



## Immunology demystified: A guide for transplant hepatologists

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### Abstract

Liver transplantation has become standard practice for treating end-stage liver disease. The success of the procedure relies on effective immunosuppressive medications to control the host's immune response. Despite the liver's inherent capacity to foster tolerance, the early post-transplant period is marked by significant immune reactivity. To ensure favorable outcomes, it is imperative to identify and manage various rejection types, encompassing T-cell-mediated, antibody-mediated, and chronic rejection. However, the approach to prescribing immunosuppressants relies heavily on clinical judgment rather than evidence-based criteria. Given that the majority of patients will require lifelong immunosuppression as the mechanisms underlying operational tolerance are still being

investigated, healthcare providers must possess an understanding of immune responses, rejection mechanisms, and the pathways targeted by immunosuppressive drugs. This knowledge enables customization of treatments and improved patient care, even though a consensus on an optimal immunosuppressive regimen remains elusive.

**Key Words:** Liver transplantation; Allograft rejection; Operational immune tolerance; Immune reaction; Immunosuppression

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**Core Tip:** Liver transplantation is standard practice for treating end-stage liver disease, requiring effective immunosuppressive medications to regulate the recipient's immune response. In the post-transplant period, vigilance is necessary to recognize and manage various rejection types (T-cell-mediated, antibody-mediated, and chronic rejection). As the majority of patients require lifelong immunosuppression while the mechanisms of operational tolerance are still being explored, healthcare providers must possess a solid understanding of immune responses, rejection mechanisms, and the targets of immunosuppressive drugs. Despite the absence of consensus on an ideal immunosuppressive regimen, customization remain crucial.

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## INTRODUCTION

Immunology plays a crucial role in liver transplantation (LT), influencing procedure success and long-term outcomes. The liver's unique immunological traits contribute to its heightened tolerogenic response compared to other solid organs [1,2]. However, despite these advantages, immunologic rejection remains a significant clinical concern[1]. The immune response involves complex interactions among various cell types, including T-lymphocytes, B-lymphocytes, macrophages, hepatocytes, and stromal cells, which produce cytokines and chemokines that govern the immune response and determine the fate of the graft[1]. T-lymphocyte activation and recognition of antigens by the recipient's immune system are critical steps in initiating the immune response against the graft resulting in T-cell mediated rejection[1]. Additionally, the production of donor-specific antibodies (DSA) represents a distinct risk factor for early and late antibody-mediated rejection (AMR) and graft loss[3]. In recent years operational immune tolerance induction in LT has gained interest, aiming to achieve long-term graft acceptance without the need for lifelong immunosuppression[2,4]. This review will further explore the main mechanisms of the immunologic reaction and types of graft rejection alongside the most commonly utilized immunosuppressive protocols.

## IMMUNOLOGICAL CONSIDERATIONS IN LIVER TRANSPLANTATION

Several important features make the liver a unique organ in the field of LT. As in the transplantation of other organs, ABO blood group matching between the donor and recipient is strongly recommended, but, in general, there is no need for human leukocyte antigen (HLA) matching. Liver transplant actively participates in tolerance induction toward itself and operational tolerance can be achieved in 20%-40% of recipients[5,6]. Nevertheless, adequate immunosuppressive therapy is a cornerstone in successful graft survival.

### ABO compatibility in LT

It is well documented that the transplantation of liver from ABO incompatible donor greatly increases the risk for graft loss due to hyperacute rejection[7,8]. In such scenario, natural antibodies against blood antigens from the plasma of the recipient may bind for blood antigens expressed in transplant, leading to activation of complement, cell destruction and inflammation. As ABO antigens are not expressed exclusively on donor red blood cells, but also on endothelial liver cells and biliary cells severe organ damage may occur[9]. The downside of ABO compatible donor selection is reduction of the pool of appropriate donors. As ABO incompatibility is not an absolute contraindication for successful transplantation, in urgent cases transplantation from ABO incompatible donors may be considered when no other options are available. Various approaches to remove ABO barrier and thus to broad the pool of available donors have been developed[10,11].

One available approach is therapeutic plasma exchange (TPE, therapeutic plasmapheresis), a form of apheresis in which the fundamental process is extracting a small portion of whole blood from either a donor or a patient and then dividing it into its constituent parts. One of the parts is gathered and preserved, while the remaining components are recombined and then returned to the individual. If performed on a patient to remove specific blood component it is called therapeutic apheresis (TA) and a process of removing different agents (antibodies, antigens, toxins) from plasma is called

plasmapheresis, the most common TA procedure. The removal of anti-A and anti-B isoagglutinins from the bloodstream of the liver recipient can be rapidly achieved, but it doesn't have the capacity to halt the generation of new antibodies by the preexisting plasma cells. Hence, after ABO-incompatible LT, repeated plasmapheresis is frequently required for patients experiencing an increase in isoagglutinin levels until the target titers are achieved[12,13]. There are different regimens and target titers of immunoglobulin M (IgM) and immunoglobulin G (IgG) isoagglutinins, but the typical isoagglutinin target ranges from less than 1:64 to less than 1:8[14,15]. When appropriate TPE protocols and immunosuppressive agents are effectively employed, along with the attainment of target levels of isoagglutinins, there is no significant contrast in transplantation outcomes between the groups with initially high and low IgM and IgG isoagglutinin levels[16]. It is noteworthy, though, that the peak titer of pre- and post-LT IgG or IgM isoagglutinin levels exhibits a notable association with intrahepatic biliary complications and graft necrosis[17,18]. Nonetheless, in the context of preoperative rituximab treatment, the significance of preoperative isoagglutinin levels lacks conclusive data, especially as some report on no significant correlation between ABO antibody titer and antibody-mediated liver rejection[13,15,19,20]. Typical complications linked to TPE are connected to factors such as the selection of anticoagulants, replacement fluids, and vascular access. These may encompass citrate-induced hypocalcemia, hemodynamic instability, and transfusion reactions[21].

Application of rituximab, an anti-CD20 specific human-murine chimeric monoclonal antibody often used in treating patients with autoimmune diseases and hematological malignancies, was first reported in context of ABO-incompatible LT 20 years ago[22]. CD20 is a B-cell marker expressed by most B cells starting from late pre-B lymphocytes as well as memory B cells, and its expression is lost in terminally differentiated plasmablasts and plasma cells[23-25]. However, certain stages of plasma cells express CD20, suggesting their potential responsiveness to rituximab treatment[23]. There are different mechanisms of rituximab action in depleting B cells upon binding to CD20 including complement-dependent cytotoxicity, complement-dependent cellular cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and direct apoptosis induction[24]. Following rituximab infusion, B cells are depleted after 24-72 h from the peripheral blood, the full effect occurs by the third month and usually lasts six to nine months. Several studies have documented the administration of rituximab monotherapy at a dosage of 300-375 mg/m<sup>2</sup> two weeks before a living donor LT[26,27]. Notably, these studies demonstrated that this approach effectively eliminated the necessity for TPE and local infusion therapy. Importantly, it was found that this strategy did not have an adverse impact on patients' survival, which holds significance due to the well-documented infection risk associated with rituximab[27].

Local infusion therapy is another option to overcome the ABO-incompatibility barrier. This method involves the insertion of a catheter into the portal vein or hepatic artery, through which a combination of methylprednisolone, prostaglandin E1, and gabexate mesilate is infused. The underlying mechanism centers on inhibiting the disseminated intravascular coagulation induced by autoreactive antibodies. However, this approach sees limited application due to associated complications and is typically reserved for emergency situations where rituximab-mediated B cell depletion is insufficient[13,14]. Intraoperative splenectomy was once considered to deplete the substantial reservoir of large B cells and plasma cells. However, it was ultimately discarded as an option due to complications, concerns about immunocompromising the patient and the observation of comparable survival outcomes in patients who did not undergo splenectomy[13,14]. Post-transplant intravenous immunoglobulins (IVIG) is another approach. IVIGs have Fab - and Fc-mediated immunomodulatory properties, affecting both B cells, T cells, dendritic cells, complement cascade and cytokine levels but the routine incorporation of IVIG into desensitization protocols faces limitations such as limited experience, the lack of long-term outcome data, high treatment expenses, and potential adverse reactions[14,28].

### HLA matching in LT

In contrast to ABO compatibility, HLA matching in LT is largely considered unnecessary and it is not routinely performed [29]. In kidney transplantation, when the organ lacks HLA-matching, allogeneic major histocompatibility complex molecules on the kidney can interact with the recipient's T cells through three distinct mechanisms[30]. One mechanism involves direct recognition occurring in the lymph nodes, where CD4+ and CD8+ T cells of the recipient directly recognize MHC-II and MHC-I molecules, respectively, on donor dendritic cells or other antigen-presenting cells. CD4+ cells and CD8+ cells differentiate into helper and cytotoxic cells, respectively - the former will secrete cytokines and help both B cells to produce antibodies and activate macrophages and the latter will directly target and eliminate graft tissue cells that display the donor's MHC-peptide complex. When alloantigen recognition is indirect, the recipient's antigen-presenting cells will internalize and process donor allogeneic MHC molecules. Subsequently, they present these processed peptides by the recipient's MHC molecules to recipient T cells. Finally, in a semidirect pathway, recipient APCs acquire and present intact donor-derived HLA[30]. In liver, however, with adequate immunosuppressive therapy MHC mismatch is well tolerated, although a minor negative effect was detected in few novel studies[29,31,32]. Some studies have even reported a positive effect of HLA class II incompatibility[33]. One of the primary explanations for the limited impact of HLA mismatch is believed to be the low expression of MHC molecules. However, it is likely that several other mechanisms promote tolerance. The presentation of antigens in the liver by dendritic cells, as well as other cell types including hepatocytes, is associated with low expression of costimulatory molecules. This leads to lymphocyte anergy and suppression of their response to the presented antigens. Furthermore, hepatocytes are able to secrete immunosuppressive cytokines such as interleukin-10. They can also promote the development of regulatory T-cells (Tregs) and stimulate apoptosis of lymphocytes through FasL and TNF $\alpha$  expression[34,35]. Persistently high plasma concentrations of MHC-I molecules originating from the allograft can potentially induce immune tolerance[36]. Despite these mechanisms of immunotolerance in liver, application of immunosuppressive drugs is necessary to prevent rejection of liver graft.

### Humoral immunity in LT

A humoral arm of immune system is also able to react on donor HLA molecules by production of DSA. While this possibility was not considered a major issue in the past, the clinical significance of DSA is being increasingly recognised [37,38]. DSA can be either preformed, existing in the patient's circulation before transplantation, or formed *de novo*, produced after transplantation. Several factors can contribute to the occurrence of preformed DSA, including previous pregnancies in female patients and frequent blood transfusions. Additionally, viral infections have been identified as a potential risk factor for DSA occurrence due to molecular mimicry. Preformed DSA can lead to acute rejection of the allograft. Detection of preformed DSAs before LT is possible, however, a positive crossmatch test does not preclude transplantation, even in cases of dual organ transplantation. *De novo* DSAs (dnDSA) are synthesized after LT and may lead to AMR. The presence of dnDSA should be suspected in case of steroid refractory rejection and when analysis of liver biopsy suggests antibody mediated rejection[39]. Younger age of the recipient and lower MELD score are known risk factors associated for dnDSA production[39,40].

## OPERATIONAL TOLERANCE

Among individuals who have undergone LT, there is a subgroup referred to as "operationally tolerant." This term is used to describe those who can cease all immunosuppressive medications for a duration of one year or longer while preserving allograft function[41]. This phenomenon is recognized as "spontaneous operational immunotolerance". Furthermore, immunotolerance can be intentionally induced through medical means, which is referred to as "therapeutic operational immunotolerance." There are excellent recent reviews available that delve into the role of liver cells in instigating tolerance, as well as studies on tolerance-related biomarkers[2,34,42,43]. This concise review provides a brief immunological overview tailored for clinicians. The liver's unique role in maintaining immune tolerance is attributed to its exposure to a variety of environmental antigens due to the portal circulation, which supplies 75% of its blood flow. The liver must distinguish between pathological and physiological antigens, and this process includes several key immune cell types including hepatocytes, Kupffer cells, liver sinusoidal endothelial cells (LSEC), liver-specific dendritic cells (DCs), and stellate cells within liver sinusoids enabling close interactions with circulating lymphocytes and maintaining a balance between defensive immune responses and immune tolerance[44]. LSECs, hepatic immune "gatekeepers," serve as unconventional antigen-presenting cells, facilitating the development of Tregs and suppressing strong immune reactions by employing inhibitory mechanisms such as programmed death ligand-1 signaling, in conjunction with stellate cells, and by inducing apoptosis *via* the Fas-FasL pathway to promote immune tolerance[2,34,42,43]. Furthermore, hepatic DCs are in an immature state, displaying reduced immunogenicity with low expression of MHC class II and co-stimulatory molecules (CD80 and CD86), similar to Kupffer cells, as well as minimal IL-12 secretion[2,34,42,43].

In addition, several alternative theories have been posited including the soluble donor MHC class I molecules, the passenger leukocyte theory, and the influence of high antigen loads. Liver allografts release significant amounts of soluble MHC class I molecules into the recipient's circulation, which may contribute to LT tolerance by inducing T cell apoptosis through direct MHC-TCR recognition in the absence of a secondary signal[34]. Additionally, the presence of donor organ-derived leukocytes in the recipient's bloodstream, referred to as microchimerism, has been demonstrated to trigger graft rejection in skin, lung, and kidney transplants, whereas in LT patients, it promotes immune tolerance[2,34,42]. Finally, it was proposed that the liver's size dilutes alloreactive T cells and cytokines, while high-load antigens favor T cell exhaustion, offering another possible explanation for liver tolerance[34].

There are numerous ongoing clinical trials to induce liver tolerance including early, staged withdrawal (up to 2 years) of immunosuppression, donor-derived regulatory dendritic cells (DCreg) infusion, donor alloantigen-reactive Treg (darTreg) therapy, low-dose recombinant IL-2 treatment or autologous Treg-enriched cell product given early post-transplant[45].

## CATEGORIES OF LIVER ALLOGRAFT REJECTION AND THEIR CLINICAL SIGNIFICANCE

Liver allograft rejection can be categorized based on various factors, including the timing of onset, histological findings from graft biopsy, impact on graft survival and response to treatment. Current knowledge indicates that approximately up to 35% of transplant recipients will experience some form of acute rejection[46]. Acute rejection can be further subcategorized into acute T cell-mediated rejection (TCMR) and AMR, depending on the dominant underlying immune mechanism. Hyperacute rejection, characterized by severe graft injury moments after reperfusion, is exceedingly rare and primarily observed in ABO incompatible transplantation, resulting from pre-existing high-titer host antibodies against donor liver antigens, leading to immediate graft dysfunction and often fatal consequences. Tables 1 and 2 provide systematic categorizations and respective characteristics of different types of rejection.

### Acute T cell-mediated rejection

Acute TCMR stands as the most prevalent form of rejection and is the primary cause of allograft dysfunction. Typically, it occurs within 90 d post-transplantation with a median onset of 8 d[47]. Prolonged cold ischemia time, female-to-male donor-recipient pairing, cytomegalo virus viremia, immune-mediated liver diseases, hepatitis C infection, and the type and level of immunosuppression are established risk factors for acute cellular rejection[48].



**Table 1 Types of acute rejection and clinical manifestations**

	<b>T cell-mediated rejection</b>	<b>Antibody-mediated rejection</b>
Time of occurrence	Within 90 d after LT with a median onset of 8 d[47]	Within the first few weeks after LT
Incidence	10%–30%[92,93]	0.3%–2%[94]
Clinical manifestations	Elevation of serum aminotransferases, alkaline phosphatase, gamma-glutamyl transpeptidase and/or bilirubin	Elevated aminotransferases; Graft injury with refractory thrombocytopenia, hyperbilirubinemia, low serum complements levels; Rapid allograft failure, hemorrhagic necrosis
Diagnostic criteria (histology needed)	Quantitative scoring - Rejection activity index (RAI): Portal inflammation - mixed (predominantly mononuclear activated lymphocytes, neutrophils, and eosinophils); Bile duct inflammation/damage; Venous endothelial inflammation; Each of these parameters is scored as 1 to 3 and thus a maximum score of 9 is possible; 0–2 is no rejection, 3 borderline (consistent with), 4–5 is mild, 6–7 is moderate and 8–9 as severe ACR[49]	Histology: endothelial cell hypertrophy, portal capillary dilatation, microvasculitis with monocytes, eosinophils and neutrophils, and portal/peri-portal edema. Microvascular involvement involving the central veins can distinguish acute AMR from other types of injury early after LT; Elevated DSA; Diffuse C4d deposition of microvasculature in ABO-compatible tissues, or portal stroma in ABO-incompatible tissues; Exclusion of other liver diseases[49]

ACR: Acute cellular rejection; AMR: Antibody-mediated rejection; C4d: Complement component 4d; DSA: Donor-specific antibodies; LT: Liver transplantation; RAI: Rejection activity index.

**Table 2 Types of chronic rejection after liver transplantation**

	<b>T cell-mediated chronic rejection</b>	<b>Antibody-mediated chronic rejection</b>
Time of occurrence	Months to years after LT[95]	
Incidence	2%–5%[96]	Unknown[65]
Clinical manifestations	Cholestatic-pattern in liver function tests – the most typical presentation; Range from mild alterations in blood tests to liver failure and death[65]	Normal liver tests despite histologic evidence of allograft injury; Abnormal liver tests during immunosuppression weaning; Graft injury and/or advanced fibrosis; Development of portal hypertension after transplantation[97]
Definition (liver histology required)	(1) Presence of bile duct atrophy/pyknosis affecting most bile ducts; OR; (2) Bile duct loss in more than 50% of the portal tracts; OR; and (3) Foam cell obliterative arteriopathy[49]	(1) Histopathological pattern of injury - both required: Otherwise unexplained and at least mild mononuclear portal and/or perivenular inflammation with interface and/or perivenular necro-inflammatory activity; At least moderate portal/periportal, sinusoidal and/or perivenular fibrosis; (2) Positive DSA within 3 months of biopsy; (3) Focal C4d positivity (> 10%) portal tracts; and (4) Exclusion of other liver insults[49]

AMR: Antibody-mediated rejection; C4d: Complement component 4d; DSA: Donor-specific antibodies; LT: Liver transplantation.

Clinical presentations of acute TCMR may range from asymptomatic to abdominal pain, jaundice, fever and anorexia. Clinically and biochemically, it is often indistinguishable from other causes of allograft injury, such as hepatic artery thrombosis, biliary tract stenosis, infection or reactivation of the underlying immune disease. The gold standard for diagnosis and assessment of the severity of cellular rejection remains histological analysis of the graft. Characteristic features include portal inflammation with mixed inflammatory infiltrate, bile duct injuries and vascular endotheliitis[49]. Each of these elements can be assigned a score ranging from 1 to 3, which collectively yields the rejection activity index (RAI), determining the severity of rejection. It is important to note that RAI does not correlate with treatment response or long-term graft survival.

### **Antibody mediated rejection**

Antibody-mediated rejection, known to be more prevalent in other solid organ transplants, occurs when host antibodies target MHC antigens of the allograft, leading to microvascular damage and graft rejection. In LT, this phenomenon is traditionally considered rare and seldom associated with graft injury, though further research is needed to fully understand its incidence and clinical significance[50]. As previously mentioned, it can manifest as hyperacute rejection, but more frequently presents as acute rejection a few weeks post-transplantation. Primary risk factors include immunological mismatch between donor and recipient and the production of DSA. Clinical presentation usually mimics that of TCMR. Elevated DSA levels, thrombocytopenia and reduced complement levels are characteristic of this form of rejection, making DSA titer determination important for diagnosis and prediction.

Diagnosis of AMR is based on four criteria: (1) Histological evidence of endothelial cell hypertrophy, portal capillary hypertrophy, microvasculitis, and periportal/portal edema; (2) elevated DSA levels; (3) diffuse C4d deposition in the microvasculature; and (4) exclusion of other conditions and complications[49]. The impact of AMR on patient and graft survival remains incompletely understood, with conflicting results in previous studies, primarily focusing on DSA titers. While some studies report a higher incidence of advanced fibrosis one year post-transplantation in cases with high DSA titers and AMR, others find no correlation[51,52]. Given the lack of consistent association between high DSA levels and

AMR occurrence, routine DSA level determination as part of pre- and post-transplant management is not currently recommended. However, in cases of treatment-resistant cellular rejection or rejection with an unclear etiology, DSA determination may serve as an indicator of AMR[53].

Most of the approaches in treating AMR have been adopted from the kidney transplantation studies[54]. The first step involves using immunosuppressive drugs (detailed later) to address cell-mediated rejection. Additionally, TPE and immunoadsorption in combination with IVIG is employed to mitigate the adverse impact of the humoral immune response. This approach has proven effective in facilitating successful transplantation for patients with positive crossmatches, and for many, it remains the primary method for desensitization before transplantation[12]. IVIG is combined to not only decrease the occurrence of infection events but also to exert immunomodulatory effects through neutralization of circulating anti-HLA antibodies with anti-idiotypic antibodies, the inhibition of complement activation, and binding to Fc receptors on immune cells[12,55]. Anti-CD20 therapy to reduce DSA remains controversial, as a recent Japanese study reported that two of the three patients with acute AMR died due to graft failure and rituximab treatment showed no therapeutic efficacy[56]. Lee *et al*[55] emphasize that IVIG is preferred over anti-CD20 agents because, although rituximab reduces circulating B cells, it does not significantly alter peripheral IgG levels in contrast to the reduction in DSAs achieved with IVIG. To address the issue of CD20 absence on plasma cells, several studies have explored proteasome inhibitors, but a drawback is their tendency to cause hepatotoxicity[12,55]. More recent efforts in the field of solid organ transplant have focused on targeted depletion of anti-HLA producing plasma cells with specific anti-CD38 antibody highly expressed on plasma cell membranes[57].

### **Chronic T cell-mediated rejection and chronic antibody-mediated rejection**

The nomenclature itself implies an inclination towards manifestation in the later stages post-transplantation; however, chronic rejection may manifest within a few months, culminating in graft failure within a year after transplantation[58]. The risk factors for chronic rejection mirror those associated with acute rejection, further accentuated in patients with a history of late-phase acute cell-mediated rejection. The incidence of chronic rejection ranges from 3%-17%, a rate significantly lower compared to other solid organ transplantations[48]. Notably, the incidence has markedly declined in the tacrolimus-dominant era of immunosuppressive therapy, currently resting at just 3.1% based on recent research[59].

Chronic rejection may assume cell-mediated or antibody-mediated forms, or even a combination thereof, resulting in chronic arterial occlusion and direct immune-mediated bile duct injury[60]. These pathological processes precipitate the loss of bile ducts, cholestasis, fibrosis, and graft insufficiency. Clinical manifestations frequently exhibit an indolent course, with patients often presenting with newly developed cholestatic graft injury. Over time, icterus, pruritus and fatigue may develop. In advanced stages, signs of liver disease decompensation emerge. In cases where chronic rejection is suspected initially, diligent evaluation should exclude hepatic artery thrombosis, biliary tree pathology, and recurrence of the underlying disease (e.g., PSC, PBC).

Key histological features of chronic rejection encompass bile duct loss without ductal response, obliterative arteriopathy and inflammation and fibrosis within zone 3 and terminal hepatic venules. These characteristics are defined and categorized according to the latest Banff criteria, as of 2016[49]. Notably, chronic rejection can be reversible, particularly in instances where bile duct loss affects less than 50% of portal spaces or in early cell-mediated chronic rejection. The recent recognition of chronic AMR has started an entirely novel field of research, the full clinical implications and graft impact of which remain areas of ongoing investigation.

Patient care after solid organ transplantation is focused on the prevention of acute rejection, as it is a clinically significant event that jeopardizes the survival of both the graft and the recipient. An exception to that paradigm was LT because the results before 2000 indicated that acute rejection after LT is not associated with graft dysfunction and patient death[48]. However, a study from 2017 involving two large cohorts of LT recipients [adult to adult living donor liver transplantation (A2ALL) and scientific registry of transplant recipients (SRTR) cohorts] found that biopsy-proven acute rejection is a clinically important event even after LT[48]. Precisely, the acute rejection within six months post-transplant in A2ALL and SRTR cohorts was associated with a higher risk of graft failure (HR 1.91, 95%CI: 1.21-3.01; and HR 1.77, 95%CI: 1.63-1.92, respectively) and death (HR 1.86, 95%CI: 1-3.47; and HR 1.66, 95%CI: 1.52-1.83, respectively)[48]. These contrasting findings can be attributed to the differences in the underlying data. The previous data were based on studies involving a small number of patients who underwent protocol biopsies, meaning that patients without apparent clinical or laboratory signs of rejection were treated earlier, resulting in improved outcomes[61,62]. Moreover, patients in both cohorts were older and had more concurrent medical conditions, rendering them more vulnerable to the impact of rejection on graft function and to the increased immunosuppression required to treat rejection[48]. Subsequently, Jadowiec *et al*[63] noted that only late TCMR (> six weeks after transplant) was associated with increased risk of mortality (HR, 1.89; 95%CI: 1.35-2.65;  $P = 0.001$ ) and graft loss (HR, 1.71; 95%CI: 1.23-2.37;  $P = 0.001$ ), whereas early mild TCMR was not associated with adverse outcomes. Furthermore, several studies have indicated that rejection occurring at a later stage, and resistance to steroid treatment are all linked to poorer graft outcomes[48,63,64].

Chronic rejection of liver grafts can result in graft failure, potentially necessitating retransplantation. Nevertheless, there is limited available data regarding both graft and patient survival after chronic rejection in LT recipients. Chronic T cell-mediated rejection precipitates graft loss in 15%-20% of cases, whereas such data remains unknown for chronic AMR [65]. Chronic rejection emerges as an independent predictor of total mortality within the 5-year post-transplantation interval, contributing to approximately 16% of retransplantations[49].

### **Emerging biomarkers in liver allograft rejection**

While liver biopsy currently serves as the gold standard for diagnosing and differentiating various types of allograft rejection, its invasive nature and associated complications limit its routine use[66]. Therefore, ongoing efforts focus on developing less invasive biomarkers to improve monitoring and diagnosis. An ideal biomarker should be highly

sensitive, specific, noninvasive, readily available, reproducible, and cost-effective[66]. Donor-derived cell-free DNA (dd-cfDNA) shows promise as a novel biomarker for identifying graft injury[67]. In one of the initial investigations, it was established that the levels of dd-cfDNA in the plasma could serve as indicators of cell death, originating from necrotic or apoptotic cells within the transplanted organ[68]. Consequently, this biomarker holds potential for predicting rejection before apparent clinical signs such as elevated liver enzymes. Furthermore, gene expression profiles, as well as serum and plasma proteins like cytokines, metabolites, and antibodies, represent potential biomarkers for identifying signatures of allograft rejection in blood samples; examination of specific T-cell and B-cell immunophenotypes in LT recipients has the potential to offer predictive insights regarding allograft rejection[69].

In conclusion, it is important to recognize both acute and chronic rejection of liver grafts as significant clinical events linked to an increased risk of graft failure and mortality. To prevent rejection after LT, it is necessary to carefully consider optimal donor and recipient selection, appropriate immunosuppression protocol and implementation of immune monitoring strategies.

## ADVANCEMENTS AND CHALLENGES IN IMMUNOSUPPRESSIVE THERAPY FOR LIVER TRANSPLANTATION

Since the first human LT in 1963, important progress has been made in the field of immunosuppressive therapy. Initially, azathioprine and corticosteroids were the main immunosuppressive drugs used. In 1982, the introduction of cyclosporin, a calcineurin inhibitor (CNI), greatly improved 1-year patient survival from 26% to 70% solidifying CNI based regimens as the cornerstone of immunosuppression[70]. Subsequent developments have led to the integration of new agents into treatment protocols. Although existing protocols are successful in preventing rejection, there is a demand for novel medications that can minimize the adverse effects of immunosuppression and strengthen the immune system's ability to fight infections and detect tumors.

In LT, immunosuppression comprises of two phases: induction and maintenance. The induction phase, initiated during transplantation, involves the administration of immunosuppressive drugs to prevent early forms of rejection and promote graft acceptance. Subsequently, a gradual reduction of immunosuppressive medication, known as tapering, is employed. The maintenance phase is then designed to sustain long-term allograft acceptance, preventing late-onset forms of rejection. This approach leverages the natural decline of the direct immunologic pathway, characterized by immediate and robust immune responses that associated with acute rejection. In contrast, the indirect pathway involves slower, less intense immune responses, typically associated with chronic rejection, as described in the preceding section.

Immunosuppression in LT targets various immunological pathways to prevent graft rejection and promote graft survival. These pathways include the activation of T-cells through stimulatory and costimulatory pathways, cytokine release, and T-cell differentiation into memory T-cells[1]. Additionally, the inhibition of the mechanistic target of rapamycin (mTOR) pathway has been shown to attenuate intracellular signaling involved in AMR[71]. The emergence of dnDSA is now recognized as a novel risk factor for graft rejection. Immunosuppressive therapy is designed to inhibit dnDSA formation by reducing plasma cells, and consequently, antibody production[3]. Other pathways targeted include B-cell mediated activation of T-cells, and Treg function[72]. The characteristics of the primary immunosuppressive drugs used in LT are presented in Table 3, with the respective mechanisms and site of action shown in Figure 1.

### Common immunosuppressive protocols in LT

The most common immunosuppressive protocol, employed in two-thirds of recipients in LT, is a triple-drug regimen, featuring the CNI tacrolimus (TAC), often combined with mycophenolate mofetil or azathioprine, and short-term steroid therapy[73]. CNIs, notably TAC, play a crucial role in preventing acute rejection and improving graft and patient survival, establishing their fundamental position in immunosuppressive protocols. Induction therapy with the administration of monoclonal anti-IL2 receptor antibodies, *e.g.* basiliximab, polyclonal anti-T lymphocyte antibodies, or anti-thymocyte antibodies, is also used in approximately one-third of recipients[74]. Tapering of immunosuppression is a common practice, typically starting with steroids, which are gradually reduced and ideally discontinued to minimize potential side effects associated with prolonged use[73]. The aim in patients with stable long-term graft function is to minimize immunosuppression. Moreover, adopting a monotherapy regimen of extended-release TAC appears to be as effective as standard twice-daily formulations, offering the added benefit of reducing the medication burden for patients with stable graft function[75].

### Efficacy and safety of mTOR inhibitors in liver transplants

While standard multidrug immunosuppression regimens are commonly used, they may not significantly reduce clinically relevant episodes of T-cell-mediated rejection and may even have counterproductive effects in low-risk transplant candidates[1,73]. Furthermore, although CNIs effectively prevent rejection episodes, they are linked to various side effects, such as nephrotoxicity, chronic renal dysfunction, increased cardiovascular disease risk, hypertension, diabetes, and malignancies. These side effects contribute to increased morbidity and mortality, making CNI-free or -sparing protocols in LT a topic of interest[76-78].

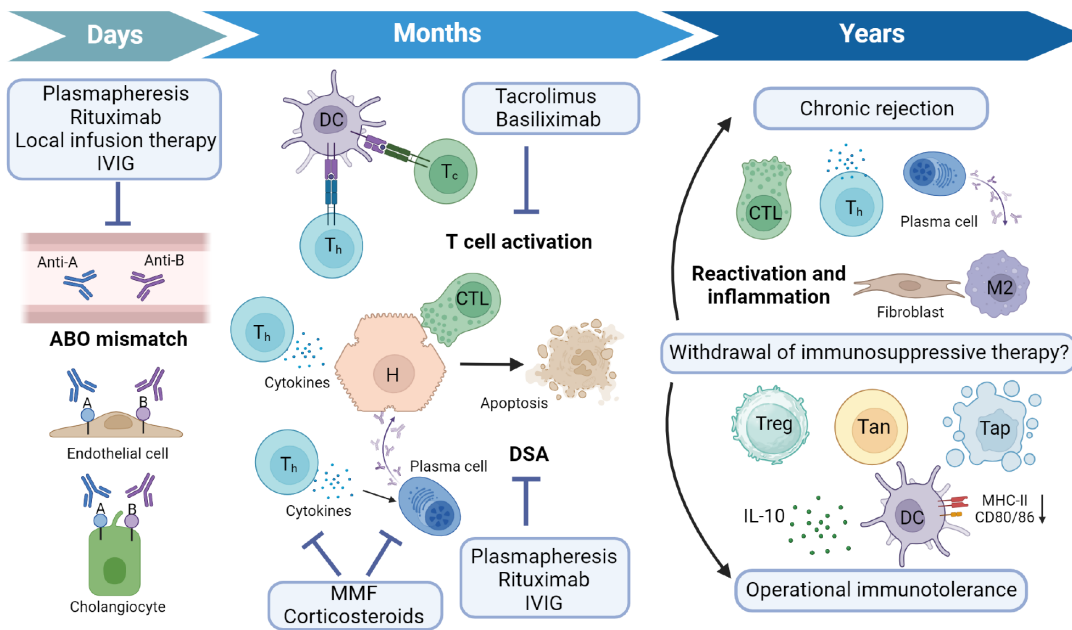
Despite initial concerns regarding the potential for hepatic artery thrombosis and decreased wound healing due to anti-angiogenic properties, numerous studies have demonstrated the safety and efficacy of mTOR inhibitors when used in conjunction with reduced TAC (rTAC) dosages, even as early as 7 d post-LT[76]. In pivotal trials like H2304 and H2307, introducing everolimus (EVR) approximately 30 ± 5 d post-OLT alongside an rTAC regimen maintained comparable

**Table 3 Immunosuppressive therapy in liver transplantation: Drugs used for induction and maintenance**

Drug name (Class)	Mechanism of Action	Dosing	Comments
<b>Induction</b>			
Basiliximab (Immunosuppressant Agent, Monoclonal Antibody)	Directed against the IL-2 receptor on activated T lymphocytes; does not cause lymphocyte depletion.	IV: 20 mg on day 0 and 4 post-LT	Induction by IL-2R antibodies is linked to less renal impairment, fewer rejection episodes, and lower post-transplant diabetes rates. Is not potent enough to be used as monotherapy, usually used in CNI sparing regimens. CNIs introduced later or at reduced doses, especially in chronic kidney disease. Used in steroid-free regimens
Methylprednisolone (Systemic Corticosteroid)	Inhibition of lymphocyte activation and proliferation.	Subject to variations across different centres and disease aetiology. Up to 1000 mg used in induction, IV	Adverse effects are common with high-doses. Delirium is a common early issue. Infections and metabolic problems (e.g. hypertension, hyperlipidemia, diabetes, obesity) pose short-term health risks
<b>Maintenance</b>			
Azathioprine (Antimetabolite)	Purine synthase antagonist inhibiting lymphocyte proliferation	Oral or IV administration. Typically, 1 to 2 mg/kg once daily as part of combination therapy. No established maximum dose; however, experts advise not exceeding 200 mg/d	Off-label use in LT
Mycophenolate (Antimetabolite)	MMF and MNa are prodrugs of MPA, a reversible inhibitor of inosine monophosphate dehydrogenase. MPA blocks the synthesis of guanosine nucleotides utilized by B- and T-cell lymphocytes for proliferation exerting a significant cytostatic effect	MMF: Oral, IV: 500 mg to 1.5 g twice daily. MNa: Oral: 360 to 1080 mg twice daily	MMF is quickly absorbed in the stomach, while MNa is a delayed-release formulation absorbed in the small intestine. Both formulations have high bioavailability, TDM is possible but not recommended due to poor correlation between drug levels and toxicity. Common side effects include bone marrow disorders and GI upset. Both MMF and MNa have teratogenic properties
Cyclosporine (CNI)	Interacts with cyclophilin in T-cells, inhibiting calcineurin, a calcium-dependent phosphatase, which in turn blocks IL-2 transcription and T-cell activation	Oral or IV administration. Oral: Starting 10-15 mg/kg daily divided into 2 doses. IV: Initial dose: 5 to 6 mg/kg/d or one-third of the oral dose as a single dose, infused over 2-6 h	TDM and tapering according to C2 or C0 is advised. Not commonly used as initial choice in modern era. Gingival hypertrophy and hirsutism can occur
Tacrolimus (CNI)	Inhibits calcineurin by binding to FKBP12, in turn blocking IL-2 transcription and T-cell activation. More potent than cyclosporine	Oral or IV administration. Oral: Starting 0.075 mg/kg daily divided into 2 doses, increased to 0.1-0.15 mg/kg daily divided into 2 doses. IV: 0.03-0.05 mg/kg/d as a continuous infusion	Extender release formulations are in use for patients with stable graft function and IS levels, conversion is done using 1:1 ratio (mg:mg) using a previously established total daily dose. Administer once daily
Prednisone, Prednisolone (Systemic Corticosteroids)	Inhibition of lymphocyte activation and proliferation.	Prednisone or prednisolone commonly used with starting maintenance dose of 20 mg daily, typically tapered and discontinued within 3-6 months. For moderate to severe rejection, common regimen is intravenous methylprednisolone (500-1000 mg daily, then tapered). In patients transplanted for AIH, low-dose prednisone (5-10 mg/day) reduces recurrence	Numerous side-effects with prolonged use, including hypertension, hyperglycemia, hyperlipidemia, weight gain, sleep disturbances, psychosis
Sirolimus (mTORi)	Inhibits the mTOR pathway which prevents IL-2 signalling to T-cells and stops T-cell proliferation	CNI minimization: Oral: 2 mg once daily in combination with CNI, adjust to a trough level of 4-10 ng/mL. CNI avoidance: Oral: 2-4 mg once daily in combination with MPA derivatives, with or without corticosteroids, adjust to trough level of 5-10 ng/mL	Despite similar structure to tacrolimus, they do not compete and can be used simultaneously
Everolimus (mTORi)	Inhibits the mTOR pathway which prevents IL-2 signalling to T-cells and stops T-cell proliferation	Oral: Initial 1 mg twice daily, adjust to a trough level of 3-8 ng/mL	Half-life is shorter than sirolimus (30 vs 60 h) which might facilitate dose adjustment

AIH: Autoimmune hepatitis; CNI: Calcineurin inhibitor; GI: Gastrointestinal; IL-2: Interleukin-2; IV: Intravenous; LT: Liver transplantation; MMF: Mycophenolate mofetil; MNa: Mycophenolate sodium; MPA: Mycophenolate acid; mTORi: Mammalian target of rapamycin inhibitor; TDM: Therapeutic drug monitoring.





**Figure 1 Key immunological events in liver transplantation.** A: A antigen; Anti-A: Anti-A isoagglutinin; Anti-B: Anti-B isoagglutinin; B: B antigen; CTL: Effector CD8<sup>+</sup> cytotoxic T cell; DC: Dendritic cell; DSA: Donor-specific antibodies; H: Hepatocyte; IL-10: Interleukin 10; IVIG: Intravenous immunoglobulin; M2: M2 macrophage; MHC-II: Major histocompatibility complex molecule class II; MMF: Mycophenolate mofetil; Tan: Anergic T cell; Tap: Apoptotic T cell; Tc: CD8<sup>+</sup> cytotoxic T cell; Th: CD4<sup>+</sup> helper T cell; Treg: Regulatory T cell. Created with Biorender.com.

efficacy and safety to standard-exposure TAC (sTAC) while preserving renal function over the long term[79]. Recent research, exemplified by the HEPHAISTOS study (NCT01551212, EudraCT 2011-003118-17), has demonstrated that initiating EVR within 7-21 d after transplantation in combination with rTAC results in comparable efficacy, safety, and renal function preservation at month 12 when compared to standard sTAC therapy[80]. The safety and effectiveness of mTOR inhibitors has been affirmed in a recent systematic review and meta-analysis[81]. Furthermore, use of mTOR inhibitors is a well-established strategy to facilitate the gradual reduction or withdrawal of CNIs ensuring the long-term renal function after transplantation[82].

In addition to their immunosuppressive properties, mTOR inhibitors exhibit antiproliferative effects, possibly reducing the risk of posttransplant recurrence and de novo malignancies[83,84]. Sirolimus seems to offer the most pronounced benefits to low-risk patients during the initial 3-5 years[85]. Furthermore, mTOR inhibitor based immunosuppression not only reduces recurrence rates but also improves overall survival in patients transplanted due to hepatocellular carcinoma [76].

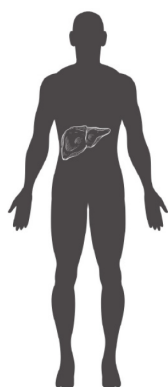
Nonetheless, certain challenges persist in the utilization of mTOR inhibitors, most notably increased infection rates and the development of metabolic syndrome[86]. Additionally, the available data on the combination of mTOR inhibitors with various concomitant therapies and their potential relationship to dnDSA formation and AMR present conflicting findings, underscoring the need for further prospective studies[3,71].

### Minimizing risk: Immune monitoring, novel medications and immunomodulatory strategies

The prevention of complications following organ transplantation is a multifaceted challenge that extends beyond managing rejection and its therapies. While transplant rejection remains a central concern, infectious complications can significantly impact post-transplant outcomes. To address this, immune monitoring strategies are gaining recognition for their potential to prevent infectious complications.

Several immune monitoring tests are available following LT, including antigen-specific assays (limiting dilution assays, mixed lymphocyte reactions, ELISPOT), Immune competence scores, Tregs, soluble CD30, and methods for identifying operational tolerant recipients. However, routine use is hindered by factors such as labor-intensiveness, inconsistent results, and the lack of sufficient validation studies, limiting their widespread applicability[87].

IgG serum level monitoring has garnered attention as a marker for identifying patients at an elevated risk of post-transplantation infections. Numerous studies have underscored the relevance of IgG levels in this context. For instance, low IgG levels have been linked to an increased susceptibility to infections in various transplant recipient groups, including heart, lung, and liver transplant recipients[88-90]. Moreover, the immunosuppressive therapies administered post-transplantation can disrupt the immune system, potentially impairing immunoglobulin development and response. Therefore, monitoring IgG levels after transplantation serves not only as a tool to assess infection risk, but also offers valuable insights into the overall immune status of the transplant recipient. Maintaining adequate IgG levels appears crucial not only for preventing infections but also for enhancing overall clinical outcomes in solid organ transplant recipients[91]. In conclusion, the development of a non-invasive and reliable biomarker to personalize immune system control after transplant, and mitigate infection risk, remains a challenge.



- Immunosuppressive regimens in liver transplantation are tailored based on factors such as age, transplant indication, and comorbidities, ensuring personalized treatment for each patient
- Significant alloreactivity during the engraftment and early postoperative period subsides, allowing tapering of immunosuppression at later stages
- Lifelong immunosuppression is typically warranted in most patients, as mechanisms of functional operational tolerance are still under investigation
- Maintaining a delicate equilibrium between over-immunosuppression (leading to infections, malignancies, and toxicities) and under-immunosuppression (resulting in graft rejection) remains predominantly subjective due to the absence of adequate biomarkers of immunological status
- Diligent monitoring, including regular assessments of drug levels and overall health, is paramount for achieving optimal outcomes

**Figure 2** Immunosuppression in liver transplantation: Personalization and monitoring.

Emerging therapies and personalized approaches to rejection management in LT have gained attention in recent years. Studies have explored innovative strategies to promote immunosuppressive drug minimization or withdrawal, such as adoptive transfer of regulatory immune cells to induce operational tolerance[2]. Therapeutic options like combined hematopoietic stem-cell transplantation and solid organ transplant, thymus transplantation and intra-thymic injection of donor alloantigens have shown promise in promoting tolerance[1]. Additionally, the use of proteasome inhibitors to deplete plasma cells and decrease antibody production is being investigated[72]. Personalized approaches aim to identify biomarkers and clinical parameters that can predict rejection and guide individualized immunosuppressive strategies. Nevertheless, challenges persist in determining the outcomes of these emerging therapies, with further research needed to optimize these approaches and improve rejection management in LT.

## CONCLUSION

In conclusion, the field of transplant immunology and LT has witnessed remarkable progress since its inception. The induction phase of immunosuppression in LT plays a critical role in preventing acute rejection and promoting graft acceptance by harnessing Tregs and creating an immunosuppressive environment. Meanwhile, maintenance immunosuppression remains essential for sustaining long-term graft survival and preventing chronic rejection, often relying on well-established agents like TAC, cyclosporine, mycophenolate mofetil, and mTOR inhibitors.

The pursuit of the ideal immunosuppressive regime persists, driven by the overarching objective of achieving optimal graft acceptance while mitigating the adverse effects associated with immunosuppression. Ongoing efforts are guided by the ultimate aspiration of attaining operational tolerance, thus eliminating the need for prolonged immunosuppressive therapy. Until the objective of operational tolerance is realized, it remains imperative to prioritize a multifaceted approach in patient care, including the principles of tailoring, tapering, and diligent monitoring of immunosuppressive therapies (Figure 2). These strategies collectively play a crucial role in optimizing transplant outcomes and patient well-being.

## FOOTNOTES

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