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Care for the organ transplant recipient on the intensive care unit

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ABSTRACT

All transplant recipients receive tacrolimus, mycophenolate and glucocorticoids and these drugs have many side-effects and drug-drug interactions. Common complications include surgical complications, infections, rejection and acute kidney injury. Infections as CMV and PJP can be prevented with prophylactic treatment. Given the complexity of organ transplant recipients a multi-disciplinary team of intensivists, surgeons, pharmacists and transplant specialists is essential.

After heart transplantation a temporary pacemaker is required until the conduction system recovers. Stiffening of the heart and increased cardiac markers indicate rejection. An endomyocardial biopsy is performed via the right jugular vein, necessitating its preservation.

For lung transplant patients, early intervention for aspiration is warranted to prevent chronic rejection. Risk of any infection is high, requiring active surveillance and intensive treatment, mainly of fungal infections.

The liver is immunotolerant requiring lower immunosuppression. Transplantation surgery is often accompanied by massive blood loss and coagulopathy. Other complications include portal vein or hepatic artery thrombosis and biliary leakage or stenosis.

Kidney transplant recipients have a high risk of cardiovascular disease and posttransplant anemia should be treated liberally. After postmortal transplantation, delayed graft function is common and dialysis is continued. Ureteral anastomosis complications can be diagnosed with ultrasound.

1. Introduction

Patients with a recently transplanted organ are often complex, with an extensive past medical history, many comorbidities, polypharmacy and transplant specific needs. As such and because of their immunocompromised status, they frequently experience (infectious) complications with possible life-threatening organ dysfunction requiring intensive care. The care for organ transplant recipient on the intensive care unit (ICU) requires specialized knowledge and cooperation with many professionals. It is the pinnacle of multi-disciplinary care, where the intensivist is supported by transplant specialists, surgeons, pharmacists and infectious disease specialists. In this article we will discuss general principals of organ transplantation, focusing on the first months after transplantation. We will discuss two hot topics and subsequently address practical considerations when caring for heart, liver, lung, and kidney transplant recipients.

2. Immunosuppressive therapy in solid organ transplantation

Immunosuppressive therapy varies between specific organs and is preferably patient-tailored, but in most cases a calcineurin inhibitor (CNI; tacrolimus or cyclosporine) forms the backbone. A CNI is usually combined with additional immunosuppressive drugs which can consist of an anti-proliferative drug (mycophenolic acid

Abbreviations: AmphoB, amphotericin B lipid complex; APACHE, Acute Physiology And Chronic Health Evaluation; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CYP3A, cytochrome P450 3A; DDIs, drug-drug interaction; EBV, Epstein Barr virus; ECMO, extracorporeal membrane oxygenator; ECRP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; ITBL, ischemic type biliary lesions; LVAD, left ventricular assist device; MTORi, mammalian target of rapamycin inhibitor; OR, odds ratio; PGF, primary graft failure; PJP, *Pneumocystis jirovecii* pneumonia; rATG, rabbit anti-thymocyte globulin.

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[MPA] or azathioprine), an inhibitor of the mammalian target of rapamycin (mTORi, everolimus or sirolimus) and glucocorticoids. During or shortly after transplant surgery, patients often receive induction therapy with either an interleukin-2 receptor blocker (basiliximab) or T lymphocyte-depleting antibody therapy (rabbit anti-thymocyte globulin [rATG] or alemtuzumab). A detailed discussion of the mechanism of action of these immunosuppressants is outside the scope of this article, but they either inhibit specific functions in lymphocytes (mainly T cells) or deplete them. [1] All immunosuppressants have many side-effects and display many drug-drug interactions (DDIs). In order to enhance efficacy and to minimize toxicity, therapeutic drug monitoring (TDM) of immunosuppressive drugs is required. With regard to CNIs and mTORis, the parameter most widely used is the drug concentration immediately before the next scheduled (morning) dose (trough concentration). An alternative, which is often used for MPA is sampling multiple time points which can then be used to determine an area-under the concentration versus time-curve (AUC). As many factors influence the level of immunosuppression especially in ICU-patients (e.g. absorption for the gut, volume and distribution and renal or hepatic clearance) we recommend to measure immunosuppressive drug concentrations 2–3 times weekly routinely and 2–3 days after dose-adjustments, changes in relevant co-medication of after changes in mode of administration.

2.1. Side-effects of immunosuppressive therapy in the early post-transplant phase

While almost every (ICU) doctor will be familiar with the side-effects of steroids, the side-effects of CNIs or MPA are not basic knowledge. The most common side-effects of CNIs that may occur early are acute nephrotoxicity and hypertension, de novo diabetes mellitus, neurotoxicity a severe complication; thrombotic microangiopathy (TMA). The side-effects of MPA mainly encompass leukocytopenia, anemia and gastro-intestinal side-effects.

The nephrotoxicity and hypertension are related to the vasoconstrictive actions of CNIs on the afferent renal arteriole. As the arteriole is constricted, glomerular filtration rate (GFR) is reduced. Moreover, CNIs have acute tubulotoxic effects and can activate the renal sodium chloride cotransporter, leading to sodium, potassium and water retention. CNI-mediated nephrotoxicity is partially exposure-dependent, improving after dose-reduction and especially the vasoconstrictive effect can be attenuated with vasodilative drugs such as calcium channel blockers. Tacrolimus-induced hypertension with hyperkalemia can be treated with any anti-hypertensive drug although thiazide diuretics (antagonizing CNIs effect on sodium chloride cotransporter) may be especially effective [2,3] Marked proteinuria is in general *not* a manifestation of CNI-mediated nephrotoxicity and should prompt the intensivist to consider other causes of acute kidney injury.

Post-transplantation diabetes mellitus may complicate transplantation in as much as 20–40% of all transplantations. Tacrolimus in particular is highly diabetogenic (decreased insulin signaling in conjunction with β-cell dysfunction), although cyclosporine, mTORi's and glucocorticoids can all be implicated. [4] Classically, glucose concentrations are elevated in the late afternoon and evening with normal fasting glucose levels. Treatment is in accordance with regular diabetic care. The experience with novel antidiabetics like sodium-glucose-linked transporter 2 inhibitors (SGLT2i) or glucagon like peptide 1 receptor antagonist (GLP-1RAs) is limited, but very interesting given their dramatic improvement in patients with heart and kidney diseases. [5]

Neurotoxicity following transplantation affect an estimated 5% of patients and can present as tremors and headache, but also as neuropathy, seizures, catatonic stupor, and cortical blindness. [6] Imaging of the cerebrum may demonstrate white matter lesions, although the exact pathophysiology of CNI-mediated neurotoxicity remains unknown but an increased CNI concentration in the central nervous system (possibly resulting from a loss of the blood-brain function) has been proposed. Significant dose reduction or cessation is the preferred treatment.

The use of CNIs can lead to a disruption of the normal endothelial function, leading to thrombotic microangiopathy (TMA), manifesting as non-immune mediated hemolysis, microthrombi leading to organ dysfunction, and thrombocytopenia. Although rare, this severe side-effect should be promptly recognized and should be distinguished from other causes of DAT-negative TMA including that associated with a hypertensive crisis and hemolytic uremic syndrome / thrombotic thrombocytopenic purpura. It requires urgent reduction in the exposure to CNIs followed by discontinuation if ineffective.

As MPA selectively inhibits the enzyme inosinemonophosphate dehydrogenase, the de-novo-synthesis of nucleotides is inhibited, often leading to suppression of the bone marrow. Most common is anemia and leucopenia, where thrombocytopenia is infrequent and could reflect an alternative diagnosis (e.g. TMA, see above) Maintaining the MPA concentration in the target exposure range is therefore important, especially in the ICU population that often suffers from cytopenia for other reasons. While diarrhea and abdominal cramps are common with MPA, it is important to exclude (atypical) infections as the cause of diarrhea.

2.2. DDI of immunosuppressive therapy

CNIs are metabolized by the cytochrome P450 (CYP) 3A enzyme system and many of their DDIs are mediated through either inhibition or induction of CYP3A enzymes. The most common drugs that have an interaction with CNIs are macrolide antibiotics (the chemical structure of tacrolimus and macrolide are highly comparable), antiepileptic drugs, amiodarone, the antifungal azoles, and rifampin. Inhibition or induction of CYP3A can cause markedly elevated or decreased exposure to CNIs, which may greatly increase their side effects or cause under-immunosuppression, increasing the chance of developing acute rejection. Avoid these combinations as much as possible, but when azole-based therapy is obligatory, a pre-emptive dose reduction of 50–60% of CNIs is required and afterwards TDM is essential, as is the consultation of a pharmacist. [7]

2.3. Route of administration

In patients who are unable to take oral medication, intravenous administration can be considered. In most cases, the first hours to days can be covered with prednisolone in a dose of 25–50 mg daily. For longer periods or more immunogenic patients or organs, intravenous forms of tacrolimus, cyclosporine, and MPA are available. MPA and steroids can be easily and safely administered, intravenous dosing of CNIs is very challenging. Pre-dose whole-blood concentrations are significantly lower than concentrations during continuous administration. Moreover, CNIs have a variable and general poor oral bioavailability, and intravenous starting doses should be approximately 1/3 of the original total daily oral dose. Given the risk of overdosing, with subsequent nephro- and neurotoxicity, intravenous CNIs should only be given if no other options exists or if the risk of rejection is thought to be high. Other routes of administration of CNIs, like topical, intramuscular, rectal, and sublingual are not recommended because of their potentially unreliable absorption in ICU-patients. Although some forms can be administered via nasogastric tube, this does not apply to prolonged release formula. [8,9]

3. Infectious complications

Transplant recipients can experience a broad spectrum of different infections, of which the clinical signs and symptoms are often atypical. Diagnosis requires specific and often invasive procedures to guide

correct treatment. Given the diagnostic and therapeutic challenges organ transplant recipients benefit from a multi-disciplinary team with consultation of an infectious disease specialist

Notwithstanding the complexity, infections occur in a general predictable pattern after solid organ transplantation. [10] In the first weeks after transplantation, mostly donor-derived and surgery-related infections occur, like wound infections, urinary catheter-related infection, and ventilator-associated pneumonia. Most transplant patients receive prophylaxis against cytomegalovirus (CMV), pneumocystis jirovecii pneumonia (PJP), and sometimes fungi (Candida of the oropharynx and esophagus) for 3–6 months after transplantation (ganciclovir or its oral prodrug valganciclovir for CMV, cotrimoxazole, atovaquone, or pentamidine inhalation for PJP, and nystatin for fungi). Where PJP-prophylaxis is universal, CMV-prophylaxis is given if the donor or recipient is CMV-seropositive and continued for longer periods when the recipient CMV-seronegative. CMV and PJP infections are uncommon during prophylaxis, although dosing of valganciclovir can be a challenge in case of fluctuating kidney function. [11] After prophylaxis has been stopped, the risk of these infections is increased, peaking at 6–12 months after transplantation, especially in seronegative recipients.

Patients experiencing graft rejection need additional immunosuppressive therapy, primarily methylprednisolone 500–1000 mg daily on three subsequent days. When first-line anti-rejection treatment fails, T-cell-depleting antibodies (see above) are given to prevent graft loss. [12-14] The effect of these antibodies on the host's immune system is more severe than methylprednisolone, with increased risk of (opportunistic) infections and latent viral and fungal infections. CMV- and PJP-prophylaxis is therefore reinstated either for a fixed period, or based on T-cell counts. The depletion of T-cells can last for months to years after treatment, and therefore even after graft loss and cessation of maintenance immunosuppression, these patients will still have a severely compromised immune system. [15]

3.1. Immunosuppression during severe infection

As sepsis is characterized by a dysregulated host (immune) response to infection, with fluctuating periods of immune activation and suppression, additional immunosuppression is undesired. [16,17] It seems logical to minimize immunosuppression during and shortly after sepsis, however infections can also-trigger a rejection episode by activating the immune response. [18] Solid data on the effects of reduction of immunosuppression during infection are lacking. The current literature is mostly limited to kidney transplantation and retrospective in nature but suggests that reduction in immunosuppression may benefit mortality. [19,20] Which medication should be stopped or reduced, for how long and when to restart is also not systematically studied nor do we have data on biopsies, re-institution or immunosuppressive therapy or rejection incidence. Given this paucity of data, there is no consensus on the management of immunosuppression during severe infections. Our strategy is to stop instead of dose-reduction given the altered and variable pharmacokinetics in ICU-patients (as mentioned before). In most patients we prefer to only stop MPA. In severe septic patients all immunosuppression is discontinued and only glucocorticoids are administered. Additional steroids just for sepsis treatment remains a controversial topic in ICU-care.

3.2. Organ transplantation and COVID-19

Mortality in organ transplant recipients with COVID-19 is about 3–4 times of the general population or 20–25% in absolute terms. Although immunosuppression was decreased in 75% of published cases and a spectrum of target therapies were given, optimal management of SARS-CoV-2 infection continues to evolve, as long-term outcomes are lacking and therefore evidence-based recommendations in organ transplant recipients remain unclear. [21-25] We are very cautious to perform transplantation which require intensive induction immunosuppression (e.g. ATG or alemtuzumab). During the first wave of the pandemic, in The Netherlands the (living donor kidney) transplant program was markedly decreased nationwide, because of shorting of staff, but also the uncertainty about risk and benefit [26]. However, analysis of French data showed that kidney transplantation program should be maintained as long as possible, both to reduce excess of deaths of candidate and avoid wasting precious donor organs [27]. When patients are treated with dexamethasone, it seems reasonable to stop MPA, but again data is lacking to support this and therefore this decision should be made after weighing risks and benefits by the multi-disciplinary team.

Given the burden of COIVD-19, vaccination is urgently needed. Vaccination, especially with mRNA-based vaccines, seems to be safe and not lead to anti-HLA formation (unpublished data from UK using AstraZeneca vaccine), although the effectiveness remains a concern. Reduced (serologic) vaccine response in immunocompromised hosts is well described after hepatitis B, influenza or pneumococcal vaccination. [28] Currently a Dutch consortium is investigating this topic for COVID-19 vaccines (RECOVAC study).

4. Transplantation of organs from hepatitis B or hepatitis C infective donors

To further increase the donor pool, especially for lung- and heart transplant recipient, previously unsuitable organ donors can now be considered for donation. The use of grafts from donors that have tested hepatitis B (HBV) positive is one of those examples. When the recipient is non-immune and the donor has anti-HBc positivity only, the graft can be accepted. Lifelong antiviral therapy is recommended in non-immune liver transplant recipients. In recipients of other organs, one year entecavir is recommended, with regular surveillance for HBV virus. Organs from HBsAg positive donors are not routinely transplanted, but can be considered in after weighing risks and benefits, given the effectiveness of entecavir. [29]

Donors with evidence of past hepatitis C (HCV) infection are often rejected since HCV is associated with hepatic and extrahepatic complications. [30] The virus has deleterious consequences in organ transplant recipients, resulting in reduced patient and graft survival. [31] In the past, antiviral therapy was based on the use of PEG-interferon-α in combination with ribavirin, with poor sustained virologic response (less than 50%) and high incidences of side-effects. [32] In contrast, modern direct acting antivirals (DAA) have shown high rates of sustained virologic response (up to 100%) in HCV infected patients with little or no side-effects or DDIs. [33] This opened the possibility to except HCV positive, even those with active infections as organ donors. Data about organ donation after active HCV infection is nonetheless limited, as this field continues to evolve. Transmission of the HCV in these cases is universal, but after 4–12 weeks of treatment all recipients cleared their HCV infections and had excellent patient and graft outcomes. [34,35] This however does not make it a 'standard procedure', and the additional risk of hepatitis C infection should be balanced by an advantage for the recipient as better organ quality of shorter waiting times. [36]. Of special interest for ICU-care is the unreliable pharmacokinetics with changing kidney function or after administration via nasogastric tube, the interactions with proton pump inhibitors, and the inability to perform TDM. Little is known about the risk of transmission to healthcare workers when caring for these recipients or handling fluids that came into contact of the infective organ, highlighting the importance of consultation with the surgeon and an infectious disease specialist.

4.1. Heart transplant patients

Immunogenic organ, high exposure of immunosuppressive medication
Early complications:

- Anastomosis leakage or tamponade
- Ischemia of electrical guiding system
- Rejection indicated by increased cardiac markers or stiffening of the heart
- Acute kidney injury

A temporary pacemaker is universal. As biopsies are performed via the right jugular vein, this vein should be preserved as much as possible.

In recent years, more patients have undergone heart transplantation after a left ventricular assist device (LVAD) implantation as bridge-to-transplant. [37] Especially in these cases, a safe entry of the chest and removal of the LVAD device is essential. The localization of the outflow graft directly posterior of the sternum may lead to severe bleeding during reopening. Pre-operative CT scanning is helpful in localizing the outflow graft and aids in determining an appropriate surgical approach. The LVAD may be very adherent to the surrounding tissue and removal may be cumbersome and lead to (prolonged) bleeding. In patients with persistent blood loss via chest tubes or with symptoms/signs suspicious for blood loss, leakage of an anastomosis or tamponade should be suspected and could need urgent intervention.

4.1.1. Primary graft failure

Primary graft failure (PGF) is a life-threating complication, with multiple organ failure, longer ICU stay, increased risk for infections, and poor short- and long-term survival. [38,39] It usually resides within days, however PGF can also take longer to recover. A distinction is made between PGF of the left and right ventricle. [39] PGF of the right ventricle can be due to pulmonary hypertension of the recipient, especially since the right ventricle is more vulnerable to ischemia reperfusion injury. As such, right ventricular failure requires specific management. Treatment consists of vasodilators in combination with dobutamine / noradrenalin and inhaled nitric oxide. In case all therapies fail, a temporary extracorporeal membrane oxygenator (ECMO) has to be implanted until graft function normalizes. [40]

4.1.2. Pacemaker

The electrical guiding system of the heart can be affected by ischemia reperfusion injury as well as by edema, therefore all patients receive a temporary pacemaker. In most of the cases, the conduction system recovers and evaluation and adjustment of pacemaker sensing thresholds is performed daily. When recovery does not occur, a permanent pacemaker is required. Dobutamine and/or isoprenaline are used to increase intrinsic electrical activity of the donor heart. [40]. As stroke volume cannot adapt shortly after transplant, heart rate should be relatively high with atrial pacing. When there is no AV sequential conduction AV sequential pacing is needed to maintain cardiac output. Depending on recovery of the conductive system, the pacing can be diminished by 5 beats per minute every day until the pacemaker is not pacing anymore. After a first heart biopsy without any signs of rejection and when the pacemaker is not pacing, the temporary pacemaker leads can be removed. [40]

4.1.3. Acute rejection

Most rejections occur within the first year, with a very variable presentation ranging from asymptomatic to arrhythmias or even cardiogenic shock. Especially antibody-mediated rejection can occur within hours after transplantation, with associated high rates of mortality. [41] Rising cardiac markers or stiffening of the heart on echocardiography can be an indicator for rejection. A biopsy is necessary for correct diagnosis. As many biopsies are performed via the right jugular vein, every effort should be made to preserve this vein (e.g. preferably no IV line placement). Complications of heart transplant endomyocardial biopsy consists of tricuspid valve damage, rhythm- or conduction disturbances, coronary fistula and heart tamponade. If patients are hemodynamically unstable with inotropic-dependence a biopsy cannot be performed and if rejection is suspected, treatment with methylprednisolone should start immediately.

4.1.4. Acute kidney injury

Acute kidney injury is a frequent complication post-heart transplantation affecting up to 70% of patients, negatively affecting patient survival especially when renal replacement therapy is needed. [42] Pre-operative high right-sided heart pressures, reduced pulmonary artery pulsatility index and pre-existent chronic kidney are strong predictors of acute kidney injury after heart transplantation. [43] This can be further aggravated after transplantation by hypotension, volume depletion, as well as the nephrotoxic effect of CNIs. Given the high immunogenicity of the heart, higher doses of CNIs are often required. By using rATG, the introduction of CNI can be delayed until a moment where the kidney function has improved.

4.2. Lung transplant patients

Immunogenic organ, high exposure of immunosuppressive medication
Early complications:

- Bleeding, especially while on ECMO
- Anxiety, breathlessness and cough while on ECMO
- High rate of (fungal) infections
- Acute kidney injury

Aspiration is common and should be proactively diagnosed as it increased the risk of chronic rejection. Active microbial surveillance and prophylactic antifungal therapy

Due to high immunogenicity, complex anatomy and high rates of infections, lung transplantation very challenging. The need for ECMO in case of right heart failure or when primary graft dysfunction manifest, even further complicates matters. In the latter situation infection or cardiogenic edema should be ruled out as other possible causes for the rapid graft function deterioration. [44] Anxiety, breathlessness and cough might be difficult to manage direct post-operatively especially on ECMO. [45-47] Anxiety and dyspnea are related, and tend to interfere with exercise while cough may interrupt blood flow to the ECMO system, adding to the anxiety and dyspnea. Treatment of cough can consist of gabapentin, cromoglycate, as well as intravenous lidocaine. [48-53] Dexmedetomidine can be effective of anxiety, and also seems to reduce dyspnea and cough. [54,55]

4.2.1. Surgical complications

Postoperative bleeding is a well know complication, affecting 5% of transplant recipients without ECMO and up to 70% with ECMO. [56] Anastomotic complications may occur on the bronchial anastomosis or vascular anastomoses. Bronchial anastomotic complications are reported to occur in 1% of lung transplants. [57] Discontinuation of direct airway blood supply by bronchial arteries is probably the main etiologic factor. Most bronchial anastomotic complications are well covered by mediastinal tissue and do not cause air leakage. These patients can usually be treated conservatively. Massive air leakage requires immediate surgical intervention. Unilateral pulmonary edema, hypoxia, or pulmonary hypertension might be indicative of venous or arterial anastomotic compromise which occurs occur in 1.8% of lung transplantations. [58] For significant lesions early surgical correction is warranted. For late vascular stenosis, catheter based angioplasty and stenting may be considered. Direct post-transplantation pleural effusion varies in extent and is thought to be caused by increased permeability of alveolar capillaries. In case of persistent significant pleural effusion, an infection or a chylothorax should be ruled out. [59]

4.2.2. Aspiration

Another challenge post lung transplantation is the occurrence of aspiration per se and subsequent pulmonary infection. Both are associated with induction of lung allograft dysfunction, and can manifest in the early post-operative phase on ICU. [60,61] A heightened awareness and early intervention for gastroparesis in ICU is warranted, as it increases the risk of chronic rejection (bronchiolitis obliterans syndrome).

4.2.3. Infections

Peri-operative antibiotic treatment should be directed towards previously cultured pathogens from the recipient and if no prior positive cultures to most common healthcare associated pathogens such as Gram negative bacilli e.g. *Pseudomonas aeruginosa* and *Staphylococcus aureus* taking into consideration local resistance patterns. [62,63] Surveillance sputum cultures in the pre-operative (both in donor and recipient) as well as post-operative phase significantly contribute to an adequate antibiotic treatment and allows further adjustment of the applied antibiotic spectrum. [63] A 15–35% occurrence rate of fungal infection is reported, mostly consisting of Aspergillus and Candida. [64] Fungal colonization vary from 20 to 50%, greatly increasing the risk for developing invasive fungal infections. [65-68] Up to 15% of patients develop this complication, typically in the first 3 months after transplantation significantly increasing risk of mortality (up to 80%). [69,70] Screening for Aspergillus species should therefore be included the standard work-up in the post-operative phase. [71] The sensitivity of serum Galactomannan is under debate in solid organ transplant recipients, although bronchoalveolar lavage Galactomannan might have a higher sensitivity. Prophylaxis for invasive fungal infections is given in the form of amphotericin B lipid (AmphoB) complex inhalation. [72,73] Duration of prophylaxis is not well studied, but we continue until complete healing of the bronchial anastomoses is observed during surveillance bronchoscopy. AmphoB inhalation should be temporarily restarted after intensification of the immunosuppressive regimen. [74] Dual therapy with AmphoB intravenously and azole therapy is given until azole resistance is ruled out. Viral infections (e.g. herpes pneumonia, CMV virus infections, EBV-reactivation) can manifest early in lung transplant recipient, due to their severe immunocompromised state, with high trough levels of CNIs. Screening for CMV and EBV viremia should therefore be performed on a weekly basis.

4.2.4. Acute kidney injury

As with heart transplant patients, the incidence of acute kidney injury is high, and multiple factors contribute to this increased risk. The lung transplant recipient who requires ECMO and develops a complication postoperatively is at highest risk for acute kidney injury, often requiring dialysis, which also portends a poor long-term renal survival.

4.3. Liver transplant patients

Immunotolerant organ, lower exposure of immunosuppressive medication, often delayed introduction of CNIs
Early complications:

- Portal vein or hepatic artery thrombosis
- Biliary complications (bile leak, anastomotic stenosis)
- Infections caused by enterococci and gram-negative bacteria
- Rejection

Recurrence of original disease mostly later after transplantation, except for HBV and HCV without prophylaxis or treatment

Compared to the other organs, the transplanted liver seems to be a privileged organ in terms of immunotolerance, lower exposure to immunosuppressive medication is needed and even spontaneous resolution of rejection has been described. [75] However, 60% of mortality in the first year can be explained by infections and surgical complication, some of which are specific for liver transplants.

4.3.1. Vascular complications

Explanting the diseased and often sclerotic liver is a major surgical procedure and combined with the coagulopathy of liver failure, massive blood loss (up to 15–20 l) can occur, although no longer common in experienced centers. Extensive blood loss and associated hemodynamic compromise, often lead to acute kidney injury (see below). Coagulopathy usually resolves as graft function is established. The incidence of hepatic artery thrombosis is relatively low, but has a dramatic effect on the graft survival with usually ischemic biliary lesions as a long-term complication. Postoperative ultrasound is performed routinely to detect portal vein thrombosis or hepatic venous outflow obstruction. It should also be suspected in patients with poor graft function or persistent ascites later after transplantation. A work-up is also provided in Fig. 1. Patients with portal vein thrombosis pre-transplantation are at increased rate of re-thrombosis. [76] One of the most feared post-operative outcomes is PGF, manifested by hepatic coma, renal dysfunction, coagulopathy, jaundice and hypoglycemia. A rapid evaluation for treatable causes, especially complications of the hepatic artery or portal vein, should be performed (see Fig. 1). Donor-derived pathology (steatosis, higher donor age) and increased ischemia times increase the risk of PGF. Prompt relisting is the only treatment option. In case of less severe early allograft dysfunction these grafts will function eventually, after intensified support and prolonged ICU care, with associated higher incidence of graft loss and mortality. [77]

4.3.2. Biliary complications

A specific problem in liver transplantation are the biliary complications which vary from bile leakage to ischemic type biliary lesions (ITBL) and anastomotic stenosis. Presentation can vary from biochemical signs of cholestasis and pruritus to fever, cholangitis and sepsis. They can be caused by arterial thrombosis or ischemia/reperfusion injury and it is one of the most common complications (15–37%), especially with grafts from donors after circulatory death. Anastomotic stenosis can be seen in around 5% of patients and is also increased in patients after partial graft transplantation (incidence up to 50%). [78] Standard treatment is ERCP, with percutaneous transhepatic drainage or hepaticojejunostomy as rescue options.

4.3.3. Infections

The first month after transplantation, most infections are related to surgical issues and hospitalization. Prolonged and complicated surgical procedures, volume of blood loss and fulminant hepatic failure at the time of transplantation are risk factors for infection and mortality. About half of the infections are of bacterial origin (increasingly enterococci in addition to Gram-negative) and empirical treatment should cover these micro-organisms. [79-81] Viral infections play a significantly smaller role, although 20–30% of liver transplant recipients will develop CMV disease. [82] Fungal infections are uncommon, but specific risk factors are increased transfusion requirement, long cold ischemia time and use of a Roux-and-Y biliary enteric anastomosis.

4.3.4. Rejection

Hyperacute rejection or antibody-mediated rejection is an extremely rare phenomenon in liver transplantation but poorly responds to therapy. Generally the only treatment option is retransplantation. [83] Acute cellular rejection is diagnosed in 15–30% of recipients mostly in the first 6 months after transplantation, with non-specific presentation of fever, increase in serum bilirubin and transaminases, thrombocytopenia or an increase in ascites [75]. Treatment options include optimization of maintenance immunosuppression in mild cases and high dose steroid induction for moderate or severe rejection, seldomly T-cell depletion therapies are used for severe or recurrent episodes. [84] Recurrence of the original liver disease has become uncommon, especially with effective antiviral therapy.

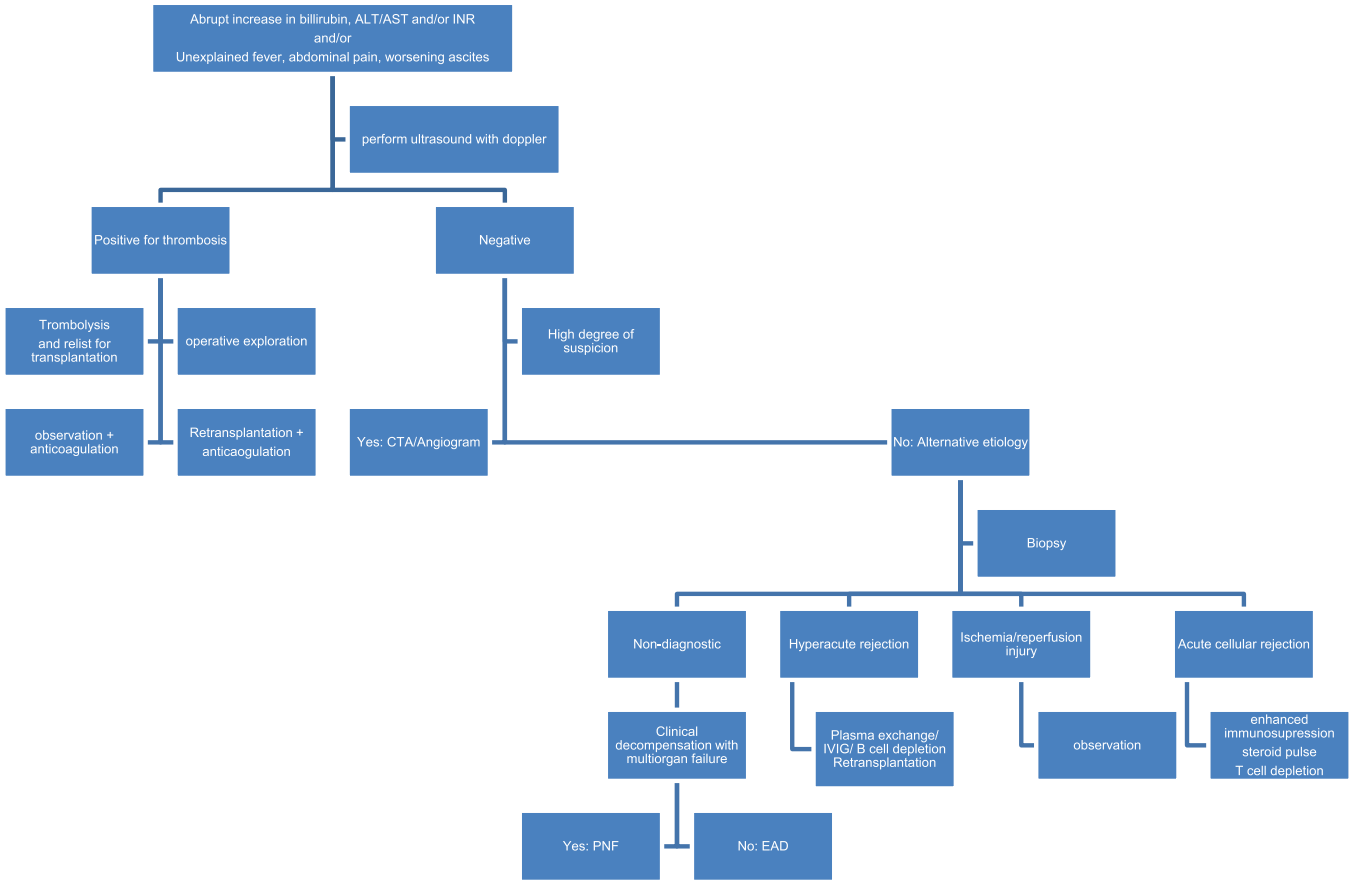

Fig. 1. Management of poorly functioning liver graft.

4.3.5. Acute kidney injury

The occurrence of acute kidney injury in patients undergoing liver transplantation is associated with reduced patient and graft survival in the peri-operative period and in long term, as 30–80% develop chronic kidney disease in the first 10 years. [75] As mentioned before, the surgery can lead to significantly reduce renal perfusion. Due to the less immunogenicity of the liver, treatment with CNIs can therefore safely be postponed to a few days after transplantation, in contrast to heart, liver and kidney transplants.

4.4. Renal transplant patients

Immunogenic organ, medium exposure of immunosuppressive medication
Early complications:

- High perioperative cardiovascular risk
- Delayed graft function in postmortal donors, during which (peritoneal) dialysis should continue
- Urinary complication (anastomosis leakage or stenosis)
- Rejection

Placement of a central venous line in the jugular vein can be a challenge, avoid the femoral vein on the side where the transplant is placed, to prevent damage to the anastomosis

Patients with kidney failures are often characterized by a history of cardiovascular disease. Their perioperative risk of further cardiovascular disease should therefore be considered universally increased, even in young patients and especially when dialysis treatment is given. Although preoperative screening is often performed, the effect on postoperative outcomes is limited and the best postoperative advise to minimize cardiovascular disease is liberal treatment of anemia (hemoglobin levels >6 mmol/l). [85] Placing central venous catheters in the jugular vein can be a challenge in renal transplant recipient if a long period of dialysis with frequent catheters or AV-fistulas compromised venous anatomy. If unsuccessful or during acute problems, the femoral vein can be used, preferably opposite to the fossa where the transplant was placed to prevent damage of the anastomosis.

Kidney grafts from living donors should function immediately and any abrupt loss urine production should prompt immediate Doppler ultrasound for arterial or venous thrombosis, even though thrombectomy is rarely successful as the graft has already infarcted. Endothelial damage during retrieval surgery may predispose to thrombosis, but most are due to technical complications with the anastomosis. Delayed graft function is common in transplantation with deceased donors. In these case oliguria or even anuria can be accepted, provided that blood pressure is adequate. Meanwhile dialysis continues. Peritoneal dialysis can also be performed, even immediately after surgery as long as the peritoneal cavity has remained intact during implantation. First cycles are frequent and with low volume, but if leakage into the fossa occurs, switch to hemodialysis. After 7–10 days without (sufficient) graft function a biopsy is performed to rule out allograft rejection. Only if no graft function has occurred after 3–4 months, the graft is considered lost.

In the first days to weeks after kidney transplantation, many other complications can occur, of which infection, rejection and urinary outflow complication are the most frequent. Being a single organ, ureter, bladder or urethral obstruction can lead to complete allograft dysfunction. Therefore any renal transplant patient with a decrease in renal

allograft function should undergo appropriate imaging like (bedside) ultrasound. Urinary complications due to leakage at the site of anastomosis of the donor ureter to bladder often present with acute onset of pain in the lower abdomen and can be readily detected on imaging (e.g. scintigraphy scan). Adequate drainage with a percutaneous nephrostomy catheter, combined with a bladder catheter is the treatment for urine leakage. If other causes of decreased allograft function have been ruled out, a percutaneous renal allograft biopsy is a relatively easy and safe procedure to establish a diagnosis.

5. Conclusion

Even after half century of performing organ transplantations, the procedure has far from become routine and patient continue to have complex problems, needing a well-educated and cooperating multidisciplinary team especially if they are admitted to the ICU. The current immunosuppressive regimen of CNIs, MPA and steroids has specific side-effects and relevant drug-drug interactions. Although many organ specific differences exist, all organ transplant patient have a high risk of infections which prompts intensive and pro-active approach to diagnosis and treatment especially in the ICU. As acute kidney is very common, preventing hemodynamic instability and reducing nephrotoxic drugs are crucial measures to improve patient outcomes. While waiting lists continue to exist and even grow, new possibilities like donation with active hepatitis C infection might increase the donor pool, but as the COVID-19 pandemic has shown, threats to the global transplant program and the individual organ transplant recipient are just around the corner.

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