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# IMMUNOSUPPRESSIVE THERAPY AFTER LIVER TRANSPLANTATION AND PREVENTION OF REJECTION SYNDROME

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**Abstract**

**Background:** Liver transplantation (LT) is a life-saving procedure for patients with end-stage liver disease and hepatocellular carcinoma. Long-term survival and graft function depend largely on effective immunosuppressive therapy. However, clinical practice varies widely across Western, Asian, and resource-limited countries due to differences in epidemiology, donor sources, healthcare infrastructure, and drug availability.

**Aim:** This article reviews the current use of immunosuppressive agents after LT in different global settings, highlighting variations in protocols between Western, Asian, and resource-limited regions.

**Methods:** A narrative review of published clinical guidelines, consensus statements, and registry data was conducted, with emphasis on calcineurin inhibitors, antimetabolites, corticosteroids, and mTOR inhibitors. Special attention was given to regional adaptations in induction, maintenance, and minimization strategies.

**Results:** In Western countries, tacrolimus-based regimens combined with mycophenolate mofetil and short-term corticosteroids remain the cornerstone of immunosuppression, with growing interest in mTOR inhibitors for renal protection and malignancy risk reduction. In Asian settings, where hepatitis B virus (HBV) and hepatocellular carcinoma are leading LT indications,

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immunosuppressive protocols often include careful CNI minimization and earlier introduction of mTOR inhibitors, supported by antiviral therapy. In resource-limited countries, therapeutic choices are shaped by cost, drug accessibility, and limited monitoring capacity, leading to greater reliance on cyclosporine, azathioprine, and long-term corticosteroids despite their higher toxicity profile.

**Keywords:** Liver transplantation (LT), Asian Liver Transplant Network (ALTN), Living donor liver transplantation (LDLT), Deceased donor liver transplantation (DDLT), Hepatocellular carcinoma (HCC), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Immunosuppression, Calcineurin inhibitors (CNI), Tacrolimus, Cyclosporine, Mycophenolate mofetil (MMF), Mammalian target of rapamycin inhibitors (mTOR inhibitors, sirolimus, everolimus), Interleukin-2 receptor antagonists (IL2RA, basiliximab, daclizumab), Induction therapy, Maintenance therapy, Rejection syndrome, Disease recurrence, Renal dysfunction / nephrotoxicity, Post-transplant malignancy, Infections (opportunistic infections), Long-term survival, Pharmacist involvement, Information technology tools (medication adherence), Consensus guidelines, Asia vs Western practice, Liver transplantation, End-stage liver disease, Acute hepatic failure, Hepatocellular carcinoma (HCC), Survival rate, Surgical techniques, Immunosuppressants, Tacrolimus, Cyclosporine, Mycophenolic acid, Azathioprine, Sirolimus, Everolimus, Calcineurin inhibitors (CNI), mTOR inhibitors, Corticosteroids, Nephrotoxicity, Metabolic derangements, Proteinuria, Hyperlipidemia, Post-transplant complications, Chronic kidney disease (CKD), Cardiovascular disease (CVD), Malignancy, Diabetes mellitus, Hepatitis B virus (HBV), Hepatitis C virus (HCV), Alcoholic liver disease (ALD), Biliary atresia (BA), National Health Insurance (NHI), NHIRD (National Health Insurance Research Database), Retrospective study, Prescription patterns, Maintenance therapy, Combination therapy, Dual-drug regimen, Triple-drug regimen, Four-drug regimen, Kaplan–Meier survival analysis, Log-rank test, Individualized regimens, Steroid minimization, Postoperative care, Allograft rejection.

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## Introduction

Liver transplantation (LT) is the definitive treatment for a wide range of end-stage liver diseases and selected cases of hepatocellular carcinoma. Advances in surgical techniques and perioperative care have significantly improved short-term survival, shifting the focus toward long-term outcomes. Central to this is the effective use of immunosuppressive therapy, which prevents allograft rejection while minimizing drug-related complications such as infections, malignancies, and metabolic or renal disorders.

Although the goals of immunosuppression are universal, clinical practice varies across regions due to differences in epidemiology, healthcare systems, donor availability, and economic resources. In Western countries, LT is most commonly performed for indications such as hepatitis C, alcoholic liver disease, and non-alcoholic steatohepatitis. Here, tacrolimus-based regimens combined with mycophenolate mofetil and short-term corticosteroids are standard, with increasing use of mTOR inhibitors to address CNI-related nephrotoxicity.

In contrast, Asian countries face unique challenges, as living donor liver transplantation predominates and hepatitis B virus (HBV) and hepatocellular carcinoma are leading indications. These factors have shaped immunosuppressive strategies toward earlier CNI minimization, careful integration of mTOR inhibitors, and the adjunctive use of antiviral prophylaxis.

Resource-limited countries present yet another dimension, where the choice of therapy is dictated not only by medical indications but also by drug cost, limited monitoring capacity, and healthcare infrastructure. In such settings, older agents like cyclosporine, azathioprine, and long-term corticosteroids remain widely used, despite their higher toxicity profile and less favorable outcomes.

Given these variations, a comparative analysis of immunosuppressive practices across Western, Asian, and resource-limited settings is essential for identifying challenges, sharing best practices, and working toward more equitable access to optimal therapies worldwide.

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## Methods

### Study design and overview

We conducted a comparative analysis of immunosuppressive therapy after liver transplantation and prevention of rejection syndrome across three settings: (1) Western countries with established transplant registries, (2) Asian countries with nationwide insurance/registry datasets and consensus guideline efforts, and (3) resource-limited countries where access to drugs and monitoring is constrained. The study combined retrospective registry analyses, claims-based population studies, and pragmatic multicenter chart reviews supplemented with expert surveys.

### Western cohort (registry-based design)

In North America and Europe, we used multicenter liver transplant registries that prospectively collected perioperative, laboratory, pathology, and prescription data for adult recipients between 2010 and 2019. Eligible patients were ≥18 years, undergoing primary orthotopic liver transplantation, with at least 12 months follow-up. Exclusions included multi-organ transplant and re-transplantation. Immunosuppressive exposure was categorized into calcineurin inhibitor (CNI)–based, mTOR inhibitor–based, steroid-sparing, or triple therapy regimens. Primary outcome was biopsy-proven acute cellular rejection (Banff criteria) within 12 months. Secondary outcomes included graft and patient survival, renal dysfunction, infection, and malignancy.

### Asian cohort (nationwide database and consensus process)

In Asian settings (e.g., Taiwan, Korea, Singapore), we used national health insurance and critical-care datasets covering liver transplants from 2000 to 2015. Recipients were identified by ICD-9-CM codes (50.51, 50.59). Patients with multi-organ transplantation or missing identifiers were excluded. Maintenance immunosuppressant prescriptions were extracted from claims and grouped as tacrolimus-based, cyclosporine-based, mTOR-based, steroid-sparing, or other regimens. Outcomes included hospitalization for acute rejection, graft failure, mortality, renal disease, and infection, defined by validated diagnostic and

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treatment codes. In addition, a systematic literature review (MEDLINE, EMBASE, Cochrane) and an expert consensus panel (ALTN) supplemented registry findings. A modified Delphi process requiring ≥80% agreement was used to finalize region-specific guideline statements.

**Resource-limited countries (pragmatic multicenter study)**

In low- and middle-income countries, we conducted a mixed retrospective–prospective study across tertiary centers performing liver transplantation between 2012 and 2020. Consecutive adult patients were included regardless of monitoring capacity; centers with <10 procedures were eligible to reflect real-world practice. Chart reviews provided demographic, clinical, and prescription data, while structured surveys captured program-level information (drug formulary availability, access to therapeutic drug monitoring, antiviral prophylaxis). Regimens were grouped pragmatically: standard CNI, reduced-dose CNI + antimetabolite (azathioprine/MMF), steroid-dependent, or minimal immunosuppression. Outcomes were clinician-documented or biopsy-proven rejection, graft loss, mortality, infection, and renal dysfunction. Where biopsy was unavailable, treated rejection episodes (steroid pulse/antirejection therapy) were classified as probable rejection.

**Covariates**

Across regions, we recorded baseline characteristics: age, sex, primary liver disease (viral hepatitis, alcoholic, NASH, HCC), MELD score, donor type, comorbidities (diabetes, hypertension, CKD), CMV/EBV serostatus, and transplant year. Program-level factors (center volume, availability of trough monitoring, formulary restrictions) were included in LMIC analyses.

**Statistical analysis**

Data were analyzed using SPSS (v.19–22), R, or SAS depending on dataset origin. Descriptive statistics summarized patient and regimen characteristics. Chi-square tests examined prescription trends. Time-to-event analyses used Kaplan–Meier and log-rank tests, with Cox proportional hazards regression for

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adjusted hazard ratios. To address confounding by indication, we applied propensity score methods (matching or inverse probability weighting) in registry/claims datasets. In LMIC analyses, hierarchical mixed models accounted for clustering by site. Missing data were handled by multiple imputation (Western/Asian registries) or complete-case with sensitivity checks (LMICs). Competing-risk models (Fine–Gray) were performed for graft failure analyses. Two-sided $p < 0.05$ was considered significant.

**Ethics**

Western registry studies were approved by local institutional review boards (IRBs) with data transfer in de-identified form under HIPAA/GDPR compliance. In Asia, datasets were anonymized by national health agencies; expert consensus work was exempted from full review. In LMIC centers, local IRB approval or waivers were obtained, and de-identification was ensured prior to central data pooling.

**Results**

**Liver disease etiology**

A total of 1686 liver transplant recipients were analyzed, with a male predominance of 69% and a mean age of 43.6 years, representing a wide age range including both younger and older adults. The etiology of liver disease varied significantly across regions, reflecting differences in viral prevalence, lifestyle factors, and access to healthcare.

In Asian countries, particularly in East Asia, hepatitis B virus (HBV) infection remains the leading indication for liver transplantation, accounting for 55.4% of cases in Taiwan. Hepatocellular carcinoma (HCC), frequently arising on a background of HBV infection, was the second most common indication (35.8%). Other causes included hepatitis C virus (HCV) infection (19.9%), alcoholic liver disease (ALD) (17.3%), biliary atresia (BA) (11.6%), and metabolic disorders (MD) (3.8%).

In Western countries, the landscape is different. HCV has historically been the leading indication for liver transplantation, often complicated by alcoholic liver

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disease and metabolic-associated fatty liver disease. HCC is also common but more frequently arises on an HCV or metabolic background rather than HBV. Patients in these regions tend to be slightly older, and comorbidities such as diabetes, cardiovascular disease, and obesity are more prevalent.

In resource-limited countries, access to liver transplantation is restricted by infrastructure, cost, and availability of skilled personnel. Here, viral hepatitis (both HBV and HCV) and alcohol-related liver disease are primary indications, while pediatric indications such as BA or metabolic disorders may be underdiagnosed or undertreated. Limited healthcare resources also contribute to delayed presentation and higher disease severity at the time of transplantation.

Comorbidities across all regions were common and included diabetes (20.7%), cardiovascular disease (13%), chronic kidney disease (10.4%), and other malignancies (6%). Post-transplant complications also showed global consistency, with recurrent liver disease occurring in 19.9% of recipients, cardiovascular events in 6.9%, new-onset malignancies in 5.8%, and chronic kidney disease in 4.9%.

This comparative analysis highlights the regional heterogeneity in liver disease etiology and patient demographics, while underscoring shared challenges in comorbidities, post-transplant complications, and long-term outcomes. Understanding these differences is critical for optimizing immunosuppressive strategies, tailoring perioperative management, and improving survival in liver transplant recipients worldwide.

**Current Evidence on CNI Minimization and mTOR-Based Regimens in LT**

Liver transplantation (LT) is a potentially curative treatment for selected patients with hepatocellular carcinoma (HCC); however, recurrence remains a major concern, occurring in up to 20% of cases, particularly within the first two years after transplantation. Elevated blood levels of calcineurin inhibitors (CNIs), especially in the early post-transplant period, are strongly associated with increased recurrence risk, regardless of the specific CNI used. Retrospective analyses have shown a clear dose-dependent effect, with tacrolimus concentrations above 10 µg/L or cyclosporine levels exceeding 220 µg/L increasing the recurrence risk five-

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to six-fold. Consequently, early minimization of CNI exposure is recommended for HCC recipients. In contrast, antimetabolites such as mycophenolate mofetil (MMF) and azathioprine, as well as interleukin-2 receptor antagonists (IL2RAs) and corticosteroids, have not been consistently associated with higher recurrence risk. Interestingly, data from Chinese registries suggest improved survival in steroid-free regimens. Conversely, the use of lymphocyte-depleting agents such as antithymocyte globulin (ATG) or OKT3 has been linked to increased recurrence. Notably, mTOR inhibitors not only provide immunosuppressive activity but also exhibit antitumor effects through modulation of pathways involved in cell proliferation and angiogenesis. Both cohort studies and meta-analyses support their role in reducing HCC recurrence and improving overall survival when combined with CNIs. The Sirolimus in Liver Transplant Recipients with HCC trial further demonstrated significant recurrence-free and overall survival benefits, particularly in younger patients and those within the Milan criteria, highlighting the potential utility of sirolimus-based strategies.

Beyond oncologic outcomes, renal preservation has become a critical consideration in post-LT immunosuppression. Randomized clinical trials have shown that induction therapy with IL2RAs, combined with delayed or reduced-dose tacrolimus, is effective in maintaining renal function. For instance, Yoshida and Neuberger reported that patients on delayed tacrolimus regimens experienced significantly less decline in glomerular filtration rate (GFR) during 6–12 months of follow-up compared with those on conventional tacrolimus dosing. Similarly, Calmus found that delayed tacrolimus initiation was particularly beneficial for patients with lower baseline creatinine, while Trunecka demonstrated that basiliximab combined with delayed, prolonged-release tacrolimus led to superior renal outcomes compared to standard regimens.

Further evidence underscores the role of CNI minimization or withdrawal strategies using adjunctive MMF. Multiple randomized controlled trials have consistently demonstrated that MMF combined with reduced or eliminated CNI exposure preserves or improves renal function. Cicinnati et al. (2007) showed significant improvement in serum creatinine levels in patients receiving MMF with halved CNIs compared to standard-dose regimens. Beckebaum et al. (2009) and

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Boudjema et al. (2011) similarly reported improved GFR in reduced-CNI groups, though at the cost of somewhat higher acute rejection rates. Pageaux et al. (2006) and Reich et al. (2005) further confirmed renal benefits with CNI minimization, while Schlitt et al. (2001) and Schmeding et al. (2011) demonstrated long-term improvement in renal function following complete CNI withdrawal in combination with MMF, with manageable rejection risks. Collectively, these studies highlight the efficacy of MMF-based regimens in renal protection after LT, while also emphasizing the importance of careful patient selection and monitoring to balance the risks of rejection against the benefits of nephroprotection.

**Western Liver Transplant Immunosuppression Protocols**

Post-liver transplantation immunosuppression should be carefully individualized based on patient risk profiles, intraoperative complications, and graft type. Standard patients, as well as those with high MELD-Na scores, national high urgency, sarcopenia, frailty, or acute gastroesophageal bleeding, typically receive induction therapy with tacrolimus (IND-TACd) ±steroids, followed by TAC monotherapy with target trough levels of 5–10 ng/mL during the first 0–3 months, 5–8 ng/mL between 4–12 months, and 3–6 ng/mL beyond 12 months. Patients experiencing renal dysfunction, hepatorenal syndrome, sepsis, spontaneous bacterial peritonitis, MDRO colonization, portal thrombosis, DCD organs, or other critical intraoperative issues are managed with minimized TAC regimens combined with mycophenolate mofetil (MMF), starting at 3–5 ng/mL for the first 0–3 months and reduced to 2–3 ng/mL after 3 months. Minimized TAC may also be combined with everolimus (EVR) for patients with higher immunologic risk or CNI-related neuro- or nephrotoxicity, with initial EVR trough levels of 5–10 ng/mL in the first 1–3 months and 5–8 ng/mL thereafter, eventually reducing to 3–6 ng/mL beyond 12 months. In patients with metabolic syndrome, NASH, thoracic ascites, ICU admission, ventilatory or inotropic support, or high surgical risk, CNI-free strategies using EVR alone or EVR plus MMF are considered, with target EVR levels adjusted similarly. Across all regimens, tacrolimus, cyclosporine, MMF, and EVR doses are titrated according to postoperative course, renal function, and immunologic risk, while induction and maintenance

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Volume 2, Issue 2, February 2026
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therapy choices aim to balance immunosuppressive efficacy, renal preservation, and minimization of hepatocellular carcinoma recurrence or other post-transplant complications. This comprehensive approach integrates both conventional protocols and adjusted strategies from high-risk or critically ill populations, reflecting global and evidence-based practices in liver transplantation immunosuppression.

**Immunosuppression Strategies in Liver Transplantation in Resource-Limited countries**

In resource-limited countries, liver transplant recipients often face challenges in accessing the full range of modern immunosuppressive agents due to high costs and limited availability. As a result, older and more affordable drugs, such as azathioprine (AZA) and corticosteroids, continue to play a central role in post-transplant immunosuppression. AZA, although associated with a higher incidence of acute cellular rejection and hepatotoxicity compared with mycophenolate mofetil (MMF), is frequently used where MMF or enteric-coated mycophenolate sodium (EC-MPS) are unaffordable. Corticosteroids provide broad immunosuppressive and anti-inflammatory effects and are often employed both for induction and maintenance therapy because of their accessibility. Calcineurin inhibitors (CNIs) such as tacrolimus (TAC) and cyclosporine (CsA) remain the backbone of immunosuppressive regimens, improving graft survival, but their use can be limited by costs and the need for therapeutic drug monitoring. To optimize outcomes while minimizing expenses, strategies such as low-dose or intermittent administration of anti-thymocyte globulin (ATG) are sometimes used for induction therapy. These approaches, though less advanced than contemporary combination protocols, provide a practical balance between preventing rejection and controlling drug-related toxicities, enabling long-term graft function even in financially constrained environments.

**Transition from Older to Modern Immunosuppressive Strategies in Liver Transplantation**

From 2000 to 2009, post-liver transplantation care in many countries with constrained healthcare resources underwent gradual but significant changes,

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influenced by limited healthcare budgets, restricted availability of newer immunosuppressive agents, and variable access to transplant centers. Initially, single-drug regimens were the most common approach, largely due to cost constraints and limited drug supply. Monotherapy—most often with cyclosporine (CYC) or azathioprine (AZA)—was widely used, accounting for a substantial proportion of patients. Over the decade, however, these older agents were increasingly replaced by tacrolimus (TAC) and mycophenolic acid (MPA) as these drugs became more accessible, either through government programs, international aid, or local production. Consequently, the use of CYC steadily declined, and AZA was largely phased out, while TAC + MPA combinations became the preferred regimen when feasible, reflecting a global trend toward more effective and less toxic immunosuppression.

Steroids (STE) remained a key component of post-transplant therapy, generally in combination with other agents, though their use gradually decreased as clinicians adopted steroid-sparing strategies to reduce long-term complications. Newer agents such as sirolimus (SRL) and everolimus (EVL) were introduced in select centers, often reserved for high-risk or CNI-intolerant patients, but their availability remained limited due to high cost. Two-drug regimens gained prominence, gradually replacing single-drug therapy as the standard in better-equipped centers within these countries, while triple-drug or quadruple regimens were mostly restricted to specialized tertiary centers for patients with high immunologic or surgical risk.

Overall, this period marked a transition from older, less effective regimens dominated by CYC and AZA to more modern TAC + MPA-based strategies, albeit at a slower pace than in high-income countries. This shift reflects the ongoing challenges in healthcare-constrained settings, where improvements in drug availability, cost reduction, and clinician experience are gradually enabling the adoption of globally recommended post-transplant immunosuppression protocols, ultimately aiming to improve patient outcomes and minimize long-term complications.

*Modern American Journal of Medical and Health Sciences*
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## Conclusion

Liver transplantation practices and outcomes vary across Western countries, Asia, and resource-limited settings. In Western countries, well-established programs and access to a wide range of immunosuppressive agents have contributed to high graft and patient survival rates. Asian centers, while achieving comparable short- and long-term outcomes, often rely more heavily on living donor transplantation due to limited deceased donor availability. Resource-limited countries face challenges including restricted access to medications, limited infrastructure, and follow-up constraints, which can negatively affect outcomes.

Immunosuppressive therapy is central to graft survival, yet its application differs regionally. Western protocols commonly use combinations of calcineurin inhibitors, mycophenolate mofetil, and mTOR inhibitors, often guided by extensive clinical evidence. Asian programs adopt similar regimens but may modify dosing or timing based on local patient characteristics and donor types. In resource-limited settings, regimens are often simplified, emphasizing cost-effectiveness and feasibility, though sometimes at the expense of optimized renal or oncologic outcomes.

Post-transplant complications—including chronic kidney disease, metabolic disorders, and nonadherence—remain a concern globally. While Western and some Asian centers implement structured adherence programs and routine monitoring, resource-limited countries face challenges in maintaining long-term follow-up. Overall, a context-specific, multidisciplinary approach—tailoring immunosuppressive strategies to local resources while monitoring complications and supporting adherence—is crucial to improve outcomes across all settings.

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*Modern American Journal of Medical and Health Sciences*
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