Transplantation

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Introduction

The necessity for high-quality intensive care units (ICUs) in abdominal organ transplantation is essential to the outcomes of these patients. In most scenarios, patients undergoing liver transplantation require a stay in the ICU, whereas kidney and pancreas transplant patients' need for ICU care may vary from institution to institution. It must be pointed out that in this era of organ shortage and higher model for end-stage liver disease (MELD) patients undergoing liver transplantation, the ICU is becoming even more critical in the pathway of successful transplants. ICU organization may vary widely, from being run by anesthesiology, surgery, or medical intensivists, but the take-home message does not change. Patients are sicker now more than ever at time of transplant, and exhaustive, detail-oriented critical care is necessary for success.

A brief word should be mentioned that in some centers, fast-tracking patients is feasible in regard to certain patients undergoing liver transplantation. Taner et al. demonstrated that only 1.9 % of patients required admission to the ICU after being fast-tracked to the ward, which is remarkable. The factors affecting ICU admission were MELD at time of transplant, BMI, operative time, transfusion requirements, and age [1, 2]. This is an exciting prospect that may be beneficial to patients and a cost-saving measure, but unfortunately this does not apply to many regions across the country who are often transplanting patients that are in the ICU on life support.

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Cardiovascular

Given that liver transplantation is such a physiological stress on the human body, close attention to blood pressure, volume status, and cardiac performance is crucial in the early postoperative period. An initial electrocardiogram is standard immediately postoperatively to help in determining any arrhythmias and assessing early electrolyte disturbances, which maybe be present when admitted from the operating room.

Furthermore, close attention to perfusion initially is important as the vascular anastomoses are at more risk to have complications when the blood pressure remains low. It should be noted that most patients with cirrhosis have lower systemic vascular resistance (SVR), and their cardiac function is often hyperdynamic at baseline. There is no set pressure at which is needed to perfuse the liver; however, abrupt changes in blood pressure can be detrimental to vascular anastomoses and to the transplanted organ itself. It should be noted that abrupt changes in blood pressure or continued hypotension should be avoided, and prompt repeat lab values must be checked with a high index of suspicion for ongoing hemorrhage. If the patient is not bleeding, the use of vasopressors or inotropes based on SVR and cardiac function should be used. In most cases, for liver transplant patients, norepinephrine and/or vasopressin is first line [3, 4].

As far as cardiac performance, many of these patients undergo placement of a Swan-Ganz catheter prior to the start of liver transplantation, and this can be used in the ICU for monitoring of cardiac function, although their use remains variable between centers. Echocardiography may be used in adjunct or to replace the use of Swan-Ganz catheters when needed. More recently during liver transplantation, uncalibrated arterial pressure waveform analysis was compared with pulmonary artery catheters; however, they did not correlate and thus is not an acceptable alternative of measuring cardiac output during liver transplantation [5].

Volume management of the post-transplant liver recipient is a complex concern, as much of the literature in ICU

N.D. Martin, L.J. Kaplan (eds.), *Principles of Adult Surgical Critical Care*, DOI 10.1007/978-3-319-33341-0_35

management of volume administration does not support the use of albumin and blood transfusion; however, we must realize that transplant patients are different and must be treated as such. Blood transfusion in the immediate postoperative period can be used slightly more liberally in transplant patients, especially when unclear whether there is ongoing bleeding. The use of albumin postoperatively for volume expansion is used fairly frequently in liver recipients as well, although its benefits remain suspect even in the transplant population [6, 7]. Additionally, it is often acceptable to use crystalloid running maintenance fluids such as 5 % dextrose with either 0.45 % or 0.9 % normal saline. One must take into account the electrolytes including sodium and potassium which may be abnormal in cirrhotic transplant recipients when choosing fluids [8].

Pulmonary

After transplantation, patients should be weaned toward extubation as soon as possible, and this may be done in the operating room. Extubation immediately after liver transplantation has been shown to be safe with no increased risk in reintubation [9–11]. Early extubation in these patients can decrease ventilator-associated pneumonia but also may decrease venous congestion through the liver. The use of positive pressure ventilation may increase the intrathoracic pressure thus decreasing flow from the intrahepatic vena cava. It should be noted, however, that not all patients are amenable to early extubation as many have been admitted in the ICU pretransplant with prolonged and debilitating encephalopathy; thus, each patient should be treated individually. It is not uncommon to have post-transplant oxygenation difficulty that may or may not have been present prior to transplant. This must be worked up using a standard algorithm that one might use for any ICU patient. Oftentimes this may be related to pretransplant volume overload, pleural effusions, iatrogenic pneumothoraxes, ascites, or change in abdominal domain [9].

Acute respiratory distress syndrome (ARDS) and transfusion-related lung injury (TRALI) are other complications that may affect the pulmonary status of transplant recipients. Factors which may influence the development of ARDS are severe reperfusion syndromes, increased blood loss, longer operative time, as well as infectious processes [12]. In severe ARDS, patients should be treated as per standard protocol with high-frequency, low-volume ventilation. The use of increased positive end expiratory pressure (PEEP) should be used with caution as it has been shown to decrease hepatic outflow, increase stasis in the portacaval system, and decrease cardiac output in these patients, but data remains controversial. It has also been shown in one study that flow was not diminished in the hepatic artery, hepatic vein, and portal vein with increased PEEP [13].

Furthermore, it is important to discuss hepatopulmonary syndrome (HPS) as many of these patients suffer from this physiologic burden and even gain exception points for transplant because of it. HPS involves an increased A-a gradient, liver disease, and lastly intrapulmonary vascular dilations. It is usually diagnosed by means of contrast echocardiography with physiology involving functional shunting as well as increased nitric oxide. The treatment begins preoperatively and includes garlic, pentoxifylline, and methylene blue, which may be restarted post-transplant, but the gold standard in therapy is liver transplantation. These patients with the improvement of ICU care have outcomes similar to patients without HPS. In one small series, there has been a reported 64 % 10-year survival after liver transplant for HPS. The quality outcomes following transplant with HPS are accompanied by long intensive care stays and aggressive pulmonary optimization. These patients should be kept volume negative if hemodynamics allow using diuresis and even initiating continuous hemodialysis as necessary along with the addition of supplemental oxygen over long periods of time [14–16].

Assessment of Graft

Post-transplant evaluation of the liver allograft function varies widely among centers with no accepted protocol. Some centers obtain routine ultrasound in the first 24 hours while others only image if clinically applicable. It is important for the surgical team to communicate in detail with the ICU team regarding any concerns they may have, as some grafts may have more tenuous vascular connections than others, which might prompt quicker evaluation and action. Intraoperative variables that increase the rate of primary nonfunction (PNF) and delayed graft function should also be relayed to the ICU and include massive transfusion, reperfusion syndrome, and prolonged warm ischemia time. In addition to communicating regarding technical aspects of the operation, the team should impart information regarding the donor quality and hemodynamic changes in the operating room especially in regard to reperfusion syndrome as these may affect liver enzymes and function in the first few days. When it comes to donor quality, one must recognize that age greater than 60, >30 % macrosteatosis, cold ischemia time >12 h, and donation after cardiac death (DCD) donors are all independent variables that are more associated with PNF [17, 18, 19]. It is important to be cognizant of the current definition of early allograft dysfunction which includes bilirubin >10 mg/dL, INR ≥1.6, and alanine or aspartate aminotransferases >2,000 IU/L all on day 7 [20]. The workup for graft dysfunction and lab abnormalities is complex, and a diagnostic and treatment algorithm is helpful in the management in these critically ill patients (Fig. 35.1).

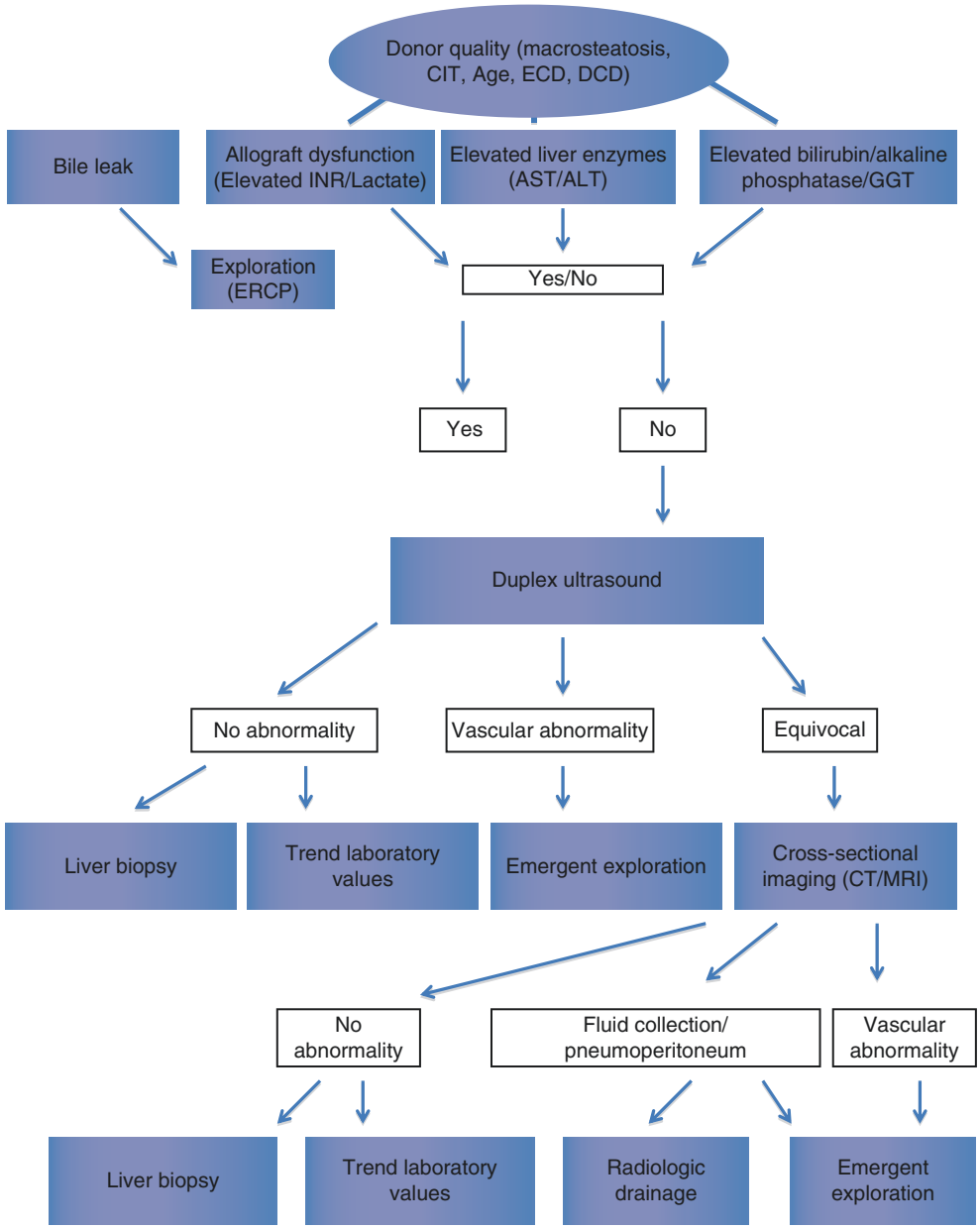

Fig. 35.1 Evaluation and management of allograft dysfunction after liver transplantation. Abbreviations: *CIT* cold ischemia time, *ECD* expanded criteria donor, *DCD* donation after cardiac death, *AST* aspartate transaminase, *ALT* alanine transaminase, *GGT* gamma glutamyl transferase, *CT* computed tomography, *MRI* magnetic resonance imaging, *ERCP* endoscopic retrograde cholangiopancreatography

Laboratory values are essential in the initial evaluation of the liver allograft; however, timing for drawing these labs may vary. It should be noted that these values will be elevated with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in the thousands at times. These levels are markers of hepatic necrosis, which may rise over the first 24–48 h but should begin to decline as the graft recovers. A graft with a greater ischemia-reperfusion injury, steatosis, or prolonged warm and cold ischemia times may play a role in the trajectory of lab trends which is why communication regarding the donor quality and intraoperative events is crucial in the understanding of lab trends [21].

Synthetic liver function in the early postoperative setting should be evaluated looking at the prothrombin time or international normalized ratio (INR). The INR, which is often elevated preoperatively, should gradually trend down as the liver begins to function and make coagulation factors. Correction of INR with fresh frozen plasma is clinician dependent but most times should be reserved for actively hemorrhaging patients or those with concerns for intracranial hemorrhage. In addition to INR, blood glucose is an important marker as glycogenolysis and gluconeogenesis rely on the new implanted allograft. Furthermore, lactate is an important marker for liver function; however, it can be elevated for a variety of reasons; thus, the entire clinical scenario must be scrutinized to rule out other causes as well [21].

Alkaline phosphatase and bilirubin may be used in the postoperative period to evaluate the excretory function of the

liver; however, they may also be elevated when the liver is injured and undergoing hepatic necrosis. For this reason, isolated increasing bilirubin or alkaline phosphatase should be further assessed as they can also be presenting factors for vascular complications. The half-life of bilirubin is considerably longer than AST and ALT, and its rise and decline may lag behind other lab values. In addition to alkaline phosphatase, γ-glutamyl transferase (GGT) is another canalicular enzyme that can be used to assess biliary obstruction. These two enzymes usually begin their rise postoperative day 4 and can rise well over three times normal, eventually declining [21].

In addition to the labs mentioned above, platelets, PTT, and fibrinogen should be checked serially to correct any ongoing coagulopathy especially in the setting of ongoing bleeding. All transplant physicians have different thresholds regarding correcting continued hemorrhage and coagulopathy; thus, adequate communication between teams continues to be ongoing theme to high-quality comprehensive care.

Imaging

Lab values that do not trend in the direction one might expect in the perioperative period deserve interrogation. The first evaluation in both liver and kidney transplantation is usually a duplex ultrasound of the transplanted graft looking for an array of possible postoperative complications. One might even perform a quick bedside evaluation in the ICU to rule out peri-graft hematoma if suspicious which could cause compression necrosis or even decrease vascular flow to and from the graft placing it at risk for failure. The use of duplex ultrasound should be the standard of care in the ICU for any concerning lab values or graft dysfunction after transplantation. Formal duplex ultrasound can evaluate the inflow of the hepatic artery and portal vein, and outflow via the hepatic veins and inferior vena cava. Ultrasound may also show biliary ductal dilatation or fluid collection, which may prompt further evaluation of the biliary system to rule out obstruction or ongoing bile leak. Ultrasound is a very versatile, quick, noninvasive, and cost-effective means of imaging in the early period and should be used as a screening tool. The use of duplex ultrasound initially after liver transplantation is most often used to rule out hepatic artery thrombosis, which occurs in up to 9 % of the recipients [22]. Normal resistive indices (RIs) are usually between 0.6 and 0.9, but one should always review the ultrasound wave forms as they can be revealing, showing some compromise with normal RIs seen in the report. The intrahepatic arteries must be evaluated in order to be a complete study and if absent should warrant further imaging or exploration if concerned. RIs greater than 0.9 may be due to resistance within the liver, which may be from injury to the liver parenchyma post-reperfusion or edema. The portal flow should be evaluated to rule out portal vein thrombosis looking at velocity, which should be greater than 25 cm/s [21].

If there are troublesome findings on ultrasound, this may prompt further studies and/or interventions. Concerning arterial findings should prompt exploration, arteriography with interventional radiology, or computed tomography (CT) depending on the clinical scenario and timing. CT should be done with contrast, but it is common for these patients to suffer acute kidney injury (AKI) post-transplant, which makes CT or arteriogram less appealing in this setting. MR angiography and venography can also be limited in the setting of AKI due to the risk of nephrogenic systemic fibrosis [23]. Due to the limitations of imaging in the setting of AKI, one might opt to explore the patient, as this is a more definitive means of assessing the vasculature. As for biliary complications, concerning findings might prompt either magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiography. Venography should also be performed when clinically indicated for possible Budd-Chiari syndrome post-transplant. It should be noted that in the early postoperative setting, operative intervention is often the key to success and should not be delayed.

Lastly, if all technical concerns have been ruled out usually over the first 24–48 h of graft dysfunction, one must consider liver biopsy to rule out acute rejection or other sources of graft dysfunction. This may be approached via the transjugular or the percutaneous approach, and the choice may be determined by the patient's clinical status. If the patient has ascites and coagulopathy, transjugular liver biopsy may be more appropriate; however, they remain more costly, require interventional radiology, and yield slightly less tissue as compared to percutaneous biopsies [24].

Renal

Unfortunately current trends are showing that more patients are being transplanted at higher MELD scores oftentimes related to rising creatinine associated with acute or chronic renal failure. More and more patients are being transplanted approaching a need for dialysis or having already begun. Hepatorenal syndrome (HRS) is a common etiology for preoperative renal failure. Diagnostic criteria include the presence of the following: ascites, creatinine >1.5 mg/dL, no improvement of creatinine after 2 days of fluid or albumin challenge with withdrawal diuretics, absence of shock, withdrawal of nephrotoxic medications, and lack of intrinsic renal disease and a normal ultrasound [25]. Roughly 40 % of patients with cirrhosis and ascites will develop HRS. It is caused by a physiologic state that includes, hyper-dynamic cardiac function, decreased SVR, low arterial blood pressure, and renal vasoconstriction [26]. The gold standard treatment for this complication of liver disease is liver trans-

plant as patients with HRS have only slightly worse long-term outcomes after LT than those without it. They do however have a higher incidence of postoperative morbidity, early mortality, and longer length of stay [27].

Renal dysfunction post-transplant may reach 17–95 % in some studies, and some patients will require renal replacement therapy for the first time after transplant, which not surprisingly increases mortality in these patients. Risk factors that have been associated with early ARF are preoperative ARF, MELD, hypoalbuminemia, duration of vasopressor support, and worsened graft function. In addition, other factors that affect the later onset of renal failure include infections, reexploration, and contrast-induced nephropathy, as imaging is common in the postoperative setting. Furthermore, drug-induced tubular injury is also a significant contributor to renal failure in these patients as calcinuerin inhibitors (CNIs) as well as aminoglycosides are commonly used for both immunosuppression and antibiosis, respectively [28]. Treatment of immediate renal failure in the post-transplant setting is multifaceted. Depending on the recipient, lowering or delayed use of CNIs may be the first step, along with management of blood glucose and blood pressure according to standard intensive care protocols. One must also rule out thrombotic microangiopathy, which can be difficult to diagnose etiology for ARF in post-transplant patients. One must recognize a hemolytic anemia and thrombocytopenia to make this diagnosis and initiate plasmapheresis if necessary. BK virus should also be ruled out as a cause of renal dysfunction in patients that undergo kidney transplant as well as simultaneous liver and kidney transplant [29].

Management of renal failure in the post-transplant setting is complicated and requires thoughtful management of nephrotoxic medications and close monitoring of fluid balance. Treatment may include fluids, diuretics, as well as continuous renal replacement and intermittent hemodialysis. Hepatic encephalopathy, MELD score, intraoperative blood loss, and deceased donor graft have all been found to be predictors for need for continuous renal replacement therapy (CRRT) post-transplant. Creatinine has been a marker that has been variable in its reliability since many of these patients have reduced muscle mass, poor protein intake, hyperbilirubinemia, and reduced hepatic synthesis of creatinine. With patients being transplanted at higher MELD scores and more marginal deceased donor grafts being used, the use of CRRT will become more commonplace in ICUs. Unfortunately the use of CRRT post-transplant has been associated with higher mortality [30].

Central Nervous System

Commonly patients undergoing liver transplantation have preoperative hepatic encephalopathy of varying degrees. Those with severe encephalopathy are often unresponsive and ventilated prior to transplant; thus, after transplant, it may take a while for their mental status to return to baseline. It is important to recognize that roughly 8–47 % liver transplant recipients have varying degrees of neurologic complications ranging from continued encephalopathy to seizures and intracranial hemorrhage [8, 31]. Patients with preoperative hepatic encephalopathy have been shown to have less brain volume and decreased cognition post-transplant [32]. In the evaluation of these patients, the clinician must have a host of information starting with preoperative grade of encephalopathy, intraoperative hemodynamics and coagulopathy, and then postoperative neurologic status as well as immunosuppressive levels in order to accurately diagnose and manage these issues. Additionally, patients with acute liver failure must be assessed frequently both before and after transplant given the high risk for cerebral edema and herniation. All treatment of neurological conditions should be done in a team setting with intensivists, neurologists, and neurosurgeons in select cases.

Unfortunately transplant patients are also at higher risk for seizures given the use of calcinuerin inhibitors such as tacrolimus and cyclosporine. Careful attention to seizure history and medications is necessary to avoid such events. Reports have documented up to 5–12 % of patients suffering seizures after undergoing LT. Administration of immunosuppressive agents must be managed with caution in patients suffering postoperative seizures, generally trying to run a lower level of calcinuerin inhibitors [33, 34].

Furthermore, intracranial hemorrhage is a known complication following liver transplant, as these patients are inherently coagulopathic often times with platelets <10 K, INR > 3, and fibrinogen <150. It can often go unnoticed and must be in the differential whenever patients do not wake up after transplantation, suffer focal deficits, or demonstrate changes in mental status. Intraoperative hypotension, massive transfusion, and coagulopathy have been shown to be potential risk factors for intracranial hemorrhage, which is why communication from the operating room to the ICU is imperative. For this reason, often centers will have some preventative transfusion parameters, but they vary from center to center [35, 36].

Sedation is another ICU problem post-transplant, as many of these patients remain encephalopathic; thus, a balance must be determined with pain control being a priority. Midazolam, propofol, fentanyl, morphine, dilaudid, and dexmedetomidine are used most commonly, but careful attention must be paid to renal and hepatic clearance of these drugs as many of these patients suffer from decreased renal function as well as delayed liver allograft function. Much like non-transplant patients, combined ventilator and sedation weaning protocols with daily sedation interruptions should be performed as this has been shown to decrease time on the ventilator, ICU stay, and mortality [37].

Infectious Disease

Diagnoses of post-transplant infections may be difficult and ultimately remain one of the most common causes of post-transplant mortality. It is important to look at temporal relationships when diagnosing infections after any solid organ transplantation, which may include donor-derived infection; thus, knowing donor serologies and cultures is necessary (Table 35.1). With regard to both kidney and liver transplant patients, those undergoing re-transplantation, on the ventilator pre-transplant, and undergoing hemodialysis and the type of biliary anastomosis are all risk factors for increased infectious processes [37–39]. Certain induction agents such as thymoglobulin, often used in kidney transplantation, may increase risk of infection; hence, communication regarding medications given in the operating room is essential.

Immediately after transplantation, the most common infections include superficial site infections (SSIs), urinary tract infections (UTIs), blood-borne infections including those associated with indwelling catheters, as well as pneumonia which are often associated with prolonged intubation both pre- and post-transplantation. Moreover, studies have shown that increased blood loss is associated with increased postoperative infection [40]. Patients in general are given standard perioperative antibiotics through the first 24 hours after surgery unless they have suspected infection at time of transplant or immediately after.

It is essential to recognize that fungal infection in the immediate postoperative period remains more common than in the standard surgical ICU patient as a result of immunosuppression. *Candida albicans* is the most frequently seen postoperative infectious fungal source; however, *Aspergillus fumigatus* must not be overlooked as a source of severe infection for patients in the post-transplant period. Patients with presumed sepsis must be immediately treated empirically, which may include third- or fourth-generation cephalosporins, piperacillin-tazobactam, quinolones, vancomycin, metronidazole, or carbapenems. In addition antifungals should be initiated with azoles such as fluconazole, itraconazole, or voriconazole or caspofungin depending on the degree of instability and suspected source [37].

As these patients remain very immunocompromised, one must be weary of activation of the herpes simplex virus (HSV) as well as cytomegalovirus (CMV) once on immunosuppression. Both these viruses can have a host of presentations and can be quite severe. Whereas HSV might normally cause oral lesions, this might manifest systemically with encephalitis, meningitis, or even hepatitis. CMV can also be a source of colitis, CNS infection, or relatively early liver dysfunction causing hepatitis and should be ruled out in the setting of elevated liver enzymes as well as signs of unsourced infection. Prophylaxis against viral infectious processes again is variable but may include acyclovir, valaciclovir, valganciclovir, and ganciclovir [41]. Clinicians must be mindful of these drugs in the ICU as they may cause neutropenia and may need to be adjusted for this as well as renal impairment.

Other opportunistic infections need to be placed into the differential as immunosuppression may trigger inactive infections including cryptococcous, toxoplasmosis, tuberculosis, histoplasmosis, pneumocystis infections, and coccidiomycosis, which can all be life-threatening. In some cases, these rare infections may present within the first month post-transplant and should be considered if etiology remains unsourced. The clinician must be mindful that many of these infections are endemic to a specific geographic region, which is helpful in the diagnosis. Risk of these infections can be lowered by the use of prophylactic agents fluconazole and trimethoprim-sulfamethoxazole being some of the more common agents used [21, 37].

Immunosuppression

Immunosuppression in transplant patients varies widely as expected with a host of agents used that have evolved dramatically over the years, and the most common classes of medications are described in Table 35.2. CNIs are almost universally used immediately after transplant, and their mechanism of action and pharmacology must be understood

Table 35.1 Infections in the early post-transplant setting

Category	Site/source	Common infections	Time period post-transplant	Common therapy
Bacterial	SSI, UTI, PNA, intra-abdominal abscess, catheter	*S. aureus*, *E. coli*, *Klebsiella*, *Proteus*, *Enterococcus faecalis*	Immediately	Vancomycin, third- and fourth-generation cephalosporins, aminoglycosides, piperacillin-tazobactam, carbapenems
Fungal	Catheter, PNA, UTI	*Candida*, *Aspergillus*,	0–2 months	Fluconazole, caspofungin, amphotericin B,
Viral	Hepatitis, CNS, PNA	HSV, CMV	HSV – immediately CMV – 1 month	aciclovir, valaciclovir
				Ganciclovir, valganciclovir, foscarnet, cidofovir, Cytogam

SSI surgical site infection, *UTI* urinary tract infection, *PNA* pneumonia, *CNS* central nervous system, *HSV* herpes simplex virus, *CMV* cytomegalovirus

in order to safely manage post-transplant patients. This class of medications is usually administered twice daily and includes cyclosporine and tacrolimus both which work similarly yet have slightly different side effect profiles.

Their mechanism of action involves the formation of complexes with cytoplasmic receptor proteins, cyclophilin with cyclosporine, and FK-binding protein 12 with tacrolimus, which then binds with calcineurin ultimately inhibiting the expression of cytokines that usually promote T-cell activation. Subsequently there is a decrease in T-cell proliferation thus diminishing the immune response to the allograft. Based on improved outcomes with regard to rejection, most people are placed on tacrolimus presently. These drugs must be monitored very closely in the early ICU setting post-transplantation as absorption may vary between patients [42, 43].

While managing transplant recipients, it is imperative that one has an understanding of the toxicities of these drugs as they can be life-threatening as they have a narrow therapeutic window [43]. First, nephrotoxicity is one of the most common toxic effects of these drugs. This is a major concern as CNIs are commonly used in the regimen for kidney transplantation. These drugs cause renal vasoconstriction damaging the renal arteriole. This is a reversible effect that is often dose related. In the ICU setting, one might evaluate this effect in terms of a similar picture as to a prerenal scenario. Overtime damage to renal parenchyma can result in end-stage renal disease and ultimately dialysis with the pathologic features of chronic interstitial fibrosis. CNIs may also cause a syndrome similar to thrombotic thrombocytopenic purpura (TTP) called thrombotic microangiopathy, and this may be primarily renal or may be systemic similar to TTP.

Next, these drugs may cause relatively severe hyperkalemia, which may require treatment. Oftentimes these patients may have baseline potassium above 5 mEq/L. The clinical picture is similar to a type IV renal tubular acidosis with a hyperchloremic acidosis. They also cause hypertension which may be present in the early postoperative period. The mechanism for new onset hypertension in these patients is multifactorial including renal vasoconstriction causing sodium retention, decrease in nitric oxide production, and activation of the renin-angiotensin-aldosterone system [44].

Some other side effects include hypertrichosis, alopecia, gingival hyperplasia, and hyperlipidemia. In addition these drugs can damage pancreatic islets, ultimately contributing to new onset or worsening diabetes mellitus. Both drugs may also cause neurotoxicity although it is more commonly seen with tacrolimus use and in some cases require a switch to cyclosporine. Findings may include tremors, headache, insomnia, and seizures and are often dose related, and levels may be adjusted both in the inpatient and outpatient setting with symptoms usually resolving [44, 45].

Lastly when discussing CNIs, it is important to discuss drug interactions as many ICU post-transplant patients are on a host of medications that may alter circulating levels of the drugs. The most common drugs that induce P-450 and may increase CNI levels include a number of calcium channel blockers, the azole family of antifungals that are often used in prophylaxis after transplant, and erythromycin.

Next mycophenolate mofetil (MMF) and mycophenolic acid (MPA) are the second agents used in most solid organ transplants. They only differ in the fact that MMF is the pro-drug of MPA and has a slightly different side effect pro-

Table 35.2 Common immunosuppressive medications: mechanisms, side effect profiles, and major interactions

Class	Drug examples	Mechanism of action	Major side effects	Major interactions
Calcineurin inhibitors	Tacrolimus, cyclosporine	Protein complex binds to calcinuerin inhibiting T-cell proliferation	Nephrotoxicity, neurotoxicity, thrombotic microangiopathy, hyperkalemia, hypertension, hypertrichosis, glucose intolerance, gingival hyperplasia	Azoles (antifungals), calcium channel blockers, erythromycin
Inhibitor of purine synthesis	Mycophenolate mofetil, mycophenolic Acid	Reversible inhibition of IMP dehydrogenase blocking de novo purine synthesis decreasing lymphocyte proliferation	Nausea, diarrhea, leukopenia, anemia, thrombocytopenia	
Corticosteroids	Methylprednisolone, prednisone	Inhibits cytokine production decreasing T-cell activation	Hypokalemia, myopathy, glucose intolerance, hypertension, lymphopenia, cataracts, weight gain, wound healing, cosmetic changes, psychological disturbances	
mTOR inhibitors	Sirolimus, everolimus	Blocks *target of rapamycin* protein inhibiting G1 to S phase of cell cycle and ultimately T-cell proliferation	Wound healing(sirolimus), hepatic artery thrombosis (sirolimus), glucose intolerance, proteinuria,	

IMP inosine-5′-monophosphate

file. MPA is a reversible inhibitor of inosine monophosphate dehydrogenase, which is the rate-limiting enzyme that is involved with production of guanosine nucleotides needed for de novo purine synthesis. This ultimately leads to decreasing proliferation of lymphocytes, as do the CNIs, but by a different mechanism. MPA is enteric coated and differs in GI profile of side effects which are often dose dependent. Diarrhea is the most common effect of these drugs, but patients may also experience nausea, bloating, and colitis. In addition to GI side effects, patients may suffer from leukopenia, anemia, as well as thrombocytopenia. In this setting, dosing must be lowered or the drug may even need to be stopped for a short period to allow recovery of blood counts.

The third class of drugs in the triple-drug regimens is corticosteroids, which have been key to immunosuppression for over 50 years. These drugs block cytokines IL-1, IL-2, IL-3, IL-6, and TNF-α and chemokines, among others. This results in lessened T-cell activation providing its immunosuppressive effect. The side effect profile for corticosteroids includes hypokalemia, myopathy, glucose intolerance, hypertension, lymphopenia, cataracts, hyperlipidemia, wound healing, cosmetic changes, and psychological effects. In the post-transplant setting, psychological effects may be sometimes confused with CNI neurotoxicity and should be carefully evaluated as changes to medications can lead to rejection and graft dysfunction [46].

Another group of drugs called mTOR inhibitors are becoming more commonly used in the current immunosuppressive regimens for renal sparing and neurotoxicity seen with higher dose CNI use. The two most commonly used drugs today are sirolimus and everolimus. The mechanism of action for these drugs are similar to CNIs, in that they bind cytoplasmic-binding proteins, which then interacts with the *target of rapamycin* protein ultimately inhibiting lymphocyte proliferation at G1 to S phase of the cell cycle [44]. The use of mTOR inhibition in liver transplantation for hepatocellular carcinoma remains an attractive option as these drugs have antiproliferative effect as well as dysregulating the mTOR signaling pathway of tumorigenesis [47].

Side effects of mTOR inhibitors differ from CNIs in that the nephrotoxicity is rarely seen when not in combination with CNIs. These drugs do however have an incidence of causing new onset proteinuria, which must be screened for prior to starting these drugs. Wound healing has been shown to be decreased with the use of sirolimus and most of the time should be delayed until after 4–6 weeks post-surgery as it can cause wound dehiscence as well as other wound complications. Much like the other medications mTOR inhibitors can cause glucose intolerance and hyperlipidemia. It is important to note also that hepatic artery thrombosis has been reported in a higher incidence with the use of sirolimus and should be considered when working up graft dysfunction [44].

Conclusion

One can understand the importance of ICU care in transplantation as many factors must be understood in order to safely manage these patients' postoperative course. The graft is sensitive to any insult thus understanding of all facets from hemodynamics to medications is essential in ferrying these people to a successful transplant. The continuing theme in this comprehensive care is communication between the transplant and ICU teams as specific knowledge of the patient and donor can guide treatment plans.

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