is not suitable for point-of-care testing, given the need for the test to be performed in the laboratory and the delay in obtaining results.

The primary contraindication to the use of heparin for CPB is a history of heparin-induced thrombocytopenia (HIT) and hypersensitivity to heparin. The Society of Thoracic Surgeons (STS), the Society of Cardiovascular Anesthesiologists (SCA), and the American Society of Extracorporeal Technology (AmSECT) recommend bivalirudin as a safe and effective alternative to heparin in these cases [126]. However, its anticoagulant effects can be challenging to reverse at the end of CPB, as there is no specific reversal agent for bivalirudin. Some investigational approaches that may allow the use of heparin in patients with HIT include performing preoperative plasma exchange to remove the offending antibodies, along with intravenous immunoglobulin (IVIg) administration to antagonize remaining antibodies, or directly inhibiting platelet activation using the rapidly acting P2Y12 inhibitor, cangrelor (The Medicines Company, Parsippany, NJ, USA) [129, 130]. Even in the absence of HIT or use of bivalirudin, a multifaceted approach is often required to manage coagulopathy and excessive bleeding after separation from bypass. This approach starts with hemostatic resuscitation with fresh frozen plasma, cryoprecipitate, and platelets, ideally using a data-driven approach using labs drawn while on bypass and point-of-care thromboelastography. In the event of uncontrollable

bleeding, additional therapies may include the use of recombinant activated factor VII, modified ultrafiltration, and hemodialysis [126].

Weaning from Cardiopulmonary Bypass

The primary objective of weaning from CPB is to transition from mechanical support to the native cardiac function to supply adequate blood flow and systemic perfusion. Following completion of the anastomoses, the patient is rewarmed to normothermia, and the heart is reperfused and filled with warm, oxygenated blood. Simultaneously, the ventilator is turned back on. The heart is evacuated of air under the guidance of transesophageal echocardiography. Inotropic agents and pulmonary vasodilators are initiated to support contractility and reduce the afterload of the right heart. Vasopressors are started to maintain adequate perfusion pressure. Prophylactic epicardial pacing wires are placed in the atrium and ventricle in the event of bradyarrythmias. The extended ischemic time of the graft often necessitates a longer period of reperfusion compared to typical cardiac surgery before attempting to wean from bypass, and the weaning process itself is often more gradual to ensure adequate graft function and prevent overloading a dysfunctional heart. Maintaining robust coronary perfusion is critical during this time and the early post-reperfusion period due to residual deleterious effects of the prolonged ischemia and high myocardial demand. Initiation of inotropes is common and does not necessarily indicate graft dysfunction, as recovery of the stunned myocardium may continue until well after ICU transfer [131]. However, mechanical circulatory support should be initiated early if there is failure to wean from CPB or evidence of severe allograft failure as indicated by the requirement for multiple high-dose inotropic agents and pulmonary vasodilator therapy. Return to bypass may also be considered if other mechanical circulatory support is not available or if there is a surgical revision that requires it, so the anesthesia team should always be prepared with additional heparin and bridging emergency drugs to facilitate reinitiation. A checklist of important factors to consider and discuss prior to weaning from bypass can be very helpful for preventing errors and ensuring preparation for the next phase of the surgery, and an example is provided in Table 5.6.

Table 5.6 Pre-weaning from the CPB checklist

Discuss any procedure- or patient-specific concerns
Confirm that the warming device(s) are on and set appropriately
Confirm that the ventilator is on and that the anesthetic is being delivered
Ensure that core body temperature is >36 °C
Review vasopressor, inotropes, and other required drips
If temporary pacing is utilized, confirm settings and lead function
Discuss the need and strategy for de-airing the heart prior to separation
Review relevant TEE findings
Discuss the plan for MCS and confirm the availability of necessary equipment
Ensure adequate time has elapsed from removal of the cross-clamp to allow sufficient reperfusion
Confirm desired filling pressures and systemic BP after weaning

Protamine for Heparin Reversal

Protamine sulfate is given at the end of CPB, just prior to decannulation, to reverse the anticoagulant effect of heparin. It is a polycationic protein derived from salmon sperm that works to neutralize heparin by forming a stable complex through ionic bonding [132]. There are several approaches to protamine dosing. The common recommendation is a fixed 1:1 (1 mg protamine to every 100 IU of heparin) ratio based on the initial dose of heparin required to establish adequate anticoagulation for CPB [133, 134]. This dosing regimen is most suitable for procedures with a CPB duration of less than 90 min [135]. For longer durations, the clearance of heparin from the circulation must be considered, and point-of-care measurements such as the heparin dose–response curve (HDRC) or heparin–protamine titration (HPT) can be used to estimate the necessary dose of protamine [126]. Point-of-care thromboelastography can also detect the residual effect of heparin after reversal, which aids in differentiating inadequate reversal from other sources of coagulopathy. The STS/SCA/AmSECT guidelines recommend limiting the dose of protamine/heparin to less than 2.6:1 [126]. Paradoxically, exceeding the recommended upper limit, especially above 5:1, can result in coagulopathy and prolonged ACT. There are several mechanisms behind this effect, including impairment of platelet function and aggregation, as well as a direct anticoagulant effect caused by the inhibition of factor V, which subsequently reduces thrombin generation [136, 137].

Protamine acts rapidly, with its heparin-neutralizing effects becoming evident within 5 min of administration [138]. Despite this quick onset, heparin rebound can occur hours after seemingly adequate heparin reversal has been achieved. This phenomenon is typically observed in cases involving high heparin doses, usually exceeding 400 IU/kg [126]. The mechanism is thought to involve heparin sequestration by fat tissue and plasma proteins. Once the circulating heparin is neutralized, the concentration gradient causes the sequestered heparin to gradually re-enter the plasma. This release of heparin persists beyond the duration of protamine's effect, as protamine has a short half-life of only 7–7.5 min [139]. Therefore, for patients requiring high heparin doses and undergoing prolonged CPB, a low-dose protamine infusion of 25 mg/h for up to 6 h after CPB cessation may be considered to mitigate this risk [126].

Protamine Reactions

Hemodynamically consequential adverse reactions to protamine that result in can generally be categorized into three types, each with its distinct mechanism and clinical presentation—isolated systemic hypotension, anaphylactic reactions, and, in severe cases, pulmonary hypertension. Rapid administration of protamine can stimulate endothelial release of nitric oxide and cyclic guanosine monophosphate, thereby resulting in isolated systemic hypotension [126, 138]. Based on the pathophysiology of the condition, this form of non-immunogenic cause of hypotension is typically treated with vasopressors. Refractory hypotension may require free radical scavengers such as methylene blue and hydroxocobalamin.

Although protamine can induce direct human connective tissue mast cell degranulation, this occurs at protamine doses that are not used in clinical practice [140].

Therefore, anaphylactoid reactions are not clinically applicable in this setting. In contrast, IgE-mediated anaphylaxis has an incidence of 0.19–0.69% [141]. Risk factors for anaphylaxis are fish protein allergy, diabetic patients with protamine-insulin treatment, prior protamine exposure, and vasectomy leading to circulating anti-protamine antibodies [142]. In addition to distributive shock, patients may also demonstrate angioedema, rashes, and bronchospasm. Therapeutic options include antihistamines, corticosteroids, and epinephrine [142].

Of the three conditions, immune-mediated pulmonary hypertension is perhaps the most severe complication following protamine administration. Protamine complexes with heparin thereafter, triggering complement activation leading to the generation of anaphylatoxin and neutrophil-mediated release of thromboxane [132]. As the pulmonary vascular resistance increases, the right heart fails to fill the left ventricle and thereby culminates in cardiogenic shock. Pulmonary vasodilators and right heart inotropic support are the treatment of choice.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) is essential during the pre-transplant and post-transplant phases of the surgery and is utilized in heart transplant patients without prohibitive risk (see Table 5.7 for a full list of contraindications). Following induction of anesthesia, TEE can be used to guide placement of a PAC, which can be particularly challenging given that this patient cohort often presents with pulmonary hypertension and severe tricuspid hypertension. According to the American Society of Echocardiography (ASE) guidelines, pre-transplant evaluation included examination for intracardiac blood stasis, as decreased blood flow may result in the formation of thrombus in the LV or LA of the recipient heart [144]. The presence of thrombus should be noted, as manual manipulation of the heart can cause thromboembolic events. Pre-transplant exam should also assess the ascending aorta for the presence of atherosclerotic disease that may influence cannulation, cross-clamp, or anastomostic sites [144].

Table 5.7 Contraindications to transesophageal echocardiography

Absolute contraindications	Relative contraindications
Perforated viscus	History of radiation to the neck and mediastinum
Esophageal stricture	History of GI surgery
Esophageal tumor	Recent upper GI bleed
Esophageal perforation, laceration	Barrett's esophagus
Esophageal diverticulum	History of dysphagia
Active upper GI bleed	Restriction of neck mobility (severe cervical arthritism, atlantoaxial joint disease)
	Symptomatic hiatal hernia
	Esophageal varices
	Coagulopathy, thrombocytopenia
	Active esophagitis
	Active peptic ulcer disease

Reproduced with permission from Hahn et al. [143], Elsevier, 2013

ASE guidelines recommend that post-transplant evaluation should include a comprehensive examination of biventricular function, valve function, and anastomotic sites [144]. LV, RV, or biventricular dysfunction can occur in up to 30% of patients [145]. The RV is generally more susceptible to injuries during OHT compared to the LV [146]. Several factors contribute to this vulnerability. Firstly, the RV has a thinner wall, which can lead to more significant temperature fluctuations during preservation. Secondly, a higher percentage of the RV's mass undergoes ischemia/reperfusion injury. Thirdly, the RV is positioned higher in the open-chest surgical setting, which means there is a possibility that it can be heated by the operating room atmosphere during implantation. Lastly, the right coronary ostium remains at the top of the circulation after graft implantation, thus making it more vulnerable to air embolism.

Tricuspid regurgitation (TR) is the most common valvular abnormality after HT, with an estimated incidence of 19–84% [147, 148]. Following TR in terms of incidence, other reported valvular dysfunction, in descending order of incidence, are pulmonary regurgitation, mitral regurgitation, and aortic regurgitation [147, 149]. The etiology of TR can be separated into functional and anatomic. In functional TR, the regurgitant jet is central and caused by distortion of the atrioventricular annular ring and malcoaptation of the valve leaflets [147]. Right atrial enlargement resulting from the combined atria in the biatrial technique is thought to exacerbate the development of TR by increasing wall tension and tricuspid annular size. However, bicaval anastomosis alone is insufficient to prevent the development of TR since tension along the bicaval anastomosis can similarly lead to wall tension and tricuspid annular distortion [148]. When the biatrial technique is utilized, a mismatch of the donor heart and recipient atrial size can also result in TR, particularly if the ratio of donor to recipient anterior wall length is >1 [150]. Additional causes of functional TR can be attributed to pulmonary hypertension and RV dysfunction [147, 149].

Intraoperative moderate to severe TR has been demonstrated to impact long-term survival. However, it is uncertain whether the presence of moderate to severe TR necessitates repair during OHT. An estimated 21% of patients have moderate to severe TR following separation from CPB; however, the majority of this cohort demonstrates regression of TR to mild or none, while only 1% undergo delayed TV repair. A prospective controlled study of bicaval OHT patients demonstrated that there was no difference in 6-year survival with the use of prophylactic tricuspid annuloplasty prior to implantation. However, there was a statistically significant improvement in cardiac mortality, the average amount of tricuspid regurgitation, and postoperative serum creatinine [151]. There are no current studies demonstrating the efficacy of prophylactic annuloplasty with the use of the biatrial technique.

Assessment of the anastomotic sites of the great vessels (ascending aorta, main pulmonary artery, IVC, and SVC) should show no discrete areas of narrowing by 2D echocardiography and demonstrate laminar flow by color flow Doppler. Pulmonary artery stenosis can be a result of size mismatch or suture constriction [144]. This is a reversible cause of RV outflow obstruction and dysfunction that must be evaluated prior to chest closure. IVC anastomotic stenosis can result in

venous hypertension and congestion of the liver and kidneys. SVC anastomotic stenosis can result in SVC syndrome, presenting as facial edema, distended neck and chest veins, airway edema, headache, and confusion [152]. The LA anastomotic suture line may appear as a prominent ridge along the posterior wall that does not necessarily produce a clinical effect. However, the presence of flow acceleration and elevated flow velocities on spectral Doppler can be an indicator of stenotic left atrial suture lines and flow obstruction, which can result in pulmonary venous hypertension and RV failure [144].

A summary of recommended TEE views and modalities is provided in Table 5.8.

Table 5.8 Recommended TEE imaging for heart transplantation

Imaging goals	Imaging views	Imaging modalities
Preprocedure		
Ascending aorta and main PA Rule out masses/thrombus at the future anastomotic site	ME: ascending aorta SAX/LAX UE: aortic arch SAX TG: basal RV, RV inflow/outflow Epicardial	2D, bi/multiplane imaging 3D
IVC and SVC Rule out masses/thrombus at the future anastomotic site	ME: bicaval (slight probe withdrawal for SVC, slight probe advancement for IVC), ascending SAX	2D, bi/multiplane imaging CFD
Evaluate for intracardiac thrombus LAA LV apex	ME: 4/5Ch, MC, 2Ch, LAX	2D, bi/multiplane imaging 3D Spectral Doppler (LAA velocities)
Extracardiac structures Pleural effusions Ascites	ME: 4/5Ch (turn probe left for left pleural space, turn probe right for right pleural space) TG views for evaluation of ascites	2D
Postprocedure		
Left ventricle Size Systolic function: Regional (wall motion abnormalities) and global (FAC, SV, EF) Diastolic function (TMF, mitral annulus velocities)	ME: 4/5Ch, 2Ch, LAX TG: basal SAX, mid-SAX, 2Ch, deep 5Ch	2D, bi/multiplane imaging 3D Spectral Doppler Tissue Doppler
Right ventricle Size (IVS and motion) Systolic function (free wall, FAC, TAPSE, RVOT SV)	ME: 4Ch, RV inflow/outflow TG: basal RV, RV inflow, RV inflow/outflow	2D, bi/multiplane imaging CFD Spectral Doppler
Comprehensive evaluation of all valves	ME and TG views	2D CFD 3D Spectral Doppler
Ascending aorta and main PA anastomosis Rule out stenosis/thrombus (absence of flow acceleration)	ME: ascending aorta SAX/LAX UE: aortic arch SAX TG: basal RV, RV inflow/outflow Epicardial	2D, bi/multiplane imaging CFD Spectral Doppler

(continued)

Table 5.8 (continued)

Imaging goals	Imaging views	Imaging modalities
IVC and SVC anastomosis Rule out stenosis/thrombus (absence of discrete narrowing, flow acceleration)	ME: bicaval (slight probe withdrawal for SVC, slight probe advancement for IVC), ascending SAX	2D, bi/multiplane imaging CFD
LA anastomosis Rule out stenosis (absence of flow acceleration)	ME: 4Ch, 2Ch, LAX	2D CFD

Adapted from Nicoara et al. [144], Elsevier, 2020
Abbreviations: *2CH* two-chamber, *4Ch* four-chamber, *5Ch* five-chamber, *2D* two-dimensional, *3D* three-dimensional, *CFD* color flow Doppler, *EF* ejection fraction, *FAC* fractional area change, *IVC* inferior vena cava, *IVS* interventricular septum, *LA* left atrium, *LAA* left atrial appendage, *LAX* long axis, *MC* mitral commissural, *ME* mid-esophageal, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow tract, *SAX* short axis, *SV* stroke volume, *SVC* superior vena cava, *TAPSE* tricuspid annular plane systolic excursion, *TG* transgastric, *UE* upper esophageal

Major Complications

Primary Graft Dysfunction

The complication of paramount concern during a heart transplant is failure of the graft itself, which is considered PGD when it occurs within 24 h of transplant and in the absence of another explanation. The International Society of Heart and Lung Transplant (ISHLT) published a report from a consensus conference that defines PGD as primarily affecting either the left ventricle (PGD-LV) or right ventricle (PGD-RV), though failure of one often leads to failure of the other. PGD differs from secondary graft dysfunction, a term used to denote cardiac dysfunction resulting from discernible causes such as hyperacute rejection, pulmonary hypertension, or known surgical complications [153]. PGD-LV can be further characterized as mild, moderate, or severe, with the latter recursively defined as dysfunction requiring MCS, not including IABP, to maintain systemic perfusion. There is no grading scale for PGD-RV resulting from the difficulty in quantifying RV dysfunction [153]. The pathogenesis of PGD is believed to be a consequence of multiple insults to the heart during the transplant process. Beginning at the time of brain death, the donor heart experiences a rapid surge in catecholamines from both endogenous and exogenous sources [153]. This influx of calcium leads to mitochondrial and cytosolic calcium overload. Consequently, programmed cell death and the activation of contractile proteins occur [154]. Simultaneously, the release of proinflammatory markers and fluctuations in serum hormone levels further impair myocardial contractility [155, 156]. Plasma levels of triiodothyronine, free thyroxine, antidiuretic hormone, cortisol, and insulin begin to decline within an hour following brain death, with several hormones reaching undetectable levels within 24 h [156]. The donor heart is then preserved in cold preservation fluid and transported on ice, which slows but

does not completely halt cellular metabolism [153]. Upon reperfusion, cardiac myocytes are exposed to oxygen-derived free radicals and an additional influx of calcium, intensifying the cumulative tissue damage [153].

The RADIAL score is the only validated predictive model for PGD [146, 153, 157]. The acronym stands for the six key variables considered in the assessment. Four of the six are related to the recipient: right artrial pressure (RAP) >10 mmHg, age > 60 years old, presence of diabetes, and inotrope dependence. The last two variables are donor age ≥ 30 years old and length of ischemic time of ≥240 min. The total score is obtained by adding one point for each of the present variables, with a significant increase in incidence with increasing score. Low score (RADIAL score 0–1), intermediate (RADIAL score 2), and high (RADIAL score > 2) correlated with PGD incidence of 12, 19, and 28%, respectively [157]. Additional risk factors for PGD are presented in Table 5.9. Severity definitions for PGD are further described in Table 5.10.

The use of intravenous levothyroxine in donors and even recipients is often used to prevent PGD, although recent evidence does not seem to support this. Based on the observation of neurohormonal disruptions, including levothyroxine, in the brain-dead donor, intravenous administration is believed to counteract myocardial energy depletion and prevent cardiogenic shock. The heart, in turn, would be more

Table 5.9 Risk factors for development of primary graft dysfunction [153, 157, 158]

Donor factors	Recipient factors	Surgical/procedural factors
Age ≥ 60	Age ≥ 30	Ischemic time
Cause of death (higher risk with intracerebral hemorrhage/ thrombosis)	Preoperative right atrial pressure ≥ 10 mmHg	Donor–recipient sex mismatch
Trauma	Mechanical support	Weight mismatch
Cardiac dysfunction	Congenital heart disease as etiology of heart failure	Non-cardiac organ donation
Inotropic support	Multiple reoperations	Experience of procurement team and center volume
Comorbidities: diabetes, hypertension	LVAD explant	Cardioplegia solution
Downtime of cardiac arrest	Comorbidities: renal dysfunction, liver dysfunction, diabetes	Increased blood transfusion requirement
Drug abuse: alcohol, cocaine, amphetamines	Ventilator dependence	Elective vs emergent transplant
Left ventricular hypertrophy	Multiorgan transplant	Longer cardiopulmonary bypass time
Valvular disease	Elevated pulmonary vascular resistance	
Hormone treatment	Allosensitization	
Coronary-artery disease, wall motion abnormalities on echocardiogram	Infection	
Hypernatremia	Retransplant	
	Inotrope dependence	

Reproduced with permission from Kobashigawa et al. [153], Elsevier, 2014

Table 5.10 ISHLT definitions of severity scale for primary graft dysfunction [153]

Type of PGD	Level of severity	Parameters for level of severity
PGD-LV	Mild	LVEF ≤40% by echocardiography, or RAP >15 mmHg, PCWP >20 mmHg, CI <2 L/min/m^2 (lasting more than 1 h) requiring low-dose inotropic support
	Moderate (must satisfy criteria 1 and 2)	LVEF ≤40%, or RAP >15 mmHg, PCWP >20 mmHg, CI <2 L/min/m2, hypotension with MAP <70 mmHg (lasting more than 1 h) Inotrope score > 10 or postoperative placement of IABP
	Severe	Dependence on left or biventricular MCS (e.g., ECMO, LVAD) excluding IABP
PGD-RV	Must satisfy criteria 1 and 2, or criterion 3 alone	RAP >15 mmHg, PCWP <15 mmHg, CI <2 L/min/m^2 TGP <15 mmHg and/or PASP <50 mmHg Postoperative placement of RVAP

Reproduced with permission from Kobashigawa et al. [153], Elsevier, 2014
Abbreviations: *RAP* right atrial pressure, *PCWP* pulmonary capillary wedge pressure, *MAP* mean arterial pressure, *TGP* transpulmonary gradient pressure; inotropic score: dopamine (×1), + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with medications dosed in micrograms/kg/min

suitable for donation and thus increase the number of organs transplanted from these donors, which early observational studies seemed to confirm. Similarly, a recipient might also receive intravenous levothyroxine if the donor had received it, based on the idea that the graft was accustomed to perhaps higher circulating T4 levels than typically present. However, a randomized trial involving 15 nationwide organ-procurement organizations (OPOs) and 852 donors found no difference in outcomes compared to placebo. Rates of transplantation of the donor heart, graft survival at 30 days, donor weaning from vasopressor therapy, donor ejection fraction, and number of organs transplanted per donor were nearly the same in both groups, with no statistical differences found. There were more adverse events in the donors on levothyroxine, including severe hypertension and tachycardia, which are likely direct effects from the infusion [159]. This remains a common practice, and there is a dearth of data for its use in recipients.

Inhaled pulmonary vasodilators like nitric oxide (NO) and the prostacyclin analog epoprostenol are mainstay treatments of pulmonary hypertension, which have been utilized for many years in heart transplants to prevent and treat PGD-RV. Unlike the LV, the RV is much more sensitive to afterload changes, and given how common pulmonary hypertension is in heart recipients, the graft RV is not adequately adapted to these elevated pressures. Therefore, the suggested benefit of prophylactic inhaled pulmonary vasodilators is to mitigate the afterload shock to the RV and prevent graft dysfunction. These agents are typically aerosolized to target their effect on the pulmonary vasculature, as intravenously administered prostacyclin analogs and phosphodiesterase inhibitors produce profound systemic vasodilation. They are usually initiated prior to separation from bypass and continued through the operative period and into the ICU admission, where they are slowly weaned off to prevent rebound pulmonary hypertension. Unfortunately, the results have been inconsistent

about their influence on outcomes. Some studies suggest they may lower pulmonary pressures and PVR while increasing cardiac index or RV ejection fraction, while a recent meta-analysis of their use in cardiac surgery patients showed no difference in RV failure compared to placebo [160]. Nonetheless, this area of research suffers from a lack of high-quality randomized trials with sufficient sample sizes, and the use of pulmonary vasodilators remains recommended by ISHLT and other organizations for the treatment of PGD-RV.

Head-to-head comparisons of the predominant inhaled pulmonary vasodilators have shown them to be more or less equivalent, so selection of a particular agent is largely dependent on the surgeon's experience and facility preference based on cost. A randomized double-blind trial of 231 patients undergoing either OHT or durable LVAD placement was randomized to receive either inhaled nitric oxide (iNO) or inhaled epoprostenol (iEPO) 15 min prior to separation from bypass. The researchers found a non-significant difference in the rate of severe RV failure requiring MCS, with an event rate of 25.0% in the iEPO group and 22.5% in the iNO group [161]. More recently, combinations of these agents have been explored to take advantage of complementary mechanisms of action and maximize clinical benefits. One such study retrospectively looked at the use of iEPO plus inhaled milrinone in cardiac surgery patients with pulmonary hypertension (PH) or evidence of RV dysfunction. Although the study was not powered for clinical outcomes, the authors reported significant improvements in hemodynamics that warrant further study [162].

There is a lack of comprehensive evidence and established guidelines for the management of PGD. ISHLT recognizes inotropic agents, systemic vasodilators, and inhaled pulmonary vasodilators as first-line treatment options for PGD. However, there is limited guidance on the optimal thresholds or sequence for initiating these therapies. Additionally, it should be noted that it is often challenging to differentiate whether the use of these pharmacological agents is part of routine post-heart transplant care or specifically intended for the treatment of PGD. Epinephrine is commonly used as a first-line inotrope given the advantage of additional alpha receptor activity for maintaining systemic blood pressure and coronary perfusion pressures. Dobutamine, milrinone or amrinone, and dopamine may also be employed, though there are no studies to date that have evaluated which of these may be preferred. The combination of a beta agonist like epinephrine or dobutamine, along with a phosphodiesterase inhibitor like milrinone or amrinone, has the potential to produce a synergistic effect as the latter prolongs the activity of the former by decreasing the elimination of cAMP, though this should be weighed against the significant systemic vasodilation caused by the phosphodiesterase inhibitors. By contrast, administering high doses of epinephrine and dobutamine may induce competitive inhibition at the beta receptor, leading to a less-than-additive effect [163].

Levosimendan (Simdax, Orion Corporation, Espoo, Finland) is an alternative inotrope that has been in use in Europe but is currently not FDA-approved in the United States and may prove helpful in the treatment of PGD. It is a calcium-sensitizing and ATP-sensitive potassium channel opener that results in positive inotropy, vasodilation, and cardioprotection [164]. A case study by Weis et al. followed 12 patients with PGD treated with levosimendan [165]. The patients showed a rapid

improvement in hemodynamic parameters, including blood pressure, cardiac output, and mean pulmonary arterial pressure. There was a reduction in inotropic requirement after 1 day of initiation, and no patients required MCS. The 30-day survival was reported as 93%; however, a subsequent follow-up study demonstrated a statistically significantly lower survival at 1 year and 3 years [166]. Its use has also been explored more broadly in cardiac surgery for the prevention and treatment of low cardiac output syndrome (LCOS)—a condition characterized by decreased cardiac function leading to reduced oxygen delivery and subsequent tissue hypoperfusion [167]. The LEVO-CTS trial, a multicenter, randomized, placebo-controlled study, explored the prophylactic use of levosimendan in patients with a left ventricular ejection fraction (LVEF) of ≤35% undergoing cardiac surgery to prevent LCOS [168]. The trial revealed that the levosimendan group experienced a statistically significant reduction in the incidence of LCOS. However, no differences were observed in 30-day mortality, the need for MCS, the incidence of myocardial infarction, or the occurrence of renal failure requiring dialysis. Similarly, the CHEETAH trial, a multicenter, randomized, double-blind, placebo-controlled study, aimed to evaluate whether levosimendan could enhance survival in patients with LCOS following cardiac surgery [169]. The study found that levosimendan did not improve 30-day survival rates compared to placebo.

When PGD is present beyond what can be treated with high-dose inotropes, MCS is the treatment of choice and has significantly improved survival rates, with 73–79% of patients now surviving to hospital discharge, compared to what was once a nearly fatal condition [113, 153, 170]. The precise timing or criteria used for MCS initiation remain to be determined, but recent studies have suggested a benefit to employing it early in dysfunction rather than as a rescue. A retrospective study of 80 patients who underwent RVAD placement associated with cardiac surgery looked at the mortality difference between so-called early and late initiation. They defined early RVAD placement as either part of the primary procedure or within 24 h of it, while the delayed cohort received an RVAD after the 24-h mark, with a median period of about 2 days. The survival between these two cohorts was drastically different, with 79% survival in the early group versus 46% in the delayed group at 90 days (Fig. 5.7) [171].

The choice of MCS in PGD varies significantly depending on patient and surgical factors, as well as device availability. In cases of PGD-LV, there is often sufficient time between recognition and decompensation to allow for a variety of MCS options based on the amount of support required, vascular access issues, and surgeon experience. However, in cases of rapid decompensation, as is often the case for PGD-RV, emergent initiation of MCS may be required, which limits the options to those immediately available. Return to CPB is always a consideration, but usually not preferred unless it is required for surgical repair, as tVAD and VA-ECMO can provide similar support but with the portability to leave the OR. Between these two options, VA-ECMO is recommended by the ISHLT given its biventricular support and oxygenation capabilities. One retrospective cohort study by Takeda et al. also found that VA-ECMO had a higher rate of successful weaning and graft recovery compared to the tVAD [113]. Percutaneous MCS

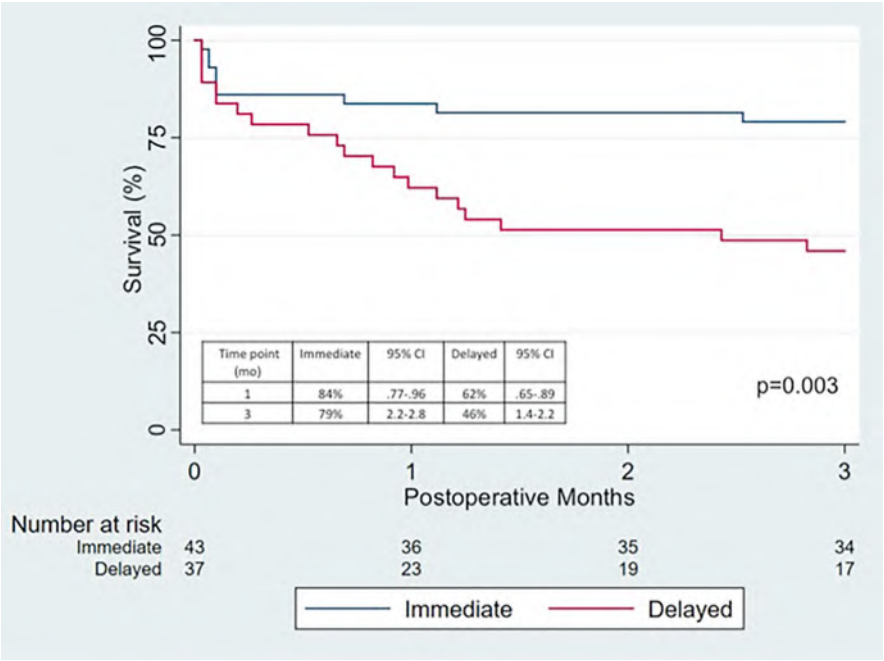

Fig. 5.7 Survival with immediate vs. delayed MCS for PGD after heart transplantation. (Reproduced with permission from Bhama et al. [171], Elsevier, 2018)

devices may also be considered but can take longer to initiate than VA-ECMO while providing less hemodynamic support. Nearly any device is viable, however, with sufficient planning and preparation; therefore, it is critically important that a plan for emergent MCS be discussed ahead of time. As good practice, this discussion should include the entire OR team and occur either during the initial patient safety time-out or prior to separation from bypass, and all required equipment should be confirmed well in advance of need.

Vasoplegic Syndrome

Vasoplegic syndrome (VS) is a state of persistent hypotension, in the setting of low systemic vascular resistance, necessitating use of vasopressors within the first 24–48 h following cardiac surgery. Diagnosis can be challenging because it often occurs alongside other etiologies, resulting in hypotension, such as hypovolemia and PGD; therefore, an adequate cardiac index should be identified before concluding the presence of VS. The pathogenesis is still being investigated but is thought to be due to cytokine release, adrenergic receptor desensitization, increased nitric oxide synthesis, activation of adenosine triphosphate-sensitive potassium channels, vascular smooth muscle cell membrane hyperpolarization, dysfunction of the

Table 5.11 Risk factors for vasoplegic syndrome [173, 174]

Patient-related factors	Surgery-related factors
Older age	Prolonged cardiopulmonary bypass time
Chronic kidney disease	Transfusion of blood products
Hypothyroidism	
Preoperative use of MCS	
Preoperative use of inotropic agents and vasodilators	

renin–angiotensin system, and injury to the endothelial glycocalyx [48, 172]. Risk factors for VS are presented in Table 5.11.

Norepinephrine is frequently recommended as the first-line agent for treatment of VS, followed by vasopressin [29]. Despite this recommendation, the Vasoplegic Shock after Cardiac Surgery (VANCS) trial lends support to the use of vasopressin as the first-line agent, as it was found to be associated with a lower occurrence of atrial fibrillation compared to norepinephrine. There were no differences in rates of digital ischemia, mesenteric ischemia, or myocardial infarction between the two treatment groups [175].

VS refractory to these agents can be followed by a single dose of methylene blue, but there are some notable contraindications that frequently preclude its use [29]. Patients with glucose-6-phosphatase dehydrogenase deficiency should not receive methylene blue, as it increases the risk for hemolysis. Similarly, methylene blue has been shown to precipitate serotonin syndrome and should be used with caution in patients on selective serotonin reuptake inhibitors, tricyclic antidepressants, linezolid, meperidine, fentanyl, tramadol, trazodone, bupropion, cocaine, or MDMA [176]. Hydroxocobalamin is an alternative nitric oxide modulator for patients with the aforementioned contraindications, though its effect on dialysate color can confuse the blood leak detector of many renal replacement and dialysis machines.

Angiotensin II (Giapreza; La Jolla Pharmaceutical Company, San Diego, CA, USA) is another treatment for vasodilatory shock, due to its potent vasoconstrictive properties and its role in the RAAS. The use of angiotensin II in this context was significantly advanced by the findings of the angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) trial, which demonstrated that angiotensin II effectively increased blood pressure in patients with vasodilatory shock who were not responsive to high doses of conventional vasopressors. The use of angiotensin II was not found to be associated with an increase in serious adverse events, including death, multiorgan failure, cardiac arrest, and respiratory failure. A post hoc analysis of the ATHOS-3 trial in 16 vasoplegic patients following cardiac surgery demonstrated similar safety and efficacy results [177]. The use of angiotensin II may be particularly beneficial for patients undergoing cardiac surgery. During CPB, blood is diverted away from the lungs, bypassing the primary site of angiotensin-converting enzyme activity. Consequently, the accumulated angiotensin I is converted by endopeptidases into vasodilatory molecules, including angiotensin 1–7 [177]. As such, the supplementation of exogenous angiotensin II can help counteract this effect.

The main barriers to its use are an unclear risk of thrombosis, as well as its very high cost relative to other vasopressors.

Management of Dysrhythmias

Dysrhythmias are very common after a heart transplant, and their management can be challenging in the context of autonomic denervation and myocardial stunning. Atrial tachyarrhythmias are estimated to occur in about 50% of heart recipients at some point, with the main risk factors including biatrial technique, cold ischemic time > 240 min, and graft dysfunction [174, 178]. While atrial fibrillation and flutter are somewhat easier to recognize, supraventricular tachycardia (SVT) can present much more of a challenge given the naturally higher resting heart rate of the post-transplant heart. The main giveaway for this condition is beat-to-beat rapid changes in heart rate as the SVT initiates and terminates suddenly, as well as extreme consistency in rate. This is in comparison to a higher-than-normal sinus rhythm that varies in rate slightly from beat to beat and with larger changes occurring more gradually. Unstable rhythms should be treated immediately with synchronized cardioversion to restore a perfusing rhythm and minimize ischemia to the graft that is characteristic of these episodes due to high myocardial oxygen demand and reduced coronary perfusion pressure. In stable situations, options include medical management and anti-tachycardic pacing. The latter is achieved by pacing an epicardial atrial lead over the rate of the dysrhythmia in an effort to induce the conduction system into an absolute refractory period that will terminate the dysrhythmia cycle. Medical management typically employs class I, III, and IV antiarrhythmics like lidocaine, amiodarone, and verapamil, respectively. Beta-blockers should be used with extreme caution, if at all, due to the graft's dependence on circulating adrenergic levels for heart rate in lieu of autonomic nerves, their negative inotropic activity, and the exquisite sensitivity to these agents in the freshly transplanted heart. Adenosine is similarly used with caution, although some recent studies have called into question whether hesitancy over its use is warranted [178].

Bradyarrythmias and heart block are also quite common, owing to lack of autonomic nerve input, conduction system ischemia or injury, and potentially resulting from prophylactic tricuspid valve annuloplasty, with some type of atrioventricular (AV) block occurring in about 10% of heart transplants [179]. Unstable bradycardia or complete heart block (CHB) can usually be treated quickly and effectively with epicardial pacing. However, when these conditions arise from graft ischemia, pacing may be ineffective until perfusion is restored. The anesthesia team must also be aware that if pacing is employed, as temporary epicardial leads are easily shorted by blood or dislodged during surgical manipulation. Common medical therapies, such as glycopyrrolate and atropine, are ineffective for a transplanted heart, as they have no parasympathetic activity to block. Instead, heart rate can be increased with a beta 1 agonist like epinephrine, or more effectively with dobutamine.

Ventricular dysrhythmias, such as premature ventricular contractions, or the more dreaded ventricular tachycardia (VT) and fibrillation (VF), can arise from

graft ischemia, myocardial irritation, and direct surgical wire placement or manipulation of the heart. Instability should be promptly treated with synchronized cardioversion in the setting of VT or defibrillation for VF. Medical therapy includes class I and III antiarrhythmics like lidocaine and amiodarone; however, care should be taken to prevent rapid administration of the latter, as it can precipitate hypotension. Determining the underlying cause of the ventricular dysrhythmia is a high priority, as many etiologies are intervenable, and particularly ischemia should not go unrecognized. Failure to quickly treat an unstable ventricular may require return to cardiopulmonary bypass or VA-ECMO to prevent significant injury to the graft.

Conclusion

Heart transplantation is an extremely valuable intervention to extend the lives of patients with advanced heart failure, but it comes with significant challenges for the anesthesiologist. Meticulous pre-listing evaluation is needed to identify impactful comorbidities, optimize therapy, and assess the need for a combined transplant. In addition to the overt cardiac pathology, preoperative management of anticoagulation and antiplatelet therapy, CIEDs, and MCS, among other factors, is critical for patient safety and procedural success. The conduct of the pre-bypass anesthetic must also consider the risk of exacerbating already very poor cardiac function through hypotension or unchecked volume administration, as well as the potential for hemorrhage in the surgically complex patient. Finally, the post-bypass period is fraught with many complications that require quick recognition and specialized care to preserve graft function and prevent further complications. Ongoing research in this field is leading to rapid development in care that also demands continued learning and growth, but this chapter has covered the foundations of knowledge needed to tackle all these challenges and will hopefully serve as a springboard into further study.

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Anesthesia for Lung Transplantation

6

Kitae Chang and Mario Pimentel

Background

The history of lung transplantation dates to the 1940s and 1950s, with the first procedures performed on canines [1, 2]. These procedures paved the way for the first human single-lung transplant to be performed on a 58-year-old male with lung cancer and emphysema by Dr. Hardy in 1963 at the University of Mississippi Medical Center [3]. Unfortunately, the patient passed 18 days after the surgery due to complications. Most early attempts at lung transplantation had similarly untoward outcomes due to infection, poor surgical techniques, and the lack of effective immunosuppressive drugs to prevent organ rejection.

With the discovery of cyclosporine in 1972 and its approval for human use in the early 1980s, there was a significant increase in graft survival rates [1, 4]. In 1983, one of the first notable markers of progress was achieved by Dr. Cooper and his group at Toronto, who performed the first successful single-lung transplants (SLTs) in patients with pulmonary fibrosis, who were immunosuppressed postoperatively with cyclosporine [5, 6]. Remarkably, multiple patients survived for far longer than previously observed. A few years later, in 1988, the same group demonstrated the first successful bilateral-orthotopic lung transplant (BOLT) using a novel sequential technique that avoided cardiopulmonary bypass (CPB) [7]. These advancements, alongside improvements in surgical techniques, donor organ preservation, and

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post-transplant care, have established lung transplantation as the therapeutic option for advanced lung disease (ALD) today.

Parallel to these developments, approaches to anesthesia for these complex surgeries have also evolved. In the early days, anesthesia for lung transplant surgery faced significant challenges, particularly in managing oxygenation and ventilation during the operation. The integration of extracorporeal life support (ECLS) and improved ventilatory strategies has helped overcome some of these issues. Today, lung transplant anesthesiology involves a multidisciplinary approach to optimize outcomes and mitigate complications of allograft rejection and multiorgan injury. Despite the progress made in lung transplantation, this procedure remains one of the most technically challenging and physiologically demanding forms of solid organ transplantation. This chapter will discuss the key perioperative considerations relevant to anesthetic management during lung transplantations, including preoperative assessment, intraoperative management, and postoperative care.

Indications

Lung transplantation is indicated for patients with advanced lung disease who are refractory to maximal medical therapy and have both a poor prognosis and significantly impaired quality of life [8]. The International Society for Heart and Lung Transplantation (ISHLT) has published consensus guidelines to help clinicians identify suitable candidates for transplantation [9]. According to these guidelines, lung transplantation should be considered in patients with chronic end-stage lung disease (ESLD) who have an estimated ≥50% risk of death from their underlying pulmonary condition within 2 years, but who also have a > 80% chance of expected post-transplant survival of at least 5 years, assuming adequate graft function. The ISHLT emphasizes the importance of early referral to transplant centers, allowing for timely evaluation and optimization of modifiable risk factors [8, 9]. The most common indications for lung transplant include interstitial lung disease, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pulmonary arterial hypertension. More recently, severe, irreversible pulmonary fibrosis following COVID-19 has emerged as an additional indication for lung transplantation in carefully selected patients [9].

Contraindications

The ISHLT guidelines outline absolute and relative contraindications to lung transplantation, emphasizing that while absolute contraindications are generally incompatible with successful outcomes, relative contraindications should be evaluated in the context of overall risk. Absolute contraindications include recent malignancy with high risk of recurrence, uncontrolled extrapulmonary infection, active tuberculosis, significant dysfunction of other organs (renal dysfunction with a glomerular filtration rate (GFR) below 40 mL/min/1.73 m^2,

recent stroke or myocardial infarction, cirrhosis with portal hypertension), active substance use (including tobacco and cannabis), progressive cognitive impairment, limited functional status (non-ambulatory) or poor rehabilitation potential, repeated medication nonadherence, lack of willingness or acceptance of transplant, and lack of a support team (Table 6.1). Relative or high-risk conditions include advanced age (>70 years), BMI extremes (>35 or <16 kg/m^2), significant coronary or cerebrovascular disease, psychiatric illness, colonization with resistant organisms, and the need for mechanical ventilation (Table 6.1). Many of these factors, although not individually prohibitive, may collectively increase the risk of poor post-transplant outcomes. Transplant centers are encouraged to assess such risks in aggregate and consider referring complex cases to specialized programs [9, 10].

Table 6.1 Absolute and relative contraindications for lung transplantation

Absolute contraindications:	Lack of patient willingness or acceptance of transplant Malignancy with high recurrence risk Significant major organ dysfunction other than the lungs GFR <40 mL/min/1.73 m^2 unless considered for multiorgan transplant Liver cirrhosis, unless considered for multiorgan transplant Unstable medical conditions (shock, myocardial infarction, stroke) Uncontrolled bleeding and coagulopathy Uncontrolled infection with multidrug-resistant bacteria Uncontrolled HIV/hepatitis with end-organ damage Active tuberculosis Active drug abuse, including alcohol, cannabis, smoking, and vaping Progressive cognitive impairment Untreated severe psychiatric illness Lack of a support team History of medication nonadherence Limited functional status or rehabilitation potential
Relative contraindications:	Age > 70 years BMI extremes (>35 or < 16 kg/m^2) Mechanical ventilation and ECMO Severe malnutrition Sepsis Hepatitis without liver damage/HIV with undetectable viral load Severe coronary artery disease Reduced ejection fraction <40% Significant chest wall or spinal deformity expected to cause restriction after transplant Extensive previous chest surgery Untreated hematological disorders Uncontrolled type 2 diabetes and hypertension Severe esophageal dysmotility A psychiatric or psychological condition that has the potential to affect medical care Lack of understanding of disease and/or transplant despite teaching Unreliable support system

Adapted from the 2021 ISHLT consensus statement [8]

Extracorporeal membrane oxygenation (ECMO), once considered a contraindication to transplantation, is now increasingly used as a bridge to transplant in select patients. This change resulted from the implementation of the Lung Allocation Score (LAS) system in 2005, which allocated organs based on disease severity rather than waitlist time. Awake and ambulatory ECMO, when feasible, has been associated with improved outcomes and is preferred over sedation and intubation. While ECMO is not an absolute contraindication, it remains a marker of substantially increased risk and should be reserved for carefully selected candidates at experienced centers. Similarly, mechanical ventilation is associated with higher perioperative morbidity and mortality but does not preclude transplant in appropriately evaluated patients [9, 10].

Preoperative Considerations

Recipient Selection

Patient selection for lung transplantation involves a comprehensive, multidisciplinary evaluation aimed at identifying candidates most likely to benefit in terms of both survival and quality of life. Appropriate selection is crucial in the context of a donor organ shortage, given the limited pool of candidates. The decision to list a patient involves careful assessment of disease severity, comorbidities, functional status, and potential for post-transplant recovery. In the United States, since 2005, the LAS system has been used to prioritize candidates based on predicted survival benefit, balancing urgency and expected post-transplant outcomes. Before the introduction of the LAS system, organs were allocated based on waitlist time rather than disease severity. Studies have shown that patients with LAS scores in the moderate range (50–79) derive the most significant net survival benefit [9, 10].

The LAS incorporates a combination of clinical variables that predict both waitlist mortality and post-transplant outcomes, including age, BMI, underlying diagnosis, pulmonary function tests (PFTs), oxygen requirements, 6-min walk test (6-MWT), need for mechanical ventilation, pulmonary artery pressures, cardiac output, serum creatinine, bilirubin, and functional status. By quantifying both urgency and benefit, the LAS aims to allocate donor lungs to those with the highest net survival advantage. The ISHLT emphasizes early referral to transplant centers, even before a patient meets listing criteria, to allow time to optimize comorbidities, provide psychosocial support, and assess candidacy for potential bridging strategies, such as awake ECMO.

Recipient Assessment

A careful and comprehensive preoperative evaluation of lung patients is not only necessary for perioperative planning, but also to minimize avoidable complications and ensure higher success of the transplantation. Pre-transplant assessment of

potential recipients is a comprehensive, meticulous, and multidisciplinary process that is more extensive than a typical pre-anesthetic evaluation, given the severity of patients' baseline lung disease, as well as the increasing age and broader range of comorbidities among recipients [11]. The following sections will discuss specific considerations and recommendations, organized by organ systems.

Neurological and Psychiatric Assessment

Studies have reported postoperative neurological complications (e.g., stroke) with an incidence as high as 80% in lung transplant recipients [12]. When these events occur, patients experience higher mortality rates [12, 13]. Delirium, which is commonly observed in critically ill patients, impacts almost half of patients who undergo lung transplantation and has been shown to be associated with a tendency for primary graft dysfunction (PGD) as well as decreased survival [14]. Risk factors most strongly associated with postoperative delirium include patient-specific characteristics, such as older age and poor baseline cognition [15]. Poor neurocognitive function is also predictive of poorer medication adherence, which has been linked to poorer outcomes. As such, establishing a detailed preoperative neurological exam, including an assessment of the cognitive status, is particularly important for lung transplant recipients. The neurological exam should also be comprehensive and well documented, as the risk for stroke is increased, as is the likelihood that these patients will require exam-obscuring sedation in the immediate postoperative period. In patients with higher risk, it is reasonable to obtain diagnostic studies (e.g., carotid duplex ultrasonography) to assess the severity of carotid disease and plan for pre-transplant intervention to mitigate the perioperative risk of stroke.

Regarding baseline psychiatric illness as a predictor for post-transplant mortality, the reported findings in the literature have been mixed. Earlier studies showed that increased baseline depressive symptoms were associated with an increased risk of mortality following transplant [16]. At the same time, a recent investigation did not find a relationship between preoperative anxiety or depression and decreased postoperative survival [17]. Nevertheless, given that a significant proportion of lung transplant patients may have acquired depression in the setting of their severe illness, it is essential to review medications they may be taking before surgery and consider restarting them as soon as it is feasible during recovery.

Pulmonary Assessment

Although the primary lung disease may no longer affect patients following lung transplantation, a thorough pulmonary assessment is an essential component of the preoperative evaluation. To safely manage patients intraoperatively, it is imperative to understand the recipient's underlying lung pathology and its implications for hemodynamic stability and ventilation management. A comprehensive pre-surgery workup includes PFTs, which measure lung volume capacities, the diffusion capacity of the lungs for carbon monoxide (DLCO), a 6MWT, and imaging studies via multiple modalities. Both chest radiographs (CXRs) and computed tomography (CT) scans of the chest enable the identification of structural abnormalities and the surveying of anatomy (e.g., chest cavity dimensions),

which can assist with surgical planning. Additionally, right heart catheterization (RHC) is commonly sought to evaluate for pulmonary hypertension and right ventricular function. Although measures of pulmonary artery systolic pressures (PASPs) can also be obtained with echocardiography, they may be less accurate compared to PASP as measured with right heart catheterization (RHC) [18]. To effectively support the physiological consequences of pulmonary hypertension, it is essential to understand the underlying etiology and distinguish between precapillary and postcapillary causes. Precapillary pulmonary hypertension originates from disease in the pulmonary arterioles and small vessels preceding the capillary beds and has a pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg. Postcapillary pulmonary hypertension results from high left-sided heart pressures, a PAWP greater than 15 mmHg, that may be due to left ventricular heart failure or valvular disease.

With more lung transplant candidates being bridged to surgery with venovenous (VV) ECMO [19], it is crucial to recognize that their pulmonary assessments may evolve through the course of their "pre-habilitation." While the patient is admitted to the intensive care unit (ICU), their gas exchange status can be monitored using serial arterial blood gas (ABG) measurements. Additionally, daily CXRs, in combination with supportive laboratory and clinical findings, should be used to screen for and appropriately treat hospital-acquired infections.

Cardiovascular Assessment

A collaborative approach, involving pulmonologists, cardiologists, anesthesiologists, and cardiothoracic surgeons, is taken before lung transplant surgery. Most components of the assessment will begin far in advance of the surgery to identify and reduce mortality-increasing risk factors, thereby maximizing optimal outcomes. Among the cardiac comorbidities that affect patients with ESLD, the conditions that must be screened for include coronary artery disease (CAD), right ventricular dysfunction, and arrhythmias.

There is a high prevalence of CAD in lung transplant recipients, even in those without traditional risk factors [9, 20]. The diagnostic workup for CAD includes a combination of information from a patient's history (e.g., symptoms such as angina, dyspnea on exertion, and chest pain) and non-invasive and invasive tests. Some non-invasive testing that should be considered includes a 12-lead electrocardiogram (ECG) to identify signs of ischemia, transthoracic echocardiography (TTE) to assess for regional wall motion abnormalities (RWMAs), and stress tests to detect reversible ischemia. Although cardiopulmonary exercise testing (CPET) is typically pursued to diagnose early signs of ischemic cardiac disease, its use in the preoperative evaluation of lung transplant patients is challenged by the poor pulmonary reserve of these patients. A more tolerable exercise test is the 6MWT, which is included in the LAS system score used to list patients for transplant. Performing left heart catheterization (LHC) is widely supported, especially in older patients, despite a lack of clear consensus in guidelines [21, 22]. While CAD was previously considered a contraindication for lung transplantation, over the last 10 years, evidence has emerged that

preoperative percutaneous coronary interventions (PCIs) or concurrent coronary artery bypass graft (CABG) surgery may not portend increased postoperative mortality [23].

Patients with a long-standing history of pulmonary hypertension are at high risk for right ventricular hypertrophy and dysfunction. Oftentimes, given that the reduced cardiac function is secondary to the underlying lung disease, in a patient who otherwise has no other cardiac pathology, some degree of right heart dysfunction can be anticipated after transplantation, particularly if the diagnosis of severe pulmonary hypertension by RHC is known before surgery. Formal assessment can be performed with an RHC, which can also provide measurements of cardiac index (CI), pulmonary artery (PA) pressures, calculated pulmonary vascular resistance (PVR), and calculated pulmonary arterial pulsatility index (PAPi). These findings can be supplemented with less invasive diagnostics, such as ECG, which can show evidence of right-axis deviation, and TTE, which may reveal quantifiable baseline structural and functional deficits that can be compared to postoperative echocardiograms.

Lastly, the most effective way to screen for rhythm abnormalities is through a patient's history, including complaints of palpitations, and by obtaining an ECG. Patients who have sustained structural remodeling due to persistently elevated right ventricular afterload are at higher risk for supraventricular tachyarrhythmias. For the subset of patients who develop preoperative atrial fibrillation requiring prophylactic anticoagulation, it is essential to review their medication history before surgery to ensure anticoagulants were held for an appropriate duration or the use of reversal agents is indicated.

Gastrointestinal Assessment

A significant portion—up to 63%—of ESLD patients have gastroesophageal reflux disease (GERD) [24], which is roughly five to six times the prevalence in the general American population [25]. The increased incidence is likely because it is a manifestation of the systemic disease causing the ESLD. For instance, it has been described that patients with idiopathic pulmonary fibrosis (IPF) experience more GERD compared to patients with other forms of chronic lung disease [24, 26]. The significance of GERD in lung transplantation is that its presence in post-surgery recipients has been shown to lead to higher mortality secondary to aspiration-induced chronic allograft dysfunction manifested as bronchiolitis obliterans syndrome (BOS) [27]. Thus, it is essential to screen patients for GERD, a modifiable risk factor for lung injury that may be addressed through either pharmacological or surgical management. Although it has not yet been accepted as standard practice, offering patients with severe GERD a Nissen fundoplication may provide some benefit [28, 29].

Concomitant liver disease, particularly due to a fibrotic process, is also seen in some patients with ESLD [30]. When the liver disease is advanced, it leads to a significantly elevated risk of perioperative complications and mortality, making patients ineligible for the surgery. Therefore, careful preoperative evaluation is necessary. Workup for liver disease includes a physical exam that could show

findings such as peripheral edema, ascites, jaundice, caput medusae, gynecomastia, and spider nevi. Baseline laboratory tests that should be checked before surgery include levels of serum liver transaminases, gamma-glutamyl transferase, albumin, bilirubin (total and indirect), platelet count, and international normalized ratio (INR). To further characterize liver disease, right upper quadrant (RUQ) abdominal ultrasonography and a CT scan of the abdomen can also be pursued.

Another important consideration for the preoperative evaluation of patients undergoing lung transplantation surgery is their nutritional status. Given the high risk of malnutrition in critically ill patients, especially for those who are hospitalized awaiting donation, it is imperative to review the patient's nutrition. Due to poor oral intake, some patients may be receiving either enteral or parenteral feeds. In patients with enteral access (e.g., small-bore feeding tube), it is recommended to hold tube feeds per standard nil per os (NPO) guidelines to minimize the risk of aspiration during anesthetic induction. Discussion and planning should be conducted with a nutritionist or dietician regarding the continuation of total parenteral nutrition throughout the perioperative period.

Functional and Musculoskeletal Assessment

Frailty is a term used to indicate a heightened risk of adverse health outcomes resulting from declines in function across multiple domains and diminished physiological capacity [31]. Across multiple patient types—including surgical, ICU, and geriatric—frailty has been associated with increased mortality. This increased risk has also been observed in the lung transplant population [32]. Also, the prevalence of frailty among transplant candidates is considerably high, with one study citing as high as 45.1% of the cohort that was followed [32]. Frailty can be assessed in various ways, ranging from a rules-based approach to one that sums deficits. One tool often cited in the literature is the Clinical Frailty Scale, a validated measure of frailty based on clinical judgment [31]. There is still no single frailty assessment tool that is supported for use in the preoperative evaluation of lung recipients. The presence of preoperative sarcopenia can also be a marker for poorer postoperative outcomes. It can be quantified using multiple modalities, such as computed tomography (CT) scans, magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA) [33].

While the success of frailty or sarcopenia interventions in different patient populations has been mixed, there is sufficient evidence to suggest that strength training and aerobic exercises can improve functional status in elderly patients [34]. As part of the preoperative assessment and optimization for surgery, it is strongly recommended that patients admitted for surgery be mobilized and engage in rigorous strength training under the guidance of experienced physical and occupational therapists. Even for patients who are peripherally cannulated for VV-ECMO, specially trained nursing staff and therapists are encouraged to mobilize these patients until the time of surgery.

Intraoperative Considerations

Sedation and Anxiolysis

Due to the fragile cardiopulmonary status of patients with end-stage lung disease (ESLD), sedatives administered before induction must be approached with caution and titrated slowly to effect. The goal is to avoid myocardial depression and reductions in systemic vascular resistance (SVR), and while there is no universally preferred intravenous anesthetic for anxiolysis or sedation, any agent used must be carefully titrated to effect.

Monitoring

Due to the complexity and potential for rapid physiological changes in patients undergoing lung transplantation, intraoperative monitoring is essential. Both standard American Society of Anesthesiologists (ASA) monitors and advanced invasive monitoring techniques are routinely used to manage these concerns [35, 36]. Special considerations should be taken for each monitoring technique. Table 6.2 lists both standard and advanced invasive monitors used intraoperatively.

Standard Monitoring

While non-invasive blood pressure (NIBP) cuffs are placed on all patients, arterial lines are preferred for continuous, precise monitoring. There is no consensus or recommendation on the site of placement for NIBP monitoring; however, the right upper extremity is often used for arterial catheterization due to the possible need for venoarterial (VA) ECMO. Given the high risk of atrial arrhythmias in this patient population [37], continuous five-lead ECG monitoring is used to detect these events early and to identify ischemic injury. Pulse oximetry is used to monitor oxygenation; however, it can be unreliable during lung transplantation due to hemodynamic instability or the absence of pulsatile flow when mechanical circulatory support (MCS) is used. During periods of signal loss, arterial blood gases (ABGs) can be drawn to measure oxygen saturation and assess adequate gas exchange. Capnography continuously measures end-tidal carbon dioxide ($ETCO_2$) and

Table 6.2 Intraoperative monitors used in lung transplantation surgery

Standard monitors:	Non-invasive blood pressure cuff 5-lead electrocardiogram Pulse oximetry Capnography Temperature probe
Advanced monitors:	Arterial line (right radial artery preferred) Central venous pressure Pulmonary arterial catheter Transesophageal echocardiography

provides insight into the adequacy of ventilation. Patients with ESLD often exhibit obstructive respiratory physiology. They are therefore found to have an elevated baseline partial pressure of carbon dioxide ($PaCO_2$), an elevated $ETCO_2$, and an increased $PaCO_2$–$ETCO_2$ gradient, due to significant dead space ventilation. Beyond ESLD patient-specific concerns, the assessment of capnography waveform patterns can assist in the early diagnosis of bronchospasm or problems such as double-lumen tube (DLT) malpositioning or kinking of the endotracheal tube. Temperature regulation is another significant challenge in lung transplantation [36]. Patients are at high risk for hypothermia due to surgical exposure, the use of cold irrigation solutions, vasoplegia after cardiopulmonary bypass, and impaired thermoregulation while under general anesthesia. Hypothermia not only impairs coagulation and drug metabolism but can also increase pulmonary vascular resistance (PVR), thereby worsening underlying right ventricular (RV) dysfunction.

Advanced Invasive Monitoring

The monitoring of central venous pressure (CVP) is made possible with a central venous catheter (CVC) that is placed either in the right or left internal jugular (IJ) vein. If the risk for the need of VV-ECMO or continuous renal replacement therapy (CRRT) is high, then the left IJ vein is usually cannulated for central line access. A pulmonary artery catheter (PAC), also known as a Swan-Ganz catheter, is another useful monitor that can be advanced through special central venous catheters (CVCs) so that its distal tip is positioned in the pulmonary artery (PA). The PAC continuously monitors pulmonary artery pressures (PAPs), cardiac output (CO), and mixed venous oxygen saturation (SvO_2), enabling real-time assessment of biventricular performance and global tissue oxygenation.

As previously mentioned, arterial catheterization via the radial artery is the preferred method for blood pressure monitoring and is typically performed before the induction of anesthesia. Continuous monitoring of hemodynamics with a pre-induction arterial line allows careful titration of induction medications and the prevention of catastrophic hypoperfusion states. Through the case, the arterial line also facilitates frequent blood sampling for ABG analysis and coagulation testing. When peripheral VA-ECMO support is used during transplantation, the right upper extremity is the preferred site for placement to monitor for differential hypoxemia, also known as “Harlequin Syndrome” or “North-South Syndrome.” This is a condition where poorly oxygenated blood ejected from the native lung and heart mixes inadequately with retrograde ECMO-oxygenated blood, leading to poor oxygenation of the proximal aorta and the organs distal to its branches [38].

Transesophageal echocardiography (TEE) is essential for lung transplant surgery. It is used in most lung transplant centers worldwide and is recommended by the American Society of Echocardiography (ASE) guidelines [39]. TEE helps evaluate preoperative findings, such as right ventricular (RV) dysfunction, and assess real-time complications that may arise during surgery. Additionally, it provides the anesthesiologist with invaluable hemodynamic information during critical portions of the transplantation (e.g., the PA clamping and reperfusion). While anastomotic complications like PA stenosis and pulmonary vein stenosis or obstruction are

exceedingly rare, TEE can also assist in their early diagnosis. Intraoperative findings concerning for stenosis include flow velocities greater than 1.0 m/s. Velocities above 1.7 m/s are highly suggestive of pulmonary vein stenosis and are a risk for PGD.

Altogether, the comprehensive and individualized approach to intraoperative monitoring in lung transplantation is vital to ensuring patient safety, optimizing graft function, and guiding perioperative management in this complex surgical population.

Surgical Steps

Lung transplantation is a high-risk surgical procedure marked by complex surgical dissection, profound physiologic stress, and frequent need for mechanical circulatory support. The procedure begins with thoracotomy, institution of single-lung ventilation, and mobilization of the diseased lung, which should be deflated. Dissection may be complicated by pleural adhesions and is associated with a significant bleeding risk, particularly in patients with a history of previous chest surgery. The pulmonary artery (PA) is clamped and stapled after systemic heparinization (50–75 units/kg) to achieve a target activated clotting time (ACT) of 180–220 seconds. PA clamping increases right ventricular (RV) afterload, often leading to hemodynamic instability, especially in patients with preexisting pulmonary hypertension or RV dysfunction. RV support is paramount and includes inotropic therapy and strict avoidance of factors that increase pulmonary vascular resistance, such as hypoxia, hypercarbia, and sympathetic stimulation. Left lung explantation frequently results in displacement or compression of the heart, necessitating volume resuscitation and inotropic support. Hemodynamic monitoring via transesophageal echocardiography (TEE) and PAC is essential to guide resuscitation and detect RV compromise. If PA clamping or one-lung ventilation is poorly tolerated, mechanical circulatory support should be initiated.

The choice of mechanical support strategy depends on the patient's cardiorespiratory reserve. Lung transplantation can be performed off-pump, on VV-ECMO, VA-ECMO, or cardiopulmonary bypass (CPB). Off-pump surgery is preferred in patients who can tolerate PA clamping and single-lung ventilation without significant hypoxemia or RV dysfunction. For patients who cannot tolerate one-lung ventilation but remain hemodynamically stable, VV-ECMO may be employed to provide respiratory support alone, though it offers no circulatory assistance. In contrast, VA-ECMO supports both gas exchange and hemodynamics and reduces RV afterload. It requires less anticoagulation (ACT 160–200 seconds) and is associated with lower rates of primary graft dysfunction (PGD) compared to CPB. Cardiopulmonary bypass, which incorporates a venous reservoir that allows blood from the surgical field to be suctioned and reinfused, offers the most comprehensive support but requires full systemic anticoagulation (ACT > 480 seconds), leading to a more pronounced inflammatory response and carrying a higher risk of coagulopathy, vasoplegia, and PGD. When VA-ECMO is used in conjunction with a cell saver, this can provide a functional alternative to the blood return capacity of

CPB, while maintaining the benefits of reduced anticoagulation and inflammation [40].

Prophylactic antibiotics and immunosuppressive agents are routinely administered during the perioperative period. While the specific agents and dosages vary according to institutional protocol and patient-specific factors, broad-spectrum antibiotic coverage and early immunosuppressive induction are standard practices. Commonly used agents may include beta-lactam or anti-pseudomonal antibiotics, antifungal prophylaxis, and immunosuppressants such as methylprednisolone, mycophenolate, tacrolimus, or basiliximab.

Once the diseased lung is removed, the donor lung is implanted in a standardized sequence: the bronchial anastomosis is performed first, followed by the pulmonary artery anastomosis, and then the pulmonary vein anastomosis to the left atrium. The graft is gently inflated and de-aired before complete reperfusion is established. This phase is often hemodynamically challenging. The reintroduction of cold, ischemic blood from the donor lung into the systemic circulation can lead to transient myocardial depression, systemic hypotension, and arrhythmias, likely due to the washout of accumulated metabolites such as potassium, lactate, hydrogen ions, and oxygen-reactive species.

To mitigate these risks, pre-reperfusion optimization is critical. Patients should be adequately volume-resuscitated, and electrolyte abnormalities, especially hypocalcemia, hypomagnesemia, and hyperkalemia, should be promptly corrected, as they can exacerbate ventricular arrhythmias. Hemodynamic support with vasopressors or inotropes may be necessary to maintain perfusion pressure and cardiac output. TEE guidance allows for real-time assessment of ventricular filling and contractility, as well as early detection of reperfusion-related complications. Controlled, gradual reperfusion, rather than abrupt unclamping, can further help blunt the cardiovascular instability commonly observed during this critical transition.

Approach to Induction

The induction of general anesthesia in patients with ESLD presents considerable challenges due to severely impaired cardiopulmonary reserve, commonly compounded by pulmonary hypertension (PH) and right ventricular (RV) dysfunction. These patients are particularly susceptible to hemodynamic instability during the peri-induction period. Even transient episodes of hypoxemia, hypercarbia, or hypotension can precipitate sharp increases in pulmonary vascular resistance (PVR), leading to acute RV failure, a complication associated with high morbidity and mortality during lung transplantation.

Anesthetic induction in this population must be performed with meticulous planning and vigilance. Invasive arterial blood pressure monitoring and secure intravenous access should be established before induction to allow for prompt detection and management of hemodynamic fluctuations. Induction strategies should aim to maintain adequate preload, minimize rises in PVR, and preserve RV function.

Medications known to increase PVR or cause systemic vasodilation or myocardial depression should be avoided or used with extreme caution. Key goals during induction include minimizing sympathetic stimulation, avoiding hypoxia and hypercapnia, and preventing abrupt changes in intrathoracic pressure or vascular tone.

In cases where the patient is too unstable to tolerate anesthetic induction, the use of mechanical circulatory support (MCS) may be clinically justified. If the patient is not already on ECMO but the anticipated need is high, femoral access may be secured pre-induction to facilitate rapid cannulation.

Airway Management

Effective airway management is critical in lung transplantation and requires careful preparation. Given the high risk for rapid desaturation and hypoxemia in patients with ESLD, minimizing apneic intervals is imperative.

For airway securement, either a single-lumen tube (SLT) or a double-lumen tube (DLT) may be used. In most practice settings, DLTs are preferred over SLTs with a bronchial blocker (BB) in both single- and bilateral-orthotopic lung transplantation surgeries due to their ease of insertion and ability to achieve lung isolation [41]. When anatomic factors (e.g., glottic narrowing, tracheal stenosis) reduce the likelihood of successfully placing a double-lumen tube (DLT), a bronchial blocker (BB) may be a preferred option. However, they are prone to dislodgement and generally require more time for proper positioning. Additionally, when the procedure is performed on cardiopulmonary bypass without the need for mechanical ventilation, SLTs can be used. Between left-sided and right-sided DLTs, left-sided DLTs are favored because they can be used for both single and bilateral lung transplants. Following the placement of any type of airway, the position must be confirmed via bronchoscopy, and this may need to be rechecked throughout the surgery [42].

After the transplant, the DLT should be replaced with an SLT. Airway exchange may be complicated by tissue swelling related to prolonged operation time and the administration of large amounts of fluids and blood products. As such, a safe approach to airway conversion is to use the Seldinger technique with a soft-tipped airway exchange catheter, either with direct or video-assisted laryngoscopy. The airway exchange catheter must be carefully inserted into the DLT bronchial lumen to the appropriate depth, avoiding injury to the airway and bronchial anastomosis [43]. Due to the risk for aspiration during the transient absence of airway protection, it is also prudent to sufficiently suction gastric contents with a nasogastric or orogastric tube. After the endotracheal tube exchange, still in the operating room, the anastomoses should be inspected via bronchoscopy, and any secretions should be cleared with lavage.

Pre-implantation

Adequate ventilation and oxygenation present significant challenges during lung transplantation, particularly in patients with end-stage lung disease. These difficulties may arise even at the onset of the procedure and tend to become more

pronounced when one-lung ventilation (OLV) becomes necessary during the recipient pneumonectomy phase. In the context of off-pump procedures, it is advisable to perform the pneumonectomy on the less perfused lung, as identified by preoperative ventilation-perfusion (V/Q) scanning. This approach ensures that the more perfused, dependent lung is responsible for gas exchange during OLV, thereby optimizing oxygenation.

Following the initiation of OLV, the physiological reflex known as hypoxic pulmonary vasoconstriction (HPV) becomes critical. HPV redirects pulmonary blood flow away from poorly ventilated regions of the lung toward better-ventilated regions, thereby enhancing ventilation-perfusion matching. Although HPV begins promptly, its full effect may take approximately 30 minutes to manifest. Anesthetic management should aim to preserve this reflex, as several intravenous vasodilators can blunt its impact. Inhaled volatile anesthetics also inhibit HPV in a dose-dependent manner. For this reason, total intravenous anesthesia (TIVA) using agents such as propofol may be preferred. Despite its systemic vasodilatory properties, propofol does not appear to interfere with the HPV response and offers a favorable profile in this context [44].

One-lung ventilation increases pulmonary vascular resistance (PVR) and pulmonary arterial (PA) pressures—physiological changes that may not be well tolerated in patients with preexisting right ventricular (RV) dysfunction or pulmonary arterial hypertension (PAH). To mitigate the risk of acute RV failure and associated hemodynamic instability, short-term ventilation strategies should be employed. These strategies should aim to prevent hypoxemia, hypercapnia, and acidosis, all of which can exacerbate PVR and compromise cardiovascular stability.

Post-implantation

Following implantation, the new lungs are highly susceptible to injury. Pulmonary edema, which is a common occurrence after pneumonectomies, is a significant contributor to acute lung injury (ALI) [45]. Additionally, injury sustained due to ischemia and reperfusion, a leading cause of PGD, is a dreaded complication following lung transplantation [46]. Thus, to mitigate the risk of either ALI or PGD, a lung-protective ventilation strategy should be used both intraoperatively and postoperatively. Postoperative ventilation strategies will be discussed in more detail below.

A protective strategy often implemented is similar to that utilized in the setting of acute respiratory distress syndrome (ARDS) and has demonstrated efficacy in improving outcomes [47]. Key recommendations include the use of low tidal volumes (typically 4–6 mL/kg of the donor ideal body weight, appropriately adjusted for OLV), application of moderate positive end-expiratory pressure (PEEP), maintenance of inspiratory pressures <20 cm H_2O above PEEP, and the lowest fraction of inspired oxygen (FiO_2) necessary to maintain oxygen saturation above 88% [48]. Moreover, it is beneficial to maintain $PaCO_2$ within the patient's pre-transplant range to prevent exacerbating RV strain. Recruitment maneuvers should also be performed to avoid atelectasis and atelectrauma, but should be done so cautiously so as not to cause barotrauma or hemodynamic instability inadvertently.

While hyperoxic injury is now a well-described clinical consequence of using higher than necessary targets for oxygenation, this is especially true during reperfusion of the implanted lung allograft. High concentrations of inspired oxygen at the time of reperfusion have been associated with an increased incidence of severe PGD [49]. To mitigate this risk, FiO_2 should be reduced to target an arterial oxygen level (PaO_2) above 70 mmHg, or corresponding to an oxygen saturation of above 88%.

Inhaled pulmonary vasodilators, including inhaled prostacyclin I_2 (epoprostenol) and inhaled nitric oxide (iNO), can be used during the pre- and post-implantation phases of the case. By reducing pulmonary vascular tone through different mechanisms of action, both agents can help decrease right heart strain in patients with ESLD who may have concomitant RV dysfunction. Furthermore, both iNO and epoprostenol may improve the ventilation-perfusion (V/Q) mismatch commonly experienced by these patients. Because iNO does not need to be aerosolized, its administration is less prone to interfere with ventilation by saturating filters with condensation. However, at most institutions, it is less available, mainly due to its higher cost. There is no demonstrable clinical superiority of one drug over the other [50].

Following lung transplantation, there has been considerable interest in the protective role of inhaled pulmonary vasodilators against PGD, particularly with the use of inhaled nitric oxide (iNO) [51]. However, a randomized controlled trial led by Ghadimi et al. in 2021 failed to show a significant difference in the incidence of severe PGD between patients who received iNO and those who received epoprostenol [52].

Postoperative Considerations

Postoperative care for lung transplant recipients is complex and requires close coordination among a multidisciplinary intensive care unit (ICU) team. The early postoperative period is a critical window for preserving graft function, maintaining hemodynamic stability, managing bleeding, supporting the immune system, and preventing infection. Intraoperative and immediate postoperative management have a significant impact on postoperative outcomes. Strategies such as judicious fluid resuscitation, lung-protective ventilation, optimal correction of coagulopathy, and support of RV function directly impact the feasibility of early extubation, hemodynamic stability, graft performance, and overall ICU morbidity [53–55].

Ventilator Management

Mechanical ventilation in lung transplant recipients must be carefully managed to preserve allograft function and minimize the risk of PGD. Lung-protective strategies are the cornerstone of care, aimed at preventing volume- and pressure-induced injury to the newly implanted lungs. These strategies include using low tidal volumes (4–6 mL/kg of ideal donor body weight), maintaining plateau

pressures (Pplat) at or below 30 cmH_2O, keeping driving pressures (Pplat minus PEEP) at or below 15 cmH_2O, and applying individualized PEEP to prevent atelectasis and optimize oxygenation. The fraction of inspired oxygen (FiO_2) should be titrated to the lowest level that maintains $SpO_2 \geq 88\%$ and PaO_2 between 60 and 80 mmHg, aiming to reduce oxidative stress, as prolonged hyperoxia has been associated with worsened PGD outcomes [56, 57]. Regular reassessment of ventilation and oxygenation using blood arterial gases is paramount. Permissive hypercapnia is acceptable if the pH remains above 7.25 and the hemodynamic status remains stable. In cases of refractory hypoxemia or early PGD, escalation strategies include increasing PEEP, administering inhaled pulmonary vasodilators (nitric oxide or prostacyclin), or initiating VV-ECMO (Table 6.3) [56–58]. VA-ECMO can be considered if there is cardiovascular compromise, particularly right ventricular dysfunction [53, 59].

Early weaning and extubation are indicated when oxygenation, ventilation, mental status, and hemodynamics are favorable. Prolonged ventilation (more than 14 days) is associated with worse outcomes, including increased risk of infection, longer ICU stay, and higher mortality [60]. Post-extubation, aggressive bronchopulmonary hygiene and participation in physical therapy are recommended to enhance secretion clearance and prevent atelectasis [55].

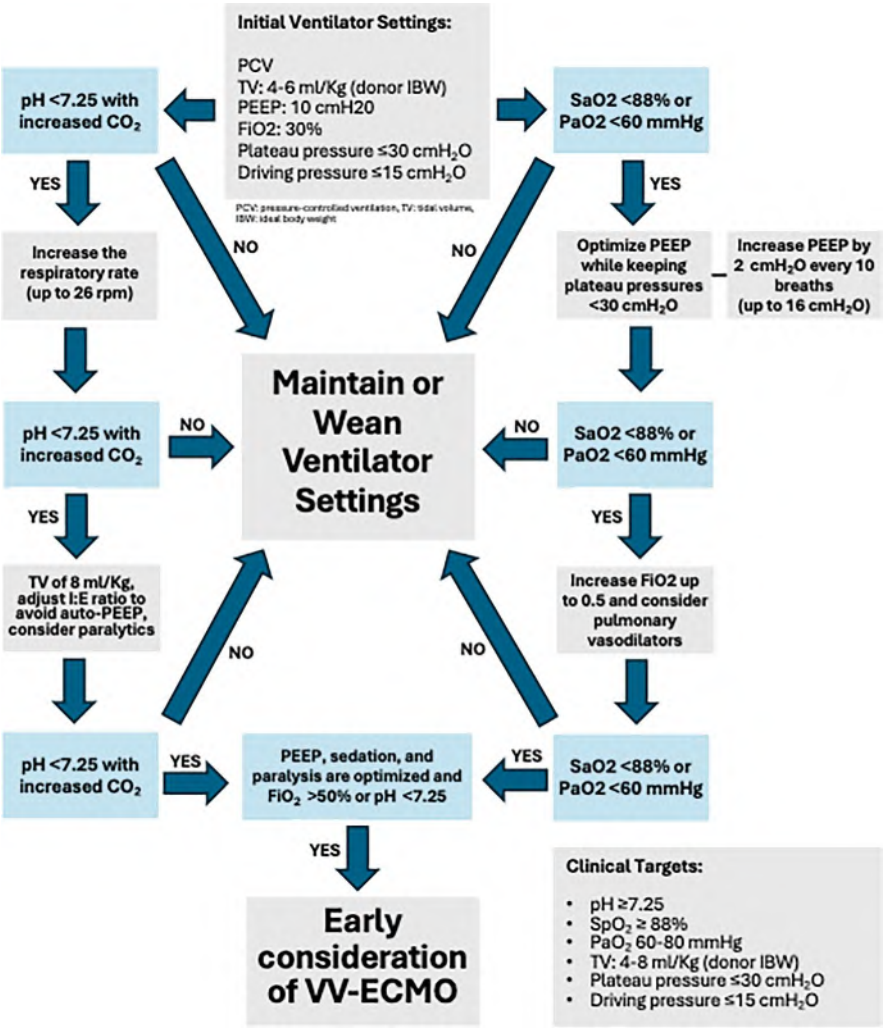
Primary Graft Dysfunction

PGD is a form of acute lung injury and the leading cause of early morbidity and mortality after lung transplantation, affecting up to 30% of recipients. It is characterized by hypoxemia and pulmonary infiltrates, with its severity graded according to the PaO_2/FiO_2 ratio and radiographic findings at 0, 24, 48, and 72 h post-transplant. Grades range from 0 (no dysfunction) to 3 (severe dysfunction), with grade 3 reflecting PaO_2/FiO_2 below 200 and bilateral infiltrates [60] (Table 6.4). Risk factors for PGD include donor-related variables (such as advanced age, smoking history, and prolonged ischemic time), recipient-related factors (elevated body mass index and preexisting pulmonary hypertension), and perioperative elements (including prolonged operative time, the use of mechanical circulatory support, and pulmonary vein stenosis) [54].

Pulmonary vein stenosis at the left atrial anastomosis is a mechanical complication that can contribute to PGD by impairing venous drainage and causing pulmonary congestion. Intraoperative TEE is essential for early detection. Findings concerning for stenosis include flow velocities greater than 1.0 m/s (above 1.7 m/s is highly suggestive), nonlaminar flow on color Doppler, and the presence of visible thrombus. Prompt recognition is critical, as this is a potentially reversible cause of PGD.

Histologically and physiologically, PGD resembles ARDS and is primarily driven by ischemia–reperfusion injury, resulting in endothelial dysfunction, increased vascular permeability, neutrophilic infiltration, activation of the inflammatory cascade, and non-cardiogenic pulmonary edema. Early diagnosis and timely

Table 6.3 Ventilator management of pulmonary grafts



Adapted from the Cleveland Clinic ICU Lung Transplant Mechanical Ventilation Guide [56–58]

Table 6.4 Primary graft dysfunction grading

Grade	PaO_2/FiO_2 ratio	Radiograph infiltrates	Disease severity
0	>300	Absent	Normal
1	>300	Present	Mild
2	200–300	Present	Moderate
3	<200	Present	Severe

Adapted from Snell et al. Report of the ISHLT on Primary Lung Graft Dysfunction (2016) [60]

intervention are essential for minimizing its impact on long-term graft function [52]. Management of PGD is primarily supportive. Preventive and management strategies include lung-protective ventilation, conservative fluid therapy, inhaled pulmonary vasodilators, and, in severe cases, ECMO to maintain oxygenation while allowing graft recovery [56].

Hemodynamics and Fluid Management

Fluid management in the postoperative period is a critical determinant of graft function and patient outcomes. Following ischemia–reperfusion injury, the transplanted lung exhibits increased capillary permeability and is highly susceptible to fluid overload, non-cardiogenic pulmonary edema, and impaired gas exchange. A fluid-restrictive approach has been associated with a reduced risk of PGD, pulmonary edema, and right ventricular strain [58, 59].

Best practice recommendations include maintaining an even or negative fluid balance after the initial resuscitative phase, early initiation of diuretic therapy, and prioritizing vasopressors over fluid boluses to sustain adequate blood pressure. Goal-directed hemodynamic monitoring—using a pulmonary artery catheter, central venous pressure, and echocardiography—should guide volume administration [53, 57].

Neurological Complications and Hyperammonemia

Neurological complications such as delirium, seizures, and stroke are common, particularly in patients with prolonged ICU stays or extended ECMO support. Preventive strategies include frequent neurological assessments, minimizing sedation, ensuring appropriate analgesia, promoting sleep hygiene, encouraging early mobilization, providing regular reorientation, and optimizing sensory input. These interventions can significantly reduce the risk of neurologic dysfunction in lung transplant recipients [55].

Hyperammonemia is a potentially fatal complication following lung transplantation, with an incidence of up to 4.1%. Its pathophysiology is multifactorial, involving excessive ammonia production, impaired hepatic elimination, and disseminated infections with urease-producing organisms such as Ureaplasma and Mycoplasma hominis. These pathogens are challenging to detect with standard cultures and may proliferate in immunosuppressed hosts, leading to ammonia accumulation through urea metabolism. Clinical manifestations typically include altered mental status, seizures, and cerebral edema. Management strategies include early initiation of dialysis, neuroprotective measures such as mannitol and hypothermia, and targeted antibiotic therapy (particularly doxycycline or azithromycin). Early recognition, prompt ammonia level monitoring in patients with altered mental status, and empiric antimicrobial coverage are critical to improving outcomes [61].

Acute Pain Management

Postoperative pain in lung transplant recipients can be severe due to extensive surgical incisions and preexisting conditions. Effective pain management after surgery is crucial for enhancing recovery, facilitating participation in physical and occupational therapies, minimizing complications, and improving overall quality of life. Multimodal analgesia regimens, including epidural analgesia, paravertebral blocks, intraoperative cryoablation techniques, and non-opioid medications, are recommended to decrease opioid consumption and associated side effects. Enhanced Recovery After Surgery (ERAS) protocols, which include preemptive analgesia and regional anesthesia techniques, have been associated with improved patient outcomes and reduced opioid use and side effects [62].

Renal Complications

Acute kidney injury (AKI) is a frequent complication after lung transplantation, driven by perioperative hypotension, exposure to nephrotoxic agents—particularly calcineurin inhibitors—and systemic inflammation related to ischemia–reperfusion injury and PGD. AKI affects up to 50% of lung transplant recipients and is associated with prolonged ICU stay, increased morbidity, and higher mortality rates [53, 54]. CRRT is commonly initiated early when urine output is inadequate or when fluid overload compromises allograft function and oxygenation [55].

Nutritional Support

Optimizing nutritional status both before and after transplantation is a key component of multidisciplinary care and is integrated into ERAS protocols for lung transplantation [62]. Malnutrition is common among transplant candidates and is associated with increased risk of infection, impaired wound healing, and prolonged hospitalization. Nutritional support should be initiated as soon as gastrointestinal function permits, ideally within 24–48 h of ICU admission. Enteral nutrition is preferred over parenteral nutrition, which should be reserved for patients with gastrointestinal intolerance or significant hemodynamic instability. Early mobilization is also strongly encouraged to prevent deconditioning, with active physical therapy ideally beginning within 24–48 h of clinical stabilization [9, 53].

Infection Control

Lung transplant recipients are immunosuppressed and therefore at high risk for infectious complications. Infection remains one of the most frequent and severe challenges in the early postoperative period, as the lung allograft is uniquely vulnerable due to disruption of airway barriers, impaired mucociliary clearance, and the

inflammatory cascade triggered by ischemia–reperfusion injury [53–55]. During the first 30 days after transplantation, the risk of bacterial pneumonia is elevated, particularly from nosocomial and multidrug-resistant organisms, especially in patients with pre-transplant colonization. In later phases, fungal infections (e.g., *Aspergillus* spp.), viral reactivations (e.g., cytomegalovirus), and other opportunistic pathogens such as *Pneumocystis jirovecii* become increasingly common [53, 54, 58].

Infection prevention strategies include antimicrobial prophylaxis, surveillance bronchoscopy with bronchoalveolar lavage cultures, and routine viral PCR monitoring. Standard prophylactic regimens typically include trimethoprim–sulfamethoxazole for *Pneumocystis jirovecii*, ganciclovir or valganciclovir for cytomegalovirus, and fluconazole, voriconazole, or echinocandins for antifungal coverage [53, 58].

Immunosuppression

The ICU team must remain vigilant for signs of acute rejection, which often present with new infiltrates on imaging, declining oxygenation, or increased lymphocytes on bronchoalveolar lavage (BAL) [53, 54]. Immunosuppressive therapy is essential for preventing both acute and chronic rejection. Most patients are managed with a triple-drug regimen, typically consisting of a corticosteroid, a calcineurin inhibitor such as tacrolimus, and an antiproliferative agent, like mycophenolate mofetil [55]. Dosing is most aggressive in the immediate postoperative period and then gradually tapered to achieve a balance between rejection risk and infectious complications. Close collaboration with infectious disease specialists, therapeutic drug monitoring, and individualized regimens are all key to optimizing outcomes [53, 55, 62].

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Anesthesia for Pancreatic Transplant

7

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Introduction

Pancreas transplantation remains a technically challenging solid organ transplant procedure, with significant anesthetic implications. Since the first successful pancreas transplant performed at the University of Minnesota in 1966, significant advancements have been made in surgical technique, immunosuppression, and perioperative management [1]. The procedure is primarily performed for patients with type 1 diabetes mellitus, with the goal of achieving insulin independence and halting the progression of diabetic complications [2].

The complexity of pancreas transplantation stems from the demanding nature of the surgery, the unique physiology of the pancreas as both an endocrine and an exocrine organ, and the high incidence of comorbidities in the recipient population [3]. Most patients have long-standing diabetes with end-organ damage, including nephropathy, neuropathy, vasculopathy, and cardiomyopathy. These complications necessitate a comprehensive and specialized anesthetic approach [4].

The anesthesiologist plays a crucial role in the multidisciplinary transplant team, managing complex hemodynamic changes, maintaining adequate organ perfusion, controlling glycemia, and ensuring optimal conditions for graft function [5]. This chapter aims to provide a comprehensive overview of the anesthetic implications and management strategies for pancreas transplantation, highlighting the unique challenges faced by anesthesiologists in this context.

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Patient Evaluation and Optimization

Comprehensive preoperative evaluation is critical for successful pancreas transplantation. Patients typically have longstanding diabetes with significant comorbidities that require thorough assessment and optimization [6]. The evaluation process begins with a detailed history and physical examination, focusing on the following.

Cardiovascular Assessment

Diabetic patients have a two to four times higher risk of cardiovascular disease compared to the general population [7]. Silent myocardial ischemia is common, occurring in up to 20–50% of diabetic patients with end-stage renal disease (ESRD) [8]. Therefore, a thorough cardiovascular assessment is essential and typically includes:

- 12-Lead electrocardiogram
- Transthoracic echocardiography
- Stress testing (exercise or pharmacological)
- Coronary angiography in patients with positive stress tests or high cardiovascular risk [9]

Diabetic cardiomyopathy, characterized by left ventricular diastolic dysfunction and hypertrophy, may be present even in the absence of coronary artery disease or hypertension [10]. This condition increases the risk of heart failure and arrhythmias during the perioperative period.

Autonomic Neuropathy Assessment

Cardiovascular autonomic neuropathy affects 30–60% of diabetic patients and significantly increases perioperative risk [11]. Clinical manifestations include the following:

- Resting tachycardia
- Orthostatic hypotension
- Reduced heart rate variability
- Silent myocardial ischemia
- Intraoperative hemodynamic instability
- Sudden cardiac death

Assessment of autonomic function should include heart rate variability tests, the Valsalva maneuver, and orthostatic blood pressure measurements [12]. Patients with severe autonomic neuropathy may require more invasive hemodynamic monitoring during transplantation.

Renal Function Assessment

Many patients undergoing pancreas transplantation have concurrent nephropathy or ESRD. Approximately 80% of pancreas transplants are performed with simultaneous pancreas–kidney (SPK) transplantation [13]. Assessment of renal function includes the following:

- Serum creatinine and blood urea nitrogen
- Estimated glomerular filtration rate
- Proteinuria quantification
- Electrolyte profile

Patients with renal dysfunction may require medication dose adjustments and specific intraoperative management strategies [14].

Airway and Pulmonary Evaluation

Diabetic patients are at an increased risk for a difficult airway due to limited joint mobility syndrome (prayer sign) and a higher incidence of obstructive sleep apnea [15]. Additionally, diabetic microangiopathy may affect pulmonary function, leading to reduced diffusion capacity and restrictive lung disease. Pulmonary evaluation should include the following:

- Airway assessment, including Mallampati score, neck range of motion, and other predictors
- Pulmonary function tests in patients with respiratory symptoms
- Arterial blood gas analysis in patients with advanced renal disease

Preoperative Assessment and Management

Medication Management

The preoperative management of medications requires careful consideration.

Insulin Management

Insulin therapy should be continued until the day of surgery, with adjustments based on fasting status and blood glucose levels [16]. Long-acting insulin is typically reduced to 50–75% of the usual dose the evening before surgery, while short-acting insulin is held on the morning of surgery. Intravenous insulin infusion may be initiated for patients with poor glucose control or those requiring emergency transplantation. Co-management with endocrinology is helpful pre- and postoperatively.

Oral Hypoglycemic Agents

Metformin should be discontinued 48 h before surgery to reduce the risk of lactic acidosis, especially in patients with renal impairment [17]. Sulfonylureas and other oral hypoglycemic agents are typically held on the day of surgery.

Antihypertensive Medications

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are commonly discontinued 24–48 h before the surgery due to the risk of intraoperative hypotension and acute kidney injury [18]. Beta-blockers should be continued perioperatively to reduce the risk of cardiovascular events. Calcium channel blockers and diuretics management should be individualized based on the patient's hemodynamic status and electrolyte balance.

Immunosuppressive Medications

Induction immunosuppression is typically initiated preoperatively or intraoperatively [19]. The anesthesiologist should be familiar with the hemodynamic and metabolic effects of these agents, which may include the following:

- Hypotension with anti-thymocyte globulin or basiliximab
- Hypertension with calcineurin inhibitors
- Hyperglycemia with corticosteroids

Laboratory Evaluation

Comprehensive laboratory assessment should include the following:

- Complete blood count
- Coagulation profile (Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR))
- Comprehensive metabolic panel
- HbA1c
- Blood group typing and antibody screen
- Viral serologies (Cytomegalovirus (CMV), epstein-barr virus (EBV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV))
- Cross-matching with the donor

Fasting Guidelines

Standard fasting guidelines apply, with special attention to glycemic control. Clear carbohydrate-containing fluids may be permitted up to 2 hours before surgery to reduce insulin resistance and prevent hypoglycemia [20]. Blood glucose levels should be monitored closely during the fasting period. For patients with gastroparesis or delayed gastric emptying, a full 8 hours of nil per os (nothing by mouth) (NPO) time may be considered.

Intraoperative Anesthetic Considerations

Induction and Maintenance

General anesthesia with endotracheal intubation is the standard approach for pancreas transplantation [21]. The choice of anesthetic agents should consider the patient's cardiovascular status, renal function, and potential for drug interactions with immunosuppressants.

Induction Agents

Propofol is commonly used for induction but may cause hypotension, particularly in patients with autonomic neuropathy or hypovolemia [22]. Dose reduction (1–1.5 mg/kg) and slow administration are recommended. Etomidate (0.2–0.3 mg/kg) provides greater hemodynamic stability and may be preferred in patients with cardiovascular compromise. However, its potential for adrenal suppression should be considered.

Neuromuscular Blocking Agents

Cisatracurium is often preferred due to its organ-independent metabolism via Hofmann elimination, making it suitable for patients with renal dysfunction [23]. Rocuronium may also be used, with dose adjustments based on renal function. Neuromuscular monitoring is essential for appropriate dosing and reversal.

Maintenance Anesthesia

A balanced technique using volatile anesthetics (sevoflurane or desflurane) with opioids and muscle relaxants is commonly employed [24]. Total intravenous anesthesia with propofol and remifentanil is an alternative approach, especially in patients with postoperative nausea and vomiting risk factors. The choice between inhalational and intravenous techniques should consider the patient's hemodynamic stability and renal function.

Hemodynamic Management

Hemodynamic management during pancreas transplantation is challenging due to several factors:

- Significant fluid shifts and potential for blood loss
- Reperfusion syndrome
- Release of vasoactive substances from the pancreas
- Pre-existing cardiovascular disease
- Autonomic neuropathy [25]

The hemodynamic goals include the following:

- Maintaining adequate mean arterial pressure (MAP >65–70 mmHg)
- Ensuring optimal organ perfusion
- Avoiding excessive afterload reduction
- Managing systemic vascular resistance changes

Invasive arterial blood pressure monitoring is standard practice, and central venous pressure (CVP) monitoring is often utilized. Advanced hemodynamic monitoring, such as pulmonary artery catheterization or minimally invasive cardiac output monitoring, may be indicated in patients with severe cardiovascular disease or pulmonary hypertension.

Inotropic and vasopressor support may be required, particularly during reperfusion. Norepinephrine is commonly used for vasopressor support, while dobutamine may be added for inotropy if needed [26]. Vasopressin may be considered in cases of catecholamine-resistant vasodilation.

Fluid and Electrolyte Balance

Fluid management during pancreas transplantation requires careful consideration of:

- Intravascular volume status
- Third-space losses
- Blood loss
- Acid–base balance
- Electrolyte abnormalities [27]

Balanced crystalloid solutions are preferred for volume replacement. Hyperchloremic metabolic acidosis should be avoided, as it may impair pancreatic function. Colloids may be used judiciously, considering their potential effects on coagulation and renal function.

The typical fluid requirement ranges from 10 to 15 mL/kg/h, with additional replacement for blood loss. Goal-directed fluid therapy using dynamic parameters (stroke volume variation and pulse pressure variation) may optimize fluid administration and reduce complications [28].

Common electrolyte abnormalities during pancreas transplantation include the following:

- Hypocalcemia (due to citrate toxicity from blood transfusions)
- Hypomagnesemia (exacerbated by diuretics and immunosuppressants)
- Hyperkalemia (from reperfusion and acidosis)
- Metabolic acidosis

Close monitoring and prompt correction of these abnormalities are essential for optimal graft function.

Glycemic Control

Glycemic management during pancreas transplantation presents unique challenges. Pre-reperfusion hyperglycemia should be controlled with intravenous insulin to maintain blood glucose levels between 100–180 mg/dL [29]. After reperfusion, careful monitoring is required as the transplanted pancreas may begin secreting insulin, potentially causing hypoglycemia.

Blood glucose monitoring should be performed every 30–60 minutes, with more frequent checks during critical periods such as reperfusion. A separate intravenous line should be dedicated to insulin administration, with prepared dextrose solutions available for rapid treatment of hypoglycemia.

Factors affecting intraoperative glucose metabolism include the following:

- Surgical stress response (increasing insulin resistance)
- Corticosteroid administration (increasing hyperglycemia)
- Catecholamine release and administration (increasing glycogenolysis)
- Pancreas reperfusion (potentially increasing insulin levels)

The anesthesiologist must anticipate these changes and adjust insulin therapy accordingly.

Coagulation Management

Coagulation abnormalities are common during pancreas transplantation due to:

- Pre-existing coagulopathy from uremia (in SPK transplantation)
- Dilutional coagulopathy from large volume fluid administration
- Consumption of clotting factors during surgery

- Fibrinolysis from pancreatic tissue manipulation
- Heparin effect from donor preservation solutions [30]

Thromboelastography or rotational thromboelastometry allows for a comprehensive assessment of coagulation and targeted blood product administration [31]. Blood product transfusion should be guided by institutional protocols and include:

- Packed red blood cells to maintain hemoglobin >7–8 g/dL
- Fresh frozen plasma for coagulation factor deficiencies
- Platelets for thrombocytopenia or platelet dysfunction
- Cryoprecipitate for hypofibrinogenemia

Antifibrinolytic agents such as tranexamic acid may be considered to reduce bleeding, but their use should be balanced against the risk of thrombosis.

Temperature Management

Normothermia is crucial during pancreas transplantation to the following:

- Optimize enzyme function and metabolism.
- Maintain normal coagulation.
- Reduce infection risk.
- Avoid cold-induced vasoconstriction [32].

Active warming methods should be employed, including:

- Forced-air warming blankets
- Fluid warmers
- Humidified and heated respiratory gases
- Elevated ambient operating room temperature

Core temperature should be maintained above 36 °C throughout the procedure.

Monitoring Considerations

Comprehensive monitoring is essential for pancreas transplantation and typically includes the following.

Standard Monitoring

- Electrocardiography (five-lead)
- Pulse oximetry
- Capnography

- Non-invasive blood pressure
- Temperature
- Urine output

Advanced Monitoring

- Invasive arterial blood pressure
- CVP and pulmonary artery catheterization (in selected cases)
- Cardiac output monitoring and Transesophageal echocardiography (in cases of severe cardiac dysfunction)
- Cerebral oximetry (in patients with cerebrovascular disease)

Laboratory Monitoring

- Arterial blood gases
- Electrolytes
- Glucose
- Hemoglobin/hematocrit
- Coagulation parameters
- Lactate
- Acid–base status

The frequency of laboratory testing depends on the stability of the patient, with more frequent assessments during critical periods such as reperfusion.

Surgical Procedure and Anesthetic Implications

Surgical Approach

Understanding the surgical approach is crucial for the anesthesiologist to anticipate challenges and plan management strategies [33]. The standard technique involves a midline incision with exposure of the retroperitoneal structures. The donor pancreas is typically placed intraperitoneally in the right iliac fossa, with vascular anastomoses to the iliac vessels.

Exocrine drainage can be managed by one of two approaches:

1. Enteric drainage: Anastomosis of the donor duodenum to the recipient's small bowel
2. Bladder drainage: Anastomosis of the donor duodenum to the recipient's bladder

Enteric drainage is more physiological but may be associated with a higher risk of intra-abdominal infections and anastomotic leaks. Bladder drainage allows for

monitoring of pancreatic enzymes in urine but can lead to metabolic acidosis, dehydration, and urological complications.

The anesthetic implications of the surgical approach include the following:

- Prolonged surgical duration (4–8 h)
- Potential for significant blood loss
- Third-space fluid losses
- Risk of inadvertent organ injury
- Need for hemodynamic stability during vascular anastomoses

Reperfusion Syndrome

Reperfusion of the pancreas is a critical period associated with significant physiological changes:

- Hypotension (due to release of vasodilatory mediators)
- Bradycardia (due to vagal stimulation)
- Hypothermia (due to cold preservation solution)
- Metabolic acidosis (due to washout of metabolic products)
- Hyperkalemia (due to release from ischemic cells)
- Hyperglycemia (due to stress response)
- Coagulopathy (due to release of fibrinolytic factors) [34]

The anesthesiologist should anticipate these changes and be prepared with:

- Volume loading (10–15 mL/kg) prior to reperfusion
- Vasopressor support (phenylephrine, ephedrine, or norepinephrine)
- Calcium gluconate for hypocalcemia and to counteract hyperkalemia
- Sodium bicarbonate for severe acidosis
- Insulin for hyperglycemia
- Anti-dysrhythmic agents for arrhythmias

Postreperfusion Management

After reperfusion, the focus shifts to the following:

- Stabilizing hemodynamics
- Optimizing graft perfusion
- Managing coagulopathy
- Maintaining normothermia
- Adjusting fluid and electrolyte balance
- Transitioning to maintenance immunosuppression

The risk of pancreatic thrombosis is highest in the immediate post-reperfusion period, necessitating careful blood pressure management and potentially anticoagulation [35]. Doppler ultrasonography may be performed intraoperatively to assess graft perfusion.

Special Considerations for Combined Kidney–Pancreas Transplantation

SPK transplantation is the most common form of pancreas transplantation, accounting for approximately 80% of cases [13]. This combined procedure presents additional anesthetic challenges.

Extended Surgical Duration

SPK transplantation typically takes 6–10 h, increasing the risks of hypothermia, coagulopathy, and fluid imbalances.

Complex Fluid Management

Balancing the fluid requirements for both organs can be challenging. The kidney benefits from liberal fluid administration to promote early graft function, while excessive fluid may increase the risk of pancreatitis and graft thrombosis [36].

Delayed Graft Function Risk

The risk of delayed graft function in the kidney necessitates careful hemodynamic management and avoidance of nephrotoxic agents.

Electrolyte Management

More complex electrolyte abnormalities may occur, particularly if the patient was on dialysis preoperatively.

Immunosuppression Considerations

Higher levels of immunosuppression may be required, potentially leading to more pronounced side effects.

The anesthetic approach should be tailored to address these challenges, with emphasis on:

- Optimizing hemodynamics for both grafts
- Careful fluid and electrolyte management
- Extended monitoring
- Anticipation of a longer recovery time

Special Considerations for Islet Cell Transplantation

Islet cell transplantation is a less invasive alternative to whole-organ pancreas transplantation, involving the infusion of isolated islet cells into the portal vein [37]. This procedure requires specific anesthetic considerations:

Procedural Approach

The procedure is typically performed under moderate sedation or general anesthesia, with ultrasound or fluoroscopic guidance for portal vein access.

Hemodynamic Management

Maintenance of portal venous pressure below 10 mmHg is crucial to prevent portal hypertension and ensure optimal islet engraftment.

Anticoagulation

Careful heparin administration is required to prevent thrombosis while avoiding bleeding complications.

Monitoring

Continuous monitoring of portal pressure during infusion is essential, along with standard hemodynamic monitoring.

Post-procedure Care

Emphasis is on preventing portal vein thrombosis and monitoring for bleeding complications.

The anesthetic management for islet cell transplantation focuses on:

- Providing adequate sedation or anesthesia for patient comfort
- Maintaining hemodynamic stability

- Facilitating optimal conditions for islet cell engraftment
- Preventing and detecting potential complications

Anesthetic Drugs and Their Effects on Pancreas Grafts

The choice of anesthetic agents should consider their potential effects on pancreatic function and graft outcomes.

Inhalational Anesthetics

Volatile anesthetics (isoflurane, sevoflurane, and desflurane) may have both protective and harmful effects on the pancreas:

- Potential for preconditioning against ischemia–reperfusion injury
- Dose-dependent inhibition of insulin secretion
- Variable effects on pancreatic blood flow [38]

Modern halogenated agents are generally considered safe for pancreas transplantation when used at appropriate concentrations.

Intravenous Anesthetics

Propofol has minimal direct effects on pancreatic function and may offer some protection against oxidative stress. Etomidate may transiently suppress adrenocortical function but has little direct effect on the pancreas. Ketamine may increase catecholamine levels and potentially affect glycemic control.

Opioids

Opioids can cause spasm of the sphincter of Oddi, potentially affecting pancreatic drainage [39]. This effect is more pronounced with morphine than with synthetic opioids such as fentanyl or remifentanil. Opioid-induced nausea and vomiting may complicate postoperative care.

Muscle Relaxants

The choice of neuromuscular blocking agents should consider renal function:

- Succinylcholine: It may be used for rapid sequence intubation if indicated, but hyperkalemia must be considered, particularly in patients with ESRD.

- Cisatracurium: It is often preferred due to organ-independent elimination.
- Rocuronium: It may have a prolonged effect in renal dysfunction.
- Vecuronium: Intermediate duration and some renal elimination.

Vasopressors and Inotropes

The effects of vasoactive agents on pancreatic perfusion should be considered:

- Norepinephrine: It preserves splanchnic blood flow at moderate doses.
- Phenylephrine: It may reduce splanchnic perfusion.
- Vasopressin: It may reduce pancreatic microcirculation.
- Dobutamine: It may improve pancreatic perfusion [26].

The selection of anesthetic agents should be individualized based on the patient's comorbidities, expected hemodynamic changes, and potential drug interactions.

Postoperative Management and Pain Control

Immediate Postoperative Care

Most pancreas transplant recipients require intensive monitoring for at least 24–48 h postoperatively. The key aspects of immediate postoperative care are as follows.

Hemodynamic Management

Continuation of hemodynamic optimization is required with goals similar to those of the intraoperative period. Close monitoring for signs of bleeding or thrombosis is essential.

Respiratory Care

Early extubation is desirable to reduce the risk of pulmonary complications, but may be delayed in cases of hemodynamic instability or significant fluid overload. Lung-protective ventilation strategies should be employed if mechanical ventilation is continued.

Fluid and Electrolyte Management

Careful fluid administration is required to maintain adequate organ perfusion while avoiding volume overload. Electrolyte abnormalities, particularly hyperkalemia and hypomagnesemia, should be promptly corrected.

Glycemic Control

Intensive insulin therapy may be required initially, transitioning to subcutaneous insulin as the pancreatic graft function stabilizes. The target blood glucose range is typically 100–180 mg/dL [29].

Monitoring Graft Function

Close monitoring of serum amylase, lipase, and glucose levels is required to assess graft function. Doppler ultrasonography may be performed to evaluate vascular flow.

Pain Management

Effective pain control is essential for patient comfort and early mobilization [40]. A multimodal approach is recommended:

- **Epidural Analgesia**
  Thoracic epidural analgesia provides excellent pain relief and may reduce the stress response. However, it may be contraindicated in patients with coagulopathy or those receiving anticoagulation for graft thrombosis prevention.
- **Patient-Controlled Analgesia (PCA)**
  Intravenous PCA with fentanyl or hydromorphone is a common alternative to epidural analgesia. Morphine should be used cautiously due to its greater effect on the sphincter of Oddi.
- **Transversus Abdominis Plane (TAP) Block**
  TAP blocks may provide effective analgesia for incisional pain while reducing opioid requirements.
- **Non-Opioid Analgesics**
  Acetaminophen can be used as part of multimodal analgesia. Nonsteroidal anti-inflammatory drug (NSAIDs) are generally avoided due to their potential nephrotoxicity. Gabapentinoids may be beneficial, particularly in patients with neuropathic pain.

- **Transition to Oral Analgesia**
  Early transition to oral analgesics should be planned as the patient recovers. Effective pain management contributes to improved outcomes by:
  - Facilitating early mobilization
  - Reducing pulmonary complications
  - Improving patient satisfaction
  - Potentially reducing the stress response

Anesthesia-Related Complications

Cardiovascular Complications

Cardiovascular events are common after pancreas transplantation, particularly in patients with pre-existing cardiac disease or autonomic neuropathy. These include the following:

- Myocardial ischemia and infarction
- Arrhythmias (particularly atrial fibrillation)
- Heart failure exacerbation
- Hypertensive crisis

Risk factors include fluid shifts, electrolyte abnormalities, sympathetic activation, and immunosuppressive medication effects. Prevention strategies include optimization of preoperative cardiac status, careful intraoperative hemodynamic management, and vigilant postoperative monitoring.

Respiratory Complications

Respiratory complications occur in 15–30% of pancreas transplant recipients and include the following:

- Atelectasis
- Pneumonia
- Pleural effusions
- Acute respiratory distress syndrome
- Pulmonary edema

Contributing factors include prolonged surgery, fluid overload, aspiration risk, and immunosuppression. Preventive measures include lung-protective ventilation strategies, early extubation when appropriate, aggressive pulmonary toilet, and early mobilization.

Renal Complications

Acute kidney injury may occur due to:

- Perioperative hypotension or dehydration
- Nephrotoxic medications
- Contrast agents
- Rhabdomyolysis

Prevention focuses on maintaining adequate renal perfusion, judicious use of potentially nephrotoxic agents, and close monitoring of renal function.

Neurological Complications

Neurological complications include the following:

- Posterior reversible encephalopathy syndrome
- Seizures
- Delirium
- Central pontine myelinolysis (from rapid correction of hyponatremia)

Risk factors include immunosuppressive agents (particularly calcineurin inhibitors), electrolyte disturbances, and pre-existing cerebrovascular disease.

Infectious Complications

The risk of infection is increased due to the following:

- Surgical complexity
- Immunosuppression
- Diabetes-related immune dysfunction
- Uremic state (in SPK transplantation)

Perioperative antibiotic prophylaxis and meticulous aseptic technique are essential preventive measures.

Graft-Specific Complications

Anesthetic management may influence the risk of:

- Graft thrombosis (from hypotension or hypercoagulability)
- Pancreatitis (from ischemia–reperfusion injury)
- Anastomotic leaks (from technical issues)
- Bleeding (from coagulopathy)

Early recognition and management of these complications are crucial for graft survival [41].

Outcomes and Prognosis

The success of pancreas transplantation has improved significantly over the past decades, with current 1-year graft survival rates of:

- 86% for SPK transplantation
- 79% for pancreas after kidney transplantation
- 76% for pancreas transplantation alone [42]

Patient survival rates are excellent, with 1-year survival exceeding 95% and 5-year survival of approximately 90% [43].

Anesthetic management may influence outcomes through:

- Optimization of perioperative hemodynamics
- Prevention of ischemia–reperfusion injury
- Maintenance of adequate graft perfusion
- Prevention of complications
- Effective immunosuppression facilitation

Quality of life improvements after successful pancreas transplantation include the following:

- Insulin independence
- Improved glycemic control
- Stabilization or improvement of diabetic complications
- Enhanced overall well-being

These benefits must be weighed against the risks of surgery and long-term immunosuppression.

Future Directions

Several emerging areas may influence the anesthetic management of pancreas transplantation in the future.

Enhanced Recovery After Surgery Protocols

Implementation of enhanced recovery after surgery pathways for pancreas transplantation may reduce complications, length of stay, and costs [44]. Key components include the following:

- Preoperative carbohydrate loading
- Minimally invasive surgical approaches, when feasible
- Goal-directed fluid therapy
- Multimodal analgesia with opioid-sparing techniques
- Early mobilization and feeding

Advances in Monitoring Technology

Novel monitoring modalities may improve perioperative management:

- Continuous non-invasive cardiac output monitoring
- Tissue oximetry
- Advanced coagulation monitoring
- Continuous glucose monitoring

Pharmacological Advances

New agents and strategies may enhance outcomes:

- Novel immunosuppressive regimens with fewer side effects
- Targeted anti-inflammatory agents to reduce ischemia–reperfusion injury
- Improved anticoagulation strategies for thrombosis prevention

Alternative Transplantation Approaches

Evolution of transplantation techniques may alter anesthetic requirements:

- Laparoscopic and robotic-assisted pancreas transplantation
- Bioengineered pancreatic tissue transplantation
- Stem cell-derived islet transplantation [37]

Artificial Intelligence and Decision Support

Integration of artificial intelligence-based decision support systems may optimize:

- Preoperative risk stratification
- Intraoperative management algorithms
- Predictive models for complications
- Personalized immunosuppression protocols

These advances have the potential to further improve outcomes and expand access to pancreas transplantation.

Conclusion

Anesthetic management for pancreas transplantation requires a comprehensive understanding of the unique challenges presented by this complex procedure. The population of patients undergoing pancreas transplantation typically has significant comorbidities, including diabetes-related end-organ damage, which necessitates careful preoperative assessment and optimization [6].

The intraoperative period demands meticulous attention to hemodynamic stability, fluid management, glycemic control, and prevention of complications [3]. The anesthesiologist must anticipate and manage the physiological changes associated with reperfusion, which can be particularly profound in pancreas transplantation [34].

Postoperative care focuses on maintaining graft perfusion, preventing thrombosis, managing pain, and facilitating the transition to immunosuppressive therapy [41]. A multidisciplinary approach involving transplant surgeons, anesthesiologists, intensivists, and transplant physicians is essential for optimal outcomes.

As surgical techniques and immunosuppressive regimens continue to evolve, anesthetic management must adapt accordingly [45]. The integration of enhanced recovery protocols, advanced monitoring technologies, and novel pharmacological approaches holds promise for further improving the success of pancreas transplantation and enhancing patient experiences.

In conclusion, the anesthesiologist plays a crucial role in the complex care of pancreas transplant recipients, with direct impact on patient and graft outcomes. A thorough understanding of the unique aspects of this procedure, combined with meticulous perioperative management, contributes significantly to the success of this life-changing intervention for patients with diabetes.

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Anesthesia for Intestinal Transplant

8

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Introduction

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Intestinal transplantation is a complex and specialized procedure performed in patients with end-stage intestinal failure (IF), following an irreversible loss of gastrointestinal (GI) tract function [1]. In addition, an intestine transplant is the least frequent abdominal organ transplant. As medical therapy for the management of IF has improved, the number of intestinal transplants has decreased over time [2]. End-stage IF results from chronic debilitating diseases such as short bowel syndrome (SBS), chronic intestinal pseudo-obstruction, or other severe, irreversible intestinal disorders, such as abdominal tumors and total parenteral nutrition (TPN)-related complications [3]. Outcomes for intestine transplant have improved over the decades and are better for pediatric patients than adults. However, the intestine graft is particularly prone to graft failure, and the rates of graft failure have remained relatively stable. Intestinal transplantation poses a unique set of challenges for the anesthesiologist due to its multifaceted physiological considerations, the surgical complexity, and the intensive and prolonged postoperative management required.

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Epidemiology of Intestinal Failure

IF is a rare but serious condition characterized by the inability of the gut to absorb sufficient nutrients, fluids, and electrolytes to sustain life without intravenous (IV) supplementation [4]. It can result from congenital, surgical, or disease-related causes, leading to significant morbidity and a healthcare burden (Table 8.1 MS) [8]. Many causes of IF ultimately can lead to short gut syndrome (SGS) and ultra-short gut syndrome (USGS) when there is a functional or anatomical absence of a portion of the small intestine. USGS is defined as <20 cm of residual small intestine in adults, or < 10 cm of residual small intestine in children, and typically is associated with a worse outcome than patients with SGS [5, 9]. Advances in nutritional support and medical therapies have improved survival; however, IF remains a challenging condition requiring specialized care such as long-term parenteral nutrition (PN). While long-term home TPN is essential for patients with irreversible IF, it incurs high recurring costs and is associated with serious complications [10]. Chronic TPN use carries significant morbidity. It can lead to cholestatic liver disease, resulting in listings for simultaneous liver and intestine transplant. Children with IF on TPN also have a high incidence of associated liver disease and are therefore often listed for combined liver and intestine transplants [9]. TPN-related complications, including recurrent life-threatening line sepsis, fungal infections, distant infections such as endocarditis or osteomyelitis, or thrombosis of the central vessels with

Table 8.1 Common indications for intestine or multivisceral transplant [2, 5–7]

Short Gut Syndrome:
Pediatric patients:
Congenital causes
Gastroschisis, malrotation, volvulus
Non-congenital causes
Necrotizing enterocolitis
Adult patients:
Inflammatory bowel disease (Crohn's disease)
Familial adenomatous polyposis
Autoimmune disease
Prior surgical resections
Trauma
Failure of TPN
IFALD
Recurrent central line-associated sepsis
Fungal sepsis
Distant life-threatening infection, such as endocarditis or osteomyelitis
Thrombosis of two or more central veins
Malignancy
Desmoid tumor most commonly
Mesenteric thrombosis/intestinal infarction
Intestinal dysmotility syndrome
Graft failure after intestinal transplant

progressive loss of central access points, can all be indications for intestine transplant [6, 11]. Intestinal transplantation, though costly upfront, may offer a more cost-effective long-term solution in selected patients by reducing reliance on home PN and its associated complications and healthcare burdens [12, 13]. Therefore, early referral to a transplant center should be considered for patients at higher risk for developing complications, such as liver disease and venous thrombosis.

Incidence and Prevalence

The epidemiology of IF varies by underlying cause, geographic region, and healthcare system. Due to its rarity and variations in diagnostic criteria, determining the incidence and prevalence of IF is challenging.

In developed countries, the annual incidence of chronic IF (requiring long-term PN) is estimated to be two to five cases per million population in adults and four to six cases per 100,000 live births in neonates [14, 15]. The prevalence of IF in the United States is 75 per million [16]. In children, IF may result from conditions such as gastroschisis, malrotation, volvulus, or necrotizing enterocolitis. In adults, IF may result from prior surgical resections, trauma, inflammatory bowel disease, autoimmune disease, familial polyposis syndrome, or other cancers [2, 5, 11]. Advances in PN and intestinal rehabilitation have significantly improved survival [17]. Approximately 70–85% of patients require parenteral nutrition within 5 years of their diagnosis [18].

IF is associated with complications such as catheter-related infections, liver dysfunction, and metabolic imbalances [19]. Intestinal transplants are most frequently done for patients with IF who develop intractable TPN-related complications [20, 21]. The survival post-transplant at 1 year, 5 years, and 10 years was 74%, 42%, and 26%, respectively [22, 23].

According to the Organ Procurement and Transplantation Network (OPTN), there were 179 candidates on the intestinal transplant waiting list in the United States as of April 2025. This figure reflects a continued decline in the number of individuals awaiting intestinal transplants. In 2022, 167 candidates were waiting for isolated intestine transplants and 180 for combined intestine-liver transplants, for a total of 347 candidates. The decrease in waiting list numbers is attributed to advancements in medical and surgical care for patients with IF, resulting in improved management and a leading to improved management and reduced need for transplants [24].

As of the most recent data from the OPTN, 95 intestinal transplants were performed in the United States in 2023. This figure includes both isolated intestinal transplants and combined multivisceral procedures, such as intestine-liver and intestine-liver-pancreas transplants. This trend suggests a potential increase in the number of transplants performed in 2024, but the exact figure will be confirmed upon the release of the 2024 data.

Indications for Intestinal Transplantation

The indications of intestinal transplantation are as follows:

1. Failure of PN, which includes complications such as chronic liver disease or end-stage liver failure due to PN-associated cholestasis, recurrent catheter-related bloodstream infections (CRBSIs), and loss of central venous access due to multiple thromboses [25, 26];
2. Severe SBS when the remaining intestine is inadequate for sufficient absorption despite optimized medical and surgical interventions;
3. Intestinal dysmotility disorders, such as chronic intestinal pseudo-obstruction, leading to persistent, severe GI dysfunction unresponsive to medical therapy [27];
4. Congenital or acquired conditions, such as extensive bowel resections from trauma, radiation enteritis, or congenital mucosal disorders that severely impair nutrient absorption;
5. IF-associated liver disease (IFALD), which occurs when there is progressive liver dysfunction secondary to long-term PN dependency [25];
6. Combination organ transplants, where patients with multi-organ failure require combined liver-intestine or multivisceral transplantation. Table 8.1 summarizes the indications of intestinal transplantation.
7. Graft failure, most commonly due to acute cellular rejection, is more frequent in intestine transplant recipients compared to other abdominal organ transplants [2]. Rejection rates for intestine transplant are related to high alloimmune sensitization and the need for complicated immunosuppression in these patients [2, 28]. As a result, approximately 20% of patients waitlisted for intestinal transplants are waiting for re-transplant.

Contraindications of Intestinal Transplantation

Contraindications for intestinal transplant include patients with non-resectable malignancies, life-threatening other non-correctable illnesses, immune deficiencies, psychological instabilities leading to potential non-compliance with immunosuppressive therapy, and the absence of adequate central venous access in the 6 months after transplantation [29, 30].

Types of Intestinal Transplantation

Intestinal transplantation is categorized into different types based on the extent of organ involvement and the underlying pathology [7, 31]:

1. **Isolated Intestinal Transplant:** The isolated small bowel graft consists of the entire jejunum and ileum, as illustrated in Fig. 8.1a. It is performed in patients

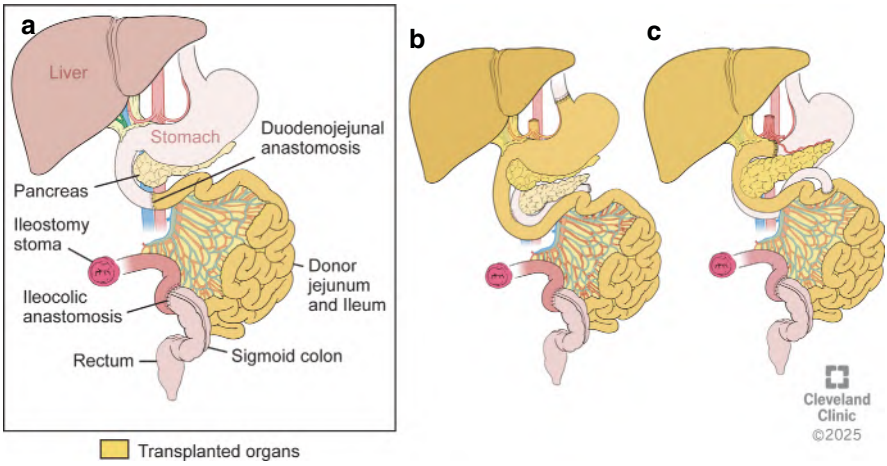

Fig. 8.1 Three main types of intestinal transplants. (**a**) Isolated intestinal transplant. (**b**) Multivisceral transplant, where the donor organs include the liver, stomach, duodenum, pancreas, and small bowel. (**c**) Combined liver-intestinal graft, which also contains, in continuity, the donor duodenum and pancreas

with irreversible IF without significant liver dysfunction. The small intestine alone is transplanted to restore enteral nutrition. For some candidates, such as those with Crohn's colitis, transplantation of the colon along with the small intestine may be necessary as well [7]. The colon has been increasingly included with the small bowel as colon-inclusive grafts have shown improved graft survival [7]. Inclusion of the left colon with intestine transplant has also been associated with a decreased risk of dehydration and diarrhea, and improved patient satisfaction [21].

2. **Multivisceral Transplant:** It involves transplantation of multiple abdominal organs, including the stomach, pancreas, liver, and intestines (Fig. 8.1b). This is considered in cases of extensive gastro-IF or abdominal malignancies requiring en bloc organ replacement. The advantage of the combined liver, small bowel, and pancreas allograft is that no hilar dissection of the graft is needed, and therefore, there are fewer risks for donor-related vascular or biliary complications [32, 33].
3. **Combined Liver-Intestine Transplant:** It is indicated for patients with IFALD due to long-term PN. Both the liver and the intestines are transplanted simultaneously without the pancreas graft [34] (Fig. 8.1c).
4. **Modified Multivisceral Transplant:** It includes transplantation of the stomach, pancreas, and intestines but excludes the liver. It is used in cases where liver function is preserved.

Intestinal Organ Allocation Policy and Current Organ Demand

Based on data from UNOS, the allocation of intestinal organs in the United States is managed by the OPTN, under the guidance of the Health Resources and Services Administration.

Organ Allocation Policy

In February 2020, the OPTN implemented a new liver and intestinal organ allocation system to improve matching between donors and recipients. This system prioritizes candidates based on medical urgency and compatibility, aiming to enhance transplant outcomes. The allocation process considers various factors, including medical urgency, immunological and physiological compatibility, and geographic location. The demand for intestinal transplants often exceeds the available supply, leading to extended waiting times for patients in need. It is important to note that only slightly more than 50% of people on the waiting list will receive an organ within 5 years, highlighting the critical need for organ donors [35].

The OPTN maintains a secure database containing national data on the candidate waiting list, organ donation, matching, and transplantation. This system helps transplant institutions effectively match waiting candidates with donated organs, ensuring equitable and efficient allocation.

Selection Committee Process

The selection process for intestinal transplantation is a highly specialized, multidisciplinary endeavor that aims to identify candidates who will derive the most significant benefit from the procedure while ensuring optimal use of limited donor organs. Evaluation begins with referral and proceeds through a comprehensive assessment by a transplant selection committee, which typically includes transplant surgeons, gastroenterologists, anesthesiologists, transplant coordinators, dietitians, social workers, psychologists or psychiatrists, financial counselors, and, when appropriate, ethicists [36]. The medical evaluation focuses on confirming the presence of irreversible IF and assessing the degree of dependence on TPN, associated complications such as liver dysfunction, recurrent sepsis, loss of venous access, and nutritional status.

Psychosocial evaluation plays a crucial role in determining the patient's ability to adhere to post-transplant care, medication regimens, and follow-up, as well as assessing social support systems and screening for psychiatric comorbidities or substance use disorders.

The surgeon's evaluation is crucial in understanding the surgical complexity and ultimately the duration of the surgery and bleeding risk. Often, intestine transplant candidates have had extensive surgical resections, leading to adhesions and

increasing the risk of bleeding during the dissection phase of the operation. Understanding the patient's GI anatomy is critical to mitigating this risk. Bleeding risk may also be increased in the setting of tumors that are invading or near major vasculature.

Additionally, a financial assessment ensures that the patient has access to the resources necessary for transplant-related care. The decision to list a patient is made collectively, with consensus from the committee, balancing clinical urgency, projected outcomes, and ethical considerations inherent in the allocation of scarce transplant resources.

Organ Selection for Intestinal Transplantation

Successful outcomes in intestinal transplantation depend heavily on the careful selection of donor organs. Multiple factors are considered to ensure graft viability, minimize postoperative complications, and improve long-term survival. A critical aspect of donor selection is matching the donor and recipient in terms of size and vascular anatomy [37]. The donor graft must be >200 cm for adult recipients or >160 cm for pediatric recipients. For deceased donors, grafts include the terminal ileum [9]. Donors must be free of malignancy, intra-abdominal infection, and bowel ischemia [11]. Patients with a history of SGS may have limited space in the abdominal cavity. Thus, graft size must account for closure of the abdominal wall, with ideal grafts coming from donors who are less than half the size of the recipient's body weight [7]. The ability to close the abdominal wall is important for preventing postoperative complications like sepsis. Additionally, a tight abdominal wall closure may lead to compartment syndrome or difficulty ventilating, as well as elevated pressure on the graft, which can ultimately compromise blood flow and viability [7]. While uncommon, size reduction of intestine grafts to improve size matching has been studied and may be of value in the pediatric population to increase the availability of smaller grafts [38].

The donor's hemodynamic stability and the duration of ICU stay are also considered, as prolonged hypotension or high-dose vasopressor use may compromise intestinal perfusion. Because the perfusion of the bowel via the splanchnic circulation is sensitive to instability and hypotension, donors who have experienced cardiopulmonary arrest must be evaluated particularly carefully [7].

The intestine is particularly sensitive to ischemia–reperfusion injury, making it essential to minimize cold ischemia time [39]. Histologic evaluation and inspection at the time of procurement are used to assess bowel viability. Evidence of edema, discoloration, or serosal injury may lead to exclusion of the graft as a suitable organ.

Because of the intestine's sensitivity to rejection, donor–recipient HLA matching is critical. Intestine transplant candidates are often sensitized due to multiple prior surgeries, infections, and transfusions, so matching can be complex [7]. Better HLA matching is associated with a decreased risk of graft failure [23].

Living Donation

Living donation is a relatively new technique for intestinal transplant and remains infrequently performed. Living donor intestine transplant shows promise in small studies, with patient and graft survival similar to those of recipients of deceased donor grafts [23, 40]. The use of live donor intestines has the potential to shorten wait times for patients listed for transplants by increasing the number of organs available for transplantation. Planned live donor intestine transplants shorten cold ischemic time, which is associated with higher quality grafts [30]. Living donation, due to its elective nature, may also allow for better HLA matching between donor and recipient [11]. Living donation may be especially indicated for rare recipients with identical twins or HLA-identical siblings [9]. For living donation, the donor operation is performed by removing the distal ileum (200 cm for adult recipients, 160 cm for pediatric recipients) and the ileocolic artery and vein. The donor retains at least 20 cm of terminal ileum and the ileocecal valve [9].

Surgical Considerations

Surgical anatomy, as illustrated in Fig. 8.2, and the nature of vascular anastomoses in intestinal transplantation present complex intraoperative challenges. The vascular supply of the intestinal graft (Fig. 8.3) primarily includes arterial inflow through the

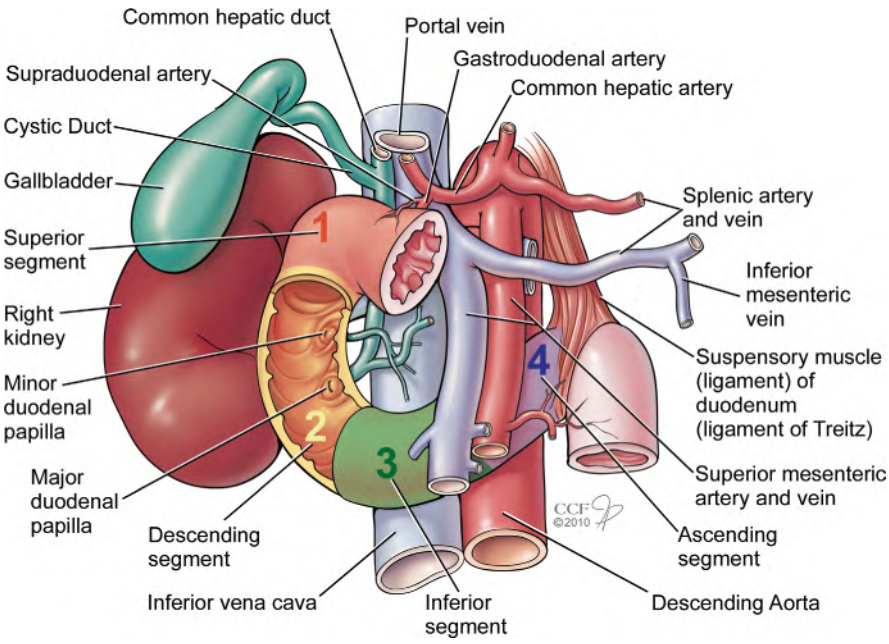

Fig. 8.2 Anatomy of the GI tract

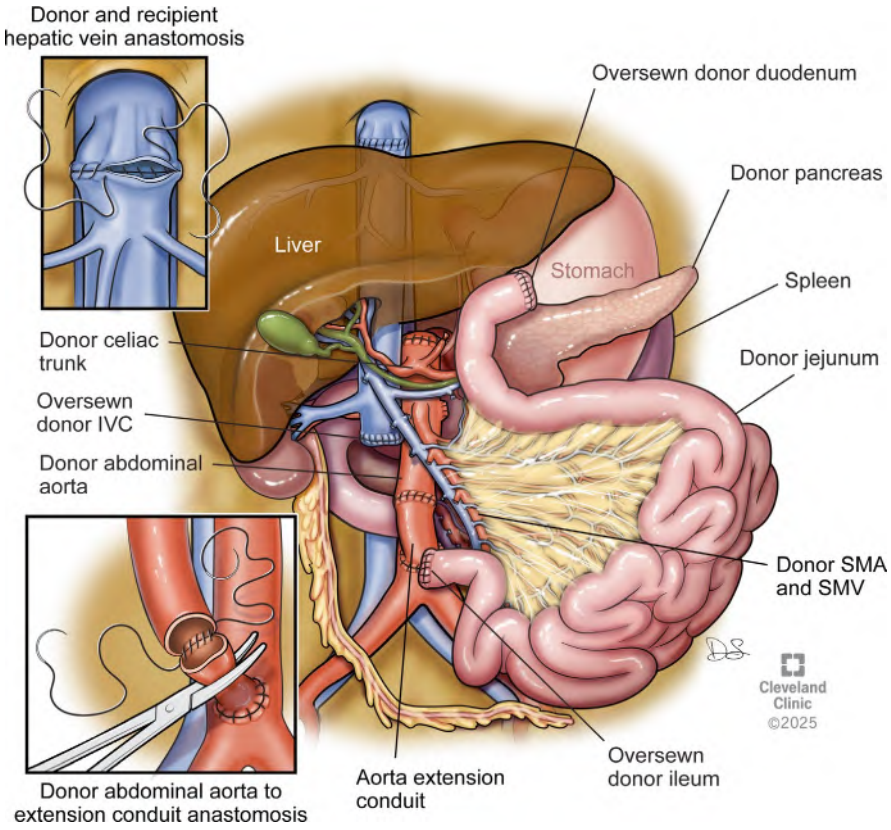

Fig. 8.3 The vascular supply of the intestinal graft

superior mesenteric artery (SMA). The donor SMA is anastomosed to the recipient's aorta or iliac artery to establish an arterial inflow. The graft venous drainage occurs through the superior mesenteric vein (SMV) or the portal vein [41]. Understanding the orientation and integration of these vascular structures is critical, and therefore, having surgeons evaluate the suitability for the recipient is paramount for the anesthesiologist to anticipate and manage significant hemodynamic changes during surgery.

Surgical technique for an isolated small intestine transplant typically consists of a large midline incision from xiphoid to pubis for exposure, with a careful and lengthy dissection phase to remove the recipient's remaining small intestine and potentially colon [21]. As the main indication for intestine transplant is SGS, most patients have substantial adhesions from prior surgeries or abdominal infections, making for a difficult dissection where risk for blood loss is high [21]. Inadvertent injury to surrounding structures can be difficult to avoid without meticulous dissection due to adhesions that may be present on major vasculature, ureters, bladder, and duodenum. Often, transplant surgeons will elect for placement of ureteral stents

before dissection to help identify the ureters intraoperatively to decrease the risk of accidental injury during dissection [21].

Once the recipient's native intestine is removed, dissection of the necessary vascular structures is performed, exposing the recipient's infrarenal aorta and inferior vena cava (IVC) [11]. The mesenteric vascular reconstruction for implanting the donor intestine may be orthotopic, heterotopic, or a combination of the two. Orthotopic mesenteric vascular reconstruction allows drainage of the donor organ into the portal circulation by connecting the donor mesenteric vessels to the recipient SMA and vein. Depending on the recipient anatomy, vascular grafts may be needed for proper flow due to the angle of the mesenteric vasculature [21]. Heterotopic implantation is achieved by using donor iliac artery and vein interposition grafts to anastomose the donor mesenteric vessels to the recipient aorta and vena cava. This heterotopic technique is frequently utilized due to thrombosis of the portal mesenteric system [7, 21]. Heterotopic reconstruction is also preferred in cases of fibrosis, vascular compromise, and liver congestion [31]. Creation of the arterial and venous conduits requires a partial cross-clamp across the infrarenal aorta, followed by partial clamping of the IVC; this has hemodynamic implications discussed below. After the arterial and venous conduits are completed, the graft vasculature is connected. Before reperfusion, a blood flush may be performed by opening the arterial inflow to the graft and flushing through the SMV anastomosis [7].

The proximal intestinal anastomosis is most commonly recipient jejunum-to-donor jejunum, but duodenum-to-jejunum or stomach-to-jejunum may be performed depending on recipient anatomy [21]. GI anastomosis may be seen more often in multivisceral transplants due to the decreased rate of rejection as compared with an isolated intestine transplant [21]. Distally, the donor intestine may be connected via ostomy or anastomosis to the recipient colon. Distal anastomosis of the graft to the recipient colon without ostomy is possible if the recipient's distal GI anatomy is viable [42]. Isolated intestine transplants more commonly utilize one or more ostomies for the distal connection of the donor intestine [21]. An ostomy provides an easily accessible biopsy site postoperatively, allowing surveillance for histologic signs of infection or rejection, which are more common with isolated intestinal transplants [43]. This approach allows early recognition of rejection, which is crucial for reversal of the rejection process [43]. Without an ostomy, the intestine graft is not as easily accessible for biopsy, and recipients must undergo serial colonoscopies for biopsies to assess for signs of graft rejection [31]. Serial colonoscopies require multiple anesthetics and carry an increased risk of perforation [31]. Recent data suggest that intestine transplant recipients without ostomies can be managed without protocolized endoscopy and biopsy, with biopsy only performed when rejection is suspected [42]. However, creation of an ostomy may increase the risk of dehydration and electrolyte disturbances from high-output GI loss, potentially lengthening hospitalization and postoperative recovery time [21]. Intestine transplant recipients without ostomies required fewer anti-diarrheal medications than those with ostomies [42]. Ostomy placement is also associated with lower patient satisfaction [21].

A hybrid ostomy, disconnected from the GI tract but connected to the primary graft via a vascular pedicle, has also been reported [21]. To accomplish this, part of the ileum is divided, creating two side-by-side layers, one of which is isolated from the rest of the GI tract and made into an ostomy, the other is anastomosed in a colon-colon fashion [31]. Hybrid ostomy allows for the recipient and donor intestinal tract to be in continuity, allowing patients to avoid the disadvantages of a functioning ostomy while maintaining the benefits of an ostomy for serial biopsies [31]. The terminal ileum is frequently the first part of the graft to show rejection on biopsy, making a hybrid ostomy at the terminal ileum the most useful location for future biopsies [21].

Preoperative Considerations

IF is a complex clinical condition characterized by the inability of the GI tract to maintain adequate nutrition and hydration [44]. It often necessitates long-term PN and carries a significant risk for multisystem organ dysfunction.

Proper preoperative evaluation of these patients is critical for risk stratification, optimization, and perioperative planning.

1. *Patient Assessment:*
   - *Neurological Considerations:* Neurologic dysfunction in patients with IF may stem from micronutrient deficiencies, metabolic disturbances, or hepatic encephalopathy. Thiamine deficiency is a recognized cause of Wernicke's encephalopathy, especially in patients with chronic malnutrition or prolonged vomiting [45]. Hyponatremia or other electrolyte imbalances may also contribute to altered mental status or encephalopathy. A careful history and physical examination should be performed, and relevant laboratory tests, especially serum sodium, magnesium, and thiamine levels, should be obtained.
   - *Cardiovascular Function:* Patients with IF often have chronic autonomic dysfunction and massive fluid shifts, which can cause hypotension and arrhythmias. Chronic anemia, central venous access complications, and the presence of high-output states (e.g., secondary to arteriovenous fistulas or chronic inflammation or associated cirrhosis) can lead to cardiac strain or failure. Sepsis-induced cardiomyopathy is another important perioperative consideration, particularly in patients with CRBSIs. A detailed cardiovascular evaluation, including an EKG and echocardiogram, is required to evaluate the baseline cardiac function. Ischemic workup in the form of stress echocardiography or left heart catheterization may be deemed necessary in patients with risk factors for ischemic heart disease. Most institutes utilize the liver transplant recipient cardiac workup protocol for intestinal transplant. Biomarkers such as BNP or troponin may aid in assessing cardiac function in selected cases [15, 33, 46].
   - *Respiratory System:* Chronic malnutrition leads to atrophy of respiratory muscles, which can reduce ventilatory reserve and increase the risk of

postoperative respiratory failure. Pulmonary complications may also arise secondary to sepsis or aspiration in patients with GI dysmotility or gastroparesis. Preoperative chest imaging may reveal infiltrates or effusions. Arterial blood gas analysis and pulmonary function tests should be considered in patients with significant respiratory symptoms or poor baseline functional status.

- *Hepatic Dysfunction:* Hepatic dysfunction is common in patients with long-term PN, and can lead to steatosis, cholestasis, or fibrosis [15, 47]. This TPN-associated liver disease results from multiple factors, including nutrient composition, infection, and lack of enteral stimulation. Laboratory evaluation should include a full liver function panel (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin) and a coagulation profile (prothrombin time (PT)/international normalized ratio (INR)). Non-invasive liver imaging or elastography may help assess the extent of fibrosis. Recognition of hepatic impairment is vital given its impact on drug metabolism, coagulation, and overall surgical risk.
- *Renal Considerations:* Renal dysfunction in IF is multifactorial and may be caused by chronic dehydration, nephrotoxic medications, or oxalate nephropathy, particularly in patients with extensive ileal resection. Volume depletion due to high stoma or ostomy outputs is a common cause of pre-renal azotemia. Furthermore, high stoma output, decreased intestinal absorption, or diarrhea can cause hypokalemia, hypomagnesemia, and acidosis, which can lead to renal dysfunction. Nutrient deficiencies, including vitamin D and vitamin B12, may lead to osteoporosis and anemia, respectively [48]. Baseline renal function should be evaluated with serum creatinine, estimated glomerular filtration rate (GFR), and electrolyte panels, including magnesium and phosphate. Urinalysis may reveal proteinuria or oxalate crystals.
- *Infection Risk:* Patients with end-stage IF are chronically immunocompromised due to the prolonged use of PN, in part because the lipid supplements often contain ω-6 fatty acids, which are pro-inflammatory and associated with suppression of the immune system [49]. Blood cultures should be obtained in febrile patients or when sepsis is suspected. The anesthesiologist should work closely with the transplant team to minimize infection risks and optimize prophylactic antibiotic therapy. Antibiotic prophylaxis should be tailored based on the patient's microbiological history and local resistance patterns.
- *Coagulopathy and Hematologic Status:* Anemia is prevalent in this population due to deficiencies in iron, vitamin B12, folate, or copper. Coagulopathy may occur secondary to vitamin K deficiency, often resulting from fat malabsorption. Malnutrition, chronic use of anticoagulants, liver dysfunction, and sepsis can all contribute to coagulation abnormalities in this cohort of patients. Evaluation should include a complete blood count, iron studies, vitamin B12 and folate levels, and coagulation parameters. A history of bleeding diathesis requires evaluation of coagulopathy, while a history of deep vein thrombosis, pulmonary embolism, or portal vein or mesenteric thrombosis requires hypercoagulability evaluation. Some patients may have components of both hyper- and hypocoagulability (Klucniks). Some of these patients may have a rare

cause of intestinal venous thrombosis, a JAK2 mutation, which can result in hypercoagulability that leads to a thrombus that results in their IF [50]. Portal vein thrombosis with or without concurrent liver disease can lead to portal hypertension and the development of intrabdominal varices, which increases the risks of rapid hemorrhage during surgical dissection. Patients with a history of thrombophilia may be on long-term anticoagulation [15]. The timing of the last dose of anticoagulant, potential strategies for reversal, and the plan to restart anticoagulation should be discussed before surgery. TPN-associated liver disease and cirrhotic coagulopathy should be assessed with platelet count, (PT/partial thromboplastin time (PTT)), and INR. Viscoelastic testing is also potentially valuable to consider for whole blood clotting [51]. The risk of significant hemorrhage is typically higher during multivisceral transplants, which include the liver, compared to isolated small bowel transplants [33, 52].

- *Nutritional Status:* Cachexia, which can include sarcopenia, is directly associated with increased mortality perioperatively. IF can lead to chronic malnutrition, with associated hypoalbuminemia and impaired wound healing, dyselectrolytemias, and micro and macronutrient deficiencies such as fat-soluble vitamins (A, D, E, and K) deficiency. Almost all patients are on PN, and PN is continued perioperatively to prevent hypoglycemia and its complications. It is critical to assess the patient's nutritional and hydration status to ensure that deficits are optimized preoperatively. Assessment of nutritional status includes serum albumin and prealbumin levels, as well as tracking weight loss and body mass index. In some cases, indirect calorimetry may be used to determine energy requirements more precisely. An assessment for sarcopenia, which can be performed noninvasively with computed tomography (CT) imaging, is also beneficial in this population and is associated with worse outcomes in a wide variety of surgeries, including solid organ transplants [53]. A multidisciplinary nutrition team should be involved to optimize preoperative support, which may include supplemental enteral or PN.
- *Metabolic Dysfunction:* Electrolyte disturbances are frequent and include hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia. These abnormalities are often exacerbated by high-output stomas or SBS. Patients are also at risk for metabolic bone disease due to chronic vitamin D and calcium malabsorption. Laboratory tests should include comprehensive metabolic panels, serum calcium, phosphate, vitamin D, parathyroid hormone levels, and bone density scans.
- *Vascular Access Considerations:* Preoperative evaluation of vascular access is a crucial component in the management of patients with IF, particularly those dependent on long-term PN. These patients often have a history of multiple central venous catheter (CVC) placements, which increases the risk of central venous stenosis or thrombosis [49]. In fact, loss of two or more central access locations is an indication for intestinal transplant [11]. Patients with central vascular thrombosis should be assessed for superior vena cava syndrome [15]. Physical examination should assess signs of venous congestion, collateral circulation, or catheter-related skin changes. Many patients will

arrive for transplant with in situ central access for TPN. These lines often have multiple access ports that can be sterilely accessed for use during the procedure [54]. Ideally, central access is obtained above the diaphragm because femoral and other lower-body access will be rendered unusable during vena cava clamping during the transplant. Preservation of viable access sites is essential, as options may become limited over time. A thorough vascular history should be obtained, including prior sites of catheter placement and complications such as infections or thrombosis. Imaging studies such as Doppler ultrasound of the neck and upper extremities, or contrast-enhanced venography, may be indicated to assess patency and identify suitable sites for future catheter placement. Advanced imaging, such as CT or magnetic resonance venography, may be necessary in patients with complex or previously occluded venous anatomy.

When surgical intervention is planned, coordination with interventional radiology (IR) or vascular surgery may be needed to ensure secure and functional central venous access perioperatively. In select cases, tunneled catheters or port placement may be done in advance of surgery to facilitate intra- and postoperative nutrition and medication administration. Patients with occluded central access points should be referred to IR for placement of central access or peripherally inserted CVCs. In one center that studied non-conventional vascular access in intestinal transplant candidates, this approach yielded a success rate of over 95%. However, procedure-related complications were 11%, including 1% procedure-related mortality [55].

2. *Optimizing Organ Function:* Before surgery, any underlying organ dysfunction (hepatic, renal, or pulmonary) should be optimized. Renal function should be monitored, as acute kidney injury is common in patients with IF due to factors such as dehydration, sepsis, and nephrotoxic drugs.
3. *Blood Product Crossmatch and Transfusion Preparation:* Intestinal transplant recipients may require multiple blood products due to preoperative anemia, blood loss during surgery, and intraoperative complications. A crossmatch should be performed with the anticipation of needing fresh-frozen plasma, platelets, or packed red blood cells. This should ideally be performed well in advance, as many of these patients have had prior transfusions and may have alloimmunization profiles that complicate and delay identification and procurement of matched units. Early communication with blood bank staff is critical to ensure that compatible products are ordered and prepared.

Intraoperative

Induction and Preparation

To properly care for these patients in the OR, the anesthesia team must be prepared to place multiple indwelling lines. Isolated intestine transplants can, in most cases, be performed with a single arterial line (for hemodynamic monitoring and arterial

blood gas analysis), a large-bore CVC, or a small-bore central line combined with a peripheral rapid infusion catheter for volume infusion. As previously discussed, patients presenting with chronic small bowel insufficiency are typically on chronic PN. As a result, these patients may have limited vascular access due to thrombotic and sclerotic/stenotic complications of chronic indwelling central lines [56, 57]. However, in these cases, they may require surgical cutdown or IR to access the IVC, hepatic veins, or even the right atrium [58]. In cases where venous access sites are limited, intraosseous access or even larger arterial access, such as the femoral artery, can provide temporary access until definitive venous access is obtained [58]. It is also possible to obtain percutaneous central access via the translumbar approach to the IVC. If the patient has patent internal jugular (IJ) veins, the most common method of access would be to obtain percutaneous IJ access and place a double-lumen CVC, in addition to large (18-gauge or larger) peripheral IV access. Should additional peripheral access be inadequate but IJs are patent, it may be necessary to place secondary central access using an introducer to facilitate large-volume resuscitation. The benefit of multiple lumens of central access is the availability of one for monitoring central venous pressure, which can assist in guiding volume resuscitation.

These cases, while infrequent, can lead to significant hemodynamic swings, and monitoring of blood gases and electrolytes is necessary throughout the case. To facilitate proper monitoring, a 20-gauge arterial line can be placed into the radial artery of either extremity. However, since this population tends to have a high rate of critical illness, the radial arteries may not be patent or may be too small to cannulate, or may be diminished from sclerosis. In these patients, intra-arterial access can be obtained via the brachial artery using the same-sized catheter, as this is a safe alternative [59, 60].

Other monitoring modalities that can be considered are non-invasive/semi-invasive cardiac output monitors, pulmonary artery catheters (PACs), and transesophageal echocardiography (TEE). While the cardiac output monitors have the benefit of either being entirely non-invasive or using the data of the already present arterial line, it should be noted that they have been found to have a significant percentage error when compared to thermodilution, which is used in PACs. [15, 33, 52, 61–63]. However, the use of PACs and TEE is typically limited to patients with significant cardiovascular risk factors, as both of these modalities carry risk of significant complications but have limited utility in the low-risk solitary intestinal transplant recipient [64]. Multivisceral transplants involving a liver graft are generally performed with the same anesthetic considerations as liver transplants and are discussed separately.

Baseline arterial blood gas analysis should be performed and repeated at regular intervals throughout the procedure. Electrolyte disturbances, acidosis, and glucose homeostasis are crucial components of anesthetic management for these procedures. Patients with known coagulation abnormalities can also be monitored with viscoelastic testing; therefore, baseline viscoelastic testing is essential [15]. Normothermia should be maintained to prevent further coagulopathy. Cross-matched blood products should be prepared in advance, with many centers preparing at least 10 units of packed red blood cells [15, 33, 52].

Choice of Anesthetic

All cases are performed with general endotracheal anesthesia. Rapid sequence induction is commonly indicated in this population due to altered intestinal anatomy and the risk of delayed gastric emptying [48]. General anesthesia may be maintained with a volatile agent or total IV anesthesia. Neuromuscular blockade is essential to optimize surgical conditions. Neuromuscular blockade should be monitored using a quantitative train-of-four [65].

Analgesia

There is minimal literature on analgesia for intestinal transplants and, therefore, no expert consensus or standard of care. Analgesia can be achieved through a variety of avenues, including IV opioids such as fentanyl, hydromorphone, or methadone. Often, patients who present with complex surgical histories may have chronic pain and can benefit from multimodal analgesia, including non-opioid analgesics such as ketamine, regional analgesia, and referral to the pain management service after transplant [48].

Peripheral nerve blocks such as transverse abdominal plane (T6–L1 dermatomes), rectus sheath (midline incision), or quadratus lumborum (T4–L1 dermatomes) blocks may be considered [66]. However, abdominal wall muscle layers may be difficult to identify with ultrasound due to altered anatomy from loss of musculature. Neuraxial analgesia with a thoracic epidural to cover thoracic and abdominal dermatomes is an excellent option for patients without contraindications [52]. Contraindications to epidural placement include coagulopathy, thrombocytopenia, cirrhosis, and patient refusal. Patients who are on chronic anticoagulation may be candidates for epidural analgesia if the medications are held for the appropriate amount of time before placement and a plan exists for restarting anticoagulation in conjunction with proper epidural management [67]. Thoracic epidurals are most commonly associated with mild complications, including postoperative nausea and vomiting, pruritus, hypotension, motor weakness, and urinary retention [68]. Regional and neuraxial analgesia may decrease postoperative opioid consumption and improve pain control [68].

Phases of the Surgery and Anesthetic Considerations

Intestinal transplantations (ITx) are long, complex operations that can be divided into distinct phases based on the steps surgeons perform. By dividing it into these phases, it is easier to organize our understanding of the surgical aspects of the procedure and how that will affect our anesthetic management.

Dissection and Organ Preparation

The first phase of the case encompasses everything from opening the abdomen to preparing the intestines for implantation on the back table. The patients who make up this population have frequently had multiple abdominal surgeries preceding their transplant, which significantly increases the surgical complexity. This complexity increases the risks of the surgeons encountering multiple abdominal adhesions and aberrant anatomy, which can substantially prolong dissection and increase the risk of significant bleeding. Those with liver disease, portal hypertension, portomesenteric thrombosis, and those with tumors near major vasculature are also at high risk for hemorrhage. This population receiving only an intestine transplant typically does not come with the associated coagulopathy as liver transplant recipients do. As such, surgeons can usually obtain hemostasis without massive loss of blood [52].

In the absence of major hemorrhage, significant fluid shifts still occur during the 10- to 15-h surgical procedure. Fluid shifts occur from evaporative losses, third-space losses, disrupted hepatic drainage, systemic inflammatory response, and sequential clamping of the aorta and vena cava [15]. Endotoxin release from abdominal infection may also occur [33]. Continual assessment of volume status and replacement of losses should be at the forefront of the anesthesia team's mind in this phase. Patients receive a median of 6–10 L of balanced crystalloid [52, 62]. Typically, if colloid is needed, patients receive a median of 1–3 L and as much as 5.5 L of 5% albumin [52, 62]. Maintenance of a target hematocrit of 25–30% is standard. Most isolated intestine transplant recipients receive red blood cells, with a median of 2 units per case [52]. In the absence of major hemorrhage, plasma, platelets, and fibrinogen are rarely necessary [52]. Furthermore, because hypercoagulability with a history of thrombosis is prevalent in this population, it is advisable to only replete clotting factors and platelets after replacement of approximately 1 blood volume, or after transfusion of more than 5 units of red blood cells has occurred [52]. Use of viscoelastic testing to guide factor repletion can serve as a guide for targeted plasma, platelet, and fibrinogen transfusion.

Fluid administration requires particular attention due to the concern that possible fluid overload may increase bowel edema, put stress on the anastomoses, and increase rates of perioperative complications. While there is little data on the volume of fluid administration and outcomes related to intestinal transplant, this question has been explored for several types of open abdominal surgery. For example, in animal studies, a correlation has been shown between increasing amounts of fluid and breakdown of the small bowel anastomosis [69]. In pancreatoduodenectomy, IV fluid administration within the first day of surgery showed thresholds of 4400 mL to 6000 mL for significant postoperative complications [70, 71]. Similar thresholds have also been observed in non-abdominal surgery and are associated with postoperative pulmonary complications [72]. However, there have also been well-done large trials showing no benefit to fluid restriction, and even increased incidence of acute kidney injury [73]. Given the fragile and high-risk nature of this population, further investigation into ideal ranges of fluid resuscitation is warranted.

Most patients will require intermittent bolus or infusion of vasopressor medications. Phenylephrine is often sufficient; however, norepinephrine and vasopressin can also be utilized [52]. Inotropic agents, such as epinephrine and dobutamine, or prostaglandins, such as prostaglandin E1, may be used to increase perfusion to the donor graft [33]. Major fluid shifts require close monitoring of arterial blood gases for electrolytes, acid-base status, and hematocrit. Furthermore, high-volume red blood cell transfusion increases the risk of hyperkalemia.

It is also during this time that the intestines will be prepared for implantation into the recipient. When the surgical team is working on donor organ preparation, there may be periods where surgery on the recipient is paused. In this case, it is essential to ensure the abdomen is covered with dressings that retain moisture to reduce unnecessary insensible losses from evaporation.

Vascular Anastomoses

Following preparation of the recipient and donated organ, the surgeons will next work on the vascular anastomoses. For the arterial anastomosis, most commonly, the donor's SMA is directly connected to the recipient's aorta, though in some recipients, a donor-to-recipient SMA anastomosis is possible. An iliac artery graft from the donor is sometimes placed between the recipient aorta and the donor graft's SMA [7]. When anastomosis to the aorta is required, the surgeons will use either a partial or a complete clamp, depending on the recipient's anatomy and surgical technique. The clamp is usually placed infrarenally to maintain uninterrupted blood flow to the kidneys. Even with infrarenal aortic cross-clamping, acute kidney injury can occur from acute tubular necrosis [48, 74]. Cross-clamping leads to a catecholamine surge, activation of the renin-angiotensin-aldosterone system, and activation of inflammatory mediators, including complement, cytokines, endotoxins, and oxygen-free radicals. Disruption in microvasculature leads to decreased oxygen uptake and consumption. Regional wall motion abnormalities may be seen on transesophageal echocardiogram but are more common with supraceliac aortic cross-clamp placement [57, 74]. Should a larger or total clamp be required, as can be seen in Fig. 8.3, the anesthesia team should anticipate an acute increase in afterload that may increase blood pressure and afterload on the heart. Therefore, it is important to have antihypertensives with a short half-life, such as nitroglycerin or sodium nitroprusside, to quickly respond to increased systemic vascular resistance. Unclamping of the aorta may lead to a spectrum of changes depending on the location and duration of the clamp and on whether the clamp was partial or total. Volume administration before unclamping may mitigate the sudden decrease in systemic vascular resistance and associated drop in mean arterial blood pressure. The drop in systemic vascular resistance can result in central hypovolemia from venous pooling in the lower extremities. This hypotension is due to the accumulation of adenosine and lactate in the areas of perfusion that have been transiently ischemic due to the cross-clamp [75]. Having rapid-acting push dose vasopressors like norepinephrine or epinephrine can help mitigate this phenomenon.

The other vascular anastomosis performed is the attachment of the donor SMV to the recipient IVC. However, the venous outflow of the graft from the donor SMV can be obtained via a donor iliac vein jump graft, which can be surgically connected to either the recipient's portal circulation (orthotopic) or systemic circulation via the vena cava (heterotopic), as mesenteric thrombosis necessitates anastomosis to the vena cava [7]. To do this, the surgeons must perform a partial IVC clamp. Typically, they can clamp a small enough portion of the IVC so that venous return to the heart is not significantly affected. This means that the hemodynamic changes tend not to be as dramatic as during liver transplantation, but they can still be significant enough to require treatment. This hemodynamic stability can be accomplished with rapidly titratable vasopressors. The use of venovenous bypass is rarely necessary for an isolated small bowel transplant [7].

Reperfusion and Completion of the Case

Following the vascular anastomosis, the anesthesia team should prepare for reperfusion. While reperfusion may not be as severe or prolonged as seen in liver transplants, there is the possibility of a post-reperfusion syndrome (PRS) manifesting shortly after unclamping of the vessels. The only means of transfer for intestines is static cold storage (SCS). Intestines are also still preserved in University of Wisconsin Solution, a high-potassium organ preservation solution, so it is possible that acute hyperkalemia and its sequelae may develop. Many centers target a pre-reperfusion serum potassium of <4 mEq/L to mitigate the risk of hyperkalemia at reperfusion [33, 52]. Hyperkalemia can be managed by shifting potassium intracellularly with the administration of calcium, insulin, and the alkalinization of the blood (sodium bicarbonate or hyperventilation). Potassium can be removed from the body intraoperatively with loop diuretics such as furosemide (though caution should be exercised in patients with renal disease), or intraoperative renal replacement therapy [48]. When a large volume transfusion is anticipated, red blood cell units can be washed to remove potassium before transfusion [48, 76]. Metabolic acidosis develops over the course of the procedure. While acidosis should generally be managed with fluid resuscitation, sodium bicarbonate may be administered to correct severe derangements. In these cases, serum sodium should be monitored, as a large volume of sodium bicarbonate can lead to hypernatremia [48].

The intestine is sensitive to ischemia–reperfusion injury, which is known to play a role in acute rejection and graft failure. Intestine ischemia and subsequent reperfusion create oxidative stress, activate inflammatory mediators (complement, cytokines, and chemokines) and the immune system (neutrophils, which produce oxygen free radicals, and mast cells), and can lead to apoptosis [77]. Ischemia–reperfusion increases the permeability of the intestinal epithelial lining, which allows bacterial translocation and endotoxin release into the systemic circulation [77].

PRS is defined as a drop of 30% or more from baseline mean arterial pressure occurring within the first 10 minutes of reperfusion and lasting at least 1 minute. However, due to variability in the definition of PRS in the literature, the incidence

of PRS in intestinal transplant (ITx) ranges widely. Some sources cite that PRS occurs nearly 50% of the time [78, 79]. In a larger study of 67 small bowel transplant recipients, 9% had PRS within 5 minutes of reperfusion [52]. Reperfusion of the intestine graft may take more time, which could account for the differences in PRS. In practice, PRS at intestinal reperfusion is insidious and manageable compared to the sudden, acute PRS known to occur at reperfusion for liver transplant. PRS is associated with longer graft cold ischemia time, increased blood transfusions, and postoperative renal failure [79]. PRS can typically be managed with bolus dosing of dilute vasopressors, particularly norepinephrine and epinephrine. Should the PRS persist for more than a couple of minutes, rapidly titratable pressor infusions can be initiated to maintain perfusion pressure.

Post-reperfusion

Following reperfusion, the surgeons will work on the anastomosis of the donor GI tract to the recipient's native GI tract. During this portion of the case, immunotherapy will be initiated. The exact agents administered can vary by institution, but typically involve multiple drugs. In the operating room (OR), induction is accomplished with a steroid (methylprednisolone), a calcineurin inhibitor (tacrolimus), and an anti-CD52 monoclonal antibody (alemtuzumab). Each of these agents has unique side effects that will need to be monitored, though most of these will not manifest until much later. Also, during this portion of the case, we should expect to see a significant rise in lactate, and that may continue to rise over time or reach very high levels. It is essential to recognize this as part of the washout of metabolites from the organ during reperfusion, rather than a manifestation of hypoperfusion. Discussion of these findings with the surgical team is crucial.

After reperfusion of the graft and completion of the GI connections, abdominal closure is performed. Care should be taken to avoid abdominal compartment syndrome. Patients with ultra-SGS may have reduced intra-abdominal space and reduced abdominal wall components, all of which can make closure exceedingly difficult. The need for major fluid resuscitation, along with expected lymphatic disruption and third-space fluid extravasation, can lead to bowel edema, further complicating closure [11]. Care should be taken to maintain deep neuromuscular blockade. Increased intra-abdominal pressure will adversely affect respiratory mechanics and may also reduce intra-abdominal perfusion. Peak airway pressures should be monitored, and increasing airway pressures may indicate tight closure, necessitating close communication with the surgical team. If primary abdominal wall closure cannot be achieved, alternative options include delayed closure, the use of prosthetic materials to extend and close the fascia (such as acellular matrix), and abdominal wall reconstruction with a rotational flap or a donor abdominal wall graft [60]. If abdominal closure is delayed, the patient will require sedation, paralysis, and ventilation in the ICU.

Fluid Management

Several considerations go into fluid management in isolated intestinal transplantation. As previously mentioned, given the duration of these cases with the abdomen entirely exposed, insensible losses alone can be significant. In addition, if there are complications with the dissection, this could lead to substantial blood loss, further contributing to hypovolemia. Historically, management consisted of aggressive replacement of these losses, resulting in ranges of 5–15 L of crystalloid and as much as 5.5 L of colloid in isolated small bowel transplantation [80].

Fluid administration requires particular attention due to the concern that possible fluid overload may increase bowel edema, put stress on the anastomoses, and increase rates of perioperative complications. While there is little data on the volume of fluid administration and outcomes related to intestinal transplant, this question has been explored for several types of open abdominal surgery. For example, in animal studies, a correlation has been shown between increasing amounts of fluid and breakdown of the small bowel anastomosis [69]. In pancreatoduodenectomy, IV fluid administration within the first day of surgery showed thresholds of 4400–6000 mL for significant postoperative complications [70, 71]. Similar thresholds have also been observed in non-abdominal surgery and are associated with postoperative pulmonary complications [72]. However, there have also been well-done large trials showing no benefit to fluid restriction, and even increased incidence of acute kidney injury [73]. Given the fragile and high-risk nature of this population, further investigation into ideal ranges of fluid resuscitation is warranted.

Postoperative Considerations

Following completion of the case, the patient will require intensive care for continued monitoring of labs and vitals and ongoing resuscitation. For straightforward cases with abdominal wall closure and minimal blood loss, extubation in the OR may be possible. The majority of patients are extubated within 72 h of surgery [52]. Much of the care following ITx can be best understood through the lens of the various complications that are likely to follow, most of which are due to the unique qualities of the intestines. One symptom common to all sources of allograft dysfunction is diarrhea, which may come from graft thromboses, rejection, or infection [1]. Therefore, it is essential that the intensivists caring for these patients be well versed in the variety of complications, their early recognition, and management.

Surgical Complications

Intestine transplant recipients have a very high rate of return to the OR, with up to 90% of recipients returning to the OR at least once in the first 30 days at one high-volume center [52]. Patients may return to the OR for hemorrhage control, infectious causes, graft thrombosis, ischemia, or technical issues [43]. Postoperative

technical surgical complications are most commonly associated with the vascular anastomoses of the graft but may also involve biliary complications or technical complications of the donor surgery [81]. These have become an increasingly uncommon reason for graft failure as surgical techniques have improved over time and medical centers have specialized in performing these types of surgeries [1]. If an ileostomy is present, recognition of vascular thrombosis (arterial or venous) may be first noted due to edematous changes, followed by parenchymal darkening [82]. Another sign that there may be ischemia is a lactate that continues to rise or does not appropriately decrease after the first 12–24 h [83]. Diagnosis is made with Doppler of the vessel anastomoses to look for adequacy of flow, aneurysmal changes, and possible obstructions [82, 83]. Many of these patients have had multiple abdominal surgeries over time, so they may also require either a delayed closure or, if closure, there should be an elevated index of suspicion for abdominal compartment syndrome [83, 84].

Infection

Given the complex environment of microorganisms that live within the small bowel, as well as the high levels of immunosuppression, this population is at significant risk of postoperative infectious complications [85, 86]. Additionally, small bowel donor grafts exhibit altered mucosal permeability, which may increase the incidence of enteric organism translocation [86]. They are susceptible to a variety of bacterial, viral, and fungal sources, so perioperatively, these patients are on broad coverage agents as a preventative measure for infection. A study on postoperative infections following intestinal transplant found bacterial infections to be the most common, followed by viral and then fungal infections. They also found that the sites of infection were primarily CVCs, followed by surgical sites and the urinary tract [86]. Once immunosuppression has been started, coverage is made sure to include anti-pneumocystis and anti-cytomegalovirus agents [86]. Intestinal transplants may also be uniquely at risk for infections from Epstein-Barr virus (and may subsequently develop B-cell lymphoma), as well as human herpesvirus 6 and 8, when compared to other solid organ transplants [85].

Renal Complications

Renal failure has been well established as a risk factor for poor outcomes among hospitalized patients. High output ostomy, pre-transplant renal dysfunction, nephrotoxic medications including immunosuppressives, and hypovolemia are associated with an increased risk of postoperative kidney injury in ITx patients [11]. Part of the reason for this risk is that patients who have been on chronic PN are subject to a declining GFR [81]. Additionally, another is that these patients frequently are hypovolemic, coupled with high-dose immunosuppression, which can lead to renal insufficiency [85]. A retrospective analysis found that up to 24.7% of ITx patients require dialysis, and this is independently associated with a significant risk of

mortality [87]. While many patients eventually recovered, 6% eventually required renal transplantation due to chronic renal failure [87]. Optimizing fluid status and decreasing trough levels of immunosuppressants like tacrolimus may help to prevent injury, but there is no decisive intervention at this time [81, 85].

Graft Rejection and Long-Term Outcomes

Due to the high lymphatic burden of the intestines, particularly within the ileum, these organs are prone to rejection and, as such, require high doses of immunosuppressive medications [85, 88]. Rejection can occur both acutely and chronically and will often require steroids and an increase in immunosuppressants, both of which have their own complications [82]. The degree of rejection and the incidence of graft loss from it have decreased over time as newer immunosuppressive agents have been developed. That said, it remains a significant contributor to the other complications seen following transplantation [41, 82]. In the most recent OPTN/Scientific Registry of Transplant Recipients data, failure rates for intestine transplantation were reported as 12.2% at 6 months, 14.6% at 1 year, 32.4% at 3 years, 55.3% at 5 years, and 70.7% at 10 years [2]. Interestingly, simultaneous intestine and liver transplantation showed failure rates reported as 36.8% at 6 months, 47.4% at 1 year, 45.0% at 3 years, 58.6% at 5 years, and 65.6% at 10 years. There are no serological minimally invasive markers of rejection at this time; diagnosis is made with endoscopic biopsy and grading. Routine endoscopy with biopsy to detect early histologic signs of rejection can allow for intervention that may improve outcomes [1, 84].

Survival rates for adult recipients of intestine transplants alone were reported as 89.8% at 1 year and 62.5% at 5 years, while recipients who also received a liver allograft had survival of 62.2% at 1 year and 50.0% at 5 years. Compared to adult recipients, survival rates in pediatric recipients were higher at 91.3% at 1 year and 78.3% at 5 years for intestine alone, and 82.1% at 1 year and 65.3% at 5 years for combined intestine and liver transplants [2]. Interestingly, intestine transplants from donors <1 year of age were associated with lower rates of graft loss and better long-term graft survival, although no difference in patient survival was found [89]. In general, factors associated with post-transplant mortality include sepsis, post-transplant lymphoproliferative disorder (PTLD), graft-versus-host disease (GVHD), rejection, thrombosis, and prolonged cold ischemia time (>8 h) [90]. High rates of PTLD are seen mainly in intestine-only transplants and are thought to be due to high immunosuppressive requirements. Pediatric patients can have increased susceptibility to PTLD, possibly due to being naïve to Epstein–Barr virus.

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Pediatric Transplant Anesthesia

9

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Liver Transplantation

✓ 2026 Edition

Pediatric liver transplantation outcomes have improved significantly over the years due to advancements in surgical technique, immunosuppressive regimens, and perioperative management. Currently, 1-year survival is greater than 90%, and 5-year survival is as high as 50% [1, 2]. With the scarcity of pediatric organs, liver transplantation can be done with a complete deceased donor graft, a partial or "split" graft, or a living donor graft.

Indications for pediatric liver transplantation vary widely but are primarily due to inherent liver disease. The most common diagnosis is biliary atresia [3, 4]. Other common diagnoses include metabolic disorders, Alagille syndrome, cystic fibrosis (CF), primary hepatic or biliary duct tumors, and fulminant hepatic failure.

Preoperative Considerations

Pediatric liver transplantation demands a multidisciplinary preoperative assessment due to the variety in patient size, physiology, and disease severity. The preoperative assessment is essential to identify the primary diagnosis as well as the myriad of multisystem complications associated with liver failure. Dedicated multidisciplinary teams, including hepatology, transplant surgery, intensive care, and anesthesiology, are essential [1, 5]. The anesthesiologist must understand the physiologic and surgical implications of the patient's age, size, primary diagnosis, and medical history to optimally care for the patient.

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The age and size of the liver transplant recipient have multiple anesthetic ramifications. Younger patients have a baseline intolerance to physiologic imbalances such as a limited respiratory reserve, a small circulating blood volume, and increased sensitivity to hypothermia and metabolic derangements. Vascular access can also be particularly challenging in smaller patients requiring ultrasound-assisted guidance, preoperative line placement by interventional radiology, or surgical placement [5]. Constant vigilance and preparation are necessary to provide care to these smaller patients safely.

The indication for pediatric liver transplantation often introduces additional anesthetic considerations. The overall health and function of the patients, preoperative location, and Pediatric End-Stage Liver Disease (PELD)/Model for End-Stage Liver Disease (MELD) score can assist the anesthesiologist in their general assessment. In addition, primary diagnoses can help the anesthesiologist anticipate intraoperative challenges. For example, patients with metabolic disorders may have marked metabolic abnormalities, especially during the anhepatic phase.

A thorough understanding of the surgical approach is essential for preparing and executing a successful pediatric liver anesthetic. Previous abdominal surgery results in abdominal scarring, which can increase surgical complexity and require early blood product transfusion. Smaller blood vessels inherent to the pediatric patient population dictate the degree to which the aorta, inferior vena cava (IVC), and superior vena cava (SVC) should be clamped and may necessitate greater vasopressor and inotropic support. Graft-size mismatch often requires a split or reduced-size graft, which can significantly increase perioperative bleeding from the transected hepatic surface [6]. Smaller vessel anastomoses require specific hematocrit and coagulopathic goals post-reperfusion, balancing tissue oxygenation while avoiding vessel thrombosis.

Intraoperative Considerations

The stages and anesthetic considerations of a pediatric liver transplant mirror those of an adult transplant. These include preparation for massive-volume resuscitation and management of coagulopathy during the pre-anhepatic phase; hemodynamic instability from IVC clamping; metabolic derangements during the anhepatic phase; and the challenges of reperfusion and post-reperfusion syndrome [3]. However, pediatric-specific considerations require constant preparation, vigilance, and anticipation on the part of the pediatric anesthesiologist [5].

Anesthesiologists should strongly consider a rapid-sequence induction given the high risk of aspiration in this population. Intravenous access includes multiple upper-extremity large-bore peripheral intravenous catheters (PIVs) or rapid-infusion catheters, an arterial line, and central venous access [5]. Blood products need to be immediately available, and equipment to both warm and rapidly infuse blood products should be prepared for use. Due to the increased potential for heat loss, small patient size, and difficult access once draped, patients should be appropriately padded, multiple forced body warmers should be placed, and all intravenous and

arterial lines should be confirmed for patency before placing the surgical drapes. Before dissection, immunosuppressive medications and antibiotics are given.

The preanhepatic, or dissection phase, begins with incision and ends with the removal of the liver [5]. Goals of the preanhepatic phase include treating coagulopathy and blood loss, maintaining normoglycemia, correcting electrolyte and acid–base imbalances, and maintaining temperature. Risk factors for massive blood product administration in pediatric patients include prior abdominal procedures, smaller or younger patients, high PELD scores, coagulopathy, and thrombocytopenia [5, 7–9]. Targeted transfusion, especially in the case of pre-existing coagulopathy, should be guided by viscoelastic hemostatic assays and clinical assessment of bleeding [10].

The anhepatic phase starts with the removal of the liver from the body and ends with the reperfusion of the new liver graft in the recipient. Many of the same anesthetic goals apply in the pediatric population as they do in the adult population with regard to reperfusion of the new graft in the recipient. These goals include correcting any hyperkalemia and managing severe metabolic acidosis prior to reperfusion [5]. Hemodynamic stability can be challenging and often requires vasopressors and/or inotropes with judicious volume replacement. However, hypervolemia should be avoided to prevent congestion of the new liver graft, as this can lead to graft failure [5]. Use of dynamic volume-estimation calculations, such as stroke volume variation or pulse pressure variation, has had varying results [11, 12]. Preparation for reperfusion requires excellent communication with the surgical team, frequent lab draws, and aggressive correction of electrolyte and metabolic abnormalities [5].

Reperfusion, or introduction of the liver graft to the systemic circulation of the recipient, results in an extreme physiologic load. The release of vasoactive substances from the graft, stagnant blood from the IVC, and cold acidotic preservation solution can cause immediate cardiac instability, including a decrease in systemic vascular resistance (SVR), an increase in pulmonary vascular resistance (PVR), and right ventricular failure [4]. Hypothermia can contribute to dysrhythmias, bradycardia, and further cardiac dysfunction [13]. Electrolyte imbalances such as hyperkalemia, hypocalcemia, and acidosis are all known negative inotropes, very common during reperfusion, and require quick correction [4]. Post-reperfusion syndrome, which can include a prolonged fall in arterial blood pressure > 30% after reperfusion, is a complex physiologic process that can cause a cascade of organ dysfunction, which may be avoided with careful volume replacement and metabolic correction [5]. Other severe complications during this time can include pulmonary hypertensive crisis, air embolism, and cardiac arrest [4].

The post-reperfusion, or post-anhepatic phase, includes the re-anastomosis of the hepatic artery and biliary reconstruction. Ongoing blood loss and the need to replace blood products and volume are common, especially with a split liver graft [4]. However, multiple studies have demonstrated that the hematocrit should not increase over 30%. Elevated hematocrit results in increased blood viscosity and raises concern for hepatic artery thrombosis, a major cause of graft failure in pediatric liver transplants [14, 15]. Aggressive correction of coagulopathy and thrombocytopenia is also avoided due to this risk [5, 16]. During this period, as the new liver graft

begins to function, many electrolyte and metabolic disturbances begin to self-correct.

Extubation in the operating room (OR) immediately after pediatric liver transplantation is an increasingly common practice that requires multidisciplinary communication and careful patient selection. Patient size-graft mismatch, medical acuity, high transfusion requirements, and fear of respiratory complications are all barriers to immediate extubation. Successful immediate extubation has been associated with older age, lower PELD/MELD score, and admission from home [17–20]. Surgical factors that determine immediate extubation success include the type of graft (whole or split), intraoperative transfusion requirements, and partial versus full abdominal closure. Overall, data suggest that early extubation, when appropriately applied, may decrease ICU and hospital length of stay and postoperative complications [21].

Assessment of coagulopathy and replacement of blood products is an essential part of liver transplant anesthesia. Recent studies have shown that the use of viscoelastic testing (VET) decreases transfusion requirements, particularly fresh frozen plasma (FFP), in pediatric liver transplant [22, 23]. VET results are rapid and can be read in real time, allowing for prompt and targeted transfusion if needed.

Postoperative Considerations

Patients should be transferred postoperatively to the intensive care unit as ongoing blood product resuscitation and close monitoring are required. Frequent assessment of the graft includes recurrent ultrasound of the hepatic vessels, lab monitoring, and hemodynamic evaluation. Antithrombotic therapy may be used to prevent vascular complications [24]. Major acute complications of pediatric liver transplant include hepatic artery or portal vein thrombosis, biliary leaks or strictures, and graft non-function [3]. Long-term complications can include chronic graft failure, infection, long-term complications of immunosuppressive therapy, and malignancies [1].

Special Considerations

Pediatric anesthesia liver transplant teams are becoming increasingly essential but not universal [5, 25]. A designated team provides the opportunity for concentrated experience, skill proficiency, and multidisciplinary communication. A recent survey of US pediatric anesthesia liver transplant teams demonstrated that most centers had a named director of liver transplant anesthesia [26]. A recent study demonstrated that the implementation of a pediatric liver transplant anesthesia team significantly increased the number of cases per team member and improved intraoperative outcomes, including early extubation and transfusion requirements [27], with similar findings in adult transplantation [28].

Pediatric Kidney Transplantation

Preoperative Considerations

End-stage renal disease (ESRD) is rare in children, and the underlying pathology is significantly different from that of adults. Pediatric transplants account for 5% of all kidney transplantations in Europe and North America [29]. The most common etiologies of ESRD are congenital anomalies of the kidneys or urinary tract in younger children and glomerulonephritis in older children [30]. Over the last decade, advances in immunosuppressive therapy, donor selection, and surgical techniques have improved graft and patient survival. The best outcomes occur with transplantation before the initiation of dialysis (preemptive transplantation), living donor transplantation, and transplantation in young recipients (age < 5 years) [31].

Renal failure can impact multiple organ systems, and a thorough preoperative assessment is essential. ESRD increases the risk of coronary artery disease, hypertension, left ventricular hypertrophy, and diastolic dysfunction [30]. A preoperative electrocardiogram (EKG) and echocardiography, in addition to history and physical exam, are necessary to evaluate cardiovascular status and myocardial function. Multifactorial hypertension is often treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in children. It is typically recommended to hold these on the day of transplantation to avoid refractory hypotension from the vasodilatory effects of anesthetics [29].

Reduced erythropoietin production and uremic platelet dysfunction result in both anemia and impaired coagulation, necessitating the availability of red blood cells for transplantation. Electrolyte derangements are also common, with hyperkalemia posing a potentially life-threatening complication of ESRD. Before transplantation, electrolyte, acid–base, and volume status should be optimized with dialysis as indicated. Additionally, bone mineralization is impaired due to hyperphosphatemia and hypocalcemia, leading to brittle bones and teeth. Malnutrition and failure to thrive are also common in pediatric patients with ESRD. Nutritional status and the use of glucose-containing fluids should be considered for those at risk [29].

Intraoperative Considerations

Transplantation techniques vary depending on the patient's and donor's sizes and the underlying pathology. As pediatric donor kidneys are rare, adult-sized kidneys are often used. In patients less than 20 kg, an intraperitoneal method with a midline incision is more common. An extraperitoneal approach via a right lower quadrant incision is typically used in older children [30]. The graft-size mismatch that occurs when a smaller child receives an adult-sized kidney results in complex physiologic management necessitating aggressive fluid or blood replacement and hemodynamic support as the allograft consumes a large portion of the recipient's blood volume at reperfusion.

Induction is commonly performed with intravenous agents, including fentanyl, propofol, and paralysis. Succinylcholine should be avoided due to the risk of hyperkalemia and dysrhythmias. Rocuronium can be safely used with sugammadex reversal. The rocuronium-sugammadex complex is excreted by glomerular filtration, and its clearance is significantly reduced by renal failure. However, the complex itself is stable, and recurarization has been found to be uncommon in patients with renal impairment [32, 33]. There is no preferred method for the maintenance of anesthesia, but a regional anesthetic technique involving truncal blocks may reduce maintenance requirements and thereby provide more hemodynamic stability.

In addition to the typical standard American Society of Anesthesiologists (ASA) monitors, hemodynamic monitoring is of the utmost importance. A recent survey found considerable variation in the type of invasive hemodynamic monitoring used during pediatric kidney transplantation anesthesia. However, the majority of centers reported using at least one type as their standard of care, with the most common being intra-arterial blood pressure, followed by central venous pressure and then cardiac output monitoring [34]. Regardless of the method used, the anesthesiologist must be prepared for volume resuscitation and hemodynamic instability. Hyperkalemia, metabolic acidosis, and hypothermia are common immediately after reperfusion and require prompt intervention. Urine output monitoring is also essential as patients will vary from anuric to polyuric, requiring accurate volume replacement throughout the intraoperative period.

Special Considerations

The debate continues as to which crystalloid solution is optimal in kidney transplantation. This is even more significant in pediatric transplantation, as a large graft-size mismatch is common and results in these patients requiring aggressive volume resuscitation due to the diversion of intravascular volume into the large transplanted kidney. Historically, normal saline (NS) was the preferred solution to avoid hyperkalemia. Several adult transplant studies have since shown that NS resuscitation promotes hyperchloremic acidosis, and this acidosis actually worsens hyperkalemia by shifting potassium extracellular [35]. Newer evidence suggests that NS may also impair graft function [36]. An international randomized controlled study, the balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids), assessed the difference in delayed graft function in patients who received balanced crystalloid (Plasma-Lyte) versus NS [37]. Delayed graft function occurred in 30% of patients receiving a balanced solution, compared with 40% in the NS group. The BEST-Fluids study included pediatric patients, specifically children over 20 kg, but these findings have not been independently validated in a pediatric-only population.

Postoperative Considerations

Immediate postoperative care often occurs in the intensive care unit, where goals include maintenance of blood volume and electrolytes and optimizing graft perfusion. Prevention of graft hypoperfusion is important as it carries a higher risk of acute tubular necrosis and graft loss [38]. Early renal Doppler ultrasound is typically used to assess for vascular complications such as thrombosis or vasospasm.

Postoperative pain management has been accomplished with a variety of techniques. While epidurals may provide favorable pain management, concerns about hemodynamic instability and epidural hematoma have prevented more widespread use. Truncal blocks, such as transverse abdominus plane blocks, have been more recently investigated to reduce the need for narcotic pain medication and provide better hemodynamic stability [39].

Long-term complications after kidney transplantation include graft failure or rejection, hypertension, infection, and malignancy. While acute graft rejection is becoming less common with improvements in immunosuppressive regimens, chronic graft failure is associated with increased ischemic time, deceased donor transplantation, and older donor recipients [29, 40]. Hypertension is present in 50–80% of recipients, even without a history of pre-transplant hypertension. Malignancy in this population is estimated to be 10 times greater than in the general population due to immunosuppressive therapy, causing opportunistic viral infection or reactivation of latent virus. Post-transplant lymphoproliferative disease (PTLD) is the most common type [38].

Heart Transplantation

Heart transplantation is an established therapy for end-stage heart failure in infants and children. Since the first heart transplantation in a child was performed in 1967, advances in surgical technique, immunosuppression, and perioperative management have improved survival of pediatric heart transplantation recipients [41]. The current 1- and 5-year survival rates after pediatric heart transplantation are 92% and 90.5%, respectively [42]. However, the availability of donor organs continues to be a significant limiting factor, and the mortality rate while on the waitlist is 17% [43].

Preoperative Considerations

Heart transplantation in infants and children accounts for 12.5% of all cardiac transplantations [44]. The main indications for heart transplantation in children include congenital heart disease (CHD), cardiomyopathy, and re-transplantation, with a distribution of 37%, 47%, and 6% of heart transplants performed in children, respectively [45]. A diagnostic indication of CHD is more common in younger patients, while cardiomyopathy is more common in older children [46]. Patients with CHD

may have lesions that are unrepairable or have failed palliation attempts [47]. Dilated cardiomyopathy is the most common form of cardiomyopathy in children requiring a transplant; however, hypertrophic and restrictive cardiomyopathies are also etiologies [48]. The most common indications for re-transplantation include coronary vasculopathy and graft failure that have developed in previously transplanted hearts [49]. Contraindications to a heart transplantation include active malignancy, uncontrolled infection, multi-organ failure, psychosocial factors, and irreversible pulmonary hypertension with a PVR > 6 Wood Units•m^{-2} [44].

The demand continues to outweigh the supply of donor hearts for pediatric patients in need of a heart transplantation [49]. The waitlist mortality for all pediatric patients is 17%, with a waitlist mortality of 25% in infants and of 15% in children and adolescents [43, 47, 50]. There is a 20% mortality rate for patients not receiving a heart transplantation after 1 year of being listed [51]. The United Network for Organ Sharing (UNOS) has a different allocation policy and listing status classification for children than for adults waiting for a heart transplantation. For pediatric patients, there is a three-tier classification listing status based on medical urgency, with status 1A for patients with the highest medical urgency, followed by status 1B and then status 2. There is also a status 7 for patients who are temporarily inactive on the waitlist due to clinical deterioration or unavailability [51].

Despite a shortage of donor hearts, 35–50% of donor hearts offered for pediatric transplantation are not accepted due to donor factors, such as older donor age, high-risk donor status, left ventricular ejection fraction less than 50%, and inotrope use [50, 52]. Transplantation centers with more selective organ acceptance rates have longer wait times [53]. The median waitlist time to heart transplantation in pediatric patients is 71 days for status 1A and 246 days for status 1B [53]. Within status 1A, patient factors contributing to longer waitlist times include weight less than 25 kg and blood type O [53]. Due to the shortage of compatible size-matched donor hearts in infants, there is a higher waitlist mortality in infants [54]. The use of ABO-incompatible heart transplantations has gained acceptance as a safe method to expand the availability of donor hearts in infants and to decrease the waitlist mortality [52, 55]. Due to immaturity of an infant's immune system, isohemagluttinins—natural antibodies to A and B blood group —are produced at low levels until 12–14 months of life [44]. Therefore, the primary factor that would lead to rejection is absent in infants, allowing ABO-incompatible heart transplantations to be an option [56]. Notably, 40% of infant heart transplantations are ABO-incompatible, and outcomes are comparable to ABO-compatible heart transplantations [52, 54–56]. Intraoperative plasma exchange may be necessary to remove any anti-A or anti-B antibodies present in a recipient [56, 57].

To develop a safe anesthetic plan for a patient undergoing an orthotopic heart transplantation, a detailed preoperative assessment must be conducted. A thorough history and physical must be performed, as well as a review of all available laboratory results and imaging studies. Pertinent imaging studies include an echocardiogram, EKG, chest radiograph, and cardiac catheterization and angiography data. Ultrasound assessment of vessel patency may be needed for patients with a history of extracorporeal membrane oxygenation (ECMO), cardiac catheterization, and

central venous lines, as well as to plan for alternative cardiopulmonary bypass (CPB) cannulation sites. Co-morbidities should be assessed in each patient with attention to possible electrolyte imbalances, arrhythmias, and coagulopathies. Patients with a failing Fontan circulation may have arrhythmias, a history of thromboembolism, protein-losing enteropathy, plastic bronchitis, or liver disease [58]. Mechanical circulatory support (MCS) is present in 37% of pediatric patients presenting for a heart transplantation, with ECMO more common in infants with CHD and left ventricular assist devices more common in patients with dilated cardiomyopathy [46]. Many patients presenting for heart transplantation are on anticoagulation medications to prevent thrombus formation with the use of MCS or in hearts with relative stasis due to severely decreased function. A discussion with the surgeon is necessary to determine when to discontinue anticoagulation medications, such as a heparin or bivalirudin infusion, or when to reverse anticoagulation, such as reversal of coumadin with vitamin K, KCENTRA®, or FFP. Certain medications may need to be held prior to anesthetizing the patient, such as angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, in order to prevent refractory hypotension under anesthesia.

Notably, 30% of pediatric heart transplantation candidates have allosensitization with the development of antibodies against human leukocyte antigens (HLAs), which may be donor-specific antibodies (DSAs) if the antigen is present in the donor heart [45, 59]. Allosensitization is associated with prior packed red blood cell transfusions, previous cardiac surgery, exposure to homograft material, previous organ transplantation, and ventricular assist devices [43, 46, 54, 59, 60]. HLA matching is not considered in the allocation of donor hearts, and there may be an HLA mismatch between the donor and the recipient [60]. The degree of HLA sensitization is measured with a panel reactive antibody (PRA) assay. A PRA level $\geq 10\%$ is considered sensitized, and the higher the PRA percentage, the greater the presence of more types of anti-HLA antibodies [43, 46, 54, 60]. There is a greater risk of antibody-mediated rejection with an elevated PRA [42, 53, 61]. Management strategies to decrease antibody levels include perioperative plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab [60]. DSAs to a transplanted heart may form after transplantation; therefore, the patient will need to be monitored for the development of DSAs and antibody-mediated rejection [52, 57].

Intraoperative Considerations

Patients presenting to the OR for a heart transplantation have varying levels of functional status and hemodynamic stability depending on the underlying anatomy and physiology, progression of disease, and the presence of MCS. Therefore, individualized anesthetic plans are necessary to maintain preload, afterload, heart rate, and contractility. Upon notification of transplantation, patients should be made NPO appropriately; however, a rapid-sequence induction may be necessary depending on the timing. If clinically stable, premedication with an anxiolytic, such as midazolam, may be needed for perioperative anxiety. Prior to

induction, the initiation of inotropes and/or vasoactive infusions may be indicated to support poor ventricular function and to maintain vascular tone and prevent hemodynamic deterioration from anesthetic agents that can decrease SVR and contractility of the heart. Standard ASA monitors should be placed prior to induction. An inhalational induction may be tolerated in some patients; however, most patients presenting for a heart transplantation require the presence of a PIV to carefully titrate induction medications that have minimal hemodynamic changes, such as ketamine and fentanyl, and to administer emergency vasoactive medications if needed. Avoiding hypoxemia and hypercarbia during induction and intubation is essential to prevent increases in PVR and subsequent alterations in the balance of pulmonary and systemic blood flow. A balanced anesthetic technique should be used during maintenance, such as a combination of isoflurane, fentanyl, and midazolam.

Adequate vascular access and appropriate invasive monitors are imperative. Many patients have had prior cardiac surgery and are at risk for bleeding during sternotomy incision and dissection. Therefore, vascular access should be obtained that can support large volume blood transfusion requirements and fluid resuscitation. An arterial line and a central venous line are required, and locations should be determined by the patient's anatomy and institutional preferences. Arterial line placement before induction may be necessary for patients with severely depressed ventricular function or with cardiac lesions with ventricular outflow tract obstructions. Transesophageal echocardiography is used to monitor function and volume status, as well as to assess the transplanted heart during weaning from CPB.

The goal of anesthetic management in the pre-CPB period is to maintain hemodynamic stability in the failing heart to support the patient until CPB is initiated. Coordination of timing to allow for adequate time for induction and vascular access placement, yet minimize the time under anesthesia prior to the initiation of CPB and explantation of the failing heart as the donor heart arrives for implantation, is an important consideration. Management of CPB for heart transplantation is similar to the management during other cardiac surgeries. Anticoagulation is most often achieved with heparin and maintained with a minimum activated clotting time of 400 s [62]. Modification of standard aortic and bicaval cannulation may be needed depending on the recipient's cardiovascular anatomy. The aorta is cross-clamped, and then explantation of the recipient's native heart is achieved by dividing the aorta and pulmonary artery, transecting the SVC and IVC, and leaving the left atrium cuff with the pulmonary veins. MCS devices and antiarrhythmic devices, such as a pacemaker or implantable cardioverter defibrillator, are removed as well [58].

Bicaval cardiac transplantation is currently the most common technique and includes preservation of the donor right atrium with anastomosis of the donor heart to the recipient's left atrial cuff, IVC, SVC, pulmonary artery, and aorta [43]. Patients who have had prior cardiac surgeries and palliative repairs are a greater technical challenge due to the need for reconstruction of vascular structures during implantation, which may increase the ischemic time of the donor heart [43, 61]. After implantation, the aortic cross clamp is removed, and the

donor heart is reperfused. Administration of lidocaine 1 mg/kg and magnesium sulfate 25–50 mg/kg when the cross clamp is removed may prevent ventricular arrhythmias as the heart reanimates. During this time, it is also important to check electrolytes and treat any abnormalities. To allow time for the donor heart to reperfuse, it is prudent to wait at least 20–30 minutes after the aortic cross clamp is removed before starting inotropes and beginning to wean off CPB. Induction of immunosuppression should be initiated when the aortic cross clamp is removed. Polyclonal anti-lymphocyte or anti-thymocyte globulin is the most common induction therapy [46, 54]. Methylprednisolone is also given in the perioperative period [52].

Donor ischemia time, which is the time between aortic cross-clamp placement during organ procurement and removal, leading to coronary artery reperfusion during implantation, should be minimized. Most donor ischemia times are less than 4 h and are rarely greater than 6 h [63]. Ischemic times less than 3.5 hours are associated with the best outcomes [50]. Ischemic times greater than 4 h are associated with lower 30-day survival and increased 1- and 5-year mortality, but not immediate rejection or post-transplant morbidities of coronary artery vasculopathy (CAV) and renal dysfunction [49, 63].

After the termination of CPB, the goals are to achieve hemodynamic stability, control heart rate and rhythm, and control bleeding. Inotropic agents, such as epinephrine and milrinone, should be started to support the donor heart [61]. Due to limited compliance of the donor right ventricle, potentially in the setting of elevated PVR in the recipient, there may be right ventricular dysfunction [62]. Risk factors for right ventricular failure after CPB during a heart transplantation include pulmonary hypertension in the recipient, longer ischemic times, and reperfusion injury [43]. Management includes milrinone for right ventricular afterload reduction and inhaled nitric oxide to reduce PVR [57]. If right ventricular dysfunction persists, then MCS may be needed with a right ventricular assist device or ECMO until myocardial recovery or reduction in PVR [44]. Vasoplegia with profound hypotension may occur and should be treated with norepinephrine or vasopressin [57]. If hypotension is refractory to high-dose vasoactive infusions, then methylene blue 1–2 mg/kg may be used as an effective treatment for vasoplegia [64]. The donor heart may need chronotropic support with a β-adrenergic agent like isoproterenol or with epicardial pacing to maintain the heart rate [61]. Atrioventricular (AV) conduction disorders affect 10% of transplanted hearts, and AV pacing with epicardial pacing leads may be needed perioperatively [57]. Bleeding should be anticipated after CPB, and blood products—such as platelets, cryoprecipitate, and FFP—should be available to control bleeding. Prothrombin complex concentrates, such as factor eight inhibitor bypass activity (FEIBA), may also be needed to achieve hemostasis. Similar to other cardiac surgeries with CPB, contributing factors for bleeding include extensive dissection, redo sternotomy, pre-existing coagulation abnormalities, preoperative anticoagulation use, and being on CPB [58]. Recipients with a failing Fontan have longer CPB times, higher donor ischemia times, need more vasoactive support after CPB, require more blood product transfusions of FFP, platelets, and coagulation factors, and have a higher mortality [65].

Postoperative Considerations

The immediate postoperative period in the intensive care unit is a continuation of intraoperative post-CPB management, including monitoring hemodynamics, titration of inotropic and vasoactive agents, and controlling bleeding. Induction immunosuppression continues for several days after transplantation and then transitions to lifelong maintenance immunosuppression. Maintenance medications consist of a calcineurin inhibitor and an antimetabolite. The most common induction agents are the polyclonal antibodies anti-lymphocyte or anti-thymocyte globulin, while the most common maintenance agents are tacrolimus, a calcineurin inhibitor, and mycophenolate mofetil, an antimetabolite [54].

Immunosuppression and surveillance protocols are institution-dependent. The gold standard for rejection surveillance and detection is cardiac catheterization with endomyocardial biopsy (EMB) and annual coronary angiography [44]. Elective EMBs for routine surveillance are safe, with a low complication rate; however, rejection is rarely detected during elective EMBs [57, 66]. Many programs have decreased the use of routine surveillance in the cardiac catheterization lab and have transitioned to non-invasive rejection monitoring in surveillance protocols, including blood sample assays such as donor-derived cell-free DNA, gene expression profiling with Allomap, and DSAs [52, 57, 67]. If rejection is suspected based on non-invasive testing results or the presence of clinical symptoms, then an urgent EMB with histopathologic evaluation of cardiac allograft tissue is necessary to diagnose acute cellular rejection, antibody-mediated rejection, or both [57, 68]. Rejection may be asymptomatic, or there may be clinical signs, such as new onset tachyarrhythmia or severe hemodynamic compromise [47, 57, 61]. An echocardiograph should be obtained for patients with suspected rejection to evaluate for potential poor myocardial function. The anesthetic technique for EMBs may be monitored anesthesia care or general anesthesia, depending on the institution's protocols and the patient's age and hemodynamic status. Inotropic agents, such as epinephrine or dopamine, should be ready and possibly started before induction. Non-elective EMBs have a small but significant risk of major adverse events, including cardiac arrest, development of arrhythmias, events requiring ECMO, and need for a blood transfusion [66]. Although rejection can happen at any point, rejection within the first year after heart transplantation affects 13% of patients and is a risk factor for mortality at 5 years [63]. Treatment for rejection depends on the type of rejection and the institution's protocols.

In addition to rejection and graft failure, other co-morbidities affect patients after heart transplantation—including CAV, malignancy, renal dysfunction, hypertension, and hyperlipidemia [44, 61, 63]. CAV is a progressive form of intimal proliferative arteriosclerosis that obliterates the lumen of large epicardial coronary arteries, coronary veins, and coronary microcirculation due to fibromuscular hyperplasia [69]. CAV is diagnosed by coronary angiography. Infant recipients have a lower rate of CAV compared to adolescent recipients. Risk factors for the development of CAV are older recipient age at the time of transplantation, older donor age, two or more episodes of rejection, black race, higher pre-transplantation PRA, and

cigarette use by the donor [46, 69]. After the development of CAV, there is a high incidence of graft failure [45, 69]. While there is no treatment to resolve CAV, statin medications have been shown to slow the development [69]. Post-transplant lymphoproliferative disorder (PTLD) is the most common malignancy in pediatric heart transplantation recipients and is associated with Epstein–Barr virus infection [54]. The development of PTLD after a pediatric heart transplantation is 3.8% by 10 years and 16% by 15 years [46, 70].

After recovery from transplantation, pediatric heart transplantation recipients undergoing an anesthetic still have special considerations in the perioperative period. Anesthetic plans should be developed based on the patient's hemodynamic status and the nature of the procedure. A thorough history and physical, and review of cardiac diagnostic imaging, is important during the preoperative evaluation. Immunosuppression medications should be continued throughout the perioperative period. Due to the immunosuppressed state, patients have a high risk of infection, and aseptic technique should be strictly followed during placement of and access to PIVs and invasive monitoring lines, such as a central line or an arterial line. Heart transplantation recipients who have developed cardiac valvulopathy should receive infective endocarditis prophylaxis if they are undergoing dental procedures involving gingival tissue or the periapical region of teeth, incision of the oral mucosa or respiratory tract, or procedures involving infected skin, subdermal tissue, or musculoskeletal tissue [71].

At the time of organ procurement of the donor heart, the heart becomes denervated with surgical interruption of parasympathetic and sympathetic nerve fibers to the myocardium [72]. The heart remains denervated once transplanted into the recipient. Intrinsic mechanisms in the donor atrium are responsible for generating the heart rate and rhythm [58]. In a patient with a transplanted heart, the heart rate at rest is higher than normal due to a lack of parasympathetic neural input to the sinoatrial node [72]. Medications with indirect effects on the heart, such as glycopyrrolate and atropine, will not affect heart rate [61]. In order to increase the heart rate, circulating catecholamines or direct-acting medications, such as epinephrine, are needed to act directly on alpha and beta receptors on the heart [61, 72]. Cardiac reinnervation occurs in 40–70% of recipients months to years after orthotopic heart transplantation and is only partial [72]. Sympathetic reinnervation can occur as early as 5–6 months, but more frequently after 18 months, while parasympathetic reinnervation can occur as early as 3–6 months, but more frequently around 2 years after transplantation [72]. Reinnervation is only partial and is detected when the resting heart rate decreases, heart rate variability increases, or heart rate increases with exercise [72]. The development of tachycardia in response to hypovolemia, pain, inadequate depth of anesthesia, and exercise is limited [44, 68]. Caution should be used when administering neostigmine and glycopyrrolate together for neuromuscular blockade reversal, as there have been reports of bradycardia and cardiac arrest due to the lack of response to glycopyrrolate [73, 74].

The outcomes of pediatric heart transplantation have improved over the years, with a median survival of 18 years after transplantation [46]. The 1-year survival of infants is 89%, 1–10 year olds is 92%, and 11–17 year olds is 94%, while the 5-year

survival of infants is 91.2%, 1–10 year olds is 92.3%, and 11–17 year olds is 88% for patients who survive past 1 year after transplantation [42]. Patients who received a heart transplantation in infancy have a more prolonged survival than patients who were 11–17 years old at the time of transplantation [46]. Recipients in all age groups with an original diagnosis of DCM have a better survival after transplantation than recipients with CHD or who required a re-transplantation [46]. After transplantation, the most common etiology of death in the first 3 years after transplantation is graft failure due to acute rejection, and after 3 years, it is CAV and graft failure [44]. Notably, 80% of surviving pediatric heart transplantation patients have regular activity or only minor limitations [45].

Special Considerations

Multiorgan transplantations, such as a combined heart–lung, heart–liver, or heart–kidney transplantation, in pediatric patients are performed infrequently [75, 76]. The perioperative risks associated with multiorgan transplantation are higher than those of single organ transplantations and include hemodynamic instability, acute kidney injury, thromboembolic events, longer OR times, need for more blood product transfusions, and longer postoperative hospital lengths of stay [75, 77]. Pediatric recipients of a multiorgan transplantation, including the heart, are more likely to have a cardiac indication of CHD than other etiologies and are older in age [75]. Patients with a failing Fontan may have Fontan-associated liver disease and benefit from a heart-liver transplantation [77]. Despite the increased risks of pediatric multiorgan transplantation and lower waitlist survival than single organ transplantation, multiorgan transplantation may be reasonable in carefully selected patients [57, 78].

As pediatric heart transplantation recipients age, prevention of medication non-adherence is important as patients become more responsible for their own health [57]. Non-adherence to immunosuppression medications is a risk factor for rejection, graft failure, and death after transplantation and may account for a lower 5-year survival in older adolescents [42, 79]. Structured educational programs and innovative communication tools have led to decreased medication non-adherence rates as adolescents transition from pediatric to adult heart transplantation programs [80, 81].

Lung Transplantation

Lung transplantation is an established therapy for end-stage pulmonary disease in infants and children. Since the first pediatric lung transplantation was performed in 1987 by Cooper, outcomes have improved due to advances in surgical technique, immunosuppression, and perioperative management [82, 83]. However, survival of pediatric lung transplantation recipients remains low, with a median survival of 5.7 years [83].

Preoperative Considerations

Lung transplantation is an uncommon procedure in infants and children, accounting for less than 5% of all lung transplantations [61]. The main indications for pediatric lung transplantation are CF, pulmonary hypertension, interstitial lung disease, obliterative bronchiolitis, and re-transplantation [83]. A diagnostic indication of a non-CF etiology is more common in younger patients, while CF is more common in older children [83]. Primary pulmonary arterial hypertension surpassed CF as the most frequent indication for pediatric lung transplantation in 2020 [84]. Advancements in CF patient care, including the introduction of CFTR modulator therapy, such as ivacaftor, are responsible for the decline in CF patients needing a transplant. The main indication for children less than 1 year old is pulmonary hypertension, followed by surfactant protein B deficiency [83]. Contraindications to lung transplantation include severe chest wall abnormalities, severe tracheobronchomalacia, severe aorta to pulmonary collaterals, and severe psychosocial issues [85].

The need for donor lungs is much greater than the supply. Patients are listed for lung transplantation after progressing to severe lung disease or pulmonary vascular disease despite maximal medical therapy [61]. Priority on the waitlist for pediatric lung transplantation is determined by the Lung Allocation Score (LAS) for children over 12 years old and considers medical urgency. A modified LAS is calculated for children under 12 years old [85]. Average waitlist times vary by patient's age and range from 20 months for adolescents to 1 month for infants [61]. The waitlist mortality is very high, with one-third of patients dying before receiving a transplant [61]. Donors are matched by ABO compatibility.

A detailed preoperative evaluation must be performed for children undergoing a lung transplantation. In addition to a thorough history and physical, all available laboratory results and imaging studies should be reviewed. Pertinent studies to review include pulmonary function tests, chest X-ray, arterial blood gas values, and echocardiogram. Patients may have right ventricular dysfunction secondary to elevated pulmonary artery pressures. For patients with pulmonary hypertension, hemodynamic data from a cardiac catheterization may be available. Patients may present on supplemental oxygen therapy, intubated and mechanically ventilated, and/or on ECMO.

Intraoperative Considerations

Patients presenting for a pediatric lung transplantation have varying levels of functional status and respiratory compromise. Therefore, individualized anesthetic plans are necessary to safely care for patients. Premedication should be used with caution due to the potential to decrease respiratory effort, leading to worse hypoxemia and hypercarbia. Induction of anesthesia is based on the patient's respiratory and hemodynamic status as well as co-morbidities. Pediatric lung transplantation is usually performed on CPB. Therefore, a single-lumen endotracheal tube is sufficient since one-lung ventilation is not needed. A balanced anesthetic technique is used for

maintenance. An arterial line and a central venous line are placed for the procedure. Mechanical ventilation settings are adjusted to achieve satisfactory gas exchange as monitored by arterial blood gases.

The most common technique for pediatric lung transplantation is bilateral sequential lung transplantation through a bilateral thoracosternotomy "clamshell" incision [85]. CPB is initiated to facilitate pneumonectomies. Cardioplegia is not used unless the patient needs an intracardiac procedure [85]. Once on bypass, the recipient's lungs are removed, and the trachea is irrigated with an antibiotic solution. The donor lungs are implanted with an end-to-end bronchial anastomosis, then the donor pulmonary artery is anastomosed to the native pulmonary artery, and then the donor left atrial cuff with pulmonary veins is anastomosed to the native left atrium [87]. If the donor lungs are smaller than the thoracic cavity, then they will expand to fit the space. However, if the donor lungs are larger than the thoracic cavity, then lung reduction is performed to prevent atelectasis [61]. After weaning from CPB, patients often need minimal inotropic support [61]. However, patients with a diagnostic indication of pulmonary hypertension may need higher inotropic and vasoactive support in order to manage right ventricular dysfunction. Ventilation parameters of the donor lungs after CPB should be based on the recipient's age and weight. Prior to leaving the OR, flexible bronchoscopy is performed to assess the bronchial anastomosis [61].

The donor ischemia time for lung transplantation is the time from when the aortic cross clamp is placed during organ procurement until reperfusion of the lung allograft. The median ischemic time is 4.5–6 hours. Ischemic time is not associated with survival at 30 days post-transplantation, the incidence of rejection within the first year, or the development of bronchiolitis obliterans syndrome (BOS). However, long-term survival is better with an ischemic time of four to 6 hours [87].

As a surgical consequence, the donor lungs become denervated, and the pulmonary lymphatic system is disrupted. Injury to the phrenic nerve, left recurrent laryngeal nerve, and the vagal nerve may happen during lung transplantation, leading to diaphragm paresis, hoarseness or vocal cord dysfunction, and gastroparesis or reflux, respectively [61, 86]. Lymphatic stasis makes patients prone to pulmonary edema, and judicious use of intravenous fluids is necessary after lung transplantation [86]. These surgical consequences not only impact perioperative management but also future anesthetics.

Postoperative Considerations

After lung transplantation, patients are managed in the intensive care unit and are mechanically ventilated for at least 24–48 hours. Patients are monitored for bleeding, airway dehiscence, vascular anastomotic stenosis, and primary graft failure [86]. Pain control postoperatively may be managed by regional anesthesia with an epidural or paravertebral catheter [61, 88].

Immunosuppression and surveillance protocols are institution-dependent. Perioperatively, most patients receive induction immunosuppression with an

interleukin-2 receptor antagonist followed by maintenance immunosuppression with tacrolimus and mycophenolate mofetil [83]. Rejection surveillance includes pulmonary function tests and fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsies [89]. The frequency of routine surveillance bronchoscopies varies by transplant center but may be performed urgently if there is a change in functional status or a decrease in forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) on a pulmonary function test. Bronchoscopies in pediatric patients are performed under general anesthesia with a laryngeal mask airway and total intravenous anesthesia for maintenance. Biopsies are often done with fluoroscopic guidance. The American College of Chest Physicians recommends platelet counts above 50×10^3/mL in order to prevent bleeding [89]. During the bronchoscopy, the airway is examined for airway stenosis, bronchomalacia, and granulation tissue. Complications of bronchoscopy with transbronchial biopsy include pneumothorax in 0.8–3.4% of patients and hemorrhage in 1–5% of patients [89].

There is a high rate of rejection episodes after pediatric lung transplantation. Notably, 26% of patients are treated for acute allograft rejection within the first year after transplantation [83]. The lowest incidence of acute rejection is in infants at 3%, and the highest incidence is in children 11–17 years old at 34% [83]. Unsuspected acute rejection or infection is diagnosed in 25% of surveillance bronchoscopies [89]. Bronchiolitis obliterans syndrome (BOS) is the most common form of chronic rejection [83]. BOS consists of obliteration of bronchiole lumens with lymphocytic infiltration and fibromyxoid deposits [61]. BOS is a significant co-morbidity after pediatric lung transplantation with an incidence of 9.2% at 1 year, 36.5% at 5 years, and 46.3% at 7 years [83]. BOS is the most common diagnostic indication for re-transplantation and is the leading cause of death after 1 year post-transplantation [85]. Other co-morbidities after lung transplantation include supraventricular arrhythmias, infection, PTLD, hypertension, and renal dysfunction [61].

The outcomes of pediatric lung transplantation have improved over the years, but the median age of survival remains low compared to other pediatric organ transplantations. The median survival of pediatric lung transplantation recipients is 5.7 years, and the conditional survival to 1 year is 9.1 years [83]. After transplantation, the most common etiologies of death within the first year are graft failure and infection, whereas after 1 year, it is BOS [85]. Risk factors for decreased survival include intubation on arrival to the OR for transplantation, pre-transplantation steroid use, and older donor age [83, 85]. The diagnostic indication and patient's age at transplantation do not impact survival at 5 years post-transplantation [85, 90]. More than 80% of surviving pediatric lung transplantation patients have normal activity or only minor activity limitations [83].

Special Considerations

The number of heart-lung transplantations has decreased over time, with currently less than five annually, as reported by UNOS [83, 91]. Previously, patients with a diagnostic indication of pulmonary hypertension or CHD with or without

Eisenmenger's syndrome were considered for heart-lung transplantation. There is a shift in practice toward lung transplantation only in patients with pulmonary vascular diseases, with potential recovery of the right ventricular dysfunction after transplantation of donor lungs with normal pulmonary artery pressures [92].

Ethics

Pediatric transplantation is no stranger to ethical concerns, especially as the need for organs continually exceeds supply. Ethics remains essential in pediatric transplantation and is centered around the four pillars of medical ethics: autonomy, nonmaleficence, beneficence, and justice [93]. In a multinational study of transplant providers, almost 40% of respondents had experienced an ethical dilemma within 2 years [94].

Upholding justice remains the major ethical cornerstone for pediatric organ allocation [95]. Despite strategies such as pediatric scoring methods, split organs, and living donors to increase organ supply, allocation remains a major ethical concern. Medical providers must balance organ supply between acutely ill high-risk transplant recipients and more stable recipients with likely higher long-term survival. Scoring systems vary by organ, but considerations include time on wait list, severity of disease, suitability of the organ, and benefit to the patient [93]. In addition, organs may be offered preferably to pediatric patients, as the length of survival and lifetime impact may be higher [96].

The second set of dilemmas pertains to the multifactorial risks associated with living donors [95]. Physicians must practice nonmaleficence, or "do no harm," while considering a major surgical procedure in an otherwise healthy patient. Living organ donation holds significant physical, emotional, and economic risks that living donors must comprehend before they agree to organ donation.

As organ donation grows worldwide, international transplant groups must ensure that local transplant centers can support the cost and medical burden of pediatric transplantation. Pediatric recipients require lifelong monitoring, medication, and specialized medical care [95]. The growth of telemedicine and virtualized care will hopefully help transplantation continue to grow throughout the world.

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Anesthesia in Living Donor Transplantation

10

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Introduction

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Living donor transplantation represents one of the most ethically complex and technically demanding areas of modern medicine, necessitating an elective surgical procedure on a healthy patient to improve the quality of life for someone else. The anesthesiologist plays a crucial role in ensuring the safety and well-being of the living donor while optimizing conditions for successful organ procurement. This unique scenario presents distinct challenges that differ significantly from both routine elective surgery and deceased donor organ procurement [1].

Most importantly, the healthy donor must be protected from any preventable morbidity or mortality while ensuring optimal organ preservation for the recipient. This dual responsibility requires meticulous planning, comprehensive preoperative assessment, and expert perioperative management [2].

Living donor transplantation has expanded significantly over the past decades to include kidney, liver, lung, pancreas, and small bowel donations. Each organ system presents particular anatomical, physiological, and technical considerations that the anesthesia team must address. The complexity is further heightened by the need to coordinate care between two operating rooms and surgical teams when simultaneous procedures are performed [3].

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Preoperative Assessment and Optimization

Comprehensive Medical Evaluation

The preoperative assessment of living donors extends far beyond standard surgical screening. Donors undergo extensive medical, psychological, and social evaluation to ensure their suitability for donation and to identify any factors that might increase their perioperative risk [4]. The anesthesiologist must review this comprehensive workup and identify any concerns that require additional optimization or contraindications to proceeding with anesthesia.

Cardiovascular assessment is paramount, as donors must have sufficient cardiac reserve to tolerate the physiological stress of major surgery and potential blood loss. Standard evaluation includes electrocardiography, echocardiography, and stress testing when indicated. Close attention must be paid to identifying subclinical cardiovascular disease that might become clinically significant under the stress of surgery [5, 6].

Pulmonary function assessment is especially crucial for lung donors but remains important for all living donors. Baseline pulmonary function tests, arterial blood gas analysis, and chest imaging provide essential information for perioperative planning. For lung donors, sophisticated pulmonary function testing is often required, including quantitative ventilation-perfusion scanning and exercise testing, both of which help predict post-donation respiratory function [7].

Renal function evaluation is crucial for all donors, not just kidney donors, as many transplant procedures can affect renal perfusion and function. Baseline creatinine, glomerular filtration rate, and proteinuria assessment establish the donor's renal reserve and guide perioperative fluid and medication management [8].

Psychological and Social Considerations

The psychological state of the living donor significantly impacts their perioperative course and recovery. Donors may experience anxiety, depression, or ambivalence about their decision, which can affect their response to anesthesia and surgery. The anesthesiologist should be aware of these psychological factors and their potential impact on perioperative management [5].

Family dynamics and social support systems influence the donor's recovery and compliance with postoperative care. Understanding these factors helps the anesthesia team anticipate potential complications and tailor their approach accordingly. The emotional stress surrounding transplantation can manifest as cardiovascular instability, altered pain perception, and delayed recovery [9].

Medication Review Optimization

All medications must be carefully reviewed for their potential impact on organ function and anesthetic management. Supplements, herbal medications, and over-the-counter drugs can have significant interactions with anesthetic agents or affect organ perfusion. Discontinuation of certain medications may be necessary, while others may require dose adjustment [10].

Anticoagulant and antiplatelet medications require particular attention, as they can significantly increase bleeding risk during organ procurement. The management of these medications or timing of interruption, if deemed appropriate, must balance the risk of bleeding against thromboembolic complications. This necessitates coordination between the surgeon, the anesthesiologist, and the prescribing physician, taking into careful consideration the indication of the medication and potential consequences of even brief cessation [11].

Multidisciplinary Committee Review

Given the combination of medical, surgical, and psychosocial complexities of organ donation and transplantation, candidates for living donation should be formally discussed within the institution's multidisciplinary transplant committee meetings. These committees are comprised of surgeons, anesthesiologists, social workers, psychiatrists, transplant coordinators, hepatologists, nephrologists, pulmonologists, and so on, who share insight from their respective fields and collaboratively make decisions regarding candidacy, with an emphasis on patient safety, ensuring optimal outcomes, and ethical considerations such as informed consent and donor motivation.

Anesthetic Considerations by Organ System

Living Kidney Donation

Kidney donation represents the most common form of living donor transplantation, accounting for over 60% of all living donor procedures. The anesthetic approach varies significantly between open and laparoscopic techniques, with modern practice favoring minimally invasive approaches when anatomically feasible [12].

Preoperative Considerations for Kidney Donors

Kidney donors typically present as healthy individuals with normal renal function and minimal comorbidities. However, subtle cardiovascular abnormalities may become apparent under the stress of surgery and anesthesia. Baseline creatinine should be less than 1.2 mg/dL in women and 1.3 mg/dL in men, with GFR >80 mL/

min/1.73m^2. Blood pressure should be well-controlled, ideally without antihypertensive medications [13]; however, a recent meta-analysis demonstrated that kidney donors with pre-existing hypertension do not have an increased risk of subsequent severe renal dysfunction or kidney failure and may warrant further consideration [14].

The choice of kidney (left versus right) influences surgical complexity and anesthetic considerations. Left nephrectomy is generally preferred due to the longer renal vein, but right-sided donation is occasionally necessary based on anatomy or findings from functional studies.

Anesthetic Management for Kidney Donation

Monitoring Requirements Most kidney donations can be managed with standard American Society of Anesthesiologists monitoring, including pulse oximetry, electrocardiogram, non-invasive blood pressure, capnography, and temperature monitoring. Invasive arterial pressure monitoring is generally unnecessary for straightforward laparoscopic cases but may be indicated for open procedures, donors with cardiovascular comorbidities, or instances where surgical complexity is increased.

Induction and Maintenance Balanced anesthesia using sevoflurane or desflurane with moderate-dose opioids provides excellent surgical conditions while maintaining hemodynamic stability. Propofol induction (1.5–2.5 mg/kg) followed by maintenance with volatile agents (0.8–1.2 MAC) allows for rapid emergence. Transabdominal plane blocks are seeing increased use to further limit the unwanted side effects of opioids [13].

Neuromuscular Blockade Rocuronium (0.6–0.9 mg/kg) or vecuronium (0.08–0.1 mg/kg) facilitates intubation and provides surgical relaxation. Complete reversal with sugammadex (2–4 mg/kg) or neostigmine/glycopyrrolate ensures full recovery of neuromuscular function.

Fluid Management Goal-directed fluid therapy targeting euvolemia is essential. Excessive fluid administration can compromise visualization during laparoscopy, while hypovolemia reduces renal perfusion. Balanced crystalloids (Lactated Ringer's or Plasma-Lyte) are preferred over normal saline to avoid hyperchloremic acidosis. Typical fluid requirements range from 3–6 mL/kg/hr., in addition to the replacement of losses.

Laparoscopic-Specific Considerations

Laparoscopic donor nephrectomy requires specialized anesthetic management for pneumoperitoneum and positioning. CO_2 insufflation of 12–15 mmHg into the abdomen can have significant effects on cardiopulmonary function by reducing preload and functional residual capacity, which can create additional challenges in anesthetic management [15].

Positioning Lateral decubitus positioning with the kidney rest elevated optimizes surgical exposure but can further compromise venous return and reduce cardiac

output. The dependent arm should be padded and positioned to prevent brachial plexus injury. An axillary roll protects the dependent axilla from compression. The non-dependent arm should be secured in a position that provides access to the surgical field but avoids hyperextension of the brachial plexus.

Ventilatory Management Controlled ventilation with tidal volumes of 6–8 mL/kg of ideal body weight minimizes barotrauma while maintaining adequate ventilation. Using positive end-expiratory pressure (PEEP) of 5–8 cmH_2O helps prevent atelectasis. End-tidal CO_2 should be maintained between 35–40 mmHg, with an increase in minute ventilation of 15–25% during pneumoperitoneum.

Hemodynamic Effects Pneumoperitoneum increases intra-abdominal pressure, potentially reducing venous return and cardiac output. Trendelenburg positioning partially counteracts these effects but may increase intracranial pressure and contribute to airway and facial edema. Careful fluid management and vasopressor support (e.g. phenylephrine 50–100 mcg boluses) maintain perfusion pressure.

Living Liver Donation

Living liver donation represents one of the most complex procedures in transplant surgery, typically involving right hepatectomy (segments V-VIII) or left lateral segmentectomy (segments II-III). The procedure requires extensive hepatic mobilization, vascular reconstruction, and precise parenchymal division, creating unique anesthetic challenges [15] and increasing the risk of donor morbidity or mortality.

Preoperative Assessment for Living Donors

Living donors undergo extensive evaluation, including hepatic volumetry to ensure adequate remnant liver parenchyma (>30–35% of total liver volume). Hepatic steatosis should be minimal (<10% on biopsy), and hepatic function tests must be normal. Portal and hepatic vein anatomy is carefully assessed to plan vascular reconstruction.

Coagulation studies, including PT/INR, PTT, platelet count, and fibrinogen level, establish baseline hemostatic function. Some centers perform thromboelastography (TEG) to assess functional coagulation status. Cardiovascular evaluation is particularly thorough, given the potential for significant blood loss and fluid shifts.

Anesthetic Management for Liver Donation

Advanced Monitoring All liver donors require invasive arterial monitoring for continuous blood pressure assessment and frequent laboratory sampling. A 20-gauge radial arterial line is typically placed after induction. Central venous access (multilumen catheter via internal jugular or subclavian approach) is essential for fluid management, drug administration, and central venous pressure (CVP) monitoring.

Large-bore peripheral intravenous (IV) access (14 or 16-gauge) is mandatory, with at least two large IVs established. Some centers place additional large-bore access via the external jugular or antecubital veins. Blood warmers and rapid infusion devices should be immediately available.

Induction and Maintenance Balanced anesthesia with careful hemodynamic control is essential. Propofol induction (1–2 mg/kg) with fentanyl (3–5 mcg/kg) provides stable cardiopulmonary conditions. Maintenance typically combines sevoflurane (0.8–1.2 MAC) with additional opioids (fentanyl 1–2 mcg/kg/hr. or remifentanil 0.1–0.3 mcg/kg/min).

Total IV anesthesia using propofol and remifentanil may be considered and offers advantages, including better hemodynamic control, reduced hepatic metabolism, faster emergence, lower emetogenic potential, decreased environmental impact, and even possible favorable immunomodulation [16]. Target-controlled infusion systems can optimize drug delivery while minimizing hepatic exposure [17].

Coagulation Management Real-time coagulation monitoring using TEG or rotational TEG (ROTEM) guides transfusion decisions. Conventional coagulation studies Prothrombin Time/International Normalized Ratio (PT/INR) and Partial Thromboplastin Time (PTT) may not accurately reflect hemostatic function during liver surgery due to consumption and dilution.

Fresh frozen plasma (FFP) is typically reserved for significant coagulopathy (INR > 1.8) or active bleeding with coagulation abnormalities. Platelets are transfused for counts <50,000/μL in the setting of bleeding or planned central line placement. Fibrinogen concentrate or cryoprecipitate may be needed if fibrinogen levels fall below 150 mg/dL.

Fluid and Blood Management Liberal fluid administration is avoided to prevent hepatic congestion and facilitate surgical dissection. Goal-directed fluid therapy using dynamic parameters (pulse pressure variation and stroke volume variation) optimizes intravascular volume while avoiding fluid overload.

Intraoperative cell salvage is routinely employed to minimize allogeneic transfusion. Salvaged blood should be processed to remove activated clotting factors and inflammatory mediators. Some centers use acute normovolemic hemodilution to further reduce transfusion requirements.

Hepatic Protection Strategies Maintaining adequate hepatic perfusion pressure (mean arterial pressure (MAP) > 65 mmHg) throughout the procedure protects both the donor remnant and the procured graft. Brief periods of hypotension during hilar dissection may be necessary but should be minimized.

Preconditioning with volatile anesthetics may provide hepatoprotection by activating protective pathways [18], and some centers administer N-acetylcysteine [19] (150 mg/kg over 4 h) as an antioxidant, although evidence of benefit for either treatment is limited. Anesthetic methods for preventing oxidative stress and ischemia–reperfusion injury remain the subject of much ongoing research.

Intraoperative Phases and Specific Considerations

Mobilization Phase Initial hepatic mobilization involves division of ligamentous attachments and may cause significant hemodynamic changes due to blood loss and surgical manipulation. Careful positioning with adequate padding prevents pressure injuries during the lengthy procedure (4–6 h).

Parenchymal Division Hepatic parenchymal transection using ultrasonic dissection or crush-clamp techniques can cause sudden blood loss. Communication with the surgical team regarding the timing of the division helps anticipate fluid and blood product needs.

Vascular Reconstruction Hepatic artery and portal vein reconstruction requires temporary occlusion that may compromise hepatic perfusion. Brief periods of controlled hypotension may facilitate microsurgical anastomoses but require careful monitoring of end-organ perfusion.

Living Lung Donation

Living lung donation, though less common, presents unique challenges due to the critical nature of respiratory function and the potential for immediate life-threatening complications. Donors typically provide a lower lobe, which can significantly impact their postoperative respiratory function [20].

Single-lung ventilation during lung procurement requires expert airway management and careful monitoring of oxygenation and ventilation parameters. The use of lung protective ventilation strategies helps prevent ventilator-induced lung injury in both the operative and non-operative lungs [21].

Hemodynamic management during lung procurement must account for the effects of lateral positioning, single-lung ventilation, and surgical manipulation on cardiac function. Changes in pulmonary vascular resistance can significantly affect right heart function and require careful monitoring and intervention [22].

Postoperative respiratory management is critical, as donors may experience temporary respiratory compromise requiring intensive monitoring and support. Early mobilization and aggressive pulmonary hygiene help prevent complications and promote recovery [23].

Organ-Specific Intraoperative Management

Kidney Donation Anesthetic Protocols

Standard Laparoscopic Nephrectomy Protocol

Premedication Midazolam 1–2 mg IV in the preoperative area reduces anxiety without significant sedation. Avoid excessive premedication, as it may delay emergence.

Induction Sequence Preoxygenation with 100% O_2 for 3–5 minutes

- Propofol 1.5–2.5 mg/kg IV with lidocaine 0.5–1 mg/kg to reduce injection pain

- Fentanyl 2–3 mcg/kg IV for analgesia
- Rocuronium 0.6–0.9 mg/kg IV for neuromuscular blockade
- Direct laryngoscopy and endotracheal intubation

Maintenance Protocol Sevoflurane 0.8–1.2 MAC in 50% O_2/air mixture
- Additional fentanyl 1–2 mcg/kg as needed for analgesia and hemodynamic control
- Rocuronium 0.15 mg/kg q45–60 minutes or as indicated by train-of-four monitoring
- Controlled ventilation: V_t 6–8 mL/kg, RR adjusted to maintain $EtCO_2$ 35–40 mmHg

Positioning and Pneumoperitoneum Management Modified lateral decubitus with kidney rest elevation
- Secure all pressure points, including both the dependent and non-dependent extremities
- CO_2 insufflation to 12–15 mmHg (lower pressure if hemodynamic compromise)
- Monitor for subcutaneous emphysema, pneumoperitoneum, or pneumothorax

Fluid Management Protocol Balanced crystalloid (LR or Plasma-Lyte) at 3–5 mL/kg/hr. baseline
- Additional fluid for blood loss replacement (3:1 ratio)
- Target urine output >0.5 mL/kg/hr. but avoid excessive diuresis
- Consider mannitol 0.25–0.5 g/kh before hilar clamping (optional)

Emergence and Recovery Reverse neuromuscular blockade with sugammadex 2–4 mg/kg
- Extubate when fully awake with adequate respiratory effort
- Multimodal analgesia: acetaminophen 1000 mg IV, ketorolac 15 mg or 30 mg if no contraindications

Open Nephrectomy Considerations

Open nephrectomy, though less common, may be necessary for complex anatomy or conversion from a laparoscopic approach. The anesthetic management differs in several key areas.

Enhanced Monitoring Arterial line placement is more commonly indicated, given the longer procedure duration and the greater potential for fluid shifts. Central venous access may be considered for donors with cardiovascular comorbidities.

Pain Management Intercostal or paravertebral nerve blocks significantly improve postoperative pain control after flank incisions. Consider performing these blocks prior to incision [24].

Fluid Requirements Open procedures typically require more liberal fluid administration due to increased surgical bleeding, insensible losses, and more prolonged exposure [25]. Monitor for signs of fluid overload, particularly in older donors.

Liver Donor Anesthetic Protocols

Right Hepatectomy Protocol

Preoperative Preparation Type and crossmatch 6–8 units packed red blood cells (PRBCs), 4–6 units FFP, 1–2 units platelets

- Activate the cell salvage device and the blood warmer
- Prepare a rapid infusion device and pressure bags for IV fluids
- Ensure the availability of coagulation factor concentrates

Advanced Monitoring Setup 20-Gauge radial arterial line after induction

- Multi-lumen central venous catheter (right internal jugular preferred)
- Large-bore peripheral IV access (14–16-gauge x 2)
- Consider additional large-bore access via external jugular
- Urinary catheter with temperature probe
- Esophageal temperature probe

Induction Protocol Anxiolysis with midazolam 1–2 mg IV if needed

- Arterial line placement under local anesthesia (optional)
- Propofol 1–2 mg/kg IV with fentanyl 3–5 mcg/kg IV
- Rocuronium 0.6 mg/kg (1.0–1.2 mg/kg IV for rapid sequence, if indicated)
- Secure airway with an endotracheal tube, confirm placement

Maintenance Strategy Balanced technique: sevoflurane 0.8–1.2 MAC with fentanyl infusion 1–2 mcg/kg/hr.

- Muscle relaxation with vecuronium 0.08–0.1 mg/kg q45–60 minutes
- FiO_2 0.4–0.5 to maintain $SpO_2 > 95\%$

Coagulation Monitoring and Management Baseline TEG/ROTEM after induction

- Repeat every 2 h or with significant bleeding
- Maintain platelet count >75,000/μL
- Keep fibrinogen >150 mg/dL
- Target INR <1.8 unless active bleeding

Fluid and Hemodynamic Management Restrictive fluid strategy until graft removal is complete: 2–4 mL/kg/hr. balanced crystalloid. If urine output becomes severely diminished, discuss the potential need for increased fluid administration with the surgeon.

- Use vasopressors (phenylephrine and norepinephrine) to maintain MAP >65 mmHg.
- CVP target 8–12 mmHg during dissection, <8 mmHg during parenchymal division.
- Systolic or pulse pressure variation <13% indicates adequate preload.

Blood Product Transfusion Triggers PRBC: Hgb <8 g/dL with active bleeding/cardiovascular disease
- FFP: INR >1.8 with bleeding or planned procedure
- Platelets: <50,000/μL of <100,000/μL for central procedures
- Cell salvage blood: Use liberally to minimize allogenic exposure.

Phase-Specific Management
Mobilization Phase (Hours 1–2)

- Maintain normothermia with forced-air warmers.
- Monitor for bleeding during adhesiolysis.
- Prepare for potential cardiovascular instability.

Parenchymal Division Phase (Hours 2–4)

- Anticipate major blood loss during transection.
- Consider controlled hypotension (MAP 55–65 mmHg) to optimize surgical conditions.
- Maintain communication regarding blood loss estimation.

Vascular Reconstruction Phase (Hours 4–5)

- Prepare for hemodynamic changes during vascular clamping/unclamping.
- Ensure adequate perfusion pressure during anastomoses.

Closure Phase (Hours 5–6)

- Ensure hemostasis and stable vital signs.
- Increase warming if hypothermic.
- Prepare for transfer to the intensive care unit versus Post-Anesthesia Care Unit (PACU) based on complexity.

Left Lateral Segmentectomy Protocol

Left lateral segmentectomy (segments II–III) is typically performed for pediatric recipients and involves less extensive surgery than right hepatectomy:

Modified Monitoring Arterial line and central venous access remain standard, but extensive blood product preparation may not be necessary due to lower blood loss risk.

Simplified Fluid Management Less restrictive fluid management may be appropriate given the simpler surgical procedure and lower risk of hepatic congestion.

Reduced Complexity Shorter procedure duration (3–4 h) and lower blood loss make this more similar to major abdominal surgery than the complex physiology of right hepatectomy.

Postoperative Care and Recovery

Immediate Postoperative Management The immediate postoperative period is critical for living donors, requiring intensive monitoring for complications while promoting rapid recovery. Pain management must be aggressive and multimodal to facilitate early mobilization and prevent chronic pain syndromes [26].

Respiratory care is particularly important, with emphasis on deep breathing exercises, incentive spirometry, and early ambulation to prevent pulmonary complications. Lung donors may require temporary respiratory support and careful monitoring of oxygenation and ventilation parameters [27].

Hemodynamic monitoring continues into the postoperative period, with attention to fluid balance, blood pressure control, and assessment for signs of bleeding or other complications. The goal is a rapid return to normal physiological function while preventing complications [28].

Pain Management Strategies Effective pain control is essential for donor recovery and satisfaction, requiring a multimodal approach that minimizes opioid dependence while providing adequate analgesia. Regional anesthetic techniques, when appropriate, can significantly improve pain control and reduce systemic opioid requirements [29]. For more invasive surgery, such as a right hepatectomy, consideration may also be given to epidural placement either pre- or postoperatively for neuraxial pain control.

Patient-controlled analgesia systems provide donors with autonomy over their pain management while maintaining safety through pre-programmed limits. The selection of opioid agents should consider individual donor factors and the potential for adverse effects [30].

Non-opioid analgesics, including acetaminophen, gabapentinoids, nonsteroidal anti-inflammatory drugs, muscle relaxants, and topical agents, play essential roles in multimodal pain management. However, their use must be carefully considered in the context of organ function and potential interactions [31].

Monitoring for Complications Living donors require vigilant monitoring for both immediate and delayed complications that may affect their recovery and long-term health. Early recognition and intervention can prevent minor problems from becoming major complications [32].

Surgical complications, including bleeding, infection, and organ-specific problems, require immediate attention. The threshold for intervention should be

low, as donor safety is paramount and any preventable morbidity is unacceptable [33].

Medical complications such as cardiovascular events, pulmonary problems, and metabolic disturbances can occur even in healthy donors subjected to major surgery. Continuous assessment and prompt treatment are essential for optimal outcomes [6].

Special Considerations and Complications

Unique Challenges in Living Donation

Living donor transplantation presents several unique challenges that distinguish it from other surgical procedures. The ethical imperative to minimize donor risk while optimizing recipient outcomes creates complex decision-making scenarios that require careful consideration [34].

The psychological impact of donation on the donor and their family can significantly affect recovery and long-term outcomes. Postoperative depression, anxiety, and regret are recognized complications that may require professional intervention [35].

Long-term follow-up of living donors is essential to monitor for delayed complications and ensure their continued health and well-being. This responsibility extends beyond the immediate perioperative period and requires ongoing commitment from the transplant team [36].

Emergency Management

Despite careful planning and execution, emergencies can occur during living donor procedures. Massive hemorrhage, cardiovascular collapse, and other life-threatening complications require an immediate coordinated response from the entire team [30].

Emergency protocols should be well-established and regularly rehearsed, with clear roles and responsibilities for each team member. Communication systems must be in place to rapidly mobilize additional resources when needed [37].

The decision to abort a donor procedure must sometimes be made to protect donor safety, even at the expense of disappointing the recipient. This difficult decision requires clear criteria and strong leadership to overcome the emotional pressure to continue [38].

Operative Room Resource Utilization

Transplant procedures, including both the donor procurement and recipient transplant, require highly specific perioperative resources, including transplant surgeons,

specially trained perioperative nursing staff and technicians, anesthesiologists, surgical equipment, and operating room availability. Furthermore, the procurement and subsequent recipient transplant procedures often occur at the same institution, potentially doubling the resources needed in a finite time span. As such, there must be thoughtful coordination between the transplant center and the operating room leadership to ensure that all necessary resources are readily available when needed. In high-volume transplant centers, there must be additional cooperation between transplant surgeons and their non-transplant surgery colleagues to ensure efficient utilization of finite resources such as operating rooms and staff availability. For ethical reasons, in circumstances where both the donor and corresponding recipient procedures are performed in the same hospital, it is not recommended that the same anesthesiologist medically direct both anesthetics.

Quality Assurance and Outcome Monitoring

Performance Metrics

Quality assurance in living donor anesthesia requires careful tracking of outcome metrics, including donor morbidity, mortality, satisfaction, and long-term health status. These metrics help identify areas for improvement and guide quality improvement initiatives [39].

Standardized protocols and checklists can improve consistency of care and reduce variability in outcomes. Regular review and updating of these protocols ensures that they remain current with best practices and emerging evidence [40].

Multidisciplinary team meetings provide opportunities to review cases, discuss complications, and identify areas for system improvements. These forums promote continuous learning and quality improvement across all aspects of donor care [41].

Continuous Quality Improvement

Living donor programs must commit to continuous quality improvement to maintain excellence in donor care and outcomes. This requires systemic collection and analysis of outcome data, identification of improvement opportunities, and implementation of evidence-based changes [41].

Benchmarking against other centers and national databases provides valuable insights into performance and helps identify best practices. Participation in quality improvement collaboratives can accelerate improvement efforts and share successful strategies among transplant centers [42].

Regular audits of processes and outcomes help identify trends and patterns that might not be apparent from individual case reviews. These systematic evaluations guide targeted improvement efforts and resource allocation [43].

Future Directions and Innovations

Emerging Technologies

Advances in surgical technique, including robotic surgery and enhanced recovery protocols, are changing the landscape of living donor transplantation. Anesthesiologists must adapt their practices to support these new approaches while maintaining focus on donor safety [44].

Monitoring technologies continue to evolve, offering new opportunities to optimize donor care by improving the assessment of physiological status and early detection of complications. Integration of these technologies requires careful evaluation of their benefits and limitations.

Pharmacological advances, including new anesthetic agents, pain management strategies, and organ protection therapies, may improve donor outcomes and experiences. Clinical trials and careful evaluation are needed to establish their safety and efficacy in this unique population.

Research Opportunities

Living donor transplantation offers numerous research opportunities aimed at improving donor safety, outcomes, and experience. Collaborative efforts between centers can provide the sample sizes necessary for meaningful clinical studies.

Biomarker development may enable better prediction of complications and optimization of perioperative care. These tools could help identify high-risk donors and guide individualized management strategies.

Long-term follow-up studies are essential to understand the full impact on donors' health and quality of life. These studies guide patient counseling and inform future practice guidelines.

Conclusion

Anesthesia for living donor transplantation represents one of the most challenging and rewarding areas of anesthetic practice. The unique responsibility of caring for healthy individuals voluntarily undergoing major surgery for the benefit of others requires the highest levels of skill, judgment, and commitment to excellence. Success in this field demands not only technical expertise but also a deep understanding of the ethical, psychological, and social factors that influence donor outcomes.

The principles of donor safety, organ optimization, and comprehensive perioperative care must guide every aspect of anesthetic management. Continuous quality improvement, ongoing education, and commitment to evidence-based practice are essential for maintaining excellence in this critical area of transplant medicine.

As living donor transplantation continues to evolve with new surgical techniques, monitoring technologies, and pharmacological advances, anesthesiologists must remain at the forefront of these developments while never losing sight of their primary responsibility to the donor. The future of living donor transplantation depends on the continued dedication of anesthesiologists to the highest standards of donor care and safety.

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Abdominal Organ Procurement: A Surgical Perspective for the Anesthesiologist

11

David A. Faber and Steven C. Kim

Introduction

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For thousands of patients with end-stage organ failure, transplant is the gold standard option for the treatment of an increasingly broad array of diseases. While the concept of transplantation has been around since antiquity, it was not until the pioneering efforts of the mid-twentieth century that longstanding immunological and technical hurdles were finally cleared, paving the way for transplantation to become a clinical reality. From those first initial steps, what was once seen as an experimental treatment is now considered routine in many instances, as organ transplantation has grown to become widely available throughout the modern world.

The development of safe, standardized, and widely available clinical organ transplant would not have been possible without the iterative development of thousands of critical components—including advancements in surgical technique, immunosuppressive medications, administrative protocols, and innovative legal standards, to name just a few—though perhaps there has not been a more critical advancement than the development of protocolized management and recovery strategies for deceased organ donors, from whom the majority of tissue for eventual transplant is sourced (while living donation provides an essential and substantial source of donor organs, this chapter will focus on deceased donors only). Yet despite the existence of well-defined and robust medical and ethical protocols, there remains substantial confusion in both providers and patient families as to the different routes to successful deceased donor organ donation. In this chapter, we will aim to address some of

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these concerns and, in doing so, define the various types of deceased organ donors; discuss the physiology of brain death and strategies for the clinical management of the deceased organ donor; and provide technical considerations for procurement and organ storage to facilitate successful transplantation of procured organs. In particular, we will focus on the abdominal organs available for transplant—the liver, kidneys, pancreas, and small bowel—as separate from the thoracic organs (heart and lungs), which are covered separately.

Background and Definitions

Although organ transplantation has become much more widely available, the demand for available organs far exceeds supply [1]. In the United States, the waiting list currently has over 100,000 candidates listed across all organ types. Yet, in 2024, a record-breaking year for organ transplants, a total of 48,149 transplants were performed—leaving more than half of listed patients waiting for a life-saving organ [2]. During this time period, thousands of patients died while awaiting an organ transplant, and thousands more continue to wait up to years for an opportunity to become an organ recipient [3]. Encouragingly, there are signs that availability continues to widen—the number of potential donors evaluated continues to increase year-over-year, as does the absolute number of transplants—yet current efforts remain inadequate to provide patients with timely access to an appropriately matched organ [4].

This inherent mismatch between supply and demand is multifactorial; medical, logistical, cultural, and legal hurdles all play a role. Access to transplant is far from uniform, with notable disparities in access across race, gender, ethnicity, and location [5]. While medical criteria relating to donor appropriateness legitimately limit the number of potential donors who progress to donation, the national organ transplant infrastructure in the United States has recently come under scrutiny for failing to procure organs from an ever-widening set of available donors [6]. With changing donor characteristics and an increasing prevalence of chronic diseases such as diabetes and hypertension that narrow donor suitability, a significant challenge is maximizing the number of donors and the number of organs recovered, while still ensuring that recovered organs are of high enough quality to provide recipients with maximal benefit, recovery, and quality of life. In this setting of increased regulatory scrutiny and an ever-growing waiting list, appropriate recognition of potential donors and their optimal management is more important than ever.

The opportunity for organ donation begins with the declaration of death in the appropriate setting. What does it mean to die? It is a surprisingly complex question to answer, with significant medical, legal, cultural, religious, and spiritual implications. For millennia, death was generally defined as the irreversible cessation of life-sustaining cardiopulmonary function leading to loss of cerebral activity [7]. However, with the advent of critical care and full cardiopulmonary support, this definition was inadequate, as modern medicine allowed a subset of patients to be maintained with a functioning cardiopulmonary system but without any discernible brain activity. In the late 1960s, when organ transplantation began to gain in popularity and there were

wide variations in donor practice nationwide, a landmark 1968 paper from the Ad Hoc Committee of Harvard Medical School established "irreversible coma" as an acceptable definition of death—reflecting the new clinical reality by defining for the first time what would later come to be better known as "brain death" [8].

In the subsequent years, consensus criteria for organ donation would be established. Two conditions must be satisfied prior to procurement of any potential organs—first, donors must be declared dead by an independent physician other than that of the recipient to avoid any conflict of interest (the so-called "dead donor rule"); and second, either the donor or their legal representative must consent to the organ procurement process (the so-called "consenting donor rule") [9, 10]. In the decades since, national transplantation policy has built upon these two bedrock principles, which have undergone little modification from their original formulation [11].

These criteria lead directly to several categories of organ donors: first, donors who are declared brain dead according to a strict set of medicolegal criteria, only after which a procurement operation can take place under controlled settings—so-called "donation after brain death" (DBD) donors. This stands in contrast to a second group of donors who do not meet formal brain death criteria, yet who have sustained injuries so devastating that they are not expected to make any kind of meaningful recovery. In this situation, patient families can consent to the planned withdrawal of all cardiopulmonary medical support, after which the patient will eventually expire and be declared dead by conventional cessation of cardiopulmonary function. Only after the declaration of death by an independent physician can organ procurement take place—so-called "donation after cardiac death" (DCD) donors.

From a strictly physiological standpoint, organs are best suited for transplant when they remain perfused with oxygenated blood at normal body temperature for as long as possible, with the shortest possible time of ischemia between procurement and implantation. As a result, DBD donors represent the ideal circumstance for organ donation. Donors are medically and legally dead but remain connected to cardiopulmonary support, which keeps all potentially transplantable organs fully perfused with oxygenated blood at normal body temperature. Surgical exposure and procurement can proceed expeditiously but need not be rushed. When exposure is optimal and cannulae have been carefully inserted, procurement can proceed under controlled circumstances.

In contrast, DCD donation proceeds in a markedly different manner. During the duration between cessation of life support and organ retrieval, organs exist at least partially in a hypoperfused state in which they remain at normal body temperature but do not receive fully oxygenated blood at a physiologic blood pressure, leading to a buildup of toxic anaerobic metabolites and irreversible organ damage. If this interval of warm ischemic time is too prolonged, it can lead to irreversible injury, rendering organs unable to be safely transplanted. As a result, from the time of declaration of death, DCD donation proceeds urgently, as exposure and cannulation must occur as quickly as possible to minimize warm ischemic time.

Although DBD donors remain the physiologically ideal organ donor, there is only a small set of narrow injury patterns that can lead to brain death alone without concurrent damage to potentially transplantable organs. As a result, many have

considered ways to augment the number and quality of DCD donors. One such approach has been termed normothermic regional perfusion (NRP) and seeks to convert aspects of DCD donation to be more similar to that of DBD donation. In NRP, DCD donors are declared dead according to local medicolegal criteria, and donation and cannulation proceed as above. Instead of procuring organs immediately as in typical DCD cases, arterial and venous cannulae are quickly inserted into the donor and connected to a cardiopulmonary bypass machine while clamping the vessels to the head, effectively restoring the circulation of oxygenated blood to all organs except for the brain. After a period of normothermic perfusion during which organs are allowed to recover from the transient ischemic period, procurement proceeds like DBD donation—surgical exposure is completed, preservative solution is flushed through the existing cannulae under controlled circumstances, and the organs can then be removed. NRP has been widely used in Europe for many years with generally excellent outcomes; it is relatively new in the United States, though it has been growing in popularity in recent years. While there exists a compelling physiologic rationale and good data from international studies, long-term outcomes in the United States have yet to be determined [12].

While the design and function of the national organ transplant infrastructure remain beyond the scope of this chapter, it is worth mentioning that donors and families remain at the forefront of the organ procurement process. Optimal care of organ donors is paramount to provide an appropriate organ for recipients. Donor families are often living through a sudden and incredibly tough situation and have to make complex medical decisions for their loved ones in extraordinarily difficult circumstances. To this end, use of the word "procurement" to describe the retrieval of suitable organs for transplant is preferred over the word "harvest," which connotes an unfeeling, aggressive, and industrial system design that does not reflect clinical reality. Organ transplantation is truly a team effort and would not be possible without the coordination of hundreds of people for each case, of which optimal care of organ donors remains a critical part.

Deceased Donor Management

Definition and Diagnosis of Brain Death

Since the first formal definition of brain death in 1968, the establishment of death by neurological criteria has been gradually legally enacted across the United States. There was, however, significant heterogeneity between states, leading to substantial confusion regarding an acceptable medicolegal definition of death by neurological criteria. To address this confusion, in 1981, the American Bar Association, American Medical Association, National Conference of Commissioners on Uniform State Laws, and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published guidelines for the determination of death in an attempt to, "provide a comprehensive and medically sound basis for determining death in all situations," including that of brain death [13]. The same document also proposed legal language for adoption by all state

legislatures, the so-called Uniform Determination of Death Act, which 37 states, the District of Columbia, and the US Virgin Islands have since enacted [14].

In sum, declaration of death by neurological criteria can be made by establishing two criteria: first, *cessation of function* of the entire brain, including the higher function of the cerebrum as well as the lower reflexes of the brain stem; and second, the *irreversibility* of this loss of function, which must be beyond recovery and persist after an appropriate period of observation. A 1995 summary statement by the American Academy of Neurology (and a subsequent 2010 update) established guidelines to make these determinations [15, 16]. Clinically, the determination of brain death must be made by correcting other causes of cerebral nonresponsiveness, including electrolyte abnormalities, acid–base disturbances, endocrine system dysregulation, drug intoxication or poisoning, and/or hypothermia. Once corrected, three clinical findings are necessary to establish a diagnosis of brain death: (1) coma (loss of clinical responsiveness to painful stimuli); (2) absence of brainstem reflexes (including pupillary, oculocephalic, corneal, and pharyngeal); and (3) apnea (no self-generated respiratory effort in response to a PaCO2 > 60 mmHg). Importantly, brain death is a clinical diagnosis—meaning that it can be diagnosed without the use of adjunctive studies (although typically it requires a ventilator and the ability to check serial arterial blood gas measurements). Should there be any question of interpretation of results, confirmatory studies (and their findings indicative of brain death) may be helpful. These may include angiography (absence of blood flow to the brain), electroencephalogram (absence of cerebral electrical activity), transcranial Doppler measurements (absence of diastolic flow to the brain), and/or cerebral scintigraphy with a Tc-99 nuclear medicine scan (absence of uptake by the brain parenchyma). Some states, although not all, require confirmatory testing to be performed by a second, separate physician after a waiting period (usually between 6 and 24 h). Similar criteria have been developed to make a diagnosis of brain death in the pediatric population, though the specifics are beyond the scope of this review.

Physiology of Brain Death

Physiologically, brain death is the end stage in the natural history of severe intracranial injury. By whatever mechanism this injury took place, the subsequent massive intracranial swelling increases the pressure within the skull, and as the bony calvarium is a fixed volume that cannot expand, the pliable brain structures are subsequently forced downward and herniate fully or partially out of the foramen magnum. This phenomenon is also referred to as “coning” of the brainstem and brain structures. As the brainstem structures herniate out of their typical anatomic positions and become progressively ischemic, they lose their ability to regulate homeostatic and autonomic functions, which are typically tightly controlled within narrow parameters. The number of structures affected and the degree to which they lose their regulatory function result in the clinical picture seen by the evaluating physician at the bedside [17].

Clinically, this loss of homeostatic and autonomic function often manifests as severe derangements to the cardiovascular, pulmonary, and endocrine systems and

may be accompanied by a massive systemic inflammatory response and coagulopathy [18]. From a cardiovascular standpoint, heart rate and blood pressure are typically tightly regulated to maintain cardiac output (CO) and mean arterial pressure (MAP), and loss of the brainstem centers controlling these variables results in considerable hemodynamic instability. The initial physiologic response to brainstem herniation attempts to raise the driving blood pressure to the brain, resulting in a catecholamine surge and unopposed sympathetic stimulation that causes elevations in systemic vascular resistance, CO, and MAP. Progression to total sympathetic denervation results in systemic loss of vascular tone and reductions in MAP that may manifest clinically as bradycardia and hypotension. Wide swings in hemodynamic variables are common as the brainstem centers progressively become locally ischemic at unpredictable rates. Controlling these variables with vasopressors or vasodilators is typically challenging in the acute setting and requires close attention [19]. The pulmonary system may be directly affected by alternating phases of vasoconstriction/vasodilation, which can cause local release of inflammatory mediators and direct injury to lung tissue at a cellular level. Additionally, lung tissue may be injured by the effects of aspiration (common in neurologically devastated patients who cannot safely maintain their airway), sequelae of the index injury (pulmonary contusion or pneumothorax from a traumatic injury, for example), or transfusion-associated lung injury [20].

Derangements of the endocrine system are the direct result of disruption of the hypothalamic-pituitary axis. The anterior pituitary is rendered unable to produce its typical suite of hormones, leading to downstream dysregulation of thyroid, adrenal, and other normal endocrine organ function. Loss of thermoregulation is common, leading to episodes of hypothermia or hyperthermia (which may lead to a fruitless search for infectious causes of fever). Loss of ACTH production may cause a relative cortisol deficiency, which may compound hemodynamic instability [21].

A systemic inflammatory response is common and is related to the widespread activation of inflammatory pathways and the release of inflammatory mediators, such as tumor necrosis factor and various interleukins. These have widespread and varied systemic effects but do significantly contribute to the unstable systemic milieu. Brain death is also associated with systemic coagulopathy, the result of direct release of prothrombotic mediators from damaged brain tissue, as well as dilution of clotting factors in the setting of large volume resuscitation. Together, these lead to an increased risk of disseminated intravascular coagulation (DIC), though to what extent this clinically affects the transplantable organs is unknown [22]. Although there is evidence to suggest that DIC may not hurt long-term kidney function, additional studies are needed to further investigate the impact of DIC on long-term organ survival [23].

Assessment of Donor Quality

In this volatile setting, it is critical that all potentially transplantable organs be fully assessed prior to procurement in order to maximize recovery rates and increase the number of organs available for transplant. The initial donor assessment is done by the treating medical team. Local protocols may vary considerably, but when the

possibility of organ donation becomes a clinical reality, treating medical teams reach out to the local organ procurement organization (OPO). Congressional mandate has divided the United States into 55 donation service areas (DSAs), each one managed by an OPO, a not-for-profit organization responsible for recovering organs from deceased donors within its DSA. OPOs perform a holistic assessment of each donor and collect detailed information related to surgical and medical history, comorbidities, and social history, including high-risk behavior such as substance abuse. Detailed information on the cause of death (in the case of DBDs) or injury (in the case of DCDs) is compiled in addition to serial bloodwork, relevant imaging, and other organ-specific information.

Once a determination of suitability as a potential donor is made, the organs that are being offered for transplant are "matched" to potential donors through the Organ Procurement and Transplantation Network database—otherwise known as the national transplant waiting list. Candidates are matched to donors according to organ-specific criteria, including blood type and immunological histocompatibility, with the sickest and closest patients typically matching higher compared to patients who are less sick and further away. All of the gathered information is then made available to the transplant centers whose patients have come up on the match run for their evaluation. Center-specific criteria may significantly impact which organs are accepted and which are not; risk tolerance for marginal organs varies considerably according to recipient center institutional knowledge, experience, and protocols. Ultimately, the decision to proceed with procurement and transplant of a potential organ is made together by the transplant surgeon and recipient at the recipient center.

While the holistic assessment of the suitability for transplant of the abdominal organs is beyond the scope of this chapter, below you will find a brief explanation of some of the donor-specific factors that contribute to this complex medical decision. Again, while there are many factors that contribute to organ assessment, the most important is the concept of matching—is this the right organ for the right recipient? Sicker recipients generally have less physiologic reserve and cannot tolerate additional insults from poorly functioning or marginal grafts, whereas healthier patients can and often do. Experience plays a significant role in evaluating overall donor gestalt and determining suitability.

Liver

Potential deceased donors are evaluated beginning with a basic review of medical history and bloodwork. Generally, donors are in good health without major comorbidities, though the presence of other unrelated medical problems, such as diabetes or hypertension, is not a contraindication to donation. Donors with a history of malignancy are generally avoided, though there are important exceptions [24]. Elevated body mass index (BMI) is not a contraindication for donation, but it increases the risk of fatty liver. While there are certain imaging findings that suggest increased fatty infiltration of the liver, a surgical biopsy of the donor graft is the gold standard to determine the degree of steatosis. Alcohol ingestion history is also assessed, though it does not preclude donation unless there are simultaneous concerns for fibrosis of the donor graft.

Bloodwork should generally reveal normal liver function and coagulation parameters—though elevated serum aminotransferases and bilirubin are common in deceased donors (especially those with a period of cardiopulmonary arrest prior to resuscitation) and do not necessarily indicate aberrant liver function. More important is the *trend* of liver function, and its return toward normal values generally indicates a graft with the potential for recovery that would make a suitable organ for transplant. Infectious diseases, including the hepatitides, are screened for; hepatitis C is no longer an absolute contraindication to donation as newer antiviral medications can cure this disease post-transplant in recipients. In fact, recent data shows that recipients receiving a DCD hepatitis C+ organ have similar 1-year outcomes to those receiving from a DBD hepatitis C− donor [25].

Anatomically, the liver must be an appropriate size match for the recipient. The right upper quadrant anterior–posterior distance is measured on cross-sectional imaging in both donor and recipient, and these measurements must be reasonably close to allow closure of the abdominal wall in the recipient. Knowledge of the vascular anatomy of the donor and recipient is also important, as this will impact both the technique of surgical procurement as well as how blood flow is re-established to the donor graft.

Surgical biopsy of the potential donor graft is typically done during the procurement operation, though theoretically, it can be done beforehand at the bedside under ultrasound imaging guidance. Intraoperative visualization and feel of the organ by the procuring surgeon is important, though it is an imperfect estimate of underlying steatosis or fibrosis. Review of biopsy specimens is conducted by an experienced gastrointestinal pathologist. Degree of macrosteatosis, presence or absence of fibrosis, degree of portal infiltration, and/or evidence of cholestasis are assessed. Generally, macrosteatosis >40% and fibrosis grade II or higher are contraindications for transplant, though there exists significant heterogeneity between accepting centers as far as absolute versus relative exclusion criteria.

Split Liver Allografts

A special consideration must be made for pediatric recipients awaiting transplantation. Because of the relative rarity of organ donors small enough to be an acceptable size for pediatric recipients, whole allografts of appropriate quality can be split in such a way that the left lateral sector of the liver is allocated to a pediatric recipient, while the right trisection of the liver is then allocated to an adult recipient. Depending on the experience and preference of the accepting pediatric transplant center, the donor liver allografts can be split either *in situ* during the warm phase of the DBD procurement operation, which adds a significant amount of necessary dissection to the operative time, or *ex situ* after the whole liver has been procured and kept cold after cross-clamping.

Kidney

Medical history prior to hospitalization is reviewed, as is the hospital course prior to organ donation. Many of the therapies utilized in the care of a hemodynamically unstable potential donor, such as vasopressors, may result in a relative

hypoperfusion of the renal parenchyma and temporary or permanent injury. Potential donors frequently require some type of temporary renal replacement for optimization of fluid status, electrolyte balance, or clearance of nephrotoxic mediators (such as myoglobin in rhabdomyolysis associated with crush injuries). If present, the trend of hourly urine output is reviewed.

Renal function prior to surgical procurement is assessed. Baseline creatinine (or if unknown, admission creatinine level) is noted, as is the trend during hospitalization. Return toward baseline generally indicates a potential for recovery. Elevated creatinine, or even absence of or reduced renal function while on temporary dialysis, is not a contraindication for donation; rather, the overall potential for recovery is assessed. Scoring systems, such as the Kidney Donor Profile Index (KDPI), have been developed that attempt to prognostically determine how long a potential donor kidney is expected to function relative to all kidneys recovered in the United States in the previous year. Donor factors such as age, weight, creatinine, cause of death, and presence or absence of diabetes and/or hypertension are mathematically combined into a percentage score, with lower numbers indicating a longer expected time of function (e.g., a kidney with a KDPI of 40% is expected to last longer than 60% of all kidneys recovered in the United States in the previous year). Patients who are highly sensitized (who have high levels of anti-HLA antibodies, which limit the number of donors from which they can receive an organ) or who are 0-ABDR mismatched to the donor (i.e., have an identical human leukocyte antigen (HLA) subset to the donor, which would minimize the potential for rejection) typically receive priority and are ranked higher on the match list. Donor–recipient matching is key; transplantation of a kidney that functions immediately may be critical for certain recipients, while it is less important in others [26].

After surgical procurement, a biopsy is sometimes performed according to local OPO protocols. Degree of glomerulosclerosis, fibrosis, and/or inflammation is assessed by an experienced pathologist; increasing percentages of these parameters are not a contraindication to transplant per se but rather generally indicate an increased risk of graft failure or nonfunction. Anatomy is assessed, including the presence and location of any supranumerary renal arteries, as well as the quality of the donor aorta and renal artery orifices. Use of *ex vivo* hypothermic machine perfusion (HMP) of donor kidneys is increasing, and review of "pump numbers"—the particular pressure and flow parameters of the donor organ—can be helpful in determining suitability for transplant (for a more detailed discussion of pumping of deceased donor kidneys, see the section *organ storage after procurement* below).

Pancreas

There are far fewer pancreas transplants performed each year compared to either liver or kidney transplants. While pancreas transplant does offer high rates of cure of type 1 diabetes, in particular in patients with end-organ sequelae of diabetes and/or hypoglycemic unawareness, the extensive surgery required, potential complications, and improving options for non-operative management have precluded widespread adoption outside of experienced centers. Moreover, the high rate of graft loss within 1 year, primarily due to technical issues, has likewise limited enthusiasm.

As a result, in previous years, deceased pancreas donors were almost universally required to be near-perfect, that is, DBD donors with low BMI, no history of diabetes, and no evidence of edema or pancreatitis on open surgical evaluation. Retrospective review of the data and the development of scoring systems such as the Pancreas Donor Risk Index and Pre-Procurement Pancreas Suitability Score have helped to systematize donor evaluation [27, 28]. Important donor factors to consider are age, BMI, cause of death from stroke, type of donor (DBD versus DCD), and serum creatinine >2.5 mg/dL. Review of the serum amylase, lipase, and hemoglobin A1c is also part of the holistic evaluation. Intraoperative mobilization and evaluation by the procuring surgeon plays an important role in assessing for edema and tissue quality that may not be apparent on cross-sectional imaging or bloodwork.

Intestine

There are several configurations of intestinal transplant, which may (multivisceral) or may not (isolated intestinal) include additional organs such as the liver and/or pancreas. Recipient factors play a significant role in determining the type of graft that would be best suited for each individual recipient. Whether or not additional organs are involved, at its core, intestinal transplant involves transplantation of the small bowel on its vascular pedicle, restoring sufficient absorptive capacity to patients who are dependent on total parenteral nutrition (TPN) due to irreversible intestinal failure.

The ideal donor is young, without additional medical problems, and has progressed to organ donation without abdominal trauma. Small bowel enterocytes are sensitive to hypoperfusion; thus, donors with mesenteric low flow states (hypotension, pressor requirements, and need for multiple blood transfusions) are often not suitable. DBD donors are required to minimize cold ischemia time. Timing of procurement and recipient exposure are critical; recipients often have hostile and multiply re-operative abdomens, which may take hours to enter safely. The amount of bowel to be recovered depends on the size of the recipient; typically, 180–200 cm is needed at a minimum in adults to provide sufficient absorptive capacity to allow attempted TPN cessation, while pediatric requirements differ substantially depending on recipient size. Intestinal grafts can be procured without affecting the ability of the liver and/or pancreas to be allocated to other recipients; the specific needs of the intestinal recipient will dictate whether or not a multivisceral transplant is planned and to what degree any kind of vascular reconstruction is required [29, 30].

Anesthesia and Technical Considerations for Abdominal Organ Procurement

Location of Surgical Organ Procurement

In the early years of transplant, all deceased donor procurements were performed at the donor hospital—that is, at the hospital in which the donor was pronounced deceased. As transplant volumes and the number of potential donors increased nationwide, the limits of this system quickly became apparent. Some of the many

drawbacks to this system include the fact that donor hospitals were frequently in isolated areas, far from airports or major highways; deceased donor procurement is a highly specialized surgical procedure requiring perioperative, anesthetic, and surgical expertise, which is often lacking in smaller hospitals which never or infrequently perform the operation; and cases often take place at odd hours to minimize interruptions to elective or emergent cases, increasing the burden on the traveling teams. The costs of this arrangement, in both monetary terms, as well as the number of organs lost to logistical or technical constraints, were significant.

To address these shortcomings, many high-volume OPOs have developed Organ Recovery Centers (ORCs), which are specialized facilities to which donors are transferred for the peri-donation management period up to and including surgical procurement. ORCs are either free-standing isolated facilities or are based within the same hospital as an existing transplant center. In either case, they specialize in organ donation and possess the necessary expertise for critical care management of potential donors, investigational studies to determine suitability for transplant, and surgical recovery of organs for transplant. The usefulness of having skilled providers and standardization during procurement has been shown to increase organ yield and help realize significant cost savings. At the time of this writing, nearly 50% of OPOs (24 of 57) utilize an ORC. Gradually, this paradigm is being adopted across the country [31].

DBD donors are most easily moved to ORCs, given that it is already known in advance that they will progress to organ procurement. In DCD donors, on the other hand, it is not known ahead of time with full certainty that donors will progress to procurement, and local treating physicians cannot accompany the patient to a distant location. As a result, DCD donation at an ORC is fraught with logistical, legal, and ethical issues. Most ORCs do not allow DCD donation, though some that are connected to an existing transplant center have the requisite staff, expertise, intensive care unit (ICU) availability, and logistical flexibility to permit DCD donation. However, regardless of the location of the donor, be it donor hospital, transplant center, or ORC, the core tenets of peri-operative, anesthetic, and surgical management remain the same, and the singular focus on donor patient care remains paramount.

Donation After Brain Death

As above, the DBD donor has been declared legally and medically dead prior to proceeding to the operating room for surgical procurement. The benefit of DBD donors lies in the ongoing perfusion of the intra-abdominal organs with oxygenated blood at a normal body temperature and the absolute minimization of the ischemic period between procurement and implantation. To this end, maintenance of blood pressure within physiologically normal ranges up until the moment of aortic cross-clamping is paramount. Vasopressor medications are continued through transport to the operating room and throughout the procurement operation as needed. Oxygenation is likewise maintained with supplemental oxygen as needed.

Avoidance of fluid overload is important beginning during the preoperative phase. While massive fluid resuscitation is often a part of the donor hospital course

prior to declaration of brain death, depending on the particular injury pattern and insult suffered, after declaration of brain death and restoration of appropriate intravascular volume, additional fluid resuscitation should be minimized and titrated to physiologic goals such as hourly urine output. Volume overload and/or anasarca can result in significant third spacing of fluids into the extravascular compartment, complicating surgical procurement. Specifically, the pancreas and liver are particularly susceptible to the effects of volume overload. The pancreas is a retroperitoneal organ and easily becomes edematous without judicious fluid use, precluding its use for transplantation. Over-resuscitation can likewise raise central venous pressure, limiting the outflow from the liver via the hepatic veins and resulting in intrahepatic venous congestion. Backup of pressure into the intrahepatic sinusoids can cause injury to hepatocytes and increase the risk for early allograft dysfunction (EAD) and/or primary nonfunction (PNF).

Once in the operating room, the patient is placed supine on the operating room table. Arms are tucked. Arterial and venous lines are arranged to be out of the surgical field. The Foley catheter is directed toward the head of the bed for monitoring of urine output. The field is widely prepped and draped, from the sternal notch to the pubic symphysis, and laterally to the level of the bed (or to the tucked arms). Once all surgical teams are present (which may include one or more thoracic and one or more abdominal procurement teams), an appropriate timeout is performed, verifying the correct donor, organs to be procured, sequence for recovery, and any additional donor-specific considerations, along with a moment of silence in honor of the donor's gift of donation.

Abdominal procurement of the liver and kidneys begins with a generous laparotomy incision from the xiphoid process to the pubic symphysis. The abdomen is carefully entered without damaging any of the underlying viscera. The round ligament is divided between the ties. The falciform ligament is divided up to the level of the hepatic veins to mobilize the anterior surface of the liver from the anterior abdominal wall. The left hepatic lobe is mobilized by dividing the left triangular ligament. The gastrohepatic ligament (pars flaccida) is opened, noting any replaced or accessory left hepatic artery and preserving it if present. A Kocher maneuver and right-to-left medial visceral rotation are performed, which mobilize the duodenum, right colon, and small bowel and bring them medially to expose the inferior vena cava (IVC) and abdominal aorta. Control of the aorta for later cannulation is accomplished with umbilical tape just proximal to the bifurcation. The inferior mesenteric vein (IMV) is isolated and controlled if an *in situ* portal flush is planned. The tissue anterior to the aorta is cleared up to the level of the crossing of the left renal vein and superior mesenteric artery (SMA). The right lobe of the liver is mobilized by dividing the triangular ligament and separating the liver from the diaphragm and retroperitoneum; care is taken to avoid injury to the retrohepatic vena cava. Dissection of the hepatic hilum is then performed with the goal of identifying the gastroduodenal artery (GDA; the final branch of the common hepatic artery) and the common bile duct (CBD). Replaced or accessory right hepatic arteries are preserved. If the liver allograft is to be split *in situ,* then at this time, the left hepatic vein and the left portal vein and left hepatic artery are identified and the parenchyma is split taking care to

identify and ligate any vessels or small bile ducts; the abdominal surgeon may elect to also perform an intraoperative cholangiogram to delineate the biliary anatomy and determine the appropriate level to divide the biliary plate. Finally, supraceliac aortic control is achieved for "cross-clamping"; this may take place in the abdomen (by dividing the left crus and isolating the aorta to the left of the spine) or in the chest (if no thoracic team is present). If cross-clamping is to be performed in the chest, a sternotomy is performed, and access to the descending aorta is achieved by medializing the left lung and accessing the aorta as it runs to the left of the spine above the diaphragm.

Pancreas procurement involves additional mobilization of the pancreas and spleen. The stomach is mobilized by entering the lesser sac through the greater omentum. The short gastric arteries are divided, and the spleen is medialized by dividing its attachments to the side wall. The transverse colon is mobilized away from the duodenum, and the splenic flexure is mobilized away from the spleen and inferior pancreatic border. The transverse colon mesentery is divided with a vessel sealing device. The pancreas is then mobilized off of the retroperitoneum, separating it from the left adrenal gland and left kidney. The stomach is divided 2–3 cm proximal to the pylorus, and the jejunum is divided a few centimeters distal to the ligament of Treitz. Any remaining posterior attachments are divided by medializing the spleen and the tail of the pancreas.

At this point, the "warm dissection" of the abdominal organs is complete, and they are ready to be removed. However, the organs must first be flushed *in situ* with ice-cold preservation solution, slowing down cellular metabolism and minimizing production of toxic anaerobic inflammatory mediators—thus reducing the risk of potentially damaging ischemia–reperfusion injury (IRI) on reperfusion in the recipient. Notably, 30,000 units of heparin are given intravenously to reduce the chance of intravascular clotting. After 3 min, the cannulae for flush are placed into the distal aorta (held in place by the previously placed umbilical tape) and IMV (if an *in situ* portal flush is planned). When all parties are ready, the aorta is cross-clamped and the flush lines are opened, allowing cold preservation solution to flow into the abdominal organs through the *in situ* vasculature. To prevent over-pressurizing the system, a "vent" is created on the venous side by opening the right atrium (if no cardiac procurement is planned) or the suprahepatic vena cava above the diaphragm. Ice is generously placed into the abdomen to surround the liver, kidney, and/or pancreas to rapidly cool them down. Typically, 4 L of solution is flushed through the arterial cannula, and up to 2 L is flushed through the portal venous cannula.

Next, the "cold dissection" proceeds to remove the organs from the abdominal cavity. The liver is removed first. The left and right diaphragm and supradiaphragmatic IVC are divided. The GDA is divided, as are the remaining lateral and posterior hilar attachments, exposing the portal vein; this is likewise divided within the pancreas below the superior mesenteric-splenic vein confluence (if no simultaneous pancreas procurement) or at the level of the coronary vein (if the pancreas is also to be procured). The IVC is divided above the level of the left renal vein, and the aorta is opened below the SMA orifice, taking care not to injure the left or right renal artery. The aorta is divided at the level of the cross-clamp. With the aorta and vena

cava completely separated from their superior and inferior attachments, the liver is lifted off of the retroperitoneum, and the remaining attachments to the retroperitoneum, pancreas, and mesenteric plexus are divided. The liver is removed from the abdomen.

The pancreas is removed next if it is being procured. Most of the cold dissection has already been performed; at this point, the remaining posterior attachments to the retroperitoneum are divided, and the pancreas is removed en bloc with the duodenum and proximal jejunum.

The kidneys are the final abdominal organ to be removed. The ureter of each kidney is identified in the pelvis, and maximal length is obtained before it is divided. The attachments to the retroperitoneum are divided, taking care to preserve the delicate plexus of vessels around the ureter. The aorta is opened along its anterior midline, and the left renal vein is divided at its insertion with the IVC (if not already done during liver procurement). The aorta is divided along its posterior midline, preserving any supranumerary renal arteries. The kidneys are mobilized from the retroperitoneum, and the aortic patch is preserved en bloc with the surrounding tissue.

On final removal of the abdominal organs, the iliac vessels are procured as well; these typically are sent with the liver and/or pancreas to serve as biologic conduits should any vascular reconstruction be required in the recipient. The common iliac artery and vein are separated from their surrounding attachments and dissected distally until both the internal iliac artery/vein and the distal external iliac artery/vein are free. They are then removed en bloc. The final tissues to be procured are lymph nodes and/or the spleen (typically part of research protocols or necessary to complete histocompatibility testing).

Donation After Cardiac Death

In contrast to DBD donors, DCD donors are not yet deceased when the decision to proceed with attempted organ procurement is made. In accordance with the "dead donor rule," DCD donors must first be declared deceased by an independent physician before any organ procurement can take place. Once consent from family has been obtained, this involves planned withdrawal of life-sustaining cardiopulmonary support, which leads to death via eventual cardiac arrest. It is important to stress that the transplant teams are not involved with any of the medical decisions made prior to the declaration of death; all care of the potential donor is under the direction of the independent treating physician who remains medically and legally responsible until the declaration of death is made.

Prior to any attempted donation, the donor must be evaluated by the recipient center and receiving surgeon. An important consideration is the likelihood of progression to death after withdrawal of cardiopulmonary support within a reasonable time frame. During the time between withdrawal of support and the declaration of death, the abdominal organs exist in an environment of "warm ischemia"—a progressively hypoxic and hypoperfused state in which they are no longer receiving oxygenated blood at a physiologic blood pressure; anaerobic metabolism begins to dominate and toxic metabolites build up in the tissues. Longer periods of warm

ischemia have been shown to correlate with worse outcomes in recipients; elevated rates of both ischemic biliary complications in liver transplant, as well as delayed graft function (DGF) and PNF in kidney transplant, have significant effects on recipient outcomes. Thus, it is critical to predict the likelihood of progression to circulatory arrest in potential donors. Scoring systems, such as the University of Wisconsin Donation after Cardiac Death Evaluation Tool, have been developed to help predict which donors will progress within a 60- or 120-min time frame; however, they have not been widely validated [32].

If the decision is made to proceed with organ recovery, cardiopulmonary support is withdrawn under controlled settings. There exists significant variability in the mechanics of DCD donation between hospitals. Ideally, withdrawal takes place in an operating room with the surgical field prepared and draped for procurement to minimize delays. However, local hospital protocols may stipulate withdrawal in the ICU or in the preoperative holding area; in these cases, after declaration of death, the patient is expeditiously brought to the operating room for procurement [33]. Wherever withdrawal takes place, 30,000 units of intravenous heparin are given prior to withdrawal, and the patient is disconnected from the ventilator (either with or without extubation, depending on local hospital protocols). Vasopressor support is stopped. Sedatives or narcotics are given for comfort at the discretion of the treating physician. Once again, all of the medical decisions regarding donor management are made independently by the treating physician without input from the procuring transplant team.

Upon withdrawal, donor vitals are closely monitored. While some donors may progress to circulatory arrest nearly immediately or within minutes, others may have a more gradual decline. Eventually, cardiac arrest results in either pulseless electrical activity or asystole (at the discretion of the treating physician). A waiting period of 5 min of "no touch time" is started in order to account for the possibility of auto-resuscitation; if, after 5 min, arrest is confirmed by the declaring physician, procurement can proceed. The time of death is noted as the time of cardiac arrest (i.e., that marking the beginning of the 5-min waiting period).

In the progression to cardiac arrest, at a certain point, the driving blood pressure is no longer adequate to maintain aerobic metabolism, and hypoxic injury begins to accumulate. Various physiological "agonal criteria" have been used to mark the onset of inadequate tissue perfusion, though none has been proven to be superior to any other. The length of this "functional warm ischemia time" (fWIT)—that is, from the onset of the agonal criteria to aortic cross-clamp—is the true determinant of ischemic organ injury and is the most important variable to assess for accepting transplant centers. There are no set criteria beyond which an organ is deemed unsuitable for transplant; rather, ischemic organ injury exists on a continuum, and each accepting center has a degree of risk that it is willing to accept in terms of the agonal criteria, fWIT, and their possible effect on function in the recipient. The author's practice is to use an onset of agonal criteria of systolic blood pressure below 50 mmHg, with a maximum fWIT of 25 min; however, we recognize the flexible nature of these artificial limits and the substantial variation that exists between accepting centers (Fig. 11.1).

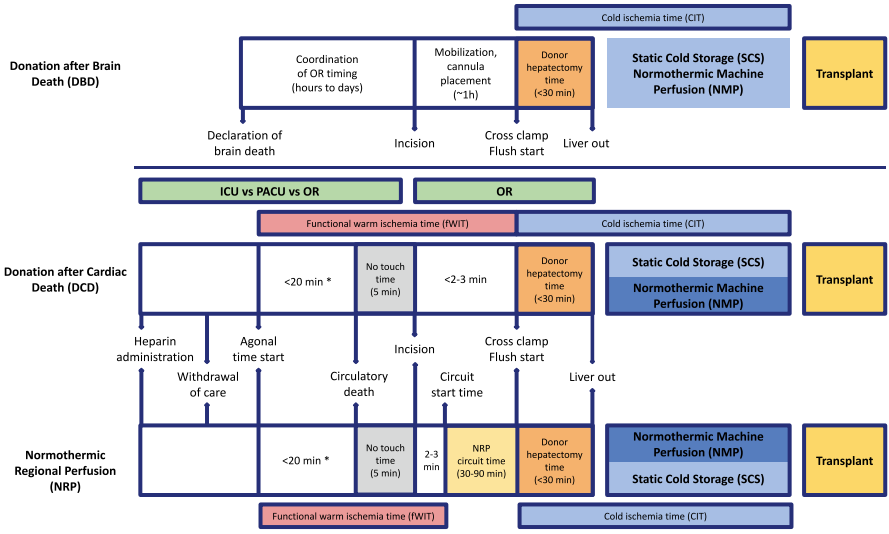

Fig. 11.1 Schematic flowchart representing the various quantifiable timepoints in DBD, DCD, and NRP organ recovery. The authors' general practice is to consider transplantation of livers with an fWIT of less than 25 min, although this limit can in theory be pushed longer depending on the individual donor and recipient circumstances*NMP is a technology that reperfuses the liver on pump with warm oxygenated blood before implantation in the recipient—as such, it is not considered part of the "cold ischemia time" in the same way as SCS, in which the liver sits on ice right up until the time of implantation

Surgical procurement then proceeds quickly. If not already done, the patient is transferred to the operating room table, and the field is widely prepped and draped. A generous laparotomy incision is made from the xiphoid process to the pubic symphysis, and the abdomen is entered sharply. The small bowel is swept out of the pelvis to expose the aortic bifurcation, the overlying tissue is divided, and the aorta is exposed. An aortotomy is made, and the arterial flush cannula is placed into the aortic lumen. An *in situ* flush with cold preservation solution is then begun. The IVC is opened at its bifurcation to allow venting. Supraceliac aortic control is accomplished either in the left chest via a sternotomy (if no thoracic procurement team) or within the abdomen at the diaphragmatic hiatus. Minimizing ischemic time is key; surgical goals include an incision-to-cannulation time of 2 min or less, and an incision-to-cross-clamp time of 3 min or less.

After the *in situ* flush has been completed, the organs are procured similarly to that described for DBD donors. The duodenum, right colon, and small bowel are medialized with the Kocher and Cattell-Braasch maneuvers; the left renal vein is identified and transected; and the IVC is divided above the insertion of the right renal vein. The CBD is divided, and the hilar structures are removed en bloc to minimize dissection time, taking care to avoid injury to any replaced or accessory hepatic vessels. The liver is disconnected from its diaphragmatic and retroperitoneal attachments and then removed from the body. The kidneys are removed as described for

DBD donors. DCD pancreas donation is limited to high-volume recovery surgeons and centers.

It should also be noted that only a subset of potential DCD donors will progress to cardiac arrest and satisfy the criteria allowing for successful procurement. Local hospital policy may allow for up to 2 h after withdrawal for progression to cardiac arrest, though durations as short as 60 min are common. Families should be notified during the consent process that if donors do not progress to arrest within the time period or exceed fWIT limits, then donation will not proceed and the donor will be brought back to the ICU for comfort care measures. Due to the substantial variation in policy between donor hospitals, we recommend that procurement teams and local treating teams are clear on hospital policies and time limits to minimize delays, ensure that local protocols are not violated, and maximize the opportunities for successful organ procurement [34].

Normothermic Regional Perfusion

Due to the ongoing organ shortage, usage of DCD donors has increased. However, the long-term effects of prolonged fWIT are unpredictable and may cause significant morbidity in recipients. Accordingly, strategies to optimize DCD donation have been developed. One such strategy, NRP, is an emerging recovery technique in the United States that has been used successfully for years in many European countries [35]. NRP takes advantage of modern cardiopulmonary bypass capability to restore circulation of normothermic oxygenated blood *in situ* after declaration of death.

In order to facilitate this approach, arterial and venous vascular access must be established. There are multiple technical variations to NRP, with the two dominant approaches being thoracoabdominal (TA-NRP, with perfusion of the thoracic and abdominal organs) and abdominal (A-NRP, with perfusion of the abdominal organs alone) [12]. As in traditional DCD donation, heparin is given prior to withdrawal of cardiopulmonary support, and donors must first be declared dead before any attempt at organ donation. Once death has been declared and the 5-min waiting period has elapsed, in TA-NRP, a sternotomy is performed to access the great vessels, and cannulae are inserted into the aorta and right atrium. The innominate, left carotid, and left subclavian vessels are clamped to prevent perfusion of the brain and upper extremities. In A-NRP, a laparotomy is performed, and the aortic/IVC bifurcation is exposed for cannulae insertion. Supraceliac aortic cross-clamping can occur in the abdomen, as in traditional abdominal organ procurement techniques, or in the chest with access via a sternotomy. In either case, once the cannulae are securely inserted, the cardiopulmonary circuit is started, and the organs are reperfused with heparinized normothermic oxygenated blood. The duration of NRP varies, but after a period of time on the circuit, procurement can proceed similarly to DBD donation, as described above; surgical dissection is completed, a preservative solution is flushed through the existing cannulae, and the organs can then be removed (Fig. 11.2).

One innovative approach to NRP involves the pre-mortem placement of arterial and venous access. In this circumstance, consent for organ procurement must include the pre-mortem placement of wire or sheath access into the femoral artery

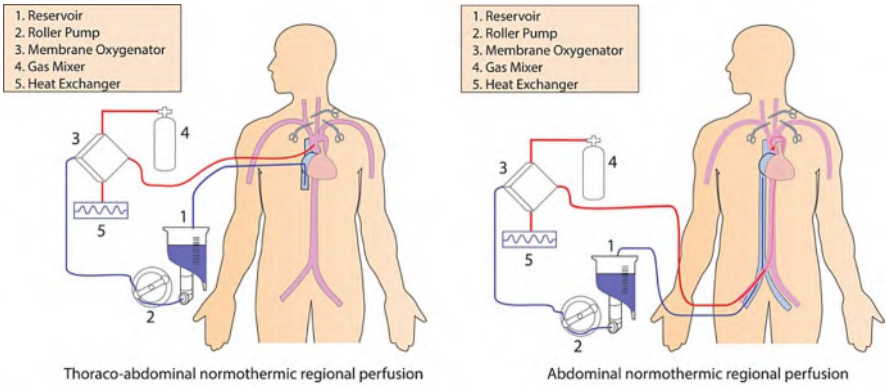

Fig. 11.2 Cannulation options—thoracoabdominal (TA) vs abdominal (A)—in normothermic regional perfusion (NRP). (Reproduced from: Alamouti-Fard et al. (June 29, 2022) Normothermic Regional Perfusion is an Emerging Cost-Effective Alternative in Donation After Circulatory Death (DCD) in Heart Transplantation. Cureus 14(6): e26437. DOI 10.7759/cureus.26437)

and vein; on the declaration of death, larger vascular access cannulae can be inserted via the Seldinger technique without a rapid laparotomy to access the larger central vessels. Cessation of blood flow to the brain is accomplished via balloon occlusion of the aorta or a sternotomy for direct aortic cross-clamping. Once the bypass circuit is re-established, surgical thoracic and/or abdominal access can be obtained without the time pressure of typical DCD procurement. One important consideration is what will happen to vascular access if the donor does not progress to cardiac arrest within local time limits. Large cannulae are cumbersome and are difficult to remove without surgical repair of the accessed vessels if placed pre-mortem; in contrast, wires or sheaths can be removed or saline locked with minimal morbidity to the donor, and are for this reason preferred [36].

Although NRP has a compelling physiologic rationale in that it limits the total warm ischemic time and quickly re-establishes physiologic normothermic flow of oxygenated blood, several limitations currently hinder its wider adoption. First, long-term outcomes of organs procured via NRP methods are lacking in the United States. The first report of TA-NRP in the United States occurred in 2020, and while NRP has been increasing in popularity and initial reports are encouraging, it remains to be seen whether the theoretical advantages (lower rates of IC in liver transplant, and of DGF and PNF in kidney transplant) are borne out in long-term follow-up data [37, 38]. Second, NRP is resource-intensive; it requires a cardiopulmonary bypass circuit, a trained perfusionist, and a procuring surgeon facile in NRP techniques. Many DCD procurements occur in smaller hospitals nationwide, many without bypass capability, limiting the availability of NRP to facilities with the requisite equipment and staff. Third, the ethical considerations brought about by NRP deserve serious and transparent consideration. Recovery techniques must comply with the dead donor rule. While recirculation of blood *in situ* after the declaration of death is generally considered to be compatible with the notion of irreversibility of

death, the possibility for cardiac reanimation *in situ* and the need for clamping of the cerebral vessels to prevent reperfusion are, for some, an ethically gray area. Many hospitals and OPOs nationwide lack a formal policy for NRP organ donation, and while many allow it, others deny it outright [39]. It is thus even more critical that consent for the particular type of NRP to be performed must include a thorough and transparent discussion of the steps, pitfalls, and alternatives with the consenting family members. Ongoing education and outreach efforts are critical to ensure broad recognition and acceptance of NRP by both healthcare workers and the public at large [40].

Organ Storage After Procurement

After surgical procurement, organs must then be transported to the recipient hospital for transplant. Since the development of regional and national organ allocation, organs may travel increasingly far distances from donor to recipient hospitals; as a result, proper storage methods are critical to ensure stability of the organ and proper function in recipients. An ideal storage method would be simple, cost-effective, and robust enough to allow for long-distance travel; it would also provide a physiologic or physiologic-adjacent environment for donor organs, permit assessment of organ quality before transplant, allow for immediate or near-immediate function after reperfusion, and be associated with good outcomes that minimize morbidity in recipients.

For years, the gold standard for organ storage was placing the organ on ice after flushing with cold preservation solution, which maintains the organ temperature at near 0 °C and slows cellular metabolism considerably, limiting the buildup of toxic anaerobic metabolites that cause damage to the graft. Known as "static cold storage," or SCS, this method was simple, cost-effective, and robust; however, it maintains a non-physiologic environment, and there is no mechanism to assess the quality of the organ until it is re-implanted and reperfused. While SCS has been associated with good outcomes on the whole, organs cannot stay on ice indefinitely; livers are ideally reperfused within 6–8 h of cross-clamp, and kidneys within 24–36 h. Longer cold ischemic times may be tolerated but are proportionally associated with an increased risk of IRI manifesting as hemodynamic instability on reperfusion, EAD, DGF, and/or PNF. To minimize these risks, and depending on the transport timing, this often results in recipient cases being performed overnight, stressing operative resources at recipient hospitals [41].

The development of machine perfusion addresses many of the shortcomings of SCS and has revolutionized organ storage after procurement. While there are many variations on machine perfusion, from temperature (hypothermic versus normothermic) to the type of perfusate used (whole blood versus preservative solution versus various combinations) to the presence or absence of oxygenation, as a whole, these devices attempt to perfuse donor organs in some form from the time of procurement to the time of transplant. In doing so, they try to reduce the risk of IRI, mitigate

hemodynamic instability on reperfusion, and reduce the risk of EAD/DGF/PNF. Thus far, machine perfusion has only been developed for kidney and liver grafts.

The first commercially available pumps were intended for donor kidneys and were hypothermic, using preservation solutions rather than blood, and were not oxygenated. Over the past three to four decades, significant experience has accumulated with kidney perfusion in all forms; while considerable heterogeneity exists in the literature, in general, HMP is associated with a lower risk of DGF, increased graft survival, and decreased cost [42, 43]. This holds in both DBD and DCD kidneys, though the addition of oxygenation to the perfusate for DCD donors >50 years of age further improves graft survival and post-reperfusion kidney function.

While machine perfusion of donor kidneys is now widespread, it was only in the past several years that machine perfusion of liver grafts has transitioned from experimental lab work to the clinical bedside. The liver, with its more complex vascular arrangement and decreased tolerance for hypoxia, proved a more difficult substrate onto which to adapt the machine perfusion paradigm. As of this writing, in the United States, there are two commercially available pumps that both offer normothermic machine perfusion (NMP) of liver grafts using blood as the perfusate, though they differ in the mechanics and location of cannulation, and the suite of services offered. The TransMedics Organ Care System (OCS) for whole liver allografts was FDA approved in 2021 and employs a full-service model; donor surgeons employed by TransMedics are available to travel to donor hospitals, perform the procurement operation and backtable preparation of the liver, and place the liver on the pump at the donor hospital to minimize cold ischemia time. An OCS technician is also provided to adjust the pressure/flow settings on the device, check serial labs, and accompany the donor organ to the recipient center until the recipient surgeon is ready for implantation. In contrast, the OrganOx Metra device, also FDA approved in 2021, employs a "back-to-base" model; organs are procured by either the recipient center or a local donor surgeon and then stored via SCS for travel back to the recipient center, during which cold ischemia time does accumulate. On arrival, the organ is prepared for cannulation on the back table and then connected to the Metra device, which generally stays at the recipient center and does not travel by air to donor hospitals. When the implanting surgeon is ready, the organ can then be removed from the pump and transplanted into place. In both cases, this has enabled recipient centers to enhance the logistics of staffing operating rooms and allocate additional time for preoperative transportation and workup for both patients and teams while the liver allograft remains perfused.

Despite its delayed rollout, liver NMP has quickly risen in popularity. The initial randomized controlled trial of the TransMedics OCS machine (published in 2022) compared NMP to SCS; not only did the trial meet the primary endpoint of reduced EAD in the NMP group (18% versus 31% in the SCS group), but use of the OCS allowed for a significantly increased rate of DCD donors, as well as a significantly decreased rate of ischemic biliary complications at both 6 and 12 months [44]. These results, as well as more recently published reports, indicate that not only is NMP at least equivalent to SCS, it can also allow increased access to liver transplant by "rescue" of marginal grafts that would otherwise have gone unused, without an

increase in ischemic biliary complications, which were previously one of the major limiting factors. As competition for donor liver allografts is only increasing, and as recipient centers increasingly field offers for marginal DCD grafts, NMP is quickly becoming the standard of care for transplant centers that perform an increasing number of DCD liver transplants.

The advent of machine perfusion has increased the decision-making complexity for recipient surgeons who now not only must decide which organs to pursue and which DCD donors are likely to progress to cardiac arrest, but also what type of recovery to employ—SCS? NMP? TransMedics surgical teams, local surgeons, or those of the recipient hospital? All of the permutations are associated with particular opportunities and monetary costs, and there is significant variability both between and within centers. In general, our practice is to utilize NMP for nearly all DCD and NRP donors, both local and remote; we typically use SCS for DBD donors, though we employ NMP if there are recipient constraints (extensive prior surgical history, complex anatomy, redo transplants, and multiple simultaneous transplants) that are expected to potentially prolong the cold ischemia time of donor grafts. This practice will undoubtedly continue to evolve as further data reveals the optimal combinations of donor type, recovery technique, and storage mechanism.

Future Directions

The iterative development of deceased donor organ transplant has led to significant advancements in all facets of the donation process—from enshrining medicolegal definitions of brain death and developing strategies for critical care management of potential organ donors, to refinements in surgical technique and the development of machine perfusion of kidney and liver allografts. As these steps forward showcase, the field continues to advance.

In the coming years, the increasing availability of NRP and machine perfusion will continue to increase the number of marginal DCD donors that can be converted into quality organ donors of both liver and kidney allografts. Whereas in previous years, many of these donors were unable to be realized, advancements in NRP and NMP have shown promise in "rescuing" many organs that were previously untransplantable. Pioneering transplant centers will continue to push the envelope in terms of donor comorbidities, agonal criteria, and fWIT limits, while robust and transparent data collection and presentation will ensure the spread of successful protocols far and wide. The costs associated with NRP and NMP may currently place these techniques outside the realm of possibility for smaller programs; costs are sure to fall in the coming years as protocols are optimized and lessons are learned. The number of surgeons trained in these techniques continues to increase, broadening access to healthcare across all parts of the country. Next-generation machine technology will continue to shrink the size and cost of devices, perhaps lowering the barriers to entry for future companies and research endeavors that seek to bring a new product to market. As has been the case for many years, organ allocation algorithms will continue to be optimized. The goal of creating the greatest benefit for the

greatest number of patients remains paramount, and as long as organs remain a scarce resource, the fairness and utility of allocation will continue to be refined.

Conclusion

While access to transplantation has, in many cases, become widespread, the ongoing critical shortage of donor organs suggests that patients will continue to wait for the opportunity to receive a life-saving organ transplant. In many cases, for those fortunate enough to receive one, that wait will end with a deceased donor organ transplant.

Because deceased donor organs make up the majority of transplanted organs in the United States, the availability of high-quality deceased donor organs will continue to play a critical role in widening access to transplantation. To that end, the appropriate identification and management of potential deceased donors and their successful transition to donation have become increasingly more critical as the demand for transplantation grows. It is incumbent on all healthcare providers, including both treatment and procurement teams, to treat donors and their families with the utmost respect and care, for it is only through their gift that the benefit of transplantation can be realized. We owe it to donors and recipients alike to make sure that every donation opportunity is fully realized.

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Thoracic Organ Procurement: A Surgical Perspective for the Anesthesiologist

12

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Introduction

Organ transplantation is a complex, multidisciplinary process that requires close collaboration among transplant surgeons, anesthesiologists, critical care teams, organ procurement organizations (OPOs), and support staff. Thoracic organ procurement, the retrieval of heart and lung allografts from a deceased donor, presents unique challenges and considerations for the anesthesiologist [1]. Donor management and intraoperative care directly impact organ viability and transplant outcomes. In recent years, advances in donation practices and preservation technology have expanded the donor pool, including increased use of donation after circulatory death (DCD) donors and novel perfusion techniques, making it more critical than ever for anesthesiologists to be familiar with current protocols. According to the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients, the number of deceased organ donors in the United States reached an all-time high of 16,989 in 2024, double the number from a decade prior [2]. Donation after brain death (DBD) remains the predominant pathway (9706 DBD donors in 2024, accounting for nearly 57% of all donors), but DCD donations have risen steadily (7283 DCD in 2024 compared to 1292 in 2014). This chapter provides a comprehensive overview of thoracic organ procurement with an emphasis on practical surgical and anesthetic considerations. Topics include the legal and ethical framework, DBD versus DCD pathways, donor pathophysiology and management, intraoperative workflow and team coordination, and current and emerging organ preservation techniques (such as normothermic regional perfusion (NRP), *ex vivo* perfusion systems, and improved preservation solutions). The goal of this

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chapter is to equip anesthesiologists, whether practicing at transplant centers or involved in occasional donor procurements, with a guide to optimize donor care and facilitate successful heart and lung retrieval.

Institutional, Legal, and Ethical Framework

Successful organ donation operates within a strict legal and institutional framework designed to ensure ethical practices and public trust [3]. In the United States, the National Organ Transplant Act of 1984 established the national organ donation system and created OPOs [4]. OPOs are regional agencies responsible for identifying potential donors, obtaining consent, and coordinating the recovery, allocation, and transport of organs. All OPOs are members of the OPTN, which is managed by the United Network for Organ Sharing (UNOS), a nonprofit organization under federal contract. The OPTN maintains the national transplant waiting list and develops policies for organ allocation and procurement. Regulatory oversight by the Department of Health and Human Services and the Centers for Medicare and Medicaid Services imposes performance standards on OPOs, including targets for donation rates and organs transplanted per donor, with periodic re-certification requirements [5, 6]. These measures aim to maximize organ recovery while ensuring quality and fairness.

Definition of Death and Consent

Because deceased donation involves recovering organs from patients who have died, a clear legal definition of death is fundamental. All US jurisdictions have adopted the Uniform Determination of Death Act, which recognizes death as either irreversible cessation of circulatory and respiratory function or irreversible cessation of all brain function (i.e., brain death) [7]. Brain death, first defined by a Harvard Medical School committee in 1968, is legally recognized as death in all 50 states [8]. The Uniform Anatomical Gift Act, originally enacted in 1968 and revised in 1987 and 2006, provides the legal framework for individuals or their next of kin to consent to organ donation and for the recovery of anatomical gifts [9–11]. Under these laws, once a patient is declared dead by either circulatory or neurologic criteria, organ procurement may proceed if valid consent or donor authorization is in place. Importantly, the “dead donor rule” is an ethical cornerstone: organs can only be removed from patients who are legally dead, and the act of organ removal must not be the cause of death [12]. Anesthesiologists must be cognizant of this principle, particularly in DCD scenarios where the line between end-of-life care and facilitating organ recovery must be carefully maintained.

Donation Pathways: DBD Versus DCD

Deceased donation is typically classified into two pathways based on the mechanism of death: DBD and DCD. In DBD, the donor has suffered a complete and irreversible cessation of brain function (brain death) but remains on mechanical ventilation and hemodynamic support, allowing organs to be perfused until surgical recovery. In DCD, the donor does not meet brain death criteria but has a non--recoverable condition; death is declared after planned withdrawal of life-sustaining therapy and subsequent cardiorespiratory arrest. Controlled DCD refers to situations where withdrawal of support is planned in a controlled setting (usually the operating room (OR) or intensive care unit (ICU)) for a patient with devastating injury or illness and prior consent for donation. Uncontrolled DCD, which is rare in the United States, involves unexpected cardiac arrest (e.g., in the emergency department) followed by rapid decision-making for organ donation. In any DCD case, strict criteria must be met to declare death: usually, cessation of circulation and respiration for a predetermined "no-touch" interval (commonly 2–5 min) is required to ensure irreversibility before the procurement team proceeds. During this standoff period, no interventions are performed, and the OR staff observes sterile technique from a distance until an independent clinician pronounces death.

Ethical Consideration

DCD pathways introduce unique ethical and practical challenges. Timing of interventions is critical; for example, administering anticoagulation or placing cannulas before death to facilitate organ preservation can be ethically sensitive. Generally, no medication or intervention intended to preserve organs should be given if it may hasten death or cause harm to the patient before death is declared. In practice, many protocols allow a dose of intravenous (IV) heparin to be given shortly before or immediately after withdrawal of life support, with the rationale of preventing thrombosis in the organs, but this must be balanced against any potential to worsen bleeding. The anesthesia team must ensure that any pre-mortem interventions comply with hospital policies and ethical norms (typically requiring explicit consent from the donor's surrogate for interventions like heparin in DCD). Another concern in DCD is the management of donor comfort during withdrawal; although brain-dead donors do not experience pain, DCD donors may have some level of awareness before asystole. Anesthesiologists may administer analgesics or sedatives for comfort during withdrawal of support, as long as the intent is purely palliative and not to expedite death. Clear communication and transparency with the donor's family about the process are essential, and institutional ethics committees are often involved in establishing DCD protocols.

OPOs and Workflow

When a potential donor is identified and consent or authorization is obtained, the local OPO coordinates the entire donation process. This includes verifying the donor's identity and consent, interacting with UNOS to allocate organs to recipients, and mobilizing transplant teams. The OPO donation coordinator is a key point of contact for anesthesiologists in donor cases. They organize conference calls between all involved transplant centers to synchronize logistics, including timing of the donor's withdrawal (for DCD) or OR time (for DBD), which transplant teams (heart, lung, liver, kidney, etc.) will be present, and any special requests (such as biopsies or pre-recovery tests). The coordinator also ensures that a thorough donor medical history, lab results, and hemodynamic data are compiled and communicated to accepting centers. Anesthesiologists should be aware that multiple surgical teams (thoracic and abdominal) will often operate simultaneously during procurement. A designated "primary recovery surgeon" (typically the heart surgeon for thoracic procurements) frequently leads the OR briefing and coordinates the sequence of organ removal. This preoperative briefing or "time-out" should involve all teams, anesthesia, and nursing, and cover key points: surgical incisions and positioning, the plan for functional assessment of organs (e.g., echocardiography of the donor heart, bronchoscopy of lungs), the order of organ flush and cross-clamp, and any planned NRP or machine perfusion procedures. The anesthesiologist plays a vital role in this briefing by clarifying the plan for intraoperative events, such as when to administer heparin, when to pause or modify ventilation, and how to manage any unexpected hemodynamic instability.

DBD: Physiology and Management

DBD has been the traditional mode of procuring of transplantable thoracic organs. Brain death, the irreversible loss of function of the brain and brainstem, triggers a cascade of pathophysiological events in the donor that can jeopardize organ function [13–15]. Understanding these changes is crucial for anesthesiologists to optimize donor management.

Autonomic Storm and Cardiovascular Collapse

The process of brain death often occurs in phases. As intracranial pressure rises and brainstem herniation begins, an intense sympathetic discharge (the "autonomic storm" or "catecholamine storm") occurs due to ischemia of the brainstem [16–18]. This results in surges of catecholamines (epinephrine and norepinephrine) that cause severe hypertension, tachycardia, and vasoconstriction. Transient hypertension and increased afterload can lead to left ventricular strain, subendocardial ischemia, and arrhythmias; many donors exhibit acute cardiac dysfunction or "stunning" during this phase. Pulmonary edema can also result from the acute

catecholamine surge (neurogenic pulmonary edema due to increased pulmonary capillary permeability) [19, 20]. This hyperadrenergic phase is usually short-lived and is followed by a precipitous collapse of sympathetic outflow as the brainstem dies. The loss of sympathetic tone causes systemic vasodilation, hypotension, and bradycardia (often profound) [21, 22]. Without intervention, the donor can progress to cardiovascular collapse and cardiac arrest due to this distributive shock state. Arrhythmias are common throughout the process. This can initially be catecholamine-driven tachyarrhythmias and later bradyarrhythmias or asystole. Autonomic instability may manifest as alternating periods of hypertension and hypotension or arrhythmias in the interval between brain death declaration and organ recovery.

Metabolic Derangements

Brain death frequently leads to endocrine failure, sometimes termed "brain death syndrome." Ischemia of the hypothalamus and pituitary causes loss of pituitary hormone release [23]. In particular, diabetes insipidus (DI) develops in the majority of brain-dead patients due to a lack of antidiuretic hormone (ADH/vasopressin) from the posterior pituitary [24–26]. The result is polyuria with massive free water loss, leading to hypovolemia, hypernatremia, and hyperosmolarity if not treated. Anterior pituitary failure causes deficiencies of thyroid hormone (T3/T4), cortisol, and insulin [27]. The lack of triiodothyronine and thyroxine contributes to reduced cellular metabolism and cardiovascular depression, while adrenal insufficiency exacerbates vasodilatory shock and impairs stress response. Insulin deficiency leads to hyperglycemia and a shift to anaerobic metabolism, resulting in lactic acidosis [23, 25]. Brain death can also abolish central temperature regulation, so donors may become hypothermic (especially when exposed in the OR) or less commonly hyperthermic. Inflammatory mediators are another factor; brain death triggers a systemic inflammatory response, with cytokine release that can injure organs (often likened to a sepsis-like syndrome without infection). For example, levels of tumor necrosis factor and interleukins may rise, contributing to cardiac and lung dysfunction and increasing the recipient's susceptibility to graft dysfunction if not mitigated.

Implications for Organ Function

The net effect of these changes is that a brain-dead donor can rapidly deteriorate if not actively managed. The heart, having potentially been "stunned" by the catecholamine surge and then deprived of adequate perfusion during hypotension, may show reduced contractility and arrhythmias [28–30]. The lungs often suffer pulmonary edema and atelectasis; neurogenic pulmonary edema and acute lung injury can cause PaO_2 to fall and lung compliance to worsen [31, 32]. Other organs (liver and kidneys) likewise experience ischemia and may release enzymes or markers of injury. Nevertheless, with aggressive donor management, many of these processes

can be counteracted or stabilized, allowing successful transplantation. The anesthesiologist's goals are to maintain perfusion to organs, optimize oxygenation and ventilation, correct hormonal deficits, and avoid additional iatrogenic injury.

Hemodynamic Management in Brain-Dead Donors

A primary focus is supporting the donor circulation through fluid resuscitation and vasoactive medications. Early, generous volume replacement is often required to counteract DI-induced losses and relative hypovolemia [31, 33–35]. Isotonic crystalloids are typically used; colloids or blood products may be given if needed (e.g., if DI causes severe hemoconcentration or if there has been bleeding) [35–37]. Invasive monitoring lines (arterial line and central venous catheter) should be placed as soon as the patient is identified as a potential donor [38, 39]. Donor management protocols set hemodynamic targets, typically systolic blood pressure (SBP) > 100 mmHg, mean arterial pressure (MAP) > 60 mmHg, cardiac index > 2.4 L/min/m^2, central venous pressure (CVP) < 12 mmHg, and pulmonary capillary wedge pressure < 12 mmHg [40]. The use of invasive monitoring, such as Swan-Ganz catheters, can help guide treatment strategies. Pulmonary edema and right ventricle (RV) overload must be continuously monitored.

In the initial phase of brain death, autonomic storm hypertension is possible. The hypertension experienced during this phase is typically brief and followed by severe hypotension. As a result, hypertension should be managed conservatively. Short-acting antihypertensives such as nitroglycerin, esmolol, and labetalol may be used [41–43]. It is critical not to overtreat hypertensive episodes such that hypotensive episodes are potentiated, which are far more common.

If hypotension occurs despite adequate volume [31], vasopressor support is instituted promptly. Vasopressin is particularly valuable in brain-dead donors because it addresses two problems at once: it is a potent vasoconstrictor (V1 receptor agonist), raising blood pressure, and it replaces the missing ADH to treat DI [44–46]. Vasopressin infusion (e.g., 0.5–4 units/h) is recommended as the first-line agent for refractory hypotension in brain-dead patients [44–46]. If additional support is needed, a low-dose infusion of norepinephrine or phenylephrine can be added for vasoconstriction. However, high doses of alpha agonists should be avoided if possible, as they can constrict renal and splanchnic circulation excessively. Notably, purely beta-adrenergic drugs (such as dobutamine or epinephrine) are double-edged in donors: while they may improve cardiac output when myocardial function is depressed, they also increase myocardial oxygen demand and can precipitate tachyarrhythmias [40]. The key is to use the lowest effective doses of vasoactive drugs and to frequently reassess perfusion (invasive pressures, urine output, lactate levels, and echocardiography if indicated).

Arrhythmias should be treated promptly, as persistent tachyarrhythmias or bradycardia can compromise organ perfusion [47]. Ventricular arrhythmias in the donor may respond to boluses of amiodarone or lidocaine [43]. Defibrillation pads should

be on the patient, and a defibrillator should be immediately available in the OR; the surgical team and anesthesia should be prepared to cardiovert or pace the heart if needed.

Endocrine Support

Given the loss of pituitary function, many centers implement a "hormonal resuscitation" protocol for DBD donors. This often includes vasopressin (as above) for diabetes insipidus (DI) and shock, plus thyroid hormone and corticosteroids [13, 14].

Thyroid Hormone (T_3 or T_4) The rationale is that thyroid hormone might improve cardiac function by enhancing myocardial energy utilization and reversing stunning. Early observational studies suggested that T_3/T_4 could increase the rate of heart donation, and thus, it became common to administer IV levothyroxine to hemodynamically unstable donors [48]. However, recent evidence has called this practice into question: a large, randomized trial found that high-dose levothyroxine did not significantly improve donor stability or increase the number of organs transplanted [49]. Despite mixed evidence, thyroid hormone replacement is still frequently used in donors with cardiac dysfunction because of its theoretical benefit and low acute risk [50].

Corticosteroids Methylprednisolone (e.g., 15 mg/kg) is commonly given to brain-dead donors [51]. Steroids may help stabilize membranes and reduce the systemic inflammatory response, potentially improving lung function and mitigating "cytokine storm" damage. Steroids also support the adrenal axis and may aid hemodynamics.

Insulin Donor hyperglycemia should be controlled with an insulin infusion to maintain euglycemia (often target glucose < 180 mg/dL) [52]. Proper glycemic control improves the metabolic environment for organs and prevents excessive osmotic diuresis.

Temperature The donor should be kept normothermic (36–37 °C) using warming blankets, fluid warmers, and ambient temperature control [33]. Hypothermia can exacerbate coagulopathy and arrhythmias.

Ventilation and Pulmonary Management

Lung viability is highly dependent on the quality of donor lung management [27]. Brain death and subsequent critical care can lead to atelectasis, pulmonary edema, or ventilator-associated lung injury if tidal volumes are excessive [53]. A lung-protective ventilation strategy is recommended for all potential lung donors [53].

This involves using low tidal volumes (6–8 mL/kg ideal body weight) and moderate positive end-expiratory pressure (typically 5–8 cm H_2O) to prevent atelectasis without causing overdistension or barotrauma [53, 54].

Bronchoscopy is a valuable procedure in donor management. Ideally performed in the ICU or early in the OR, bronchoscopy allows suctioning of secretions, clearance of mucus plugs, and direct inspection of airway anatomy and lung secretions. Anesthesiologists often perform this, either with a flexible scope through the endotracheal tube or in conjunction with the surgical team, to ensure the airways are clean. It is recommended to communicate bronchoscopic findings (such as purulent secretions or structural anomalies) to the lung procurement team and the accepting transplant center, as this may influence lung acceptance. Bronchoscopic pulmonary toilet can significantly improve oxygenation and lung mechanics in donors with collapse or consolidation. Another standard practice is the "oxygen challenge test": ventilating the donor with 100% O_2 and a standardized setting (tidal volume 6–8 mL/kg, positive end expiratory pressure (PEEP) 5 cm H_2O) for 15 min and then drawing an arterial blood gas (ABG). A $PaO_2 > 300$ or 350 mmHg on 100% FiO_2 and PEEP 5 cm H_2O is traditionally considered a sign of acceptable gas exchange capacity. However, if the PaO_2 is lower, it does not automatically rule out lung donation as recruitment maneuvers and adjustments can sometimes improve it, and some marginal donors with PaO_2/FiO_2 ratios < 300 mmHg have been successfully transplanted (especially if *ex vivo* lung perfusion is planned) [55]. Still, anesthesiologists should strive to optimize oxygenation (e.g., ensure adequate lung inflation, correct ventilator settings, and perform suctioning) before the oxygen challenge that is often done just before procurement, as the results are reported to the transplant centers.

Multidisciplinary Coordination

Throughout the donor maintenance phase, it is imperative that anesthesiologists (or ICU physicians) communicate frequently with the OPO coordinator and surgical teams regarding the donor's status. If any critical deterioration occurs (e.g., refractory hypotension or pulmonary failure), the transplant teams will need to know, as it could affect organ acceptance. Conversely, the accepting teams might request specific management steps, such as antibiotics or steroids, for lung donors. A collaborative approach, where anesthesia, surgery, and OPO staff continually reassess and address issues, yields the best outcomes. Active donor management during the ICU phase is therefore strongly encouraged; the anesthesiologist plays a critical role in these cases in optimizing hemodynamics, oxygenation, and metabolic state while maintaining stability up to the point of organ recovery. This ensures that by the time the surgical teams are ready to flush and explant the organs, those organs are in the best possible condition for transplant.

DCD: Protocols and Special Considerations

DCD has become an important pathway to expand the donor pool, especially for lungs and, increasingly, hearts [56]. DCD donors undergo a distinct process that differs significantly from DBD, and it poses additional challenges for the anesthesiology team. In 2024, the United States recorded 7283 DCD donors (nearly half of all deceased donors), compared to only 1292 in 2014, reflecting the steady increase of this practice [2]. While historically DCD organs were considered more at risk of ischemic injury, improvements in technique, including the advent of NRP, have markedly improved outcomes such that transplant results from DCD can approach those of DBD in certain contexts [57, 58].

Controlled DCD Procedure

In a controlled DCD scenario, a patient with severe irreversible neurologic injury or end-stage disease (who does not meet brain death criteria) has life-sustaining therapy withdrawn per the decision of the care team and family. If the patient dies within a feasible timeframe and under conditions suitable for donation, organs are then recovered. The anesthesiologist's involvement in DCD is somewhat paradoxical: once life support is withdrawn, the focus shifts from patient care to organ preservation, yet no action can be taken until death is declared. Typically, the process is as follows:

1. ***Preparation:*** All necessary teams (including the anesthesiologist) gather for a pre-donation huddle to clarify roles. If consent for DCD is in place, the patient is usually transported to the OR or a location near it to minimize the time between death and organ recovery. The patient is continually monitored and mechanically ventilated during transport. Necessary preparatory steps may include placing additional IV access if needed, ensuring fluids and drugs are immediately available, and, in some cases, administering heparin. Many centers will administer a bolus of unfractionated heparin (30,000 units IV) just before extubation or immediately after circulatory arrest to prevent damage in organs during circulatory arrest. The exact timing is discussed in the pre-op briefing and agreed upon by all teams. If heparin is given before death, it is typically 3–5 min before withdrawing support so it can circulate; however, some protocols wait until after cardiac arrest (acknowledging limited distribution). This practice is institution- and case-dependent, balancing ethical concerns.
2. ***Withdrawal of Life Support:*** The critical care or primary physician (not the procurement surgeon) will perform the withdrawal. This usually involves discontinuing mechanical ventilation (extubation). Once the ventilator is turned off, the patient can potentially progress to bradycardia, hypotension, and apnea over minutes [59]. The anesthesia practitioner and ICU team simply observe supportive measures; no active measures to resuscitate are taken (unless the process is aborted due to failure of the patient to expire in a reasonable timeframe).

3. ***Determination of Death:*** The patient is observed until cardiorespiratory arrest occurs. By protocol, a period of asystole (or pulseless electrical activity with no arterial pulse) must be maintained for a preset duration to prevent autoresuscitation. This hands-off interval is usually 2–5 min in the United States. During this time, the anesthesia provider, surgeons, and nurses do not touch the patient. Often, an independent ICU physician or anesthesiologist will document the exact times of oxygen cessation, cardiac arrest, and the elapsed hands-off period. After the interval, a physician examines the patient to confirm the absence of pulse, heart sounds, and respirations, and then pronounces death.
4. ***Rapid Organ Recovery:*** Once death is declared, the procurement teams enter the donor OR. The anesthesiologist's role at this juncture is to assist the surgeons if needed. In a typical thoracic DCD without NRP, the steps are extremely rapid to minimize warm ischemic time (WIT). The surgical team will make a sternotomy incision immediately. The anesthesia team may be requested to reintubate the patient and resume ventilation to protect the lung graft.

In DCD heart or lung recovery, speed is paramount. For lungs, the surgical team will instill cold preservation solution (pulmoplegia) in the pulmonary artery within minutes of death. For the heart, an aortic cross-clamp is applied, and cold cardioplegia is delivered as soon as possible after the stand-off time to protect the heart. The WIT in DCD is defined as the interval from circulatory arrest to the start of cold perfusion of the organ [60]. This WIT is injurious to organs because they undergo ischemia at body temperature. Hearts are particularly sensitive; clinical experience suggests that if the donor's systolic blood pressure was < 50 mmHg for more than 30 min before or during the agonal phase, the heart may not be usable [60, 61]. Lungs, on the other hand, tolerate warm ischemia relatively well, as some oxygen can still diffuse into alveolar cells from residual air, and they have lower metabolic demands. There are usually no absolute time cutoffs for lung WIT, though long WIT may correlate with an increased risk of primary graft dysfunction [62].

Normothermic Regional Perfusion

In DCD organ recovery, NRP is an increasingly used technique to restore circulation to organs after death is declared, thereby resuscitating and preserving them *in situ* [2]. NRP involves establishing cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) on the donor after circulatory arrest, to perfuse either the abdominal organs (A-NRP) or both thoracic and abdominal organs (TA-NRP), while excluding blood flow to the brain so that death status is not reversed. In A-NRP, for example, femoral arterial and venous cannulas are placed and connected to an ECMO circuit that perfuses the abdominal aorta. The thoracic aorta is cross-clamped (usually at the diaphragm level) to prevent any blood from reaching the heart or brain. This restores oxygenated circulation to the abdominal organs (liver, kidneys, and pancreas) at near-normal temperatures, greatly reducing warm ischemic injury. TA-NRP goes a step further by also allowing reperfusion of

the heart and lungs in the donor's body. In TA-NRP, typically a median sternotomy is performed immediately after death, and the arch vessels (brachiocephalic, left carotid, and left subclavian) are surgically ligated or clamped to isolate cerebral circulation. Then, central cannulation (aorta/right atrium) is performed, and the circuit is connected to a perfusion pump to reanimate the heart and lungs with warm, oxygenated blood. The heart will usually begin beating again, and the lungs will be ventilated and perfused. It is crucial to occlude all vessels to the brain before initiating TA-NRP to avoid any blood flow to the brain, which would violate the dead donor rule [12, 63–65]. In fact, procurement surgeons often transect or tie off the arch vessels as the very first step in the sternotomy, before cannulation. TA-NRP allows observation of heart function in the donor reanimation (similar to a DBD functional assessment) and limits heart and lung WIT to the brief stand-off interval, thereby markedly improving the viability of these organs.

From the anesthesiologist's perspective, NRP protocols require additional preparation and coordination. During TA-NRP, the heart will resume activity. The anesthesiologist should monitor the electrocardiogram (ECG) and arterial pressures. If the heart does not restart in normal sinus rhythm, defibrillation or pacing might be needed (these should be anticipated with defibrillator pads in place). Often, the heart will fibrillate upon reperfusion and require a DC shock or overdrive pacing to convert to a perfusing rhythm. Low-dose inotropes might be given on the circuit to aid myocardial function (e.g., a small dose of epinephrine infusion directly into the perfusate if contractility is poor), but generally, the aim is to let the heart recover without excessive pharmacologic stimulation. The lungs can be ventilated with 100% oxygen during NRP.

Ethical and Logistical Issues With NRP

While NRP has shown tremendous promise in improving organ utilization, it remains ethically complex. The practice of restarting circulation after death raises the question: Does restoring cardiac activity undermine the declaration of death? Ethicists argue that since cerebral circulation is prevented, the state of brain death (or permanent cessation of brain function) remains; thus, the patient is still dead even if the heart is reanimated. Nonetheless, some critics voice concern that NRP blurs the line and could erode public trust [64]. From a regulatory standpoint, no US federal law prohibits NRP, but policies are still evolving. Anesthesiologists should be aware of their own institution's stance and any state guidelines. Another consideration is consent: some OPOs explicitly inform the donor's family about NRP and allow them to opt out of that method if it makes them uncomfortable (because it involves restoring some bodily circulation after death). On the other hand, many families simply consent to donation, and the details of NRP versus standard recovery are handled by medical teams. As NRP has become more common (over 400 DCD-NRP cases in the United States in 2023, up from only a few dozen a decade ago [2]), a consensus is gradually forming that it can be performed ethically with proper safeguards. Key safeguards include stringent isolation of cerebral circulation (e.g., ligating vessels as described), transparency in the consent process, and involvement of hospital ethics committees to approve protocols.

Anesthesiologists involved in these cases should feel free to voice any concerns and ensure they are comfortable with the procedure, as their participation is part of the ethical conduct as well.

Surgical Technique for Heart and Lung Procurement

Once the donor has been appropriately managed and the decision has been made to proceed with organ recovery, surgical teams for each organ system will commence the procurement operation. Thoracic (heart and lung) recovery often occurs simultaneously with abdominal organ recovery (liver, kidneys, etc.), so a coordinated approach is necessary to avoid conflicts in the operative field and to ensure each organ is protected. The anesthesiologist's awareness of the surgical steps allows anticipation of critical moments when specific anesthetic actions are required (such as performing ventilatory recruitment maneuvers, resuscitation, or administering medications). Below is an overview of the typical surgical sequence for heart procurement and lung procurement, noting points of intersection with anesthetic management.

General Setup

The donor is positioned supine on the OR table, with arms tucked. For heart and lung retrieval, a median sternotomy is performed, often extended into an upper laparotomy if abdominal teams are working concurrently. The chest and abdomen are sterilely prepped and draped together. Just before the sternotomy, the anesthesiologist should pause ventilation and allow the lungs to deflate. This is to reduce the risk of lung injury from the oscillating sternal saw and to prevent cutting into inflated lung tissue, which could be pressed up against the sternum. The surgical team will usually ask for confirmation that ventilation is off; they then perform the sternotomy and use cautery and bone wax to achieve hemostasis on the cut edges of bone. Once the chest is open, a sternal retractor is placed to retract the sternum. The pleural cavities are entered bilaterally to fully expose the lungs. This incision can be extended laterally along the costal-diaphragmatic junction if additional visualization is necessary, although care is taken not to injure the adjacent liver or stomach accidentally. At this point, the anesthesiologist may resume ventilation. The surgeons will then open the pericardium and expose the heart.

Initial Inspection and Assessment

The heart is examined for any signs of trauma, ventricular hypertrophy, coronary disease (if not already known from imaging), valvular thrills (as a sign of significant valvular regurgitation), and overall biventricular function. Cardiac function is most commonly assessed visually and by manual palpation, but can also be supplemented

with the use of portable echocardiography. Particularly when lifting the heart to evaluate the left ventricle, the patient may become hypotensive or arrhythmogenic, and communication between the anesthesiologist and surgeon is critical to prevent significant donor decompensation.

The lung surgeon will likewise inspect the lungs. They visually check for contusions, edema, pneumonia, consolidations, or infarctions from pulmonary embolism. Furthermore, they will request that the anesthesiologist perform a Valsalva or inflation hold to fully expand the lungs, observe their expansion, and resolve any atelectasis. The lung surgeon will also request that the ventilator be fully disconnected to check for appropriate lung recoil. The anesthesiologist should additionally be wary of any hemodynamic instability that can occur when reflecting the lungs out of the thoracic cavity during these inspections. The lung team may request an ABG to clarify donor suitability further. This can be done via a peripheral ABG sample or through direct sampling of the left and right superior and inferior pulmonary veins, which can provide a detailed assessment of each lobe (particularly if there are heterogeneous visual characteristics of the lungs). This is commonly done on the aforementioned baseline ventilatory settings (tidal volume 6–8 mL/kg, PEEP 5 cm H_2O), although temporary recruitment with a higher PEEP may be requested.

Any concerning findings are communicated to the recipient teams for final acceptance decisions. Once all recipient teams confirm they are ready to proceed (i.e., the organs have been accepted and the recipient is being prepared), the procurement moves into the organ preservation and division phase.

Donor Thoracic Organ Preparation

Key surgical steps for the heart include mobilizing and isolating the aorta, pulmonary artery, superior vena cava (SVC), and inferior vena cava (IVC). These can be encircled with umbilical tapes, if necessary. During SVC mobilization, the azygous is identified and ligated to reduce venous return during the eventual cross-clamp period. Consideration of left atrial venting typically occurs at this point (essential to reduce pulmonary edema and left ventricular dilation). Communication between heart and lung surgeons is critical if both teams are present. Common venting locations include Sondergaard's groove (also known as Waterston's groove), the left atrial appendage, or, if the lungs are not being procured, the intrapleural locations of the bilateral pulmonary veins. Sondergaard's groove is of particular interest to the anesthesiologist. This fat plane on the right lateral aspect of the heart, adjacent to the right superior pulmonary vein, is developed to separate the right and left atrium. The heart is typically manually reflected to the left for exposure, which can lead to hypotension. Furthermore, the use of electrocautery at this location may cause cardiac arrhythmias, particularly atrial fibrillation. The surgical team should inform the anesthesiologist of this dissection; significant hypotension may require a temporary pause of these maneuvers, while the development of arrhythmias may mandate electrical cardioversion (having working defibrillation paddles on the field and a code cart easily accessible is recommended).

Cross-Clamp and Administration of Organ-Specific Preservation Solutions

Once thoracic and abdominal teams have completed their respective organ assessments (with official acceptances) and preparations, all members will agree on the timing of heparization and aortic cross-clamp. Since the aortic cross-clamp is, for all intents and purposes, irreversible, clear communication is paramount. Team members may request a cross-clamp delay due to operative complexities on the recipient side (e.g., left ventricular assist device (LVAD)-explant, redo-transplant). However, excessive delays (> 1 h) should be minimized for professional courtesy and to prevent potential donor instability from accumulating blood loss, catecholamine storming, and cooling of the core temperature. The anesthesiologist should also be mindful of unexpected acute hemodynamic instability or significant blood loss that may require early and rapid cross-clamping in an effort to preserve as many organs for donation.

Just prior to aortic cross-clamping, a number of things happen nearly simultaneously:

- **Heparinization:** A large dose of heparin is administered IV by the anesthesiologist (commonly 30,000 units). In DBD donors, heparin is given at least 3 min before cross-clamping to ensure adequate drug circulation. The anesthesiologist should announce when heparin is given.
- **Plegia Catheter Placement**: A catheter is placed directly in the ascending aorta and main pulmonary artery to allow for the administration of antegrade cardioplegia (heart preservation) and pulmoplegia (lung preservation), respectively.
- **Ventilation Management:** The lungs should remain ventilated during the pulmonary artery flush to ensure uniform distribution of the preservation solution.
- **Prostaglandin Administration:** For lung donors, prostaglandin E1 (PGE_1) is given into the pulmonary circulation just prior to flush. Typically, 500 μg of PGE_1 is injected into the main pulmonary artery by the lung surgeon. PGE_1 causes pulmonary vasodilation, which helps flush out the pulmonary capillary blood and improves preservation solution distribution, but may also lead to systemic hypotension [66].
- **Venous Venting:** The SVC is ligated, and the IVC is cut to allow blood to drain out. The left atrium is incised (either via Sondergaard's groove or the left atrial appendage) to vent the left side of the heart. These maneuvers prevent the heart from distending when cardioplegia is given and provide an exit for bronchial circulation, blood, and preservation fluid. Essentially, multiple vents are created so that when cold solutions are injected, pressure does not build up and blood can escape, helping with cooling.

Once everything is prepared, the aortic cross-clamp is applied, which halts blood flow to the abdominal organs and allows the antegrade cardioplegia solution to preferentially flow down the coronary arteries to arrest the heart and provide myocardial protection. The cardioplegia solution is typically an iced crystalloid solution (e.g., UW or Celsior solution) with high potassium via a pressure bag that induces

diastolic arrest. It is often given as 2 L under pressure, and the heart usually stops within seconds of starting. Simultaneously, antegrade pulmoplegia is started for the lungs: the lung preservation solution (commonly a low-potassium dextran solution such as Perfadex) is infused into the pulmonary artery by gravity drainage. Similar to the myocardial protection afforded by cardioplegia preservation solutions, pulmoplegia works to cool the lung tissue, thereby reducing the metabolic activity, providing sufficient energy substrate to maintain aerobic metabolism and reduce pulmonary edema [67–70]. Unlike cardioplegia, which is pressurized, the lung flush is usually not pressurized to avoid barotrauma; it flows by gravity from an elevated bag, typically 3–4 L. The anesthesia team can assist by ensuring the table is level (to prevent gravity drainage) and by monitoring fluid amounts.

As cold preservation solution floods the heart and lungs, the donor's core temperature will drop rapidly. The heart will turn flaccid and pale as cardioplegia takes effect. The lungs will blanch as well with adequate perfusion. After the flush is complete, the surgical teams proceed with organ removal:

- **Heart Explantation:** If the lungs are also being recovered, care is taken with incising the left atrium: typically, the left atrium is cut at the interatrial groove to free the pulmonary vein inflow in a way that leaves cuffs of atrial tissue attached to the pulmonary veins for the lung transplant anastomoses (i.e., the posterior wall of the left atrium remains with the lung graft). If there is no lung team, the heart explant can include most of the left atrium. Next, the aorta and pulmonary artery are cut (the aorta distal to the clamp site, and the PA either just before the bifurcation or higher if lungs are taken). The vena cava is cut (if not already), and the heart is lifted out. The heart is then placed into a basin of ice slush on the back table for packaging. The clock for cold ischemic time starts at the moment of cross-clamp, so the team will note that time (either the OPO coordinator or anesthesiologist records the cross-clamp time and heart-out time for documentation). The heart is immediately immersed in a preservation solution placed on ice. If a transportable perfusion device (e.g., TransMedics OCS Heart) is being used, the team might instead take the heart directly to that machine to initiate warm perfusion.
- **Lung Explantation:** With the heart now explanted, the lung team can entirely remove the lungs. In addition to the initial 3–4 L antegrade flush via the PA, they often perform a retrograde pulmoplegia flush: additional cold Perfadex into the pulmonary veins (via the left atrial openings) to flush blood out of the pulmonary microcirculation from the opposite direction. Typically, 500 mL will be instilled retrograde into each of the four pulmonary veins. The anesthesiologist might see blood-tinged perfusate or a clot spilling from the PA during this, which should gradually run clear if the flush is effective. All the while, the lungs can be kept inflated at a low level. Following this, the trachea needs to be divided. To facilitate this, the anesthesiologist is asked to withdraw the endotracheal tube partially (so the endotracheal cuff is not near the carina) and then perform an inspiratory hold to inflate the lungs to 20–30 cm H_2O. This inflation ensures that some air remains in the alveoli after removal (oxygenating the tissue and reducing

atelectasis during transportation). The surgeon then fires a surgical stapler across the trachea, sealing it and cutting it. The lungs are then freed from the chest cavity by cutting the remaining pleural attachments and lifted out. They are immediately placed in a basin with cold Perfadex preservation solution for inspection and packaging. Once the lungs are removed, the anesthesiologist can cease mechanical circulation, and the active portion of their duties has concluded.

Communication

Throughout the procurement, team coordination and constant communication are essential. The anesthesiologist should promptly announce critical hemodynamic changes: e.g., "lungs seem to be getting stiff" or "blood pressure dropping now, giving vasopressors now." Conversely, surgeons should alert the anesthesia team of maneuvers that might cause changes (like lifting the heart may cause vagal responses or blood return fluctuations). When warned, the anesthesiologist can compensate with volume resuscitation, vasopressor boluses, or temporary Trendelenburg positioning.

Clear communication is particularly important during dynamic moments of the operation. If the heart is being evaluated, often by direct palpation or portable echocardiography, transplant teams may request a temporary reduction of vasoactive infusions to better assess native function. Conversely, the anesthesiologist may request additional time before proceeding (e.g., "wait to lift the heart while we catch up on volume"). During organ preparation, any unexpected issues, such as bleeding or technical difficulty, should be communicated immediately. In rare cases of massive hemorrhage (e.g., atrial tear), the anesthesiologist may need to administer volume or blood products during the procurement to maintain perfusion until organ recovery is complete.

In practice, donor surgery is fast-paced and can be somewhat chaotic, often involving multiple surgical teams working simultaneously. The anesthesiologist frequently serves as a stabilizing presence, tracking vital signs, anticipating physiologic changes, and announcing key events. Calling out "cross-clamp on, time noted at 14:32" helps all teams accurately document ischemic time, while sharing relevant clinical data, such as "the last blood gas PaO_2 was X on these ventilator settings," can guide organ-specific decision-making. Although the anesthesiologist's direct patient care role effectively ends once the organs are recovered, they may still assist with documentation and coordination until the teams depart. In summary, understanding the surgical flow and maintaining continuous, bidirectional communication allows the anesthesiologist to deliver seamless support and help ensure the donor's stability throughout the procurement.

Organ Preservation and Transport Technologies

After organ removal, the focus shifts to preserving organ viability during the time between procurement and implantation. Traditionally, thoracic organs are simply stored on ice in a cooler with a preservation solution (static cold storage method),

which is the most common cardiac preservation technique used in the United States and worldwide [71].

Once the heart or lung is removed from the donor body, it is brought to the back table where additional inspection of the graft is performed, specifically to ensure that the donor sewing cuffs are adequate. They are then placed into one or more sterile bags surrounded by ice (4 °C environment) [71, 72]. Hypothermia has been shown to reduce metabolic activity in a stepwise manner; at 4 °C, the heart's metabolic activity is roughly 10% of baseline [73, 74]. Hypothermic reduction of metabolic activity is also the cornerstone for successful lung preservation and transplantation [75]. The metabolic activity of the explanted lungs is decreased to 5% compared to baseline when cooled to 4 °C [76].

While effective for short periods, cold storage has limitations regarding the duration organs can tolerate ischemia. Traditionally, the acceptable ischemic time for hearts is 4–6 h, while for lungs, it is tolerable for 6–8 h [77, 78] using conventional static storage. In recent years, multiple technologies have emerged to preserve these organs better. Here, we review the key preservation strategies for heart and lung grafts, including static cold storage devices and perfusion systems.

Heart Preservation Advancements

Alternative Static Cold Storage

Portable cooling devices have been developed to better regulate temperature than an ice cooler. For example, the Paragonix SherpaPak (Paragonix Technologies Inc., Braintree, MA, USA) is a cardiac transport box that keeps the heart in a temperature-controlled environment between 4 and 8 °C [79, 80]. It uses an inner canister where the heart is submerged in a cold solution, placed inside an insulated outer container with ice packs. The SherpaPak has been shown to maintain a consistent hypothermic temperature and has demonstrated equivalent or improved outcomes compared to traditional cooler transport [79–82]. Indeed, registry data presented in 2024 indicated that about half of all DBD donor hearts in the United States were transported using this device, and its use was associated with a lower rate of severe primary graft dysfunction and improved 2-year survival (94% versus 89%) [83]. Whether due to better thermal control (minimizing myocardial injury from direct topical freezing) or other factors, modern cold storage devices are helping extend acceptable ischemic times and distances for heart transport; one report described a heart successfully transplanted after over 7 h using a SherpaPak, covering nearly 3000 miles of transport [84].

Normothermic Machine Perfusion (OCS Heart)

The TransMedics Organ Care System (OCS, Transmedics Inc., Andover, MA, USA) is a portable *ex vivo* perfusion device that keeps the heart beating and perfused with warm, oxygenated blood during transport [57, 85–88]. Often dubbed the "heart in a box," the OCS Heart has an onboard pump, oxygenator, and monitors. After the donor heart is excised, it is quickly connected to the OCS circuit: an aortic cannula

delivers oxygenated donor blood (mixed with a nutrient solution) into the coronary arteries, and venous blood is drained from the right atrium via a PA cannula (coronary sinus effluent) back into the circuit. The device maintains normothermia (~37 °C) and allows the heart to beat. The system measures aortic pressure and coronary flow and can be used to monitor lactate trends as a surrogate for myocardial metabolism. If the heart has an electrical standstill initially (as can happen if the cross-clamp was prolonged), the team can defibrillate or pace the heart on the OCS until it beats adequately. The advantage of OCS is twofold: it limits cold ischemic time by providing continuous perfusion and offers an opportunity to assess and resuscitate the heart. For example, in DCD hearts that may have had 10–20 min of warm ischemia, the OCS can be used to assess the heart's functional recovery (e.g., if it ejects well, maintains pressure, and shows declining lactate levels, it is potentially a suitable organ for transplant).

In 2022, the FDA-approved OCS Heart after trials showed safety and efficacy. In the PROCEED II trial (a randomized study of OCS versus ice for standard criteria hearts), 30-day outcomes were similar between OCS and cold storage [85]. More importantly, the OCS has been applied to extended-criteria donor (ECD) hearts that might otherwise be discarded. The OCS Heart EXPAND trial investigated hearts from older donors, donors with mild coronary disease or longer downtimes, and so on, and reported that 86% of these high-risk donors were successfully transplanted after evaluation and transport on OCS; 1-year survival in recipients of these ECD hearts was 89%, comparable to national averages [88].

OCS has also facilitated DCD heart transplantation. The first DCD heart transplants (pioneered in Australia and the United Kingdom around 2014) used an OCS to perfuse the heart after removal. In current US practice, DCD hearts are either recovered via NRP or directly procured and placed on OCS for resuscitation. The combination of NRP (*in situ* reperfusion) and/or OCS (*ex situ* reperfusion) has enabled hundreds of DCD heart transplants over the last few years.

Hypothermic Oxygenated Perfusion—The XVIVO Heart Preservation System

An emerging technology blends the benefits of cold storage and perfusion. The XVIVO Heart Preservation System (XHPS, XVIVO Inc., Gothenburg, Sweden) is a device that perfuses the heart with a cold (8 °C), oxygenated cardioplegic solution continuously during transport [89]. Essentially, instead of a static cold flush and ice, the heart is bathed and perfused with a low-flow, oxygen-rich solution to further prolong viable storage time beyond what static cold can achieve. Preclinical studies have shown that hypothermic machine perfusion can extend safe preservation times and reduce ischemia-reperfusion injury [90–92]. The XHPS device uses a specialized perfusate (mixed with a small amount of blood for oxygen carrying) that is circulated through the coronaries at 8 °C under low pressure. The solution contains nutrients and hormones intended to metabolically support the myocardium. Because metabolism at 8 °C is greatly reduced, even a low perfusion flow with dissolved oxygen can meet tissue needs without accumulating lactate.

Early reports from phase 1–2 studies in Europe have been promising, showing feasibility and no adverse outcomes in hearts preserved with XHPS versus standard care [89, 93]. A larger multi-center trial (the PRESERVE trial) is ongoing in the United States and Europe [93]. If successful, this technology could enable heart preservation for more than 4–6 h, which would be transformative for organ sharing across long distances. As anesthesiologists, encountering an XHPS in practice would mainly involve awareness that, after the heart is removed, the team might spend a few more minutes connecting it to this device on the back table rather than packing it in ice.

Lung Preservation Advancements

Alternative Static Cold Storage

LUNGguard (Paragonix Technologies Inc., Braintree, MA, USA) is a portable cooling device like SherpaPak, designed for alternative static cold storage of lung allografts. LUNGguard uses the same dual-cannister technology to maintain a consistent temperature-controlled environment (4–8 °C) with real-time monitoring of temperature and pressure. The GUARDIAN-Lung Registry reported lower rates of severe primary graft dysfunction, ECMO, and dialysis requirements with LUNGguard compared with ice [94]. Like SherpaPak, LUNGguard extends the acceptable ischemic time to up to 12 h [95].

Central *Ex Vivo* Lung Perfusion (Stationary EVLP)

Ex vivo lung perfusion was developed to evaluate [99] and rehabilitate lungs after retrieval, especially from extended-criteria donors, thereby expanding the usable donor pool and limiting cold-ischemic time [96–98]. Cypel et al. [99] first demonstrated > 12 h preservation using acellular, normothermic perfusate, low perfusion pressures, left-atrial pressures of 3–5 mmHg to stent the microvasculature, and a centrifugal pump responsive to changing pulmonary resistance. On these circuits (e.g., Toronto/XVIVO), the lungs are ventilated at 37 °C while compliance, pulmonary vascular resistance, airway pressures, gas exchange, and edema are continuously monitored for 4–6 h or longer. The landmark HELP trial reported that 80% of high-risk lungs initially declined were transplanted after EVLP with outcomes comparable to conventional grafts [100, 101]. Beyond assessment, EVLP is evaluating potential therapeutic interventions (currently being studied): terbutaline to enhance alveolar fluid clearance [102], surfactant lavage for aspiration injury [103], high-dose antimicrobials [104, 105], and experimental gene or cell therapies targeting inflammation and endothelial integrity [106, 107].

Lung OCS (Mobile EVLP)

The OCS Lung (TransMedics) applies the same normothermic perfusion principles on a portable platform, allowing continuous perfusion and ventilation during transport instead of static cold storage. After retrieval, lungs are connected to an acellular, nutrient-rich circuit that maintains pulmonary-artery pressures of 10–20 mmHg

and left-atrial pressure of 3–5 mmHg while real-time measurements of compliance, gases, and lactate guide acceptance decisions. The INSPIRE trial demonstrated non-inferiority of OCS Lung compared with traditional cold storage for standard-criteria lungs, and its mobility extends the safe ischemic window while providing the same ability to re-evaluate borderline grafts [98].

Transport Considerations

Organs are usually transported by a combination of ground and air. The OPO coordinator handles the logistics, but anesthesiologists should be aware of one particular concern: barometric pressure changes for lung transport by air. If lungs are inflated and sealed in a container at sea-level pressure, flying to high altitude (lower external pressure) can cause the trapped gas in the lungs to expand (Boyle's law), potentially over-distending and injuring alveoli. To mitigate this, lung teams often ensure that the lungs are not overly inflated in the transport bag or will release a bit of air if needed. Some transport coolers also have vent valves to equalize pressure (BAROguard) [108].

Intraoperative Anesthetic Management and Team Coordination

From the induction of donor surgery to the point at which the organs leave the hospital, the anesthesiologist is a central figure in maintaining stability and ensuring smooth coordination. Many aspects of donor management have been covered in preceding sections. Here, we summarize the specific intraoperative anesthetic considerations and the teamwork elements crucial for a successful thoracic procurement.

Monitoring and Access

By the time the donor is in the OR, invasive monitors (arterial line and central venous line) and adequate IV access (at least two large-bore IVs) should be in place. If not, the anesthesia team will obtain these immediately after inducing (if the patient was not already intubated) or upon arrival. Most donors are already intubated and ventilated from the ICU, so no induction is necessary; anesthesia in a DBD donor is mainly continuation of sedation/analgesia as needed. Standard American Society of Anesthesiologists monitors (ECG, pulse oximeter, and capnograph) are used. A temperature probe may help track core temperature, as donors can become hypothermic when exposed.

Hemodynamic Goals

The targets discussed (SBP > 100, MAP > 60) remain in effect in the OR. Continuous infusion of vasopressors (like vasopressin) is titrated to maintain these pressures, although the addition of agents with inotropic effects (epinephrine, norepinephrine, dopamine, etc.) should be discussed with the surgical team. Volume resuscitation is ongoing; the anesthesia provider should be frequently assessing volume status (CVP trends, urine output, and surgical field bleeding) [33–35]. If, during the surgical dissection, there is blood loss (e.g., from the mediastinum or great vessels), it should be replaced promptly with crystalloid or blood as needed. Blood transfusion in donors is somewhat controversial: transfusing banked blood can introduce anti-HLA antibodies that might affect organs. It is generally preferable to use fluids and vasopressors to maintain pressure, and only transfuse if absolutely required (e.g., hemoglobin has dropped very low, or there is substantial hemorrhage) [35–37]. Coagulopathy is uncommon unless the donor had trauma, but if noticed (oozing in the field), lab checks and products (fresh frozen plasma and platelets) might be needed.

Ventilation Management

The anesthesiologist should continue lung-protective ventilation. Typical settings might be tidal volume 6–8 mL/kg (ideal body weight) and PEEP 5 cm H_2O [41, 109]. Watch peak pressures: if the chest is open, lung compliance improves, so tidal volumes may need adjustment to avoid too large excursions. Recruitment maneuvers should be done, especially after sternotomy. The lung team might request a specific deflation test to evaluate how well the lungs collapse for recoil assessment. Bronchoscopy, if not done earlier, should be done to remove significant secretions and identify any abnormal endobronchial lesions.

Medications

Aside from vasoactive drips and hormone therapy (which are continued), the anesthesiologist should ensure adequate anticoagulation (heparin) prior to aortic cross-clamping. If the donor is volume overloaded (right ventricular distention) or pulmonary edema is suspected, a dose of diuretics (furosemide) might be given during the case to improve heart and lung conditions, provided blood pressure tolerates.

Arrhythmias and Emergencies

It bears reemphasizing that donors can arrest in the OR, typically from arrhythmia, hypotension, or severe vagal response, which may preclude organ donation. Usually,

if a donor arrests in the OR before planned aortic cross-clamping, the surgical team might immediately cross-clamp and flush to salvage organs rather than do prolonged cardiopulmonary resuscitation (CPR). If atrial fibrillation, ventricular fibrillation, or ventricular tachycardia occurs, urgent defibrillation is warranted, and amiodarone or lidocaine can additionally be given. For bradycardia or asystole, pacing might be attempted, or epinephrine could be used. Typically, in these cases, the heart is declined for inadequate quality, but other organs, including the lungs, could remain viable.

DCD-Specific Intraoperative Notes

In controlled DCD, the anesthesiologist's intraoperative role was outlined earlier. If withdrawal is in the OR, make sure that the monitors are visible to the physician who will declare death. After death has been declared, the anesthesia provider might help by re-intubating and restarting mechanical ventilation. This is sometimes done concurrently with pulmoplegia flush to help lung cooling.

Documentation and Handoff

After the organs are out, the anesthesiologist, along with the OPO coordinator and surgeons, completes documentation. This includes recording the cross-clamp time (critical for ischemic time calculation), the time each organ was placed on ice, and any intraoperative medications. All donor medications given in the last 24 h (including drips, antibiotics, and blood products) are typically recorded and passed on. The anesthesiologist often has the anesthetic record, which becomes part of the donor's chart (transplant centers will refer to this for details such as vasopressor doses and last vital signs). A concise transplant center briefing is usually provided by the procurement surgeon en route or upon arrival, but anesthesiologists may also provide input if something notable occurred. Such communication ensures that the recipient team is not caught off guard by any donor instability that could affect organ function.

Finally, a word on the emotional aspect: Organ donation is a procedure that, while routine in the medical field, often carries deep emotional significance for the donor's family and even the staff. Anesthesiologists might find themselves as the last physician caring for the donor patient as a person. It is not uncommon to observe a moment of silence or respect in the OR when the donor passes. Maintaining professionalism and empathy through this process, for example, treating the donor's body with dignity after organ removal, is part of the unwritten duties of the team. Many institutions have protocols for an honor walk or a moment of honor for the donor, during which anesthesiologists may participate before entering the OR.

Conclusion

Thoracic organ procurement is a procedure that encapsulates the intersection of critical care, anesthesia, and surgery. Anesthesiologists play a crucial role in this process by maintaining the donor's physiologic stability, managing hemodynamics, performing interventions such as bronchoscopy, and coordinating closely with surgical colleagues. In DCD cases, the anesthesiologist must navigate the delicate balance of compassionate end-of-life care with the urgency of organ preservation, all while adhering to ethical guidelines. The growth of organ donation, primarily through expanded criteria donors and DCD, has increased the demand for donor management. Potential donors today may be older, have more comorbidities, or have sustained more instability than in the past, requiring astute and proactive management by the ICU and anesthesia teams. Technological advances such as NRP and *ex vivo* perfusion are exciting developments that promise to improve transplant outcomes and expand the donor pool.

Ultimately, the success of thoracic organ procurement, measured by the viability of the heart and lungs and the outcomes in the recipients, is a team success. It relies on seamless integration of efforts by critical care physicians optimizing the donor pre-OR, anesthesiologists managing intraoperative physiology, surgeons executing surgical technique, and OPO staff coordinating the process. By understanding the entire continuum and the rationale behind each step, anesthesiologists can provide guideline-based, high-quality care that honors the gift of organ donation and maximizes the benefit to transplant recipients.

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Advances and Future Directions in Transplant Anesthesia

13

Elizabeth A. Wilson

2026 Edition

Abbreviations

CPB	cardiopulmonary bypass
DBD	donation after brain death
DPIPB	deep parasternal intercostal plane block
DPP	direct procurement and perfusion
ECD	extended-criteria donors
ECMO	extra-corporeal membrane oxygenation
ESOT	European Society for Organ Transplantation
ESPB	erector spinae plane block
GGTA1-KO	1,3 alpha galactosyltransferase knockout
HCV	hepatic C infection
HMP	hypothermic machine perfusion
HOPE	hypothermic oxygenated perfusion
ICU	intensive care unit
IVC	inferior vena cava
MP	machine perfusion
NIHP	*ex vivo* non-ischemic heart preservation
NMP	normothermic machine perfusion
OCS	organ care system
OHT	orthotopic heart transplantation
OLT	orthotopic liver transplantation
PEC	pectoralis plane block
PFIB	pectointercostal fascial block (PFIB)
PONV	postoperative nausea and vomiting

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QL	quadratus lumborum
ROS	reactive oxygen species
SAPB	serratus anterior plane block
TAP	transversus abdominal plane
UNOS	United Network for Organ Sharing Database
VAS	visual analog pain scores

Regional Anesthesia Peri-transplantation

Regional anesthesia is associated with decreased opioid consumption, improved postoperative outcomes, increased patient satisfaction, and decreased hospital costs [4, 5, 6]. In transplantation, concern for coagulopathy, hemodynamic instability, metabolic deficiencies, immunosuppression, and infection historically discouraged anesthesia providers from utilizing regional anesthesia. Advancements in regional anesthesia, however, have improved the safety and efficacy of regional blocks, offering numerous anesthetic options to ameliorate pain after transplantation (Table 13.1 and Fig. 13.1) [4, 5, 7]. New ultrasound-guided techniques, which enable real-time visualization of anatomic structures, block needles, and local anesthetic spread, have facilitated the development of new perioperative fascial plane blocks. Complications associated with inadvertent needle placement, causing pneumothorax or peritoneal perforation, for example, are very rare with fascial plane blocks [8, 9].

Choice of block and single versus continuous administration depends on the specific postoperative concerns associated with each type of transplantation and patient [4, 5]. Transplants with faster recovery times, such as kidney and pancreas, may benefit from shorter regional blocks; while transplants with longer recovery times, such as heart, lung, and liver, may benefit from longer regional blocks. Interestingly, one study examining TAP blocks in laparoscopic living donor nephrectomy surgeries demonstrated continuous catheter infusion provided no additional analgesic benefit over a single injection [10].

Multiple studies have reported the possible duration of indwelling catheters used in various transplant surgeries, such as 1–3 days for transversus abdominal plane (TAP) blocks [11], 3–5 days for erector spinae plane blocks (ESPBs) [12–14], 4 days for rhomboid intercostal and sub-serratus (RISS) plane blocks [15], 4–9 days for paravertebral blocks (PVBs) [16], and 8 days for serratus anterior plane blocks (SAPBs) [17]. Continuous regional or neuraxial anesthesia via catheter placement may improve analgesia over an extended period but must be weighed against the possible risk of infection, hematoma formation [18], bleeding, and local anesthetic toxicity [4, 5]. In a retrospective registry analysis, prolonged catheter use was associated with infection, particularly after 4 days [19], but this has not been validated in transplantation. Pain from a hematoma is associated with increased medical costs and decreased patient satisfaction [18, 20]. Patients with cirrhosis may be at a higher risk for bleeding after regional or neuraxial anesthesia, but this has not been

Table 13.1 Regional anesthesia blocks for transplantation (Ander)

Block	Location	Nerves	Target	Corresponding type of transplant surgery
ESPB	Posterior, lateral, and anterior chest and/or abdomen of the chosen dermatomal level	Dorsal and ventral rami of thoracic spinal nerves	Posterior aspect of the transverse process of the chosen dermatomal level, deep to the erector spinae muscle	Heart Kidney Liver Lung Pancreas
EOIFPB	Anterolateral upper abdominal wall	Anterior and lateral branches of the intercostal nerves	Deep to the external oblique muscle, superficial to the sixth rib or intercostal muscle, at the mid-clavicular line	Liver Pancreas
II/IH	Low abdomen, L1 dermatome	II and IH nerves	Deep to the internal oblique fascia, superficial to the transversus abdominis muscle, close to the anterior superior iliac spine	Kidney
PVB	Unilateral dermatomes of the thorax and abdomen	Unilateral spinal nerve roots	Area between transverse processes, deep to the superior costotransverse ligament, superficial to the pleura	Heart Kidney Liver Lung Pancreas
PIFB/ DPIPB	Anterior chest (sternotomy pain)	Anterior intercostal nerve branches	Deep to the pectoralis major fascia, superficial to the intercostal muscle between the 3rd/4th and 4th/5th ribs	Heart
Pectoralis (PEC) I	Anterolateral chest (does not include parasternal area)	Long thoracic, medial and lateral pectoral, intercostal, and possibly thoracodorsal nerves	Deep to the pectoralis major fascia, superficial to the pectoralis minor muscle at the level of the third rib	Heart
Pectoralis (PEC) II	Anterolateral chest (does not include parasternal area)	Long thoracic, medial and lateral pectoral, intercostal, and possibly thoracodorsal nerves	Deep to the pectoralis minor fascia, superficial to the serratus anterior muscles at the level of the fourth rib	Heart
QL	Posterior, lateral, and anterior chest and/or abdomen of the chosen dermatomal level	Dorsal and ventral rami of spinal nerves	Lumber interfascial triangle, posterior to QL, lateral to erector spinae, anterior to latissimus dorsi muscles	Kidney Liver Pancreas

(continued)

Table 13.1 (continued)

Block	Location	Nerves	Target	Corresponding type of transplant surgery
RS	Cutaneous nerves of the chosen dermatomal level, midline incisions	Anterior cutaneous abdominal nerves	Posterior to the RS fascia, superficial to the transversalis fascia, superior and inferior to the umbilicus bilaterally	Liver Pancreas
RISS plane block	Anterolateral thorax	Lateral cutaneous branches of the intercostal nerves covering T2–T9 dermatomes	T2–T7 coverage: Deep to rhomboid fascia, superficial to intercostal muscle T7–T9 coverage: Deep to serratus anterior fascia, superficial to intercostal muscle	Lung
SAPB	Anterolateral thorax	Thoracic intercostal and long thoracic nerves	Deep to the latissimus dorsi fascia, superficial to the serratus anterior muscle at the level of the fourth–fifth ribs	Heart Lung
Thoracic epidural (TE)	Bilateral dermatomes of the thorax and/or abdomen of chosen levels	Bilateral spinal nerve roots	Epidural space, deep to ligamentum flavum and vertebral lamina, superficial to dura mater, medial to vertebral pedicles	Heart Kidney Liver Lung Pancreas
TAP	Abdominal cutaneous nerves	Lateral and anterior abdominal cutaneous nerve branches from T6 to L1	Between internal oblique fascia and the transversus abdominis muscle, near the posterior limit of the transversus abdominis muscle	Kidney Liver Pancreas
Transverse thoracic muscle plane/SPIPB	Parasternal chest wall	Anterior cutaneous branches of the intercostal nerves	Deep to the internal intercostal fascia, superficial to the transversus thoracic muscle	Heart

Abbreviations: *DPIPB* deep parasternal intercostal plane block, *EOIFPB* external oblique intercostal fascial plane block, *ESPB* erector spinae plane block, *II* ilioinguinal, *IH* iliohypogastric, *PEC* pectoralis, *PIFB* pectointercostal fascial block, *PVB* paravertebral block, *QL* quadratus lumborum, *RS* rectus sheath, *RISS* rhomboid intercostal and sub-serratus, *SAPB* serratus anterior plane block, *SPIPB* superficial parasternal intercostal plane block, *TE* thoracic epidural, *TTMP* transverse thoracic muscle plane

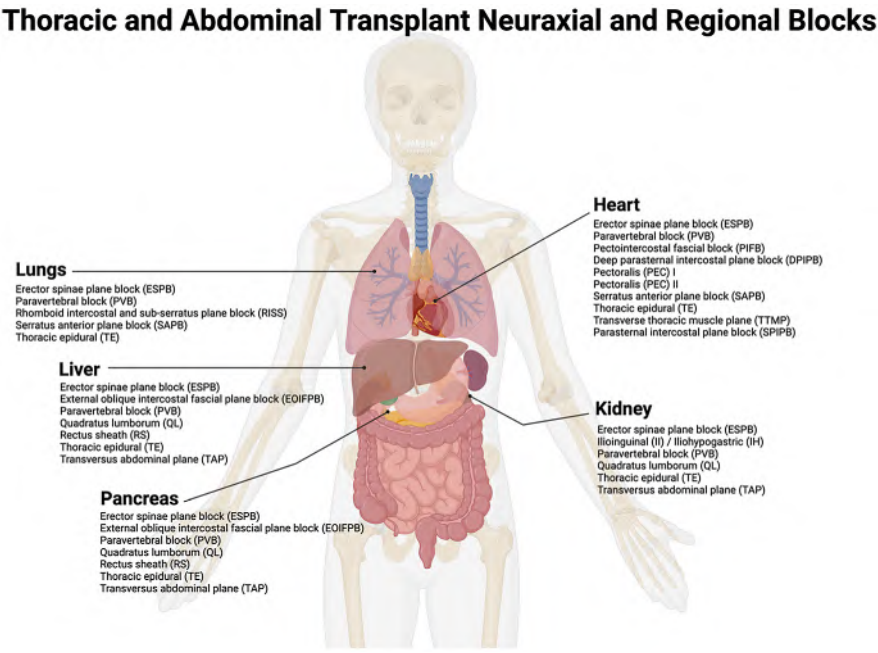

Fig. 13.1 Neuraxial and regional for thoracic and abdominal transplantation (Ander). Abbreviations: *DPIPB* deep parasternal intercostal plane block, *EOIFPB* external oblique intercostal fascial plane block, *ESPB* erector spinae plane block, *II* ilioinguinal, *IH* iliohypogastric, *PEC* pectoralis, *PIFB* pectointercostal fascial block, *PVB* paravertebral block, *QL*, quadratus lumborum, *RS* rectus sheath, *RISS* rhomboid intercostal and sub-serratus plane block, *SAPB* serratus anterior plane block, *SPIPB* superficial parasternal intercostal plane block, *TE* thoracic epidural, *TTMP* transverse thoracic muscle plane. (Graphic created in Biorender.com)

extensively examined in the medical literature [5]. Additionally, patients with cirrhosis may have impaired local anesthetic metabolism, increasing their risk of local anesthetic toxicity, but this also has not been extensively studied in the medical literature [5]. Future research is thus needed to investigate the effect and risk of complications associated with regional and neuraxial anesthesia in each type of transplantation specifically.

Regional Anesthesia for Heart Transplantation

Few studies examine regional anesthesia in heart transplantation. Neuraxial remains controversial due to the risk of bleeding, need for anticoagulation, and potential for hemodynamic instability. Other possible complications include placement failure with rates as high as 6.7%, postoperative catheter malfunctions with rates as high as 12.7%, epidural abscesses or hematomas with an incidence of <0.09%, and spinal abscesses or hematomas with an incidence of <0.03% [21, 22]. Alternatively, many

fascial plane blocks have been examined in other cardiac and thoracic surgeries that may be suitable in heart transplantation [21, 23–25], including PVB, pectointercostal fascial plane blocks (PIFBs), deep parasternal intercostal plane blocks (DPIPBs), superficial parasternal intercostal plane blocks (SPIPBs), pectoralis plane blocks (PEC), SAPBs, and ESPB.

PVBs were equivocal to thoracic epidurals and associated with a lower incidence of postoperative nausea and vomiting (PONV), hypotension, and urinary retention in a systematic review and meta-analysis including 23 randomized control trials with 1120 participants [26]. PFIBs were associated with significantly decreased visual analog scale pain scores, though opioid consumption and postoperative delirium rates were equivocal, compared to the control group in a single-center, prospective, randomized, placebo-controlled, blinded trial of 80 patients requiring sternotomy for cardiac surgery [27]. DPIPBs were associated with less opioid and non-steroidal anti-inflammatory drug (NSAID) consumption, shorter time to extubation, and reduced hospital and intensive care unit (ICU) length of stay compared to the control group in a randomized, controlled, double-blind study of 108 patients undergoing valve replacement surgery via median sternotomy [28]. SPIPBs, a type of DPIPB in which local anesthetic is administered deeper into the transversus thoracic plane through the intercostal muscles, can also provide adequate pain control for median sternotomies. SPIPBs were associated with significantly reduced postoperative opioid and NSAID consumption, time to extubation, time to first bowel movement, improved sleep quality, and duration of hospital and ICU length of stay compared to the control group in a randomized, double-blinded study of 60 patients undergoing median sternotomy for cardiac surgery [29]. PEC blocks and SAPBs are also safe and effective in cardiac surgery patients [30, 31]. PEC blocks were associated with decreased duration of ventilator support, pain scores after extubation, and need for rescue analgesia compared to the control group in a randomized study of 40 patients undergoing coronary artery bypass grafting or valve surgeries with a median sternotomy [30]. Bilateral single-shot ESPBs were associated with a statistically significant reduction in postoperative pain scores after cardiac surgery in a prospective, randomized, controlled trial [32]. Another study demonstrated ESPBs had similar postoperative pain scores compared to thoracic epidurals with no difference in clinical outcomes [33].

Regional Anesthesia for Lung Transplantation

Pain after lung transplantation can contribute to poor pulmonary compliance and decreased graft expansion, increasing the risk of postoperative complications such as atelectasis and pneumonia. Multiple regional anesthesia blocks have been shown to improve postoperative outcomes, including thoracic epidurals, PVBs, ESPBs, SAPBs, and RISS plane blocks. Intraoperative cryoablation of intercostal nerves has also been shown to lower postoperative pain scores and opioid use [34].

Due to their efficacy and relatively low complication rate, thoracic epidurals are a common component of the multimodal approach to pain management during and after lung transplantation [35]. Compared to opioids alone, epidural infusions with

a combination of local anesthetic and opioid are associated with a significant reduction in pain scores and breakthrough analgesic requirements [36].

The optimal timing of thoracic epidural placement, however, remains debatable. The primary concerns with preoperative placement are the risk of epidural hematoma while anticoagulated for extra-corporeal membrane oxygenation (ECMO) or cardiopulmonary bypass, if used, and hypotension, which is often exacerbated by strategic fluid restriction intraoperatively. Despite these concerns, preoperative thoracic epidural placement has been associated with decreased postoperative mechanical ventilation compared to postoperative placement or no placement at all in some studies [6]. An additional single-center retrospective study of over 100 lung transplant patients demonstrated lower pain scores at 48 and 72 h postoperatively with preoperative epidurals compared to postoperative epidurals [37]. Interestingly, there was no difference in primary graft dysfunction, length of mechanical ventilation, or adverse pulmonary events. Importantly, no incidents of epidural hematoma, paralysis, or infection were reported [37]. The primary concerns with postoperative placement are the missed opportunity to treat pain intraoperatively, possible anticoagulation, and positional challenges if sedated, intubated, and connected to mechanical ventilation. Many studies have shown improved analgesia without serious complications, such as epidural hematoma or abscess formation [38].

Alternatively, PVBs can also provide safe and effective pain management during lung transplantation [39]. In a retrospective study involving 44 patients, PVBs demonstrated comparable postoperative opioid requirements with shorter ventilation time and fewer adverse events, including hypotension and urinary retention, compared to thoracic epidurals [40]. When a thoracic epidural and PVB are contraindicated, fascial plane blocks, which are further from the spinal cord and thus a safer place in the setting of anticoagulation or coagulopathy, are also viable options that are associated with fewer hemodynamic changes. ESPBs can provide somatic and visceral pain coverage as the local anesthetic administered can spread to the paravertebral, epidural, and possibly dorsal rami spinal nerve spaces [41]. SAPBs cover post-thoracotomy pain at the T2–T9 anterior thoracic wall dermatomal levels, and catheter placement has been shown to provide lasting relief for 4–8 days postoperatively [17, 42]. One case report demonstrated adequate pain control with a RISS block catheter at T5–T9 dermatomal levels for 3 days [15].

Regional Anesthesia for Liver Transplantation

Concerns regarding coagulopathy, hemodynamic instability, and metabolic deficiencies have largely precluded the widespread use of neuraxial anesthesia in liver transplantation. Interestingly, one 10-year retrospective single-center study in 685 liver transplant recipients with a low risk coagulation profile (INR < 1.5 and platelets >100 x10^9/L) demonstrated thoracic epidural use was associated with increased extubations in the operating room at the end of surgery and decreased intraoperative opioid requirements, postoperative pain scores, incidences of pneumonia, and ICU length of stay without major complications such as epidural hematoma [43].

Given their lower risk profile, peripheral fascial plane blocks are becoming increasingly popular in liver transplantation in the setting of new ultrasound-guided techniques. A retrospective study of 26 liver donors demonstrated reduced postoperative pain scores with ultrasound-guided PVBs compared to those without them [44]. Similarly, TAP blocks, which typically cover T10–L1 dermatomal levels but extend coverage to T6 using an oblique subcostal approach, are associated with significantly decreased opioid consumption and lower rates of PONV compared to intravenous analgesic therapy alone (Hebbard [45] and Amundson [46–50]). A retrospective cohort study of 24 living donor hepatectomy patients showed that ESPBs catheters reduced intraoperative and postoperative opioid consumption compared to 51 control patients [51]. External oblique intercostal fascial plane blocks (EOIFPBs), quadratus lumborum (QL), and rectus sheath (RS) blocks are also options, though there is limited data in the literature examining their efficacy. Ultrasound-guided EOIFPBs, which target the fascial plane deep to the external oblique muscle and superficial to the sixth rib or intercostal muscle at the mid-clavicular line, are easy to perform pre-emergence and cover the anterolateral upper abdominal wall.

Regional Anesthesia for Kidney Transplantation

There are a plethora of studies examining the beneficial effects of both neuraxial and fascial plane blocks in kidney transplantation and donor nephrectomy [52]. Possible blocks include thoracic or lumbar epidural (depending on incision site), PVB, ESPB, TAP, QL, and ilioinguinal (II)/Iliohypogastric (IH) blocks.

Epidurals and PVBs have been shown to be effective analgesia for both kidney transplantation and donor nephrectomy in multiple studies (Suarez-Sanchez [53], Oliveira [54, 55]). Interestingly, a 2020 prospective randomized study in 60 donor nephrectomy patients examining continuous epidural infusions versus continuous TAP block catheters demonstrated better pain control over 24 h, fewer complications, and earlier Foley catheter removal, ambulation, and hospital discharge in the TAP catheter group compared to the epidural group [56]. Additionally, a 2012 prospective randomized study examining single-shot TAP blocks with bupivacaine versus placebo saline injections in 46 laparoscopic donor nephrectomy patients demonstrated reduced pain scores, postoperative opioid requirements, PONV interventions, and faster return to a regular diet in the bupivacaine group compared to the placebo group [57]. Two retrospective studies demonstrated decreased intraoperative opioid requirements, 24-h opioid requirements, discharge opioid requirements, and PONV with either TAP or QL blocks dosed with a one-time administration of 20 mL Bupivacaine 0.25% or 0.5% [58, 59]. A 2020 prospective randomized trial demonstrated reduced pain scores and opioid requirements in patients who received QL blocks compared to placebo [60]. QL is a newer fascial plane block with increasing popularity, given its coverage of lower abdominal incisions, but it is more challenging to perform than a TAP block. II/IH blocks have been associated with decreased pain scores and opioid requirements, but their efficacy and complication rates are higher compared to other fascial plane blocks [61, 62].

Regional Anesthesia for Pancreas Transplantation

There is a paucity of studies examining the efficacy of regional anesthesia in pancreas transplantation. However, there is an abundance of evidence to support both neuraxial and fascial plane blocks in pancreatic surgery in general [63]. Many studies demonstrate a reduction in opioid consumption, pulmonary complications, and ileus [64]. A prospective randomized controlled trial of 40 patients undergoing pancreatic surgery demonstrated superior postoperative pain control and a lower incidence of opioid-related adverse effects with thoracic epidurals compared to intravenous analgesia [65]. Additionally, a systematic review and meta-analysis of pancreatic surgery patients in 2021 demonstrated equivocal pain and surgical outcomes with thoracic epidurals, TAP blocks, and opioid PCA pain control [66]. A retrospective study of 197 pancreatic surgery patients found that TAP blocks, whether single-shot or as a continuous infusion, were associated with lower opioid requirements and faster time to intestinal recovery compared to an intravenous opioid pain regimen alone [67]. A small retrospective cohort study in pancreatic transplant patients examining continuous RS block catheters demonstrated similar pain control compared to thoracic epidurals [68].

Technological Advancements in Organ Preservation

Organ preservation methods have improved beyond conventional static cold storage (SCS), in which the allograft is preserved in a bag of solution surrounded by ice. During donation after circulatory death (DCD) procurement, normothermic regional perfusion (NRP) has mitigated the effects of donor warm ischemia time. During allograft storage, normothermic and hypothermic machine perfusion (MP) has enabled the early re-introduction of oxygen, decreasing total ischemia time. Unfortunately, MP is expensive and not easily accessible in certain parts of the world. Alternatively, new preservation methods such as Paragonix do not facilitate the early re-exposure to oxygen but provide stabilizing cooling techniques in a controlled and monitored environment to prevent allograft freezing and uneven temperature distribution (Fig. 13.2).

Normothermic Regional Perfusion

Similar to veno-arterial ECMO, *in situ* NRP is a mode of mechanical circulatory support that maintains organ perfusion, with the exception of the brain, and attenuates warm ischemic injury during DCD procurement (Fig. 13.2). There are two types of NRP, thoracoabdominal and abdominal, which vary by the position of occlusive clamps or balloon catheters that isolate specific vascular beds. Thoracoabdominal NRP is performed postmortem, after the cessation of life support. Abdominal NRP can be performed either pre- or post-mortem. A postmortem schematic of the timeline of events during DCD procurement with NRP can be

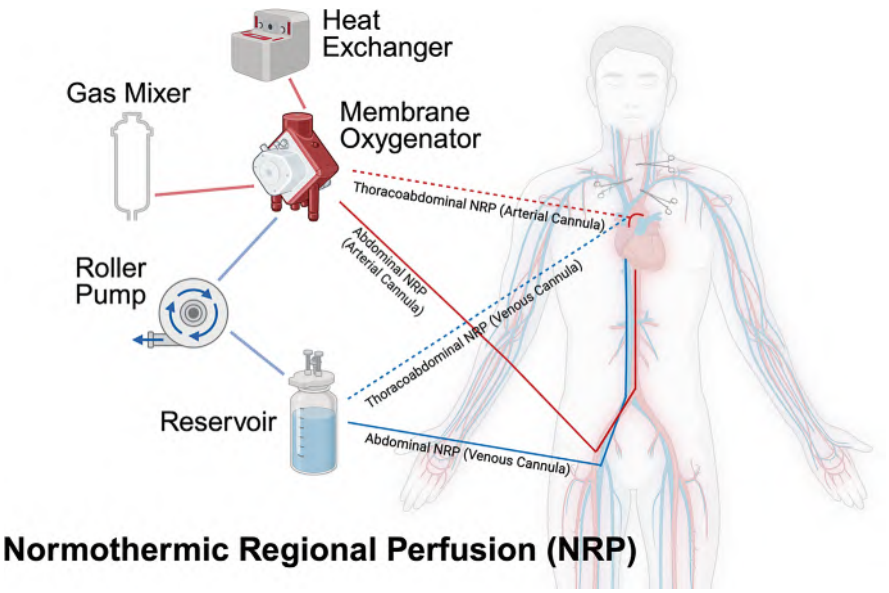

Fig. 13.2 Normothermic regional perfusion (NRP). The two types of NRP, thoracoabdominal and abdominal, vary by the position of occlusive clamps or balloon catheters that isolate specific vascular beds. (Graphic created in Biorender.com)

found in Fig. 13.3. NRP can be used with or without *ex vivo* MP of the allograft prior to implantation in the recipient.

There is a plethora of evidence to support the use of NRP as a novel technique to improve thoracic and abdominal organ preservation. In heart transplantation, NRP has been associated with improved survival. Benkert et al. retrospectively examined 918 heart donors and recipients in the United Network for Organ Sharing (UNOS) registry from January 2019 to December 2023, including 296 (32%) NRP and 622 (68%) direct procurement and perfusion (DPP) patients, and found NRP was independently associated with improved short-term recipient survival (HR: 0.39 [95% confidence interval (CI): 0.22–0.70]; p = 0.002) [69]. Furthermore, there was a cumulative survival benefit to NRP after propensity-score matching on recipient and donor factors (log-rank p = 0.006) [69]. Interestingly, Ran et al. demonstrated no significant difference in 1-year post-transplant survival between NRP and DPP (93.1% for NRP versus 91.1% for DPP, p = 0.79) [70]. However, the authors suggest that NRP should be the preferred procurement technique, given its beneficial impact on abdominal transplantation [70].

In lung transplantation, thoracoabdominal NRP use has been limited by the concern for the development of post-transplant recipient pulmonary edema and its potential deleterious impact on graft function. Many institutions have created lung-protective protocols during thoracoabdominal NRP that minimize functional donor warm ischemia time, total NRP time, and allograft pulmonary edema [71]. In one

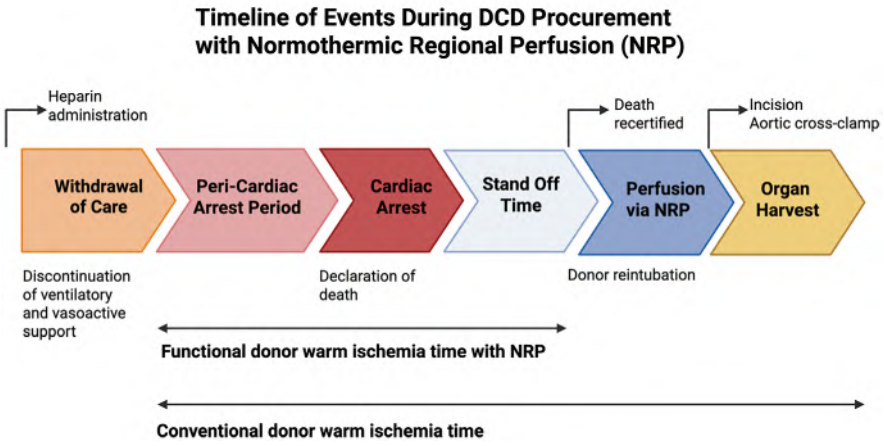

Fig. 13.3 Schematic of the timeline of events during DCD procurement with NRP. Abbreviations: *DCD* donation after circulatory death, *NRP* normothermic regional perfusion. (Graphic created in Biorender.com)

study examining 627 DCD donors in the UNOS database, DCD donor lung allograft procured with NRP demonstrated lower rates of ECMO (7.7% versus 17.0%, $p = 0.26$) and mechanical ventilation (34.6% versus 47.2%, $p = 0.29$) at 72 h and similar 6-month survival rates (85.7% versus 89.1%, $p = 0.67$) compared to directly procured donors [72]. Similarly, another study conducted a national retrospective review of lung transplants from DCD donors and found that those procured with NRP had a lower likelihood of ventilation after 48 h (23.5% versus 51.3%, $p = 0.027$) and similar rates of predischarge acute rejection, need for ECMO at 72 h, hospital length of stay, and 30, 60, and 90 day survival post-transplant [73]. These studies suggest that DCD lung procurement with NRP warrants further investigation and may be a safe and effective means to expand the deceased donor pool.

In liver transplantation, NRP has been shown to decrease the risk of EAD [74], biliary complications, allograft loss [75], post-reperfusion syndrome, and ischemic cholangiopathy [76] compared to conventional DCD recovery and a comparable incidence of EAD with donation after brain death (DBD) [76]. Specifically, Watson et al. [77] found a reduction in EAD (12% for NRP versus 32% for non-NRP livers, $p = 0.0076$), 30-day allograft loss (2% NRP versus 12% non-NRP livers, $p = 0.0559$), ischemic cholangiopathy (0% NRP versus 27% non-NRP livers, $p < 0.0001$), and anastomotic strictures (7% NRP versus 27% non-NRP livers, $p = 0.0041$). NRP remained significantly associated with reduced ischemic cholangiopathy ($p < 0.0001$) after adjustment in multivariate analysis [77]. These data suggest NRP during DCD liver procurement may lead to better or similar outcomes compared to conventional organ recovery and DBD, respectively [3].

Similarly, NRP has been shown to significantly increase the utilization rate of liver, kidney, and pancreas procurements from DCD donors with similar or improved outcomes compared to conventional procurement after transplantation [78]. In a retrospective analysis of DCD donors in the United Kingdom between January 2011 and December 2019, a mean of 3.3 organs per donor were transplanted when NRP was employed compared with 2.6 organs when NRP was not employed [79]. After adjustment for organ-specific donor risk profiles, NRP increased the odds of all abdominal organs being transplanted, specifically 3-fold for liver, 1.5-fold for kidney, and 1.6-fold for pancreas [79]. Notably, 12-month liver transplant survival was higher in recipients of NRP allografts with a 51% lower risk-adjusted hazard of transplant failure (HR = 0.494) [79]. After risk adjustment, kidneys procured via NRP had a 35% lower chance of developing delayed graft function than non-NRP kidneys (odds ratio (OR) = 0.65; 95% CI: 0.465–0.901). Furthermore, in pancreas transplantation, the European Society for Organ Transplantation (ESOT) published a consensus statement in 2023 suggesting NRP is a reliable and reproducible method for DCD procurement and has the potential to expand the donor pool [80]. Based on nine studies, it is recommended that NRP should be maintained for 1–4 h, and further studies are warranted for allograft quality assessment and outcomes [80].

The evidence thus suggests NRP is beneficial for all abdominal organs and may help bridge the gap between long transplant waitlists and available allografts.

Machine Perfusion

Ex vivo MP is an artificial allograft storage technique used for organ preservation. The two types of MP are [1] normothermic MP (NMP), which uses an oxygenated blood-based perfusate at physiologic temperature, and [2] hypothermic MP (HMP), which uses an oxygenated non-blood-based perfusate at hypothermic temperatures (Fig. 13.4). Both techniques maintain continuous circulation and moderate shear-stress within the allograft to sustain endothelial functionality. With the early reintroduction of oxygen, MP may attenuate the impact of IRI by extending organ preservation time, increasing organ utilization, allowing the functional assessment of marginal allografts that may have otherwise been declined [81], and reducing rates of EAD [82].

Normothermic Machine Perfusion

NMP uses an oxygenated blood-based perfusate at physiologic temperature to re-establish allograft cellular metabolism during extended preservation. NMP maintains circulation in either a pulsatile or continuous fashion and preserves the sinusoidal endothelium, replenishes ATP [83] and glycogen stores [84], and can facilitate the alteration of gene expression involved in liver regeneration and control of inflammation [85]. NMP can assess allograft viability via macroscopic appearance, lactate clearance, bile production, and perfusate transaminases [86, 87].

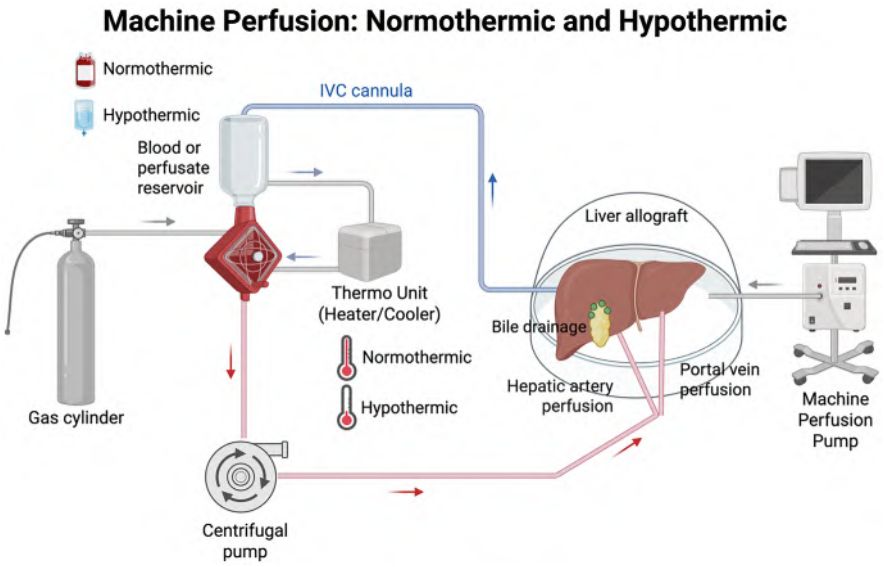

Fig. 13.4 Machine perfusion (MP): normothermic MP (NMP) and hypothermic MP (HMP). *Ex vivo* MP is an artificial allograft storage technique used for organ preservation. The two types of MP are [1] NMP, which uses an oxygenated blood-based perfusate at physiologic temperature, and [2] HMP, which uses an oxygenated non-blood-based perfusate at hypothermic temperatures. (Graphic created in Biorender.com)

Advancements in NMP technology have facilitated the development of clinically effective devices for heart, lung, liver, and kidney transplantation. New innovative NMP platforms for *ex situ* preservation of the pancreas, intestine, uterus, and ovaries are currently in development [88].

In the prospective, international, multicenter Organ Care System (OCS) Heart EXPAND Trial, NMP was associated with an 87% extended-criteria donor (ECD) DBD utilization rate, patient survival was 93%, 89%, and 86% at 6, 12, and 24 months, respectively, and outcomes were comparable to concurrent non-randomized control patients [89]. A meta-analysis examining 12 studies involving 741 orthotopic heart transplantation recipients, of which 260 received OCS Heart System NMP (173 DBD and 87 DCD) and 481 received SCS, demonstrated equivocal outcomes, including early and late survival, primary graft dysfunction, length of stay, rejection, and vasculopathy [90].

In lung transplantation, 80% of donor lungs are discarded due to primary graft dysfunction or other factors [91]. Grade 3 pulmonary graft dysfunction is associated with markedly elevated 30-day mortality rates and bronchiolitis obliterans syndrome [91]. Evidence suggests *ex vivo* lung perfusion (EVLP) may help bridge this gap and increase organ utility. The randomized, controlled, open-label international lung trial with the organ care system technology (INSPIRE) clinical trial demonstrated normothermic EVLP was non-inferior to SCS with a lower incidence of grade 3 graft dysfunction and similar 30-day survival rates [92]. The OCS Lung

INSPIRE Trial demonstrated an 87% utilization rate for ECD and DCD donor lungs with equivocal or improved long-term outcomes with normothermic EVLP compared to standard criteria donor lungs preserved via SCS [93].

In liver transplantation, the Consortium of Organ Preservation in Europe demonstrated a 50% reduction in AST level and organ discard with 54% longer mean preservation times with NMP compared to SCS [83]. In the prospective, international, multicenter OCS Liver PROTECT randomized clinical trial, 293 patients were randomized to either the OCS group using NMP ($n = 151$) or the conventional SCS group ($n = 142$) [94]. Compared to the SCS group, the OCS group with NMP was associated with a significant reduction in EAD (27 of 150 [18%] compared to 44 of 141 [31%]; $p = 0.01$), reduction in histopathologic evidence of IRI (9 of 150 [6%] versus 18 of 141 [13%]; $p = 0.004$), increased utilization of DCD donor allografts (28 of 55 [51%] versus 13 of 51 [26%]; $p = 0.007$), and decreased ischemic biliary complications at 6 months (1.3% versus 8.5%; $p = 0.02$) and 12 months (2.6% versus 9.9%; $p = 0.02$) [94].

Interestingly, the success of *ex situ* NMP in liver transplantation also facilitated the discovery of completely ischemia-free OLT with *in situ* NMP [95], in which perfusion begins within the donor's body before procurement instead of after the allograft is removed as in *ex situ* NMP. One randomized controlled trial of 68 DBD recipients demonstrated a decreased incidence of EAD in the ischemia-free *in situ* NMP group compared to the conventional procurement and storage group (6% versus 24%, difference −18%; 95% CI: −35% to −1%, $p = 0.044$) [96]. This novel technique, however, requires further investigation and refinement prior to broad implementation.

There are a few studies examining NMP in kidney transplantation. One randomized controlled trial examined kidney allografts after SCS with 1 h of NMP and SCS alone [97]. The rate of delayed graft function, defined as the need for dialysis within 1 week of transplant, was 82 of 135 (60.7%) in NMP kidneys versus 83 of 142 (58.5%) in SCS kidneys (OR = 1.13; 95% CI: 0.69–1.84; $p = 0.624$) [97]. However, NMP demonstrated feasibility and safety with no increase in transplant thrombosis, infectious complications, or other adverse events [97].

There are no clinical studies currently available regarding NMP in pancreas transplantation. The ESOT examined the preclinical evidence and published a Consensus Statement in 2023 recommending NMP at a maintenance pressure range of 25–50 mmHg for longer than 1 h between 34 °C and 37 °C [80]. It also recommends diversion of exocrine secretions to prevent tissue injury [80]. Endocrine function can be assessed by hormone secretion levels, but perfusate amylase and lipase levels are not reliable exocrine markers for tissue viability or injury [80].

Hypothermic Machine Perfusion

HMP uses an oxygenated non-blood-based perfusate at hypothermic temperatures between 4 °C and 12 °C to reduce allograft metabolic activity. Hypothermic oxygenated perfusion (HOPE) maintains a continuous flow of oxygen, reaching PaO_2 levels as high as 450–600 mmHg, which decreases the release of reactive oxygen

species, restores mitochondrial ATP within 2 h, and reduces the inflammatory response during reperfusion [98–100]. The perfusion technique used in HMP is technologically simpler and cheaper than that used in NMP [98]. However, HMP requires a high perfusion pressure to offset the cold-induced high resistance to flow within the allograft, which may lead to sinusoidal endothelial damage [101].

In *ex vivo* non-ischemic heart preservation (NIHP), or HMP for heart transplantation, heart perfusion is maintained via a continuous supply of oxygenated cold cardioplegic solution enriched with hormones, nutritional components, and red blood cells, maintaining a hematocrit of 8% [102]. Unlike NMP, HMP does not allow the examination of allograft lactate levels, coronary perfusion pressure, or cardiac contractility. Preclinical studies in porcine hearts suggest heart preservation with NIHP can be safely maintained for 24 h, with sustained endothelial function for at least 8 h [103]. The first human study was a non-randomized, open-label, phase 2 trial, which demonstrated reductions in myocardial damage and allograft rejection at 6 months compared to SCS [104]. An international, randomized, controlled clinical trial in heart transplantation with DBD donation demonstrated HMP with HOPE, compared to SCS, correlated with a risk reduction of 44% (hazard ratio 0.56; 95% CI: 0.32–0.99, log-rank test $p = 0.059$) of a composite of either cardiac-related death, moderate or severe primary graft dysfunction of the left or right ventricle, acute cellular rejection, or graft failure (with the use of mechanical circulatory support or re-transplantation) within 30 days after transplantation [105].

Interestingly, HMP with HOPE is not a common preservation method for lung transplantation. EVLP, the established preservation method for lung transplantation, is largely normothermic, with the exception of Lung Assist, a commercially available type of EVLP, which is an isolated perfusion device that can be performed in either normothermic or hypothermic conditions. There is a paucity of data examining the safety and use of hypothermic EVLP.

In liver transplantation, HOPE after DCD procurement has been shown to reduce rates of biliary complications and improve 1-year allograft survival compared to SCS controls [106]. One multicenter randomized controlled trial found that HOPE significantly decreased early allograft injury, 90-day complication rates, and ICU and hospital length of stay and improved outcomes in extended criteria brain death donors compared to SCS [107]. In a meta-analysis of nine studies, HMP was found to reduce the odds of EAD (OR 0.51, 95% CI 0.34–0.76; $p = 0.001$; $I^2 = 0\%$) and non-anastomotic biliary strictures (OR 0.34, 95% CI 0.17–0.67; $p = 0.002$; $I^2 = 0\%$) compared to SCS [108].

There is a plethora of evidence to support the use of HMP in kidney transplantation. A Cochrane Database systematic review and meta-analysis demonstrated that HMP reduces the risk of delayed graft function compared to SCS with high-certainty evidence [109]. Moreover, HMP reduces the risk of delayed graft function in kidney from DCD donors (7 studies, 772 participants, relative risk (RR) 0.75; 95% CI: 0.64–0.87; $p = 0.0002$) and DBD donors (4 studies, 971 participants, RR 0.78, 95% CI: 0.65–0.93; $p = 0.006$) [109]. To prevent one instance of delayed graft function, 7.26 and 13.6 in DCD and DBD kidneys, respectively, required MP [109].

Currently, there are no reported clinical studies on the use of HMP in pancreas transplantation. The ESOT examined the preclinical evidence and published a Consensus Statement in 2023, which recommends HMP up to a pressure of 30 mmHg in a colloid solution for 1–6 h between 4 °C and 12 °C [80]. It also suggests a decrease in resistance index may be correlated with better preservation of the whole pancreas during HMP [80].

Paragonix

Freezing and uneven temperature distribution during SCS is associated with allograft hepatocellular damage [110]. To prevent this, Paragonix Technologies developed multiple organ preservation systems that use stabilizing cooling techniques and digital tracking and monitoring. These devices, such as SherpaPak for heart transplantation, LUNGguard for lung transplantation, LIVERguard for liver transplantation, and KidneyVault for kidney transplantation, are composed of a rigid outer shell, proprietary phase-change materials, a temperature probe, and GPS technology to maintain a consistently stable thermal environment and facilitate real-time monitoring and tracking during organ transport.

In heart transplantation, early data suggests that DCD cardiac allografts after thoracoabdominal NRP can be safely maintained via SherpaPak for at least 3.5 h with satisfactory post-transplant function [111]. Preliminary data in a descriptive propensity-matched cohort of 254 DBD liver transplant recipients (127 with LIVERguard and 127 with SCS) from the GUARDIAN-Liver Registry (funded by Paragonix Technologies) from 2021 to 2024 demonstrated a 27% reduction in acute kidney injury (p = 0.016), 44% reduction in EAD (p = 0.074), and 48% reduction in new hemodialysis post-transplant (p = 0.37) (data presented by Dhanireddy et al. during the 2025 American Society of Transplant Surgeons Winter Symposium). Paragonix systems are a cost-effective and promising means of organ preservation, and their effect on transplant outcomes long-term requires further study.

Xenotransplantation

The global demand for allotransplantation of all types exceeds the supply of suitable allografts. Xenotransplantation, or animal-to-human organ transplantation, is an experimental, though promising, means to increase the pool of transplantable

organs. Pig organs are the best candidates for xenotransplantation due to their similar size and physiology [112]. Preclinical studies are largely performed in non-human primates, and there is a developing number of human case reports. Critical barriers to xenotransplantation include a high risk of rejection due to cross-species molecular incompatibilities and the possibility of transmission of xenogeneic infections [112–114].

Innovation in gene editing techniques contributed to the initial success of xenotransplantation, particularly with the breakthrough of 1,3 alpha galactosyltransferase knockout (*GGTA1*-KO) via deletion of α-Gal epitopes in donor pigs. Humans have natural antibodies against pig cell-surface carbohydrate xenoantigens, including galactose-α1,3-galactose (α-Gal), *N*-glycolylneuraminic acid (Neu*5*Gc), and Sda. Anti-α-Gal antibodies are the most critical as they make up about 1–4% of circulating immunoglobulins [112]. Upon porcine xenotransplantation, human anti-α-Gal antibodies form immune complexes with α-Gal xenoantigens, which activate complement via the classical and alternative pathways. Complement activation subsequently triggers membrane attack complexes and leads to xenograft cell lysis and hyperacute rejection. Deletion of the α-Gal xenoantigen, referred to as *GGTA1*-KO, and transgenic expression of human complement regulatory proteins may prolong the survival of pig-to-human xenografts as seen in primates [112]. Additionally, several non-α-Gal antibodies and innate and adaptive immune responses contribute to humoral and cellular xenograft rejection.

Multiple genetically modified pig lines have been developed to address issues of immune rejection, coagulation dysregulation, and xenogeneic infections [112]. In 2022, a genetically modified pig-to-human cardiac xenotransplantation was performed in a 57-year-old man with non-ischemic cardiomyopathy [115]. The cardiac xenograft functioned normally until 49 days postoperatively, at which point it developed sudden myocardial thickening and failure, and the patient died on postoperative day 60 [115]. The authors report that the cardiac xenograft failure may have been antibody-mediated, complement-dependent, or related to porcine cytomegalovirus transmission [112, 115]. Over the last year, multiple 10-gene knockout pig xenografts (Fig. 13.5) have been transplanted into living humans [112]. To date, the longest a human has survived with a kidney xenograft is 130 days.

Considerable progress has been made in cardiac and kidney xenotransplantation, paving the way for further gene modifications. Studies in lung and liver xenotransplantation are also underway, but xenotransplantation is more challenging in this context due to lung and liver anatomy and vasculature. Xenotransplantation nonetheless remains a promising future direction to alleviate the global organ shortage problem.

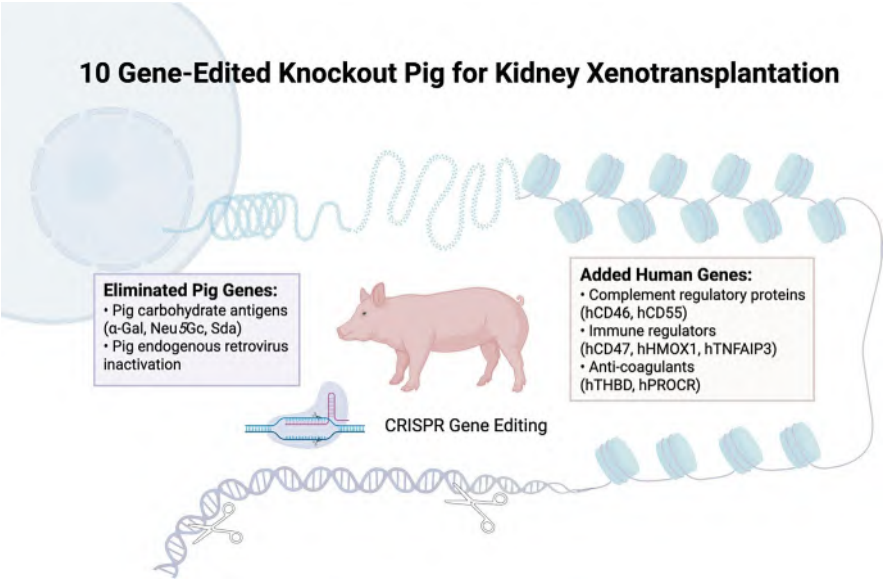

Fig. 13.5 Gene-Edited Knockout Pig. In kidney xenotransplantation, 10-gene knockout modifications in pig xenografts include deletion of carbohydrate antigens, endogenous retrovirus inactivation, and the addition of human complement inhibitors, anti-coagulants, and immune regulators. (Graphic created in Biorender.com)

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