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## REVIEW



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*REVIEW*

# Innovative immunosuppression in kidney transplantation: A challenge for unmet needs

Maurizio Salvadori, Aris Tsalouchos

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## Abstract

Due to the optimal results obtained in kidney transplantation and to the lack of interest of the industries, new innovative drugs in kidney transplantation are difficult to be encountered. The best strategy to find the new drugs recently developed or under development is to search in the sections of kidney transplantation still not completely covered by the drugs on the market. These unmet needs are the prevention of delayed graft function (DGF), the protection of the graft over the long time and the desensitization of preformed anti human leukocyte antigen antibodies and the treatment of the acute antibody-mediated rejection. These needs are particularly relevant due to the expansion of some kind of kidney transplantation as transplantation from non-heart beating donor and in the case of antibody-incompatible grafts. The first are particularly exposed to DGF, the latter need a safe desensitization and a safe treatments of the antibody mediated rejections that often occur. Particular caution is needed in treating these drugs. First, they are described in very recent studies and the follow-up of their effect is of course rather short. Second, some of these drugs are still in an early phase of study, even if in well-conducted randomized controlled trials. Particular caution and a careful check need to be used in trials launched 2 or 3 years ago. Indeed, is always necessary to verify whether the study is still going on or whether and why the study itself was abandoned.

**Key Words:** New drugs; Unmet needs in kidney transplantation; Delayed graft function; Long-term outcomes; Kidney inflammation; Anti-human leukocyte antigen antibodies

**Core Tip:** Finding new innovative drugs for kidney transplantation is not easy but looking for unmet needs it is possible to find new interesting drugs and opportunities to use in kidney transplantation. Many of these drugs are just at the beginning of their process toward the approval and should be careful checked until the finish of their path. Principal unmet needs are treatment and prevention of delayed graft function, improve the long-term outcomes, desensitization and treatment of acute antibody-mediated rejection. Finding new drugs in these fields results extremely important to face new kind of transplantation as transplant from non-heart beating donor and transplant in ABO incompatibles pairs.

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## INTRODUCTION

Little progress has been made over the past decade in the development of new therapeutic measures in clinical kidney transplantation, chiefly because of a lack of interest by industries and providers and because most centers have reached optimal outcomes with the drugs used today[1]. However, a strategy may be adopted to identify new immunosuppressant drugs in kidney transplantation.

New immunosuppressant drugs may be found looking for identified unmet therapeutic needs.

These new drugs may also be adopted as new immunosuppressive treatments or new strategies for special kidney transplantation scenarios such as ABO incompatibility, non-heart-beating donor (NHBD) transplantation and transplantation from high-risk donors.

### *Drugs for unmet therapeutic needs*

These drugs may be categorized as follows: (1) Therapy for ischemia-reperfusion injury (IRI) that results in delayed graft function (DGF); (2) Therapy to preserve optimal kidney function over the long-term; and (3) Therapy for desensitization and antibody-mediated rejection (ABMR).

## THERAPY FOR DGF

DGF refers to acute kidney injury (AKI) occurring in the first week of transplantation that cannot not be ascribed to acute rejection[2].

DGF is associated with increased immune activation, complement activation and release of damage-associated molecular patterns, such as hypomethylated DNA, hyaluronic acid, heparin sulfate, fibrinogen and heat shock proteins. Consequently, nuclear factor κB is activated and induces inflammatory cytokines such as interleukin (IL)-1, IL-6, tumoral necrosis factor alpha and interferon beta[3].

Due to this complex mechanism, although several drugs to treat DGF have been tried, many of them failed to prove their effectiveness. Indeed, DGF has also been called the graveyard of drugs for transplantation.

However, new drugs have recently emerged and they are still in randomized controlled trials (RCTs) to control DGF.

### *Anti-apoptotic strategies*

Apoptosis plays an important role in shaping DGF. Indeed, the pro-apoptotic gene p53 is activated by hypoxia and induces cell cycle arrest and apoptosis[4].

QPI-1002 also known as 15 NP, is a short interfering RNA that inhibits the expression of p53. The results of a phase I/II clinical trial in kidney transplant recipients demonstrated beneficial effects on IRI/DGF in humans[5]. Additionally, two studies reported good results in mice[6,7]. However, the RCT was terminated in 2018 without positive results because of a lack of documented efficacy.

### *Pegylated carboxyhemoglobin*

Carbon monoxide (CO) is involved in regulating endothelial cell survival and proliferation. It also plays roles in protecting against DGF through IRI, vessel relaxation and inhibition of proinflammatory responses[8-10]. The infusion of pegylated carboxyhemoglobin delivers CO to organs. CO is a very powerful anti-apoptotic substance and has anti-inflammatory effects. In animal studies, CO is extremely effective in both cold and warm ischemia.

The use of pegylated carboxyhemoglobin is currently the object of a phase 2/3 study to analyze the efficacy and safety of SANGUINATE for reducing the DGF rate in patients receiving a kidney transplant

[11,12]. In a recent study by Thuillier *et al*[13], 3 oxygen transporters, HBOC-201, BbV and M101, were tested in organ preservation[13-15].

### Relaxin

In DGF, relaxin (RLX) has an anti-inflammatory effect by reducing the expression of intracellular adhesion molecule 1, inducing the expression of Notch 1 in macrophages and reducing neutrophil adhesion through increased synthesis of nitric oxide[16-18]. Additionally, RLX causes vasodilatation through increased NO production and inhibition of endothelin 1 production[19]. Two studies[18,20] documented improved renal function, histologic improvement in damaged tissue after DGF, and a reduced number of apoptotic cells.

### Hepatocyte growth factor

ANG-3777, formerly BB3, is a hepatocyte growth factor mimetic that binds to its transmembrane tyrosine kinase receptor, cMET[21]. In preclinical studies, ANG-3777 was renoprotective in a variety of animal models of AKI, exerting anti-inflammatory and regenerative effects and preventing tubular cell apoptosis, epithelial to mesenchymal transition and fibrosis[22,23]. In a randomized, placebo-controlled phase 2 trial on oliguric patients after kidney transplantation, patients treated with ANG-3777 had a larger increase in urine output, a greater reduction in C reactive protein and neutrophil gelatinase-associated lipocalin and a higher estimated glomerular filtration rate (eGFR)[24]. More recently, Vincenti *et al*[25] started the Graft Improvement Following Transplant (GIFT) trial, which is a phase 3 trial on the hepatocyte growth factor mimetic ANG-3777 in kidney transplant recipients with DGF. The aim of GIFT is to generate data to advance the treatment of DGF. In addition, the authors stress that a significant factor is that ANG-3777 may also be effective when administered after AKI-related DGF.

### Complement inhibition

Complement activation plays a significant role in IRI, which causes and precedes DGF. The most studied among the complement inhibitor drugs to minimize DGF has been Mirocept (APT 070), which inhibits C3/C5 convertases and C1 esterase inhibitors.

Mirocept, still in a phase 1 trial (ISRCTN49958194)[26], is a potent membrane-localizing complement inhibitor and may be administered *ex vivo* to the donor kidney prior to transplantation. However, a recent dose finding study in animals[27] documented that a high dose of Mirocept might be needed to achieve adequate complement inhibition. More promising results have been obtained with C1 esterase inhibition.

This drug may also be administered as a donor pretreatment strategy in high-risk recipients (NCT02435732)[28], but the trial results are still unknown. Better results have been obtained by administering C1 esterase inhibitors to recipients of kidneys from high-risk donors or in the case of donation after circulatory death (DCD)[29-31]. A recent study from Huang *et al*[32] studied the three-year outcomes of patients treated with C1 esterase inhibitors to avoid DGF in a randomized controlled study. The study found that the treatment was associated with a lower incidence of graft failure.

Table 1 summarizes representative drugs in the categories described above used to prevent DGF and their targets.

### Improving perfusion techniques

Improving perfusion techniques is not drugs in the sense of the word but rather a different strategy to prevent IRI and DGF by improving kidney perfusion at the time of kidney transplantation.

In a recently published study, Urbanellis *et al*[33] documented that continuous normothermic *ex vivo* kidney perfusion significantly improved early kidney function compared with hypothermic anoxic machine perfusion and static cold storage (SCS) in a porcine kidney auto-transplantation model.

A more interesting study was performed by Niemann *et al*[34]. The authors documented that reducing the body temperature by 2 °C of the deceased donor achieved a significant reduction in DGF rates and that the effect was more significant in the extended criteria donors.

Finally, in a recent review[35], it was documented that active oxygenation during hypothermic machine perfusion is the most beneficial in cases involving the use of DCD kidneys when applied starting from kidney procurement until transplantation. Active oxygenation improves preservation and subsequent early graft function.

## THERAPY TO PRESERVE RENAL FUNCTION

These drugs may be divided into the following categories: (1) Therapy to avoid nephrotoxicity, usually by elimination of calcineurin inhibitors (CNIs); (2) Therapy to control inflammation and fibrosis (principally when inflammation overlaps fibrosis); and (3) Therapy to prevent donor-specific antibodies (DSAs) and treat chronic ABMR (cABMR).

**Table 1 Therapies targeting delayed graft function in kidney transplantation**

| Drug | Molecular target | Mechanism of action |
|---|---|---|
| 15NP or QPI-1002 | p53 | Inhibition of apoptosis |
| Pegylated carboxyhemoglobin | Cytochrome C oxidase; cytochrome P450; HMGB-1; P38 MAPK pathway | Inhibition of oxidative injury, inflammation, and apoptosis |
| Relaxin | ICAM-1; neutrophil adhesion | Vasodilatation; inhibition of apoptosis |
| ANG-3777 (BB3) | Tyrosine kinase receptor cMET | Antinflammation; inhibition of epithelial to mesenchymal transition |
| Mirocept (APT 070) | Inhibition of C3/C5 convertase | Inhibition of complement activation |
| C1 esterase inhibitor | C1 esterase | Inhibition of complement activation |

HMGB-1: High mobility group protein box-1; MAPK: Mitogen-activated protein kinases; ICAM 1: Intercellular adhesion molecule 1.

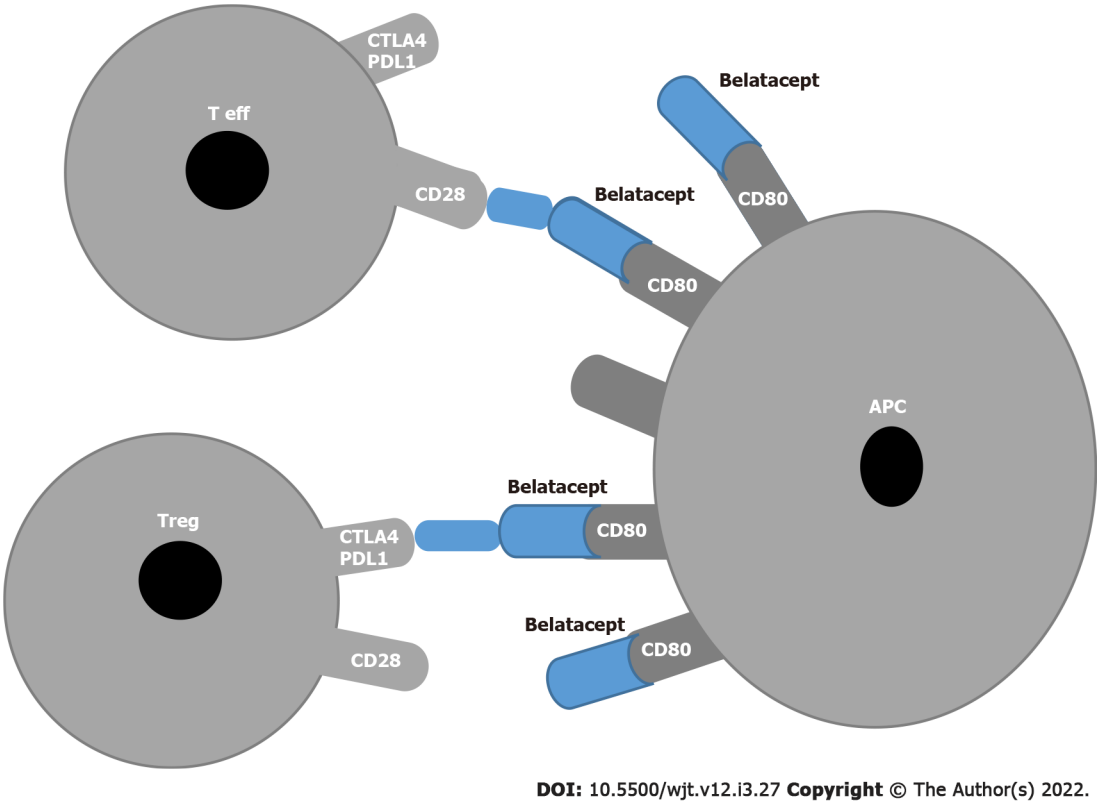


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**Figure 1 Block of co-stimulation with Belatacept.** APC: Antigen presenting cell; T eff: T effector; T reg: Regulatory T cells; PDL1: Programmed cell death receptor ligand 1; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4.

### *Therapy to avoid nephrotoxicity induced by CNIs*

Until recently and even today, the two main strategies for a CNI-free regimen have been as follows: Mammalian target of rapamycin inhibitor-based immunosuppression; belatacept based immunosuppression.

Several studies have documented the efficacy of everolimus therapy in conjunction with low-dose CNIs[36-39]. The study by Pascual *et al*[36] "the Advancing renal TRANSplant eFficacy and safety Outcomes with eveRoliMus based regimen (TRANSFORM)" was a randomized open label, two-arm study with 2037 *de novo* kidney transplant recipients recruited in 186 centers worldwide. Everolimus efficacy was demonstrated, but the administration of low-dose tacrolimus (TAC) was needed.

The complete withdrawal of CNIs is difficult to achieve and is only appropriate for low-risk patients and donors and for living donors, and in the absence of DSAs[40].

The use of belatacept or other agents blocking the costimulatory pathways is the other method to avoid CNIs.

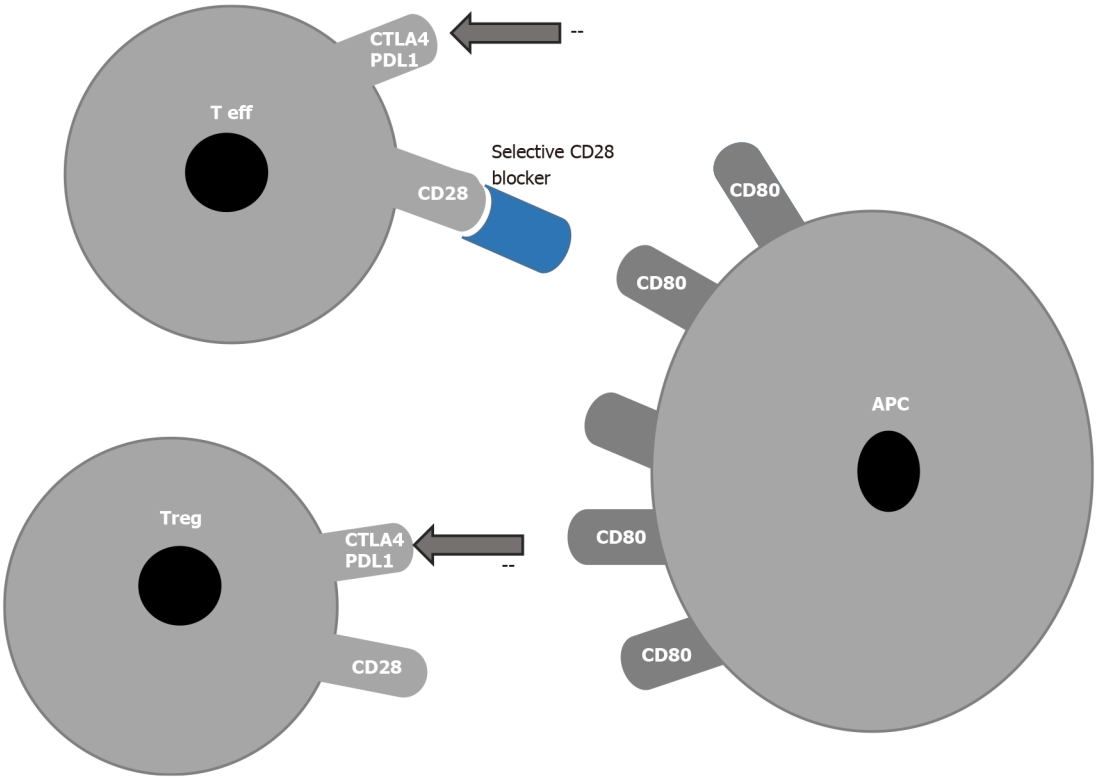


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**Figure 2 Block of co-stimulation with anti CD28.** APC: Antigen presenting cell; T eff: T effector; T reg: Regulatory T cells; PDL1: Programmed cell death receptor ligand 1; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4.

The blockade of CD28/cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T effector lymphocytes and CD80/CD86 on antigen presenting cells (APCs) was the first pathway to be targeted in the trials BENEFIT and BENEFIT-EXT[41,42] . Independent of well-preserved kidney function, the use of belatacept in a subset of patients was associated with an increased number of severe rejections[43, 44] and an increased number of opportunistic infections[45] , including cytomegalovirus[46]. In addition a correlation between the incidence of post-lymphoproliferative disease and Epstein-Barr virus seronegative patients in the belatacept group was found[47].

These drawbacks are related to the fact that belatacept, which binds to CD80 and CD86 on APCs, blocks not only the T effectors that represent the positive signal but also the regulatory T (Tregs) that constitute the inhibitory signal (Figure 1).

In 2015, a report showed that the blockade of CD28 on effector T cells without inhibition of Treg cells prolonged survival in a nonhuman primate kidney transplant model. In this way, effector cells can be inhibited without inhibiting Tregs because selective CD28 blockade allows inhibitory signals *via* CTLA-4 and programmed cell death ligand-1 to remain intact while blocking T cell activation by CD28[48] (Figure 2).

Selective targeting of the CD28 antigen on T cells might be a more effective immunosuppressive therapy than belatacept, since this blockade leaves the inhibitory signal of CTLA-4 intact and may preserve Treg functions[49-51].

Currently, two monovalent antibodies, FR104 and lulizumab-pegol are under development for clinical application. These antibodies have antagonistic activity against CD28 alone[52,53]. To date, an RCT has been conducted at the University of California to modulate Tregs with combinatorial treatment with CD28 and IL-6 receptor antagonists[54] (Figure 3). The addition of an IL-6 receptor antagonist (tocilizumab) aims to further stimulate Treg cells and exert an anti-inflammatory effect. In the CTOT24 trial, after induction with thymoglobulin, steroids are administered from the beginning, lulizumab is started at the beginning and then continued weekly through day 77, belatacept is started on day 84 and administered every 4 wk, tocilizumab is started at the beginning and continued every 2 wk through day 168, and everolimus is started on day 14 and administered twice daily.

A different way to block costimulation is to block the interaction between CD40 and CD40 L. A first attempt was made to block the CD 40 receptor, but the studies were interrupted because of a number of thromboembolic complications[55,56]. This was because CD40 L is also expressed on platelets, which causes thromboembolic complications.

In 2014, Okimura *et al*[57] reported that ASKP 1240, a fully human antibody targeting human CD40, had a potent immunosuppressive effect that did not interfere with platelets.

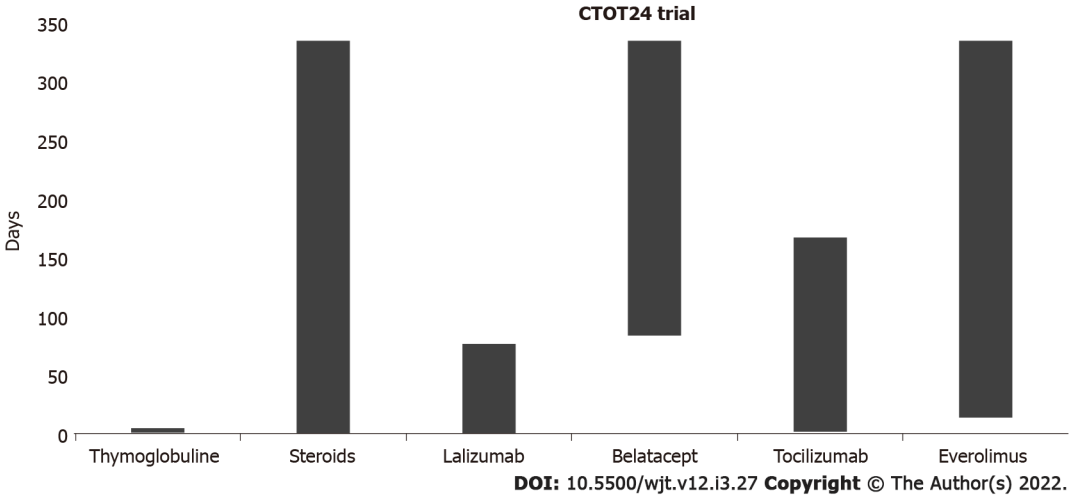


**Figure 3 CTOT24 trial.**

Recently, in a phase 1b study, the safety and efficacy of bleselumab, a fully human anti-CD40 monoclonal antibody, was documented by Vincenti *et al*[58]. The results were confirmed by a phase 2, randomized, open label, noninferiority study by Harland *et al*[59].

Novartis claimed to have developed another anti-CD40 monoclonal antibody (CFZ-533, Iscalimab). The antibody was characterized by several studies[60,61] . The antibody is the object of an RCT in *de novo* renal transplantation[62] to demonstrate comparable efficacy to and better renal function than TAC in *de novo* CNI-free kidney transplantation.

Until recently, it was believed that the main cause of kidney injury over time after transplantation was primarily due to CNI nephrotoxicity.

The first study questioning this opinion was the DeKAF study by Gaston *et al*[63] . The study documented that the decline in kidney function was not only due to CNI nephrotoxicity but also due primarily to the presence in the recipient of DSAs and the consequent activation of the humoral response[64]. Indeed, long-term graft survival was lower in patients with DSAs in the serum and C4d, a marker of immune response activation on the glomerular capillary wall. The role of DSAs and ABMR was further documented by Sellarés *et al*[65] and Lefaucheur *et al*[66]. A separate study documented that both *de novo* and pre-existing DSAs caused ABMR and reduced graft survival[67].

A more recent study by Stegall *et al*[68] examined 575 surveillance biopsies of kidney transplants from living donors on low-dose TAC therapy and found that 82% of patients whose grafts survived 10 years were affected by inflammatory lesions not related to CNI toxicity or to immunological mechanisms.

Preserving renal function requires other therapies in addition to safely reducing or withdrawing CNIs.

### *Therapy to control inflammation and fibrosis not related to immunological causes*

Several factors, such as hyperuricemia, glucose intolerance, arterial hypertension, dyslipidemia and infection, may induce an inflammatory state in kidney transplant patients[69]. In addition, chronic hypoxia mediated by IL-1 and IL-6, angiotensin II and transforming growth factor beta may result in the accumulation of extracellular matrix, which can lead to interstitial fibrosis. In particular, several studies [70-72] document that IL-6 leads to allograft injury by acute inflammation, adaptive cellular/humoral responses, innate immunity and fibrosis. All these studies indicate that IL-6 is a mainstay in inducing inflammation and allograft injury.

Several drugs have been proposed to control the graft inflammatory state, including low-dose aspirin, statins, renin-angiotensin inhibitors, and xanthine-oxidase inhibitors, but no prospective trial with these drugs has been conducted in kidney transplantation. The only drug object of an RCT is the IL-6R inhibitor.

Currently, available agents for IL-6 signaling inhibition include monoclonal antibodies against IL-6 or IL-6R and Janus kinase inhibitors. The most often studied is tocilizumab, an IL-6R blocker. In a study conducted by Chandran *et al*[73], IL-6 blockade with tocilizumab increased Tregs and reduced T effector cytokines in renal graft inflammation. Tocilizumab-treated patients showed an improved tubulointerstitial Banff score and an increased Treg frequency.

### *Therapy to control chronic humoral rejection*

Important advances have been made in the treatment of ABMR, but less effective treatments are available to control cABMR, which is a slowly progressing disease in which grafts are primarily injured

by *de novo* DSAs[74].

Until recently, attempts to treat cABMR had been limited to a combination of plasmapheresis and intravenous immunoglobulins (IVIGs)[75] and rituximab (RTX)[76,77]. Recently, proteasome inhibitors such as bortezomib[78] and carfilzomib[79] have also been studied, but these drugs were not as effective as anticipated.

In addition, complement inhibitors such as C1 inhibitors (C1-INH) and eculizumab, failed to control cABMR[80,81] probably because antibodies may injure the endothelium in a complement-independent pathway. Better results have been obtained with the use of IL-6R or IL-6 inhibitors.

In a previous study, Shin *et al*[82] documented the efficacy of tocilizumab in blocking monocyte activation in an *in vitro* model, to inhibit the inflammatory cascade induced by alloantibodies. In a more recent study, Shin *et al*[83] documented a beneficial effect of tocilizumab on cABMR owing to a reduction in antibody production by B cells.

Similarly, Choi *et al*[84] documented a reduction in DSAs and cABMR and stabilization of renal function in patients with cABMR, DSAs and transplant glomerulopathy treated with tocilizumab. A phase 4 RCT in patients with cABMR was recently designed[85].

Clazakizumab is a humanized monoclonal antibody directed against IL-6. In a study by Dobere *et al*[86], clazakizumab reduced DSAs and demonstrated beneficial effects on cABMR and renal function.

## THERAPY FOR DESENSITIZATION AND ACUTE ABMR

Desensitization and treatment of ABMR are the two faces of the same coin. It has already been discussed how DSAs play a relevant role in inducing AKI and graft failure. DSAs may already be present before transplantation, or they may appear *de novo* after kidney transplantation. In both conditions, they may cause ABMR.

Desensitization is the treatment to reduce or, when possible, completely eradicate DSAs before or at the time of transplantation. Treatment of ABMR includes powerful drugs aimed at controlling this severe complication.

To better understand the mechanism of action of these drugs, Figure 4 represents how DSAs are formed and where the immunosuppressant drugs may act[87]. Naïve CD4+ T cells recognize the antigen presented by APCs. Activated CD4+ cells process antigens, which are presented to naïve B cells. Costimulatory molecules mediate the presentation through CD80/86 and CD28. B cell maturation and development into B-memory cells and plasma cells (PCs) is regulated by cytokines (principally IL-6 and IL-21), B cell activating factor (BAFF) and a proliferation-inducing ligand that interact with B cell maturation antigen. PCs produce antibodies that bind to donor-specific human leukocyte antigen (HLA) molecules, activate complement and initiate injury leading to ABMR. Agents capable of interfering with this complex system are numerous and act at different levels.

Several studies and reviews have described the drugs used in desensitization and in the treatment of ABMR[88-93].

Novel agents will be discussed in this chapter. New agents acting on costimulatory signals have already been discussed[48,49,57,59]. Similarly, anti-IL-6/IL-6R agents have been discussed[83-86].

Obintuzumab is a type 2 anti-CD20 antibody that induces more robust B cell depletion than RTX. To date, the drug has been evaluated in a phase 1b study to induce desensitization[94].

Belimumab belongs to the anti BAFF family. The drug is effective in treating systemic lupus erythematosus[95] but less effective in treating ABMR[96] due to possible infective complications. Proteasome inhibitors such as bortezomib and carfilzomib act on PCs, but are not as effective as anticipated. Carfilzomib has been studied in desensitization in a nonhuman primate model[97].

Drugs acting directly on PCs target CD38. Several studies or case reports have documented the efficacy of daratuzumab in the treatment of ABMR[98-100]. Isatuximab is effective on PCs and other immune cells, such as Tregs and Bregs. This fact may limit its applicability in the treatment of ABMR [101].

Inebilizumab is a humanized anti-CD19 monoclonal antibody approved for neuromyelitis optica [102].

An RCT with inebilizumab for pretransplant desensitization[103] was suspended due to the coronavirus disease pandemic.

Finally, another fully human monoclonal antibody, anti-CD38, is the object of an RCT for the treatment of ABMR[104].

In ABMR, the activation of the complement cascade is triggered by ligation of the C1 complex to HLA antigens that are bound by DSAs. Several drugs are capable of blocking complement activation (Figure 5). The C1 complex is activated upon antibody binding. The humanized monoclonal antibody BIVV009 (sutinlimab) targets its enzymatic subcomponent C1 s and this therapy blocks C4 and C2 cleavage and the formation of C3 convertase.

A phase 1 study with this drug[105] was concluded, and Eskandary *et al*[80] studied 10 kidney transplant recipients with ABMR. Repeated biopsies documented a reduction in C4d deposition even if DSA levels and microvascular inflammation were unchanged.

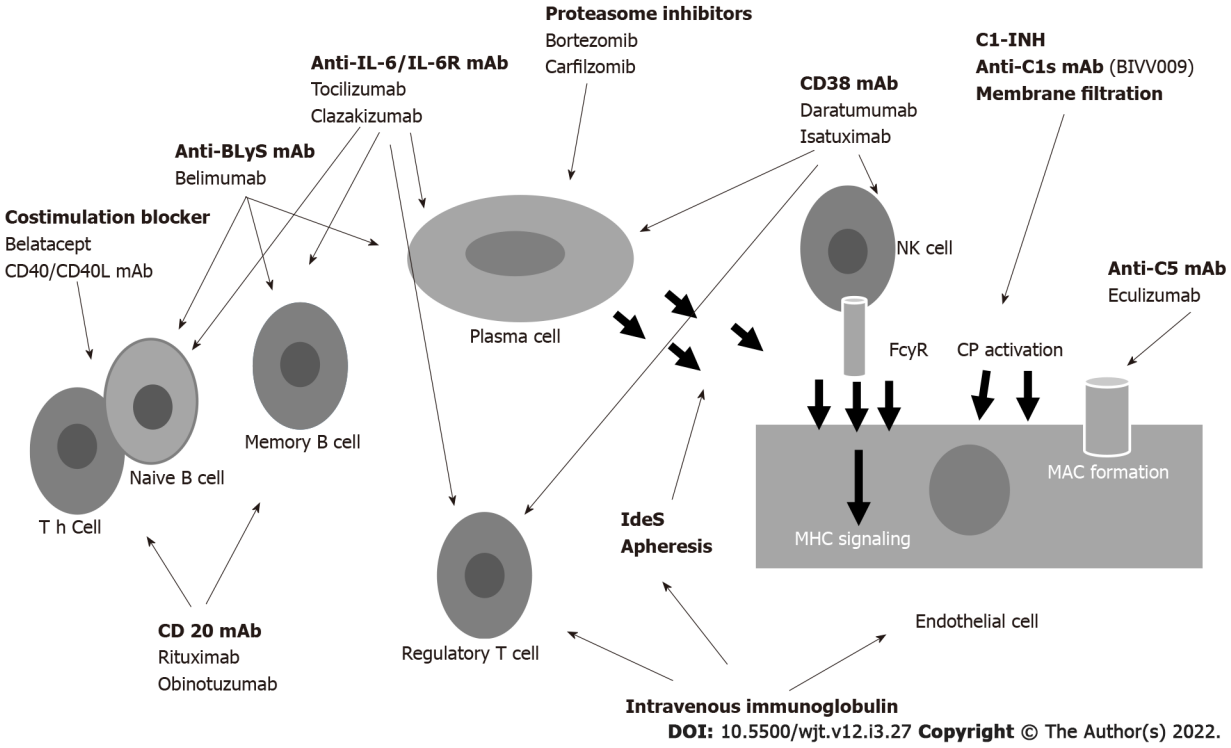


**Figure 4 Drugs acting at different levels to control the antibody formation.** BLyS: B Lymphocyte stimulating factor; mAb: Monoclonal antibody; C1-INH: C1 inhibitors; NK: Natural killer; Cp: Complement; FcyR: FcyReceptor; MAC: Membrane attacking complex; MHC: Major histocompatibility complex; IL: Interleukin.

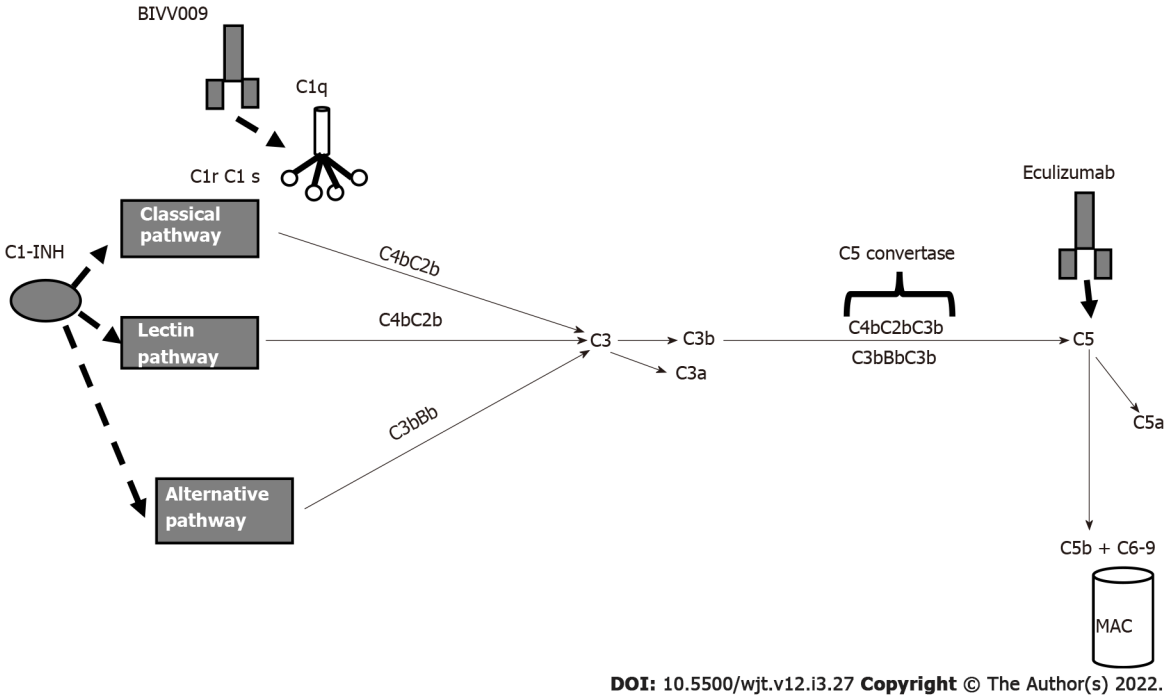


**Figure 5 Principal drugs affecting complement.** C1-INH: C1 inhibitor; MAC: Membrane attacking complex.

C1-INH regulates several pathways that contribute to complement activation and cause ABMR.

In 2015, in a phase I/II placebo-controlled trial, Vo *et al*[106] reported the efficacy of C1-INH in the prevention of ABMR in HLA-sensitized patients. Later, Montgomery *et al*[107] in a randomized controlled pilot study, documented the efficacy of C1-INH in controlling ABMR. More recently, two more studies are ongoing to document the efficacy of human plasma C1 esterase inhibition as an addition to the standard of care for the treatment of ABMR[108,109].

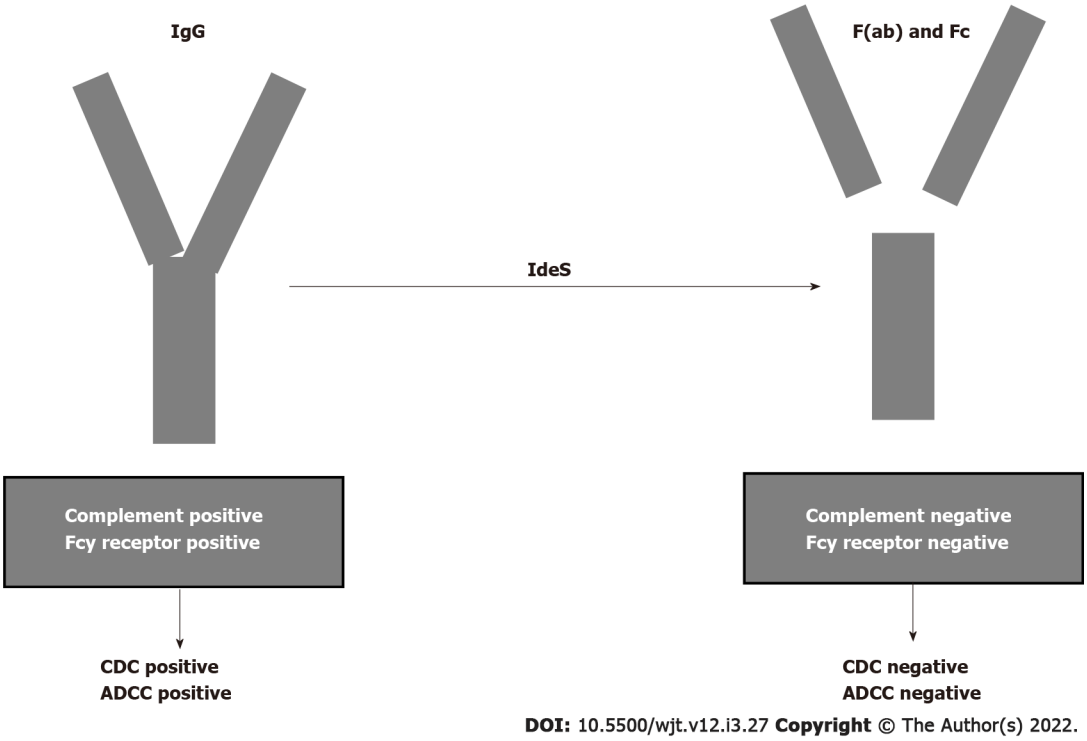


**Figure 6 Cleaving intact immunoglobulin G by imlifidase.** CDC: Complement dependent cytotoxicity; ADCC: Antibody dependent cell cytotoxicity; F(ab): Fragment ab; Fc: Fragment c; Ides: Imlifidase; IgG: Immunoglobulin G.

The humanized monoclonal antibody eculizumab binds to C5 with high affinity and prevents C5 convertase-mediated cleavage to C5a and C5b. In the past, several studies documented the efficacy of eculizumab in treating ABMR[110-112]. Recently, other studies documented the efficacy of eculizumab in treating and preventing ABMR[113,114]. Antibody removal is another therapeutic technique that may be applied primarily to desensitize patients with preformed DSAs before transplantation. Until recently, antibody removal and/or inhibition have been performed by plasmapheresis and IVIGs. Recently, it was documented that imlifidase (IdeS), a recombinant cysteine protease derived from Streptococcus pyogenes, rapidly cleaves IgG in the lower hinge region to a Fab fragment and a dimeric Fc fragment [115] (Figure 6). In addition to eliminating HLA antibodies, Ge *et al*[116] demonstrated that IdeS is a potent inhibitor of antibody-dependent cell cytotoxicity. A drawback of IdeS treatment is antibody recurrence after the interruption of the treatment. Incorporation of plasmapheresis and RTX to this treatment may overcome this drawback.

An international phase 2 trial was conducted in five transplant centers[117] for desensitization of cross-match-positive, highly sensitized kidney transplant recipients. Antibody rebound occurred 3-14 d after lipopolysaccharide administration, but graft survival at six months was 88.9%. The study conclusion was that IdeS converted positive cross matches to negative cross matches and achieved the transplantation of high-sensitized patients with optimal results at 6 mo.

In a more recent study, Kjellman *et al*[118] documented that lipifidase treatment administered to 39 cross-match-positive patients accomplished a 3-year graft survival of 93% with an ABMR incidence of 38% in the first month post-transplantation.

## CONCLUSION

Lack of interest by industries and optimal outcomes reached by the drugs used to date has resulted in little progress in finding new drugs. However, examining unmet needs in the field of kidney transplantation may help us to find new drugs. Needs not optimally covered by current drugs are control of DGF, improvement of the long-term immunosuppression with graft outcomes reduced by chronic damage and the control of desensitization and ABMR. The control of these needs is of outmost importance, considering the expanding numbers of new kinds of kidney transplantation as transplantation from older donors and from NHBDs and transplantation from antibody-incompatible donors.

In the first kind, controlling or reducing DGF is essential; in the latter kind, the reduction of antibodies against HLA is essential.

DGF may be controlled either with optimal management of the donor before or during kidney removal or with drugs attempting to target one of the multiple pathways involved in causing the IRI that is conducive to DGF.

New drugs are also emerging to control or reduce the antibody serum level. Several steps are involved in antibody generation and for each of those steps new drugs will be found.

In addition, drugs are able to reduce the nephrotoxicity induced by the long-term use of CNIs and to control kidney inflammation that may contribute to a worse graft outcome.

The majority of these drugs have been very recently found and are still in RCTs. Therefore, trials with novel agents require a careful approach and these new agents in transplantation face many challenges, but may provide a hopeful pipeline in this issue.

## FOOTNOTES

**Author contributions:** Salvadori M and Tsalouchos A contributed equally to the manuscript; Salvadori M designed the study, performed the last revision and provided answers to the reviewers; Tsalouchos A collected the data from literature; Salvadori M and Tsalouchos A analyzed the collected data and wrote the manuscript.

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*MINIREVIEWS*

# New onset hypertension after transplantation

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## Abstract

It has been reported that up to 90% of organ transplant recipients have suboptimal blood pressure control. Uncontrolled hypertension is a well-known culprit of cardiovascular and overall morbidity and mortality. In addition, rigorous control of hypertension after organ transplantation is a crucial factor in prolonging graft survival. Nevertheless, hypertension after organ transplantation encompasses a broader range of causes than those identified in non-organ transplant patients. Hence, specific management awareness of those factors is mandated. An in-depth understanding of hypertension after organ transplantation remains a debatable issue that necessitates further clarification. This article provides a comprehensive review of the prevalence, risk factors, etiology, complications, prevention, and management of hypertension after organ transplantation.

**Key Words:** New onset; Hypertension; Organ; Transplantation; Renal

**Core Tip:** This article provides a comprehensive review of the prevalence, risk factors, etiology, complications, prevention and management of hypertension after organ transplantation.

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## INTRODUCTION

The systolic blood pressure of more than 130 mmHg or diastolic blood pressure of above 80 mmHg leads to the development of hypertension requiring medical management *via* antihypertensive medications[1]. The primary and secondary blood pressure elevations potentially increase the risk of various cardiovascular complications. Secondary hypertension develops under the impact of several morbidities and comorbidities. Organ transplantation based on heart, kidney, lung, bone marrow, and liver predisposes 70%-90% of the treated patients to hypertension that potentially impacts their overall survival[2]. The development of posttransplant hypertension also leads to graft-related complications. The systematic prevention and control of organ transplant-related hypertension are paramount to reducing the risk of morbidity/mortality. This review elaborates on the complications, etiology, risk factors, prevalence, incidence, and medical management of hypertension occurring after organ transplantation.

## KIDNEY TRANSPLANTATION

Most of renal transplant recipients are already hypertensive before transplant. The prevalence of hypertension in end stage renal disease is around 70%-80%. Hypertension improves in some patients after renal transplantation with the improvement of the renal functions, many patients continue to have renal transplantation related hypertension after transplantation[3].

The renal transplantation-related hypertension prevalence among 47%-82% of children and 50%-80% adults potentially deteriorate their prognostic outcomes. However, the variations in hypertension prevalence between the patient populations potentially deteriorate their medical management and treatment outcomes. More than 27.6% of patients experience hypertension within one year of their organ transplantation. The utilization of immunosuppressants, organ rejection, graft dysfunction, long surgery duration, and advanced donor age are the significant factors that increase the risk of organ transplantation-related hypertension[4]. Other predisposing factors include post-biopsy arteriovenous fistula, post-transplantation glomerulonephritis/renal artery stenosis, and family history of hypertension among organ donors[5].

## HEART TRANSPLANTATION

Seventy percent of patients who receive heart transplants experience hypertension and its clinical complications[6]. The elderly hypertensive patients with heart transplant status often experience a marked reduction in estimated glomerular filtration rate and elevation in serum creatinine levels. The findings by United Network for Organ Sharing database indicate hypertension predisposition among heart transplant recipients with age sixty years or above compared to other age groups[7]. The clinical studies reveal a reduction in hypertension incidence among patients who undergo heterotrophic cardiac transplants[8]. The patients who receive an orthotopic heart transplant, however, experience a high risk for hypertension. The obese patients undergoing heart transplantation also remain highly predisposed to hypertensive heart disease. The dependence on steroids, calcineurin inhibitors, and other immunosuppressants further increase the risk of hypertension among heart transplant recipients. Medical literature correlates 70%-90% incidence of hypertension with the use of calcineurin inhibitors among heart transplant patients[9].

## LUNG TRANSPLANTATION

A reportable number of patients develop new-onset/episodic hypertension after undergoing lung transplantation. Medical literature confirms the cumulative prevalence of new-onset hypertension among 45% (at one year), 56% (at two years), and 63% (at three years) of lung transplant recipients. These patients frequently develop comorbidities, including diabetes mellitus and hypercholesterolemia [10]. The lung transplant patients who receive cyclosporine treatment or encounter blood pressure elevation (before transplant) also develop hypertension in many clinical scenarios[11].

## LIVER TRANSPLANTATION

Liver transplantation is the gold standard in a patient with end-stage liver disease. Immunosuppressive therapy is required to reduce rejection after transplantation[12]. Unfortunately, more than half of the liver transplant patients develop hypertension that impacts their prognosis and treatment outcomes six months after surgery. In addition, post-transplant hypertension develops among liver transplant patients based on their calcineurin inhibitor/steroid use, family history of hypertension, obesity, and older age. However, the tacrolimus use, and race of liver transplantation patients do not increase their risk for episodic hypertension[13].

## BONE MARROW TRANSPLANTATION

Approximately 2.4% of bone marrow transplant recipients develop pulmonary hypertension that potentially deteriorates their quality of life, life expectancy, and quality-adjusted life-years[14]. The progressive elevation in pulmonary vascular resistance often triggers right ventricular dysfunction and mortality among bone marrow transplant patients. Hemopoietic cell transplantation among adults and children predisposes them to systemic hypertension during the initial two years of their recovery. Sixty-one percent of adults/children experience new-onset hypertension within one month of their hemopoietic cell transplant[15,16].

### *Etiology*

The surgical interventions, immunosuppressive therapy/immune system deterioration, and recipient/donor factors potentially impact the hypertension etiology in patients with organ transplant status.

### *Donor factors*

Hypertension among organ transplant patients also develops under the impact of deceased donor renal graft[17]. Medical literature provides inclusive findings concerning the impact of donor hypertension on the hypertension predisposition of organ transplant patients; however, it independently increases the risk for renal allograft failure[18]. The donor's age often determines the post-transplant hypertension risk of the organ transplant candidates[19]. The kidney transplant patients whose donors exhibit a history of familial hypertension experience ten times greater risk of blood pressure elevation than the patients whose donors do not report a family history of hypertension[12]. The differences between the donors' age and body surface area and their organ recipients also predispose them to episodic hypertension. The nephron underdosing due to reduced recipient/donor body weight ratio potentially triggers chronic inflammation among organ transplant patients, which eventually predisposes them to diabetes mellitus, post-transplant hypertension, and chronic rejection of transplanted organs[20].

### *Recipient factors*

The clinical studies provide inconclusive evidence concerning the impact of behavioral patterns of organ transplant patients on their hypertension predisposition. However, alcohol consumption, smoking, salt intake, and obesity deteriorate the clinical outcomes of organ transplant patients and increase their risk of hypertension compared to the general population. The organ transplant candidates with pretransplant hypertension and obesity experience a high risk of posttransplant hypertension[17-22]. Stable kidney transplant patients with hypovolemia experience a high risk of elevated mean arterial/diastolic/systolic blood pressures[23]. Post-transplant hypertension also develops under the impact of comorbidities (including endocrine tumors and obstructive sleep apnea) and the age of the recipients.

### *Transplant renal artery stenosis*

The development of transplant renal artery stenosis (TRAS) under the impact of renal artery stenosis reduces the vascular supply to the allograft. TRAS triggers hypertension among 1%-5% of renal transplant recipients[24,25]. The initial six months to two years after organ transplant predispose the treated patients to TRAS-related complications[26]. TRAS manifests with transplant dysfunction,

water/salt retention, renal function deterioration, and refractory hypertension. The organ transplant patients eventually experience acute pulmonary edema and hypertensive crisis[26]. TRAS-induced hypoperfusion triggers renin-angiotensin-aldosterone system (RAAS) that potentiates renovascular hypertension in patients with organ transplant status[26]. The potential causes of transplant renal artery stenosis include immune-mediated endothelial deterioration, recipient/donor artery trauma, suturing techniques, donor artery atheroma, and renal artery lesions[27]. TRAS assessment relies on conventional angiography; however, TRAS correction and enhancement of blood pressure/renal perfusion warrants renal vascularization *via* PCTA (percutaneous transluminal coronary angioplasty)[26].

### Acute rejection and chronic allograft injury

Hypertensive crisis in organ transplant patients correlates with acute and chronic allograft injury. However, clinical studies provide inconclusive evidence concerning a causal relationship between hypertension and allograft deterioration[22].

### Acute rejection

The cases of acute organ rejection warrant diagnostic assessment concerning post-transplant hypertension. The therapeutic management of acute organ rejection often corrects the systolic and diastolic blood pressure elevations in organ transplant patients. These outcomes substantiate the acute organ rejection attribution of hypertension in organ transplant scenarios[22].

### Chronic graft injury

The chronic renal allograft injury emanates from recurrent glomerular disease, thrombotic microangiography, tubular atrophy, interstitial fibrosis, and chronic antibody-mediated organ rejection. The focal segmental glomerulosclerosis predominantly associates with hypertension in patients with organ transplant status. The current body of evidence provides inconclusive evidence concerning the cause-and-effect relationship between renal allograft dysfunction and hypertensive crisis among organ transplant patients. However, the findings from a preclinical study advocate the potential of hypertension to cause allograft deterioration in organ transplant scenarios[28].

### Immunosuppressive drugs

The toxic effects of immunosuppressive drugs often elevate the risk of hypertension among organ transplant patients.

### Steroids

The organ rejection prevention protocol concerning transplantation scenarios relies on the systematic administration of methylprednisolone and prednisone. Corticosteroid maintenance therapy potentially triggers a range of morbidities and comorbidities among patients with organ transplant status. It also increases their risk of hypertension to multiple folds. A plausible mechanism concerning steroid-induced hypertension attributes to volume expansion/sodium retention due to mineralocorticoid receptor overstimulation in organ transplant patients. The exclusion of steroids from the immunosuppressive therapy to mitigate the risk of hypertension could, however, trigger organ rejection and its fatal complications. A recently reported meta-analysis confirmed a 48% incidence of acute organ rejection in patients who did not receive steroids with their immunosuppressive therapies compared to 30% organ rejection incidence among patients who received steroid-controlled immunosuppressive treatments[29].

### Calcineurin inhibitors

The multifactorial characteristics of calcineurin inhibitor-induced hypertension are widely debated in the medical literature. The calcineurin inhibitors impact the function of the sodium-potassium pump/sympathetic nervous system and vascular tone that eventually triggers a hypertensive crisis in patients with organ transplants. They further induce nitric oxide metabolism by triggering nicotinamide adenine dinucleotide phosphate oxidase-induced angiotensin-II release in the context of intrarenal renin-angiotensin system activation[30]. Furthermore, renal/systemic vasoconstriction often develops under the impact of cyclosporine therapy[31]. The endothelial receptor type A across preglomerular arteries triggers endothelin production that eventually leads to renal vasoconstriction in organ transplant recipients[29,32]. The clinical studies demonstrated cardioprotective effects of tacrolimus compared to cyclosporin in the setting of organ transplantation[33]. They also reveal the superiority of tacrolimus over cyclosporin in controlling blood pressure elevations among organ transplant patients [21]. Research evidence confirms blood pressure elevation in organ transplant recipients on cyclosporin treatment after increasing their dietary sodium intake. This increase in blood pressure indicates the incidence of sodium-dependent hypertension among patients after their organ transplantation[34]. However, the clinical studies do not provide conclusive evidence related to the sodium retaining effects of calcineurin inhibitors in organ transplant scenarios[35]. However, the medical literature indicates the potential of cyclosporin inhibitors in elevating the activity of sodium-potassium chloride/sodium chloride cotransporters for maximizing sodium reabsorption in organ transplant patients[36]. The clinical studies also emphasize the possibility of replacing calcineurin inhibitors with sirolimus based on

its safety profile and least impact on the 24 h systolic blood pressures of patients with organ transplant status.

## PREVENTION MEASURES

Organ transplant-related hypertension prevention warrants the mitigation of risk factors that potentially aggravate systolic and diastolic blood pressures in the treated patients. These risk factors include native kidneys, donor hypertension, smoking, drug use, obstructive sleep apnea, and obesity[37,38]. The findings from various clinical studies recommend lifestyle/behavioral modifications and weight reduction strategies for organ transplant recipients to minimize their risk of postprocedural hypertension. They also advocate the need for evaluating suprarenal masses based on their hypertension attribution[39].

The long-term use of calcineurin inhibitors, including tacrolimus and cyclosporine among organ transplant patients, clinically correlates with their hypertensive crises. The clinical studies reveal a reduced impact of tacrolimus (compared to cyclosporine) on the blood pressure levels of organ transplant patients[40]. The organ transplant recipients who receive tacrolimus also exhibit a limited dependence on antihypertensive drugs for managing their blood pressure levels[37]. The clinicians accordingly recommend tacrolimus over cyclosporine for the medical management of organ transplant patients. The medical literature alternatively recommends the selective T-cell co-stimulation blocker (Belatacept) to control T cell proliferation and cytokine production in renal transplant patients for effectively managing their episodic hypertension[41].

The clinical studies further advocate the deleterious impact of corticosteroids on the blood pressure management of organ transplant patients. They provide substantial evidence concerning the dose-dependent relationship between corticosteroid utilization and hypertensive crisis in organ transplant scenarios. The clinicians accordingly recommend minimal dosages of steroids (for example, 5 mg per day dose of prednisone) to achieve long-term immunosuppression in organ transplant patients without increasing their risk for episodic hypertension[42].

The worsening of hypertension in kidney transplant patients clinically correlates with their antibody-mediated and acute cellular organ rejection[43]. The subsequent administration of immunosuppressive therapy (based on thyroglobulin, immunoglobulins, and steroids for reversing organ rejection) further exacerbates the hypertensive crisis[44]. These findings necessitate the development of comprehensive treatment protocols to minimize hypertensive crisis without compromising the outcomes of immunosuppressive therapies in organ transplantation scenarios.

The clinical studies reveal the impact of expanded criteria donor recipient status on worsening cardiovascular complications and hypertensive crises in patients with organ transplant status[45]. Organ transplant patients prevalently develop diabetes, chronic rejection, and hypertension under the impact of reduced donor/recipient body weight ratio[20]. Posttransplant hypertension also triggers under the impact of aortorenal donor atheroma in various clinical scenarios[19]. The medical literature accordingly recommends selecting young and normal-weight donors without a confirmed diagnosis of hypertension or atherosclerosis to minimize the risk of hypertension among organ transplant patients.

A range of genetic factors contributes to the development of hypertensive crises in organ transplant patients. The presence of apolipoprotein L-1 variants in deceased African American donors potentiates early graft dysfunction and eventual blood pressure elevation in the recipients of transplanted organs. The polymorphisms in CYP3A5, ABCC2, and ABC1 transporters further attribute to posttransplant hypertension and poor graft survival in organ transplant scenarios[46,47]. The assessment of these genetic mechanisms and factors is paramount to minimizing the risk of posttransplant hypertension among organ transplant patients.

Post-transplant hypertension also develops under the impact of transplanted renal artery stenosis following kidney transplantation[48]. The clinical studies reveal substantial improvements in blood pressure levels of organ transplant patients after the medical management of their renal artery stenosis [49]. These findings substantiate early diagnosis and therapeutic management of renal artery stenosis to reduce the incidence of posttransplant hypertension and its critical complications.

The therapeutic management of posttransplant hypertension relies on the systematic administration of calcium channel blockers, beta-blockers, and loop diuretics (for volume optimization). The normalization of serum potassium levels and enhancement of kidney function of organ transplant patients further depends on angiotensin receptor blockers and angiotensin-converting enzyme inhibitors[38].

The hypertension risk factors among liver transplant recipients include new-onset hepatic steatosis, alcoholic cirrhosis, and rapamycin use[50]. These findings advocate the need for monitoring organ transplant patients on mTOR inhibitor therapies to reduce their incidence of hypertensive crises.

The patients with allogenic hematopoietic stem cell/bone marrow transplant experience a high risk of hypertension based on several factors including graft *vs* host disease, mycophenolate/calcineurin inhibitor therapies, and lymphoma/Leukemia history[51]. Other hypertension predisposing factors concerning stem cell transplant scenarios include serum creatinine elevation, sinusoidal obstruction syndrome, amphotericin-B therapy, and the young age of the patients in pediatric hematopoietic stem

cell transplant[15]. The clinical studies accordingly advocate consistent monitoring of the bone marrow transplant patients based on their dependence on amphotericin-B, mycophenolate, and calcineurin inhibitors.

## DIAGNOSTIC PARAMETERS

The diagnostic assessment of hypertension in organ transplant scenarios relies on 24 h ambulatory/home/office blood pressure monitoring interventions. The office blood pressure assessment warrants the recording of three consecutive blood pressure readings and calculation of their mean value. The home blood pressure monitoring requires averaging two blood pressure readings obtained at home within a tenure of 4 days. The 24 h ambulatory blood pressure assessment relies on averaging various blood pressure readings obtained within a day's duration *via* a digital blood pressure monitor[1]. The 24 h blood pressure evaluation also helps categorize systolic/diastolic blood pressure levels based on their reverse dipping, dipping, and non-dipping patterns.

The clinical studies emphasize marked differences between clinical blood pressure monitoring, home blood pressure assessment, and ambulatory blood pressure monitoring. These studies also advocate the requirement of practicing care and caution while measuring the blood pressure levels of organ transplant patients. The clinical findings prioritize the use of ambulatory blood pressure monitoring for investigating the occurrence of whitecoat/masked/nocturnal hypertension to rule out the risk of cardiovascular complications[52].

The medical literature reveals a substantial increase in night-time systolic blood pressure following kidney transplantation[53]. The 24 h ambulatory blood pressure monitoring effectively tracks nocturnal blood pressure variations in organ transplant patients[54]. This blood pressure evaluation approach is the method of choice for tracking posttransplant hypertension and is recommended over home/office blood pressure monitoring interventions[55].

The diagnostic affirmation of posttransplant hypertension thoroughly relies on the appropriate use of blood pressure recording interventions. The blood pressure monitored at the physician's office may not give an accurate outcome based on the risk of masked/whitecoat hypertension and circadian variation/diurnal rhythm. Masked hypertension could increase the risk of native kidney disease among renal transplant patients[56]. However, clinical studies do not provide conclusive findings determining the impact of masked hypertension on the outcomes of renal transplant patients. These diagnostic intricacies warrant the use of automated electronic devices for blood pressure monitoring to minimize the risk of masked hypertension and the whitecoat effect in organ transplant scenarios[57].

The medical literature advocates optimizing blood pressure cutoff limits to accurately identify the existence or absence of hypertension and initiate antihypertensive therapies for organ transplant patients. The diagnostic parameters for assessing hypertension in posttransplant scenarios rely on the following parameters[4]: Office blood pressure reading of greater than 140/90 mmHg.

An ambulatory blood pressure reading of greater than 135/85 mmHg (awake state) and 120/70 mmHg (sleeping state) The recommendations by KDIGO (Kidney Disease Improving Global Outcomes) advocate the need to administer antihypertensive therapies to kidney transplant patients following their blood pressure elevation above 130/80 mmHg[58].

## MAJOR COMPLICATIONS

Approximately 50%-80% of adult organ transplant recipients develop hypertension and its clinical complications. The past medical history of hypertension further increases the incidence of post-transplant hypertension. Additionally, the old age of donors, elevated body mass index, male gender, and African American race include the significant demographic factors attributing to the development of hypertension among organ transplant patients[43].

### *Types of complications*

Medical literature reports a 50% prevalence of hypertensive among patients with organ transplant status[43]. Posttransplant hypertension predominantly triggers graft dysfunction and cardiovascular events in organ transplant patients that eventually lead to their renal failure. The cardiovascular complications related to posttransplant hypertension include coronary artery disease and congestive heart failure. Uncontrolled hypertension in the setting of kidney transplants potentially disrupts cardiorenal outcomes by impacting the overall functions of the heart and renal allograft[21,59].

### *Cardiovascular complications due to post-transplant hypertension*

The recipients of kidney transplants experience a 3%-5% incidence of non-fatal/fatal cardiovascular episodes. They further experience a 50-fold predisposition to cardiorenal complications compared to the general population[60]. Posttransplant mortality often attributes to critical cardiovascular complications

emanating from hypertensive crises. The cardiovascular compromise develops under the impact of posttransplant hypertension and elevates the incidence of morbidity/mortality among the treated patients. The cardiovascular episodes attribute to forty percent of patient deaths in the setting of a kidney transplant[4]. The predominant cardiovascular complications emanating from posttransplant hypertension include stroke, arterial narrowing, coronary artery disease, congestive heart failure, and ischemic heart disease. The kidney transplant scenarios also report a high incidence of diastolic dysfunction, left atrial enlargement and left ventricular hypertrophy. Heart failure with decreased left ventricular ejection fraction potentially increases the mortality risk among organ transplant patients. The clinical studies reveal a strong association between nocturnal hypertension and left ventricular hypertrophy in various organ transplant scenarios[4].

### *Graft dysfunction due to post-transplant hypertension*

The graft dysfunction in posttransplant scenarios predominantly develops under the impact of hypertensive crisis. The deterioration in renal function also correlates with blood pressure elevation in the setting of organ transplants. The renal allograft injury triggered by posttransplant hypertension-induced kidney failure further aggravates episodic hypertension and its potential manifestations[43]. The clinical studies continue to examine the relationship between independent allograft survival and blood pressure levels of organ transplant patients.

The retrospective study by Opelz *et al*[61] (1998) based on 29571 renal transplant recipients revealed the adverse impact of posttransplant hypertension on the renal allograft injury patterns[61]. Another clinical study indicated improvements in cardiovascular mortality and renal allograft function after therapeutic management of systolic blood pressure of patients within 1-3 years of their kidney transplantation[22]. The study outlined positive clinical outcomes in organ transplant recipients with a marked reduction in systolic blood pressure (below 140 mmHg).

A clinical study revealed improvements in renal transplant survival rates among patients with reduced diastolic pressures (ranging between 89-99 mmHg). The study findings advocated the need for monitoring mean arterial/diastolic/systolic blood pressures of the renal transplant patients until one year after transplantation to enhance their allograft survival. The study outcomes further correlated the risk of allograft failure for every 10 mmHg diastolic/systolic blood pressure elevation[61]. The clinical studies also indicate blood pressure reduction is a protective factor for kidney transplant recipients during the initial year of their recovery[4,22]. The evidence-based findings clinically correlate graft failure/chronic allograft nephropathy, renal failure, and cardiovascular compromise with posttransplant hypertension. Organ transplant patients with hypertension accordingly experience a high risk of morbidity and mortality[61].

## MEDICAL MANAGEMENT

The treatment guidelines for managing posttransplant hypertension do not differ from the therapeutic protocols adopted for treating hypertension/blood pressure elevation among patients with a high risk for cardiovascular complications (Table 12-3). The clinical studies reveal the impact of diabetes/proteinuria and cardiovascular conditions on the blood pressure elevation in organ transplant patients. The maintenance of systolic/diastolic blood pressure below 140/90 mmHg is highly necessary to reduce the risk of posttransplant hypertensive crisis. The multifactorial origin of posttransplant arterial hypertension in renal transplant cases warrants its systematic monitoring and medical management. Posttransplant hypertension/hypertensive crisis further intensifies under the impact of allograft nephropathy and immunosuppressive therapies. The diagnostic interventions to track and evaluate the causative factors of posttransplant hypertension include assessing 24 h urinary sodium, proteinuria, 24 h urine clearance, renal function tests, and hepatic panel. The candidates for kidney transplantation qualify for renal ultrasound in the context of evaluating their urinary tract blockage and renal artery stenosis.

The pretransplant hypertension of kidney transplant recipients warrant antihypertensive therapy. The clinical studies reveal rare cases (concerning kidney transplantation) that achieve normotensive status in the absence of antihypertensive therapy. These outcomes necessitate pharmacological management of hypertension of kidney transplant patients to reduce the risk of their cardiovascular complications[22]. The non-pharmacological approaches for hypertension management in kidney transplant scenarios rely on lifestyle modification, stress reduction, weight management, smoking cessation, low-salt diet, and exercise management. Clinical studies need to explore the complex interplay between pharmacodynamics and pharmacokinetics of antihypertensive medications to optimize their use in organ transplant scenarios. They also need to investigate drug-drug interactions and their impact on comorbidities and hypertension management of organ transplant patients[62].

The renal transplant scenarios report a high incidence of hypertension emanating from corticosteroid therapy. The novel organ transplantation protocols advocate the exclusion of corticosteroid treatment to minimize the risk of hypertensive crises or episodic hypertension[22]. However, the clinical studies provide inconclusive evidence concerning the discontinuation timings of steroid therapies for renal

**Table 1 Management for hypertension following renal transplantation**

| Blood pressure management | Interventions | Comments |
|---|---|---|
| Non-pharmacological management | Dietary sodium restriction; Weight reduction; Exercise; Smoking cessation; Stress reduction | |
| Pharmacological therapy | Antihypertensive medications: -Diuretics; -Calcium channel blockers; -Beta-blockers; -Renin-angiotensin aldosterone system blockade; -Alpha1 antagonists; -Alpha 2 agonists | Medication choice depends on patient characteristics, adverse effects, tolerability |
| Invasive interventions | -Transplant renal artery angioplasty +/- stenting; -Continuous positive airway pressure; -Bilateral native nephrectomy; -Native renal denervation | -Transplant renal artery stenosis; -Obstructive sleep apnea; -Failed native kidney; -Sympathetic overactivity |
| Adjustment of Immunosuppressive Medication | -Steroid withdrawal protocol; -Minimize dose of calcineurin inhibitors; -Replace CsA by using less hypertensive and less nephrotoxic drugs | Other drugs that can be used: -MMF: Mycophenolate mofetil; -Tacrolimus; -Sirolimus |

**Table 2 Target Blood pressure guideline for kidney transplant recipients**

| Medical Society/Guideline | Recommended BP target |
|---|---|
| ACC/AHA[65] | < 130/80 mm Hg |
| JNC 8 (2014)[66] | Not defined |
| Kidney disease outcomes quality initiative (KDOQI)[67] | -Goal of 125/75 mm Hg for transplant recipients with proteinuria. -Goal of 130/85 in the absence of proteinuria |
| Kidney disease: Improving Global outcomes (KDIGO)[68] | < 130/80 |
| European Best Practice Guidelines for Renal Transplantation 2002[19] | Target BP ≤ 125/75 mm Hg in proteinuria patients |
| Canadian Society of Nephrology[69] | Patients with significant proteinuria; Target Blood pressure is < 130/80 mm Hg |
| British Renal Association[70] | < 130/80 mm Hg |

A reasonable target blood pressure is < 140/90 mmHg for transplant recipients who do not develop proteinuria. (Are you sure about the recommended first line agents?)

transplant patients. The researchers continue to debate regarding the early or late withdrawal of steroid treatments in organ transplant scenarios. Few clinical studies alternatively negate the contention related to the impact of steroid therapies on the hypertensive crisis of organ transplant patients[37].

The medical literature provides some evidence concerning the need for manipulating the currently deployed immunosuppressive therapies to optimize the hypertension management of patients with organ transplant status. This belief reciprocates with the adverse impact of immunosuppressive treatments on posttransplant hypertension. Clinical studies showed that cyclosporine increases the risk of posttransplant hypertension compared to tacrolimus[63]. Furthermore, clinical studies also confirm a marked reduction in systolic/diastolic blood pressures following the dose reduction of cyclosporine or its replacement with tacrolimus in organ transplant scenarios[41]. These findings warrant investigation concerning the hypertension induction effect of cyclosporine in organ transplant patients. The impact of cyclosporine on renal sodium retention probably triggers vasoconstriction of glomerular arterioles leading to posttransplant hypertension[43].

Posttransplant hypertension management primarily relies on first-line therapies based on dihydropyridine calcium channel blockers since they effectively minimize calcineurin-induced vasoconstriction. The beta-blocker therapies further improve the survival rate of organ transplant recipients irrespective of their predisposition to cardiovascular complications[64]. The antihypertensive therapies in organ transplant scenarios must exclude ACE (angiotensin-converting enzyme) inhibitors during the initial 3-6 mo based on the risk of hyperkalemia, anemia, and reduction in glomerular filtration rate[2].

The medical literature provides evidence concerning the development of posttransplant hypertension despite administering antihypertensive therapies. The evidence-based findings elaborate on the necessity for renal arteriography to rule out renal artery stenosis in organ transplant patients. The patients who develop more than 80% renal arterial stenosis qualify for percutaneous transluminal angioplasty. Renal denervation is another viable therapy with the potential to manage refractory hypertension in organ transplant scenarios[4].

**Table 3 Studies regarding the management of posttransplant hypertension**

| | Study type | Title | Ref. | Intervention | Outcome | Conclusion |
|---|---|---|---|---|---|---|
| 1 | Four cross-sectional Retrospective analysis | Treatment of Hypertension in Renal Transplant Recipients in Four Independent Cross-Sectional Analysis | Kuxmiuk-Glembin *et al*[64], 2018 | -Beta-blockers 80%); -Calcium channel blockers (53%); -Diuretics (37%); -Alpha-blockers (35%); -Angiotensin-converting enzyme inhibitors (ACEi) (32%); -ARB (7%) | Blood pressure controlled using BB (43.9 controlled, 56.1 not controlled $P$ = 0.007); -Number of antihypertensive agents: 2.43 +/- 1.3 (controlled BP); 1.88 +/- 1.5 (Uncontrolled BP) $P$ < 0.001. -ACEI &/ARB: Yes: 57.1 (controlled, 42.9 (Uncontrolled); No ACEI/ARB: 48 (Controlled), 52 (uncontrolled) $P$ = 0.08 | The commonly used monotherapy agents:-BB followed by CCB. -Use of ACEI, diuretics, and alpha-blockers was about the same. -ARB therapy was least utilized. -Significant increase was observed in the mean number of antihypertensive drugs per patient in subsequent years |
| 2 | Randomized controlled trials systemic review | Antihypertensive treatment for kidney transplant recipients | Cross *et al* [71], 2009 | 60 studies involving 3802 recipients. -29 studies (2262 participants) compared calcium channel blocker to placebo/no treatment. -10 studies (445 participants) compared ACEi to placebo/no treatment. -7 studies (405 participants) compared CCB to ACEi | -CCB compared to placebo/no treatment reduced graft loss (RR 0.75, 95%CI: 0.57-0.99) and improved glomerular filtration rate (GFR), (MD, 4.45 mL/min, 95%CI: 2.22-6.68). -ACEi versus placebo/no treatment were inconclusive for GFR (MD -8.07 mL/min, 95%CI: -18.57-2.43) and variable for graft loss, precluding meta-analysis. -Direct comparison with CCB, ACEi decreased GFR (MD -11.48 mL/min, 95%CI: -5.75 to -7.21), proteinuria (MD -0.28 g/24 h, 95%CI: -0.47 to -0.10), hyperkalaemia (RR 3.74, 95%CI: 1.89-7.43) | CCB may be used as first-line agents for hypertensive kidney transplant recipients. ACEi have few detrimental effects in kidney transplant recipients |
| 3 | Double-blind, randomized, placebo-controlled trial. | Angiotensin II blockade in kidney transplant recipients. | Ibrahim *et al*[72], 2013 | -The effect of losartan compared to placebo and initiated within three months of transplantation | Doubling of renal cortical volume – Measure of interstitial fibrosis/tubular atrophy | -Use of losartan tended to be protective, with an odds ratio (OR) of 0.39 (95%CI: 0.13–1.15, $P$ = 0.08). -Losartan had no significant effect on time to a composite of ESRD, death, or doubling of creatinine level. The mean time to doubling of serum creatinine was longer in the losartan group, compared with placebo (1065 versus 450 d [hazard ratio (HR) 7.28, 95%CI: 2.22–32.78]) |
| 4 | Prospective Controlled Trial | Converting-enzyme inhibitor versus calcium antagonist in cyclosporine-treated renal transplants | Mourad *et al*[73], 1993 | -6 mo after transplantation, patients were randomly allocated to treatment by the angiotensin-converting enzyme inhibitor lisinopril (ACEI, alone or associated with frusemide; $n$ = 14), or the calcium antagonist, nifedipine (CA, alone or associated with atenolol; $n$ = 11) | -Before initiation of antihypertensive therapy, the two groups had similar mean arterial pressures and GFRs. -Both ACEI and CA treatments were associated with no change in renal function, a similar change in mean arterial pressure (ACEI -18 +/- 3; CA -13 +/- 5 mm Hg), and identical trough blood levels cyclosporine | In cyclosporine-treated transplant recipients, satisfactory control of hypertension was obtained by ACEIs based on their potential to minimize arterial pressures |
| 5 | Prospective Randomized Trial | Randomized trial of steroid withdrawal in kidney recipients treated with mycophenolate mofetil and cyclosporine | Pellitier *et al*[74], 2006 | -121 patients were randomized either to discontinue or remain on steroids (60 patients per group) | There were no significant differences in patient and graft survival rates at 1 year or at last follow-up (approximate 3.7y). -Incidence of acute and chronic rejection as well as graft function were the same within 1 yr | Steroid withdrawal in low-risk kidney transplant recipients is safe and ameliorates many of the unwanted side effects of steroid use |
| 6 | Retrospective study | Lack of long-term benefits of steroid withdrawal in renal transplant recipients | Sivaram *et al*[75], 2001 | -Retrospective review identified 58 patients administered cyclosporine, azathioprine, and prednisone who underwent complete steroid withdrawal | -Post-steroid withdrawal follow up: 7.6 +/- 1.9 years; -9 patients restarted therapy; 3 patients lost their graft (2 of which are those who restarted prednisone therapy). -2 died with functioning grafts | When prednisone dosage was tapered from 10 mg/d to 10 mg every other day, clinically significant improvements were seen in weight, systolic and diastolic blood pressures, glycosylated hemoglobin levels, and diabetes-related outcomes |

## CONCLUSION

Posttransplant hypertension increases the risk of graft-related complications in patients with a known history of (pretransplant) hypertension. Steroids, cyclosporine, calcineurin inhibitors, and other immunosuppressive drugs further increase the predisposition of organ transplant patients to hypertension. Hemopoietic cell transplantation predominantly adds to the 2-year risk of systemic hypertension in children and adults. The donor factors for episodic hypertension attributes to the donors' age and body surface area. The recipient factors, however, include hypovolemia and pre-existing comorbidities. TRAS-induced hypoperfusion triggers RAAS that potentiates renovascular hypertension in organ transplant patients. Posttransplant hypertension is a significant cause of cardiovascular complications and graft dysfunction. The 24 h blood pressure monitoring is, therefore, necessary to effectively manage hypertensive crises in organ transplant recipients. The evaluation also helps categorize systolic/diastolic blood pressure levels based on their reverse dipping, dipping, and non-dipping patterns.

## FOOTNOTES

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MINIREVIEWS

# In memoriam of Thomas Earl Starzl, the pioneer of liver transplantation

Sezai Yilmaz, Sami Akbulut

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## Abstract

Starzl's nearly 3000 publications that contribute to the science of transplantation in every field have been the most important resources for every scientist working in this field. For those of us who work in the liver transplant field, his contributions throughout his life have shaped our career and passion, even for those who have never met, spoken to, or worked with him. If we are able to help patients with liver failure today by offering them the chance of transplantation, it is because of Starzl's passionate work and efforts. Thanks to Starzl's scientific legacy, hundreds of scientists serve humanity and thousands of patients can hold on to life. It has been an honor for us to write this article about Professor Starzl.

**Key Words:** Liver transplantation; Thomas Earl Starzl; Pioneer of liver transplantation



**Core Tip:** Starzl's nearly 3000 publications that contribute to the science of transplantation in every field have been the most important resources for every scientist working in this field. Thanks to Starzl's scientific legacy, hundreds of scientists serve humanity and thousands of patients can hold on to life thanks to this legacy. It has been an honor for us to write this article about Professor Starzl.

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## INTRODUCTION

Thomas Earl Starzl was born March 11, 1926, in LeMars, Iowa[1]. He received his medical degree from Northwestern University[1]. He worked at the University of Colorado as a surgeon from 1962 until 1981. Thomas Earl Starzl, MD, PhD, a surgeon who was a pioneer of liver transplantation (LT) died at the age of 91 years on Saturday, March 4, 2017 at his home in Pittsburgh, Pennsylvania[1,2]. Starzl is called "the Father of Modern Transplantation"[1-3]. Starzl's death deeply saddened all liver transplant surgeons around the world. A better understanding Professor Starzl, requires mentioning his biography and the first liver transplant.

He performed the world's first liver transplant in Denver on March 1, 1963 in a child, named Bennie Solis[4,5]. Bennie Solis belonged to a Spanish American family, and suffered from biliary atresia. Bennie's donor was another child who died during open heart surgery. The donor was already on a heart-lung machine for artificial circulation and the body temperature was cooled for organ preservation until the family gave consent for donation of the liver. Starzl and colleagues had performed nearly two hundred LTs in dogs. It took several hours just to make the incision and enter the abdominal cavity. Dissection was very difficult due to high-pressure venous collaterals as a result of portal hypertension. Previous operations resulted in highly vascularized and rough scar tissue that encased the liver. Bennie also had severe coagulopathy. Pharmaceutical or other human-derived factors that should have been used to prevent hemorrhage and deficiency of coagulation factor were not easily available. Bennie bled to death as Starzl tried everything to stop the hemorrhage. The transplantation could not be performed. Despite the fact that Bennie was three years old, he spent every day of his short life in agony. When his wound was closed and his body was washed and prepared the surgical team burst into tears. Starzl and his team remained in the operating room for a long time without saying a word. Starzl has always stated "it was not the last time that I would see this scene, both in my dreams and in reality". Ever since, I have not heard anybody describe it as a case of Solis or the first human LT.

The efforts made during the process of initiating kidney transplants in research laboratories should now be made for LT which is a more difficult procedure. The main lesson to be learned from Bennie Solis's surgery was dealing with the clotting problems in severe liver disease. An expert named Von Kaulla who was working on the coagulation pathway at the time was recruited to the team. Von Kaulla made important contributions such as the definition of fibrinolysis and recommending the use of epsilon amino caproic acid and specific coagulation agents in LT[6]. Moreover, the prompt transplantation of a well-functioning liver graft was essential.

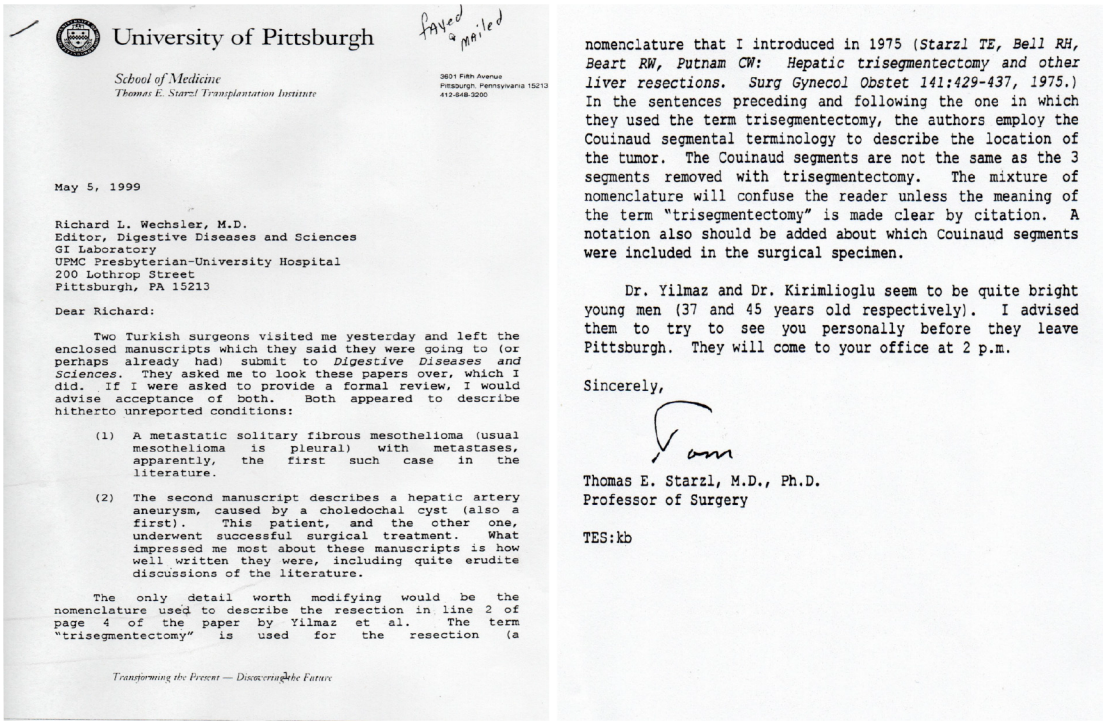
After the first 7 unsuccessful liver transplants (5 were performed by Starzl), a voluntary moratorium was declared that lasted for 3.5 years. Starzl then performed the first successful liver transplant in 1967 with long-term survival, after having experienced this battle many times and having been defeated in each time[7]. An 19-mo-old girl named Julie Rodriguez underwent LT for hepatoblastoma. Julie lived 400 d and unfortunately passed away due to metastatic recurrence of her tumor.

In 1968, the liver transplant program at the University of Colorado was bolstered by the liver transplant program initiated by Roy Calne at Cambridge University. Starzl particularly emphasized the following statements "the fate of liver transplantation would depend on an unspoken transatlantic alliance between Cambridge and Denver". Calne has made undeniable contributions related to the use of 6-mercaptopurine, azathioprine, and cyclosporine in transplantation[8,9].

Professor Starzl then went to the University of Pittsburgh which became the busiest transplant center in the world. In 1996, the transplant institute was renamed in Starzl's honor. Starzl combined azathioprine and prednisone as a strategy that made renal allograft transplantation possible. He repeated the same steroid strategy to improve the success of LT. Starzl pioneered the use of cyclosporine in the 1970s and tacrolimus in the 1990s[10-12]. The success of these treatments has revolutionized all organ transplants. Starzl performed baboon-to-human liver xenotransplantation in 1992[13]. This patient lived 72 d. It was also a milestone for future generations. Thomas Starzl's worked on organ preservation, abdominal multi-visceral transplantation, chimerism or immunotolerance are all revolutionary advances in the field of transplantation[14]. Thanks to his work, the National Institutes of Health's consensus report stated that liver transplant is now an acceptable treatment for end-stage liver disease.

### *Special comment (Professor Sezai Yilmaz)*

I would like to briefly talk about my story regarding Professor Starzl. In the last months of 1998, I was assigned to University of Pittsburgh Medical Center (UPMC) as a visiting research fellow to initiate the LT program at Inonu University as a general and gastrointestinal surgery specialist. The director of the UPMC Thomas Starzl Transplantation Institute at that time was Professor John Fung. I received great help from Professor John Fung and transplantation surgery fellow Dr Daniel Katz during the registration and initial periods of my clinical work. This is how I met Starzl: Dr Vedat Kirimlioglu, my colleague from Malatya Inonu University had come to Pittsburgh for a period of one month. We made an appointment with Starzl's secretary and went to visit him. It was actually a courtesy visit. Dr Kirimlioglu presented embroidered copper gifts to Professor Starzl, which were local art items he had brought from Turkey. I presented the dried apricots and pistachios that I planned to give to Starzl and Fung on my way from Malatya. In his 2-storey wooden office located on Fifth Avenue, opposite UPMC



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May 5, 1999

Richard L. Wechsler, M.D.
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Dear Richard:

Two Turkish surgeons visited me yesterday and left the enclosed manuscripts which they said they were going to (or perhaps already had) submit to *Digestive Diseases and Sciences*. They asked me to look these papers over, which I did. If I were asked to provide a formal review, I would advise acceptance of both. Both appeared to describe hitherto unreported conditions:

(1) A metastatic solitary fibrous mesothelioma (usual mesothelioma is pleural) with metastases, apparently, the first such case in the literature.

(2) The second manuscript describes a hepatic artery aneurysm, caused by a choledochal cyst (also a first). This patient, and the other one, underwent successful surgical treatment. What impressed me most about these manuscripts is how well written they were, including quite erudite discussions of the literature.

The only detail worth modifying would be the nomenclature used to describe the resection in line 2 of page 4 of the paper by Yilmaz et al. The term "trisegmentectomy" is used for the resection (a nomenclature that I introduced in 1975 (*Starzl TE, Bell RH, Beart RW, Putnam CW: Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 141:429-437, 1975.*) In the sentences preceding and following the one in which they used the term trisegmentectomy, the authors employ the Couinaud segmental terminology to describe the location of the tumor. The Couinaud segments are not the same as the 3 segments removed with trisegmentectomy. The mixture of nomenclature will confuse the reader unless the meaning of the term "trisegmentectomy" is made clear by citation. A notation also should be added about which Couinaud segments were included in the surgical specimen.

Dr. Yilmaz and Dr. Kirimlioglu seem to be quite bright young men (37 and 45 years old respectively). I advised them to try to see you personally before they leave Pittsburgh. They will come to your office at 2 p.m.

Sincerely,

Thomas E. Starzl, M.D., Ph.D.
Professor of Surgery

TES:kb

*Transforming the Present — Discovering the Future*

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**Figure 1 Letter from Professor Starzl to the editor of Digestive Diseases and Sciences (original version).**

Presbyterian Hospital, he welcomed us with his secretary and his dog. We spent a very long and pleasing time together that day. He offered us coffee. We even talked about the Bosnian War, which was taking place in those years. Afterwards, we sat outside on the terrace and even took pictures there with the three of us and his dog. Later, I stated that I had prepared two medical articles and wanted to get his comments on them. Starzl took the printed-out articles and said he would evaluate them. We said goodbye to him and left. Early the next day, while I was at my home, I received a phone call from Starzl's secretary who said that Starzl was waiting for me in the office at 1:00 pm. I was so surprised. I quickly got ready and went first to the hospital and then to Starzl's office. He greeted me again with a smile and said that he liked my articles. He told me that I needed to make some corrections regarding hepatectomy terminology. He gave me a letter and asked me to forward it to Richard Wechsler at the Gastrointestinal Laboratory a few hundred yards away. I left after thanking him. The envelope was open. The letter consisted of 2 separate pages and had 2 copies. He probably made a copy for me. It was there that I learned that Richard L. Wechsler was the editor of Digestive Diseases and Sciences. When I got to Wechsler's office, he immediately accepted me. I realized that Starzl had already talked to Wechsler about me. I handed him the letter and had a coffee then left. I read the letter line by line without missing a word. I would like to summarize Starzl's statements.

"Two Turkish surgeons visited me yesterday and left the enclosed manuscripts. They asked me to review these papers, which I did. If I were asked to provide a formal review, I would advise acceptance of both. Both appeared to describe hitherto unreported conditions (metastatic solitary fibrous tumor of liver and hepatic artery aneurysm caused by choledochal cyst). Dr Yilmaz and Dr Kirimlioglu seem to be quite bright young men (37 and 45 years old, respectively)" (Figure 1). Both these articles were published in the first issue of Digestive Diseases and Sciences[15,16]. This was an unforgettable moment for me and I was faced with the image of an exemplary scientist-mentor. Later, I met Starzl several times while visiting his transplant ward and at interesting coffee shops in Pittsburgh during those years. I have always seen his kind, loving and affectionate personality.

## CONCLUSION

In conclusion, Professor Starzl's nearly 3000 publications that contribute to the science of transplantation in every aspect and has been the most important resources for every scientist working in this area. For those of us who work in the liver transplant field, his lifetime contributions have defined our career and passion. Even for those individuals who have never met, talked to, or worked with him are affected by this work and efforts. If we can help patients with liver failure today by offering them the chance of LT, this is because of the passionate work and efforts of Starzl. Thanks to Starzl's scientific legacy, hundreds of scientists serve humanity and thousands of patients can hold on to life. It has been an honor for us to

write this article about Professor Starzl.

## FOOTNOTES

**Author contributions:** Yilmaz S and Akbulut S wrote the manuscript; Akbulut S and Yilmaz S reviewed the final version.

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*MINIREVIEWS*

# Autoimmune hepatitis and liver transplantation: Indications, and recurrent and *de novo* autoimmune hepatitis

Murat Harputluoglu, Ali Riza Caliskan, Sami Akbulut

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## Abstract

Autoimmune hepatitis is a chronic inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum globulin levels. Liver transplantation may be required for patients with acute liver failure, decompensated cirrhosis, and hepatocellular carcinoma. Recurrence is defined as development of the same disease in the allograft following liver transplantation. Autoimmune hepatitis recurs in 36%-68% of the recipients 5 years after liver transplantation. *De novo* autoimmune hepatitis is the development of autoimmune hepatitis like clinical and laboratory characteristics in patients who had undergone liver transplantation for causes other than autoimmune hepatitis. Diagnostic work up for recurrent and *de novo* autoimmune hepatitis is similar to the diagnosis of the original disease, and it is usually difficult. Predniso(lo)ne with or without azathioprine is the main treatment for recurrent and *de novo* autoimmune hepatitis. Early diagnosis and treatment are vital for patient prognosis because *de novo* autoimmune hepatitis and recurrent autoimmune hepatitis cause graft loss and result in subsequent retransplantation if medical treatment fails.

**Key Words:** Liver transplantation; Autoimmune hepatitis; Recurrence autoimmune hepatitis; *De novo* autoimmune hepatitis

**Core Tip:** Autoimmune hepatitis is a chronic inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum globulin levels. Liver transplantation may be required for patients with acute liver failure, decompensated cirrhosis, and hepatocellular carcinoma. *De novo* autoimmune hepatitis and recurrent autoimmune hepatitis are known causes of late graft dysfunction following liver transplantation which should be included in the differential diagnosis.

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## INTRODUCTION

Autoimmune hepatitis is a chronic inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum globulin levels. This disease may manifest as elevated liver transaminases, acute hepatitis, cirrhosis or acute liver failure[1]. Autoimmune hepatitis is classified into types 1 and 2. Patients with positive antinuclear antibody (ANA) and/or anti-smooth muscle antibody (anti-SMA) are classified as type 1, whereas type 2 is defined by the presence of anti-liver-kidney microsomal type 1 antibody (anti-LKM-1) or anti-liver cytosol type 1 antibody (anti-LC-1) positivity. Autoimmune hepatitis is mainly treated with immunosuppressive drugs such as glucocorticoids and azathioprine (AZA). In this review, indications for liver transplantation in patients with autoimmune hepatitis and the diagnosis and treatment of recurrent autoimmune hepatitis after liver transplantation are discussed. Additionally, *de novo* autoimmune hepatitis, which can be seen in patients who have received liver transplantation for indications other than autoimmune hepatitis, are discussed.

### *Indications for liver transplantation for patients with autoimmune hepatitis*

Liver transplantation may be indicated for patients with autoimmune hepatitis if one of the following conditions are present: (1) Acute liver failure; (2) Decompensated cirrhosis (Model for End-Stage Liver Disease score ≥ 15); or (3) Hepatocellular carcinoma. Liver transplantation may be required if there is a failure to diagnose and treat autoimmune hepatitis, inadequate response or intolerance to immunosuppressive therapy, or if the patients are not compliant with the treatment. Ultimately, 10%-20% of patients with autoimmune hepatitis eventually need liver transplantation[2,3].

Autoimmune hepatitis accounts for approximately 5% and 2%-3% of liver transplants in the United States and Europe, respectively[4,5]. The frequency of acute and chronic rejection after liver transplantation for autoimmune hepatitis is more frequent compared to other liver diseases[6]. Five-year patient and graft survivals for autoimmune hepatitis are reported to be 80%-90% and 72%-74%, respectively[7].

### *Clinical manifestations associated with autoimmune hepatitis after liver transplantation*

**Recurrence of autoimmune hepatitis after liver transplantation**: Recurrence is defined as reappearance of the disease in the liver allograft. Autoimmune hepatitis recurs in 8%-12% of patients within the first year and 36%-68% within 5 years following liver transplantation[6]. Recurrent autoimmune hepatitis frequency is not significantly affected by the graft type (either living related or cadaveric)[8]. Diagnostic workup of recurrent autoimmune hepatitis is similar to diagnosing the original disease and it is equally challenging. The main reason for the complexity in diagnosis is the absence of a specific marker for diagnosis. In addition, immunosuppressive therapy may mask some features of the original disease. The disease progression may differ and may lead to an atypical presentation. Transplant recipients with recurrence of autoimmune hepatitis usually have elevated transaminases, fever, fatigue, jaundice, abdominal pain, skin rash, and joint pain upon presentation[9]. Nevertheless, the presentation of recurrence of autoimmune hepatitis is not specific and can be seen in other complications of liver transplantation. Hypergammaglobulinemia is defined as increased serum IgG levels, and together with positivity of ANA and SMA, make up the serological findings of the disease. The pathophysiology of recurrent autoimmune hepatitis is not comprehensively understood and is similar to the mechanisms involved in the development of classical autoimmune hepatitis. The main histopathological feature of recurrent autoimmune hepatitis is prominent lymphocytic interface activity with or without plasma cell infiltration. Other pathological findings are acute lobular hepatitis with focal hepatocyte necrosis, acidophil bodies with lymphoplasmacytic cells, pseudo-rosetting of hepatocytes, perivenular lymphoplasmacytic inflammation, and confluent and bridging necrosis with lymphoplasmacytic infiltration (severe inflammatory activity)[10]. Cellular and antibody-mediated forms of cytotoxicity are involved in the pathogenesis of the disease. These features may be less evident or absent in certain instances. The differential diagnoses include rejection, drug hepatotoxicity, *de novo* steatohepatitis, and viral hepatitis,

including hepatitis E. The diagnosis is performed by excluding other possible etiologies.

Many risk factors such as the effects of immunosuppressive therapy as well as recipient- and donor-related factors play an important part in the recurrence of autoimmune hepatitis in the liver allograft. Early corticosteroid withdrawal for reasons such as nonadherence or physician recommendation, high titers of autoantibodies at the time of liver transplantation, coexisting autoimmune disorders, association of human leukocyte antigen (HLA)-DR3 and HLA-DR4 mismatch, and severe necroinflammatory activities in the explant liver at the time of liver transplantation are some of the reported risk factors of recurrence[9]. Figure 1 summarizes the factors implicated in the development of recurrent autoimmune hepatitis.

Recurrent autoimmune hepatitis needs prompt treatment because nearly half of cases are resistant to therapy and result in graft failure. Treatment is usually empirical. In mild cases, only increasing compliance with immunosuppressive therapy and increasing immunosuppressive doses are sufficient. In severe cases, predniso(lo)ne (30 mg/d) and AZA (1-2 mg/kg/d) are required. The combination of corticosteroids and mycophenolate mofetil (MMF) may also be the initial therapeutic approach[6]. When laboratory values improve, the dose of corticosteroids is tapered to 5-10 mg within 1-2 mo[9,11]. Patients who do not respond to this combination are considered for other immunosuppressive agents such as calcineurin inhibitors or inhibitors of mammalian target of rapamycin. In cases with severe liver failure, retransplantation may be required. It has been reported that retransplantation is required in 33%-60% of patients with recurrent autoimmune hepatitis[6,12,13].

***De novo* autoimmune hepatitis:** *De novo* autoimmune hepatitis is the development of autoimmune hepatitis in patients who underwent liver transplantation for reasons other than autoimmune hepatitis. In its latest update, the Banff Working Group for liver allograft pathology proposed replacing the term *de novo* autoimmune hepatitis with plasma cell-rich rejection[14]. *De novo* autoimmune hepatitis is more common in children than in adults (5%-10% *vs* 1%-3%)[6,11]. Clinical findings in *de novo* autoimmune hepatitis are similar to those observed in recurrent autoimmune hepatitis and autoimmune hepatitis. Serum aspartate aminotransferase, alanine aminotransferase, and IgG levels are high. One of the most striking features of *de novo* autoimmune hepatitis is detection of newly developed autoantibodies. Patients with *de novo* autoimmune hepatitis may have ANA, antimitochondrial antibody, anti-SMA antibodies and also anti-LKM-1, anti-LC, antibodies to gastric parietal cells, and atypical anti-liver/kidney cytosolic antibody targeting the antigen glutathione-S-transferase T1 (GSTT1) may be positive. The main histological feature in *de novo* autoimmune hepatitis is interface hepatitis with lymphocytes and plasma cells. Other histopathological features are spotty necrosis, portal fibrosis, and bile duct injury[15].

Older donors, the mismatch of GSTT1 genotype of donor and recipient, the use of antilymphocyte antibodies, treatment with tacrolimus or MMF are associated with a higher risk of *de novo* autoimmune hepatitis[16]. Cyclosporine A and granulocyte colony-stimulating factor treatment is reported to be protective against *de novo* autoimmune hepatitis. The pathogenesis of *de novo* autoimmune hepatitis is still unknown. Although it has been suggested that antibodies against GSST1 antigen may play a role in the development, it may also develop in the absence of these antibodies. Therefore, the role of antibodies against GSST1 antigens in pathogenesis is not fully established. One of the possible mechanisms for the development of *de novo* autoimmune hepatitis is the release of autoantigens from the damaged tissue during reperfusion which exacerbates the autoimmune response after liver transplantation. Other possibilities are due to molecular similarities; in other words, exposure to microorganisms that share amino acid sequences with autoantigens causing crossreactive immunity. In fact, viral infections (which are common after transplantation) can cause autoimmunity by various mechanisms[17]. In addition, interferons used for hepatitis C have potent immunomodulatory effects and can trigger autoimmune disorders in immunosuppressive patients. Today, since interferon-free treatment regimens are used in the treatment of hepatitis C after liver transplantation, hepatitis C patients are now safer in terms of the risks of interferon after transplantation.

While the results of treatment of *de novo* autoimmune hepatitis are promising, poor outcomes such as cirrhosis and graft loss can be seen if these patients are not treated properly. Therefore, early diagnosis and treatment of this disease has paramount importance. Predniso(lo)ne with or without AZA continues to be the mainstay of treatment for *de novo* autoimmune hepatitis. If there is no response to these agents, then MMF can be given instead of AZA[11].

### *Long-term use of corticosteroids after liver transplantation*

The risk of acute and chronic rejection in patients undergoing liver transplantation for autoimmune hepatitis is higher than in patients who are transplanted for other indications. Corticosteroids may prevent development of rejection or relapse on the long term however, usually they are tapered to reduce the risk of infections and adverse effects of steroids. Corticosteroids have many side effects, including infection, depression, osteoporosis, diabetes, hypertension and adrenal suppression, which significantly affect the quality of life in recipients following liver transplantation[18]. The issue of how long corticosteroids should be given to prevent rejection and relapse in patients with autoimmune hepatitis remains a controversial issue. There have been few studies on the long-term administration of corticosteroids after transplantation in autoimmune hepatitis patients. In a study involving 73 patients

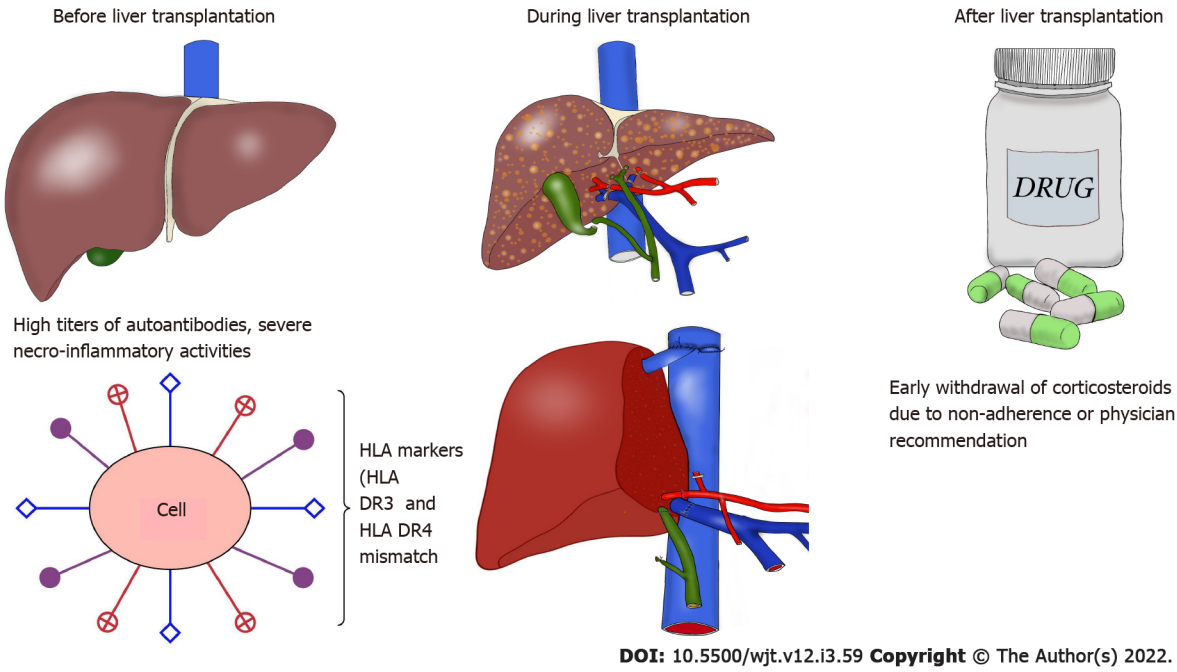


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**Figure 1 Summary of the factors implicated in the development of recurrent autoimmune hepatitis after liver transplantation.** HLA: Human leukocyte antigen.

with autoimmune hepatitis who underwent liver transplantation, it has been shown that long-term treatment with low-dose corticosteroid in combination with other immunosuppressive medication reduced recurrence rates of autoimmune hepatitis[19]. The recent American Association for the Study of Liver Diseases (AASLD) guidelines emphasize that the data supporting the long-term administration of corticosteroids to prevent post-transplant rejection, graft loss and recurrent autoimmune hepatitis are limited and the treatment is not justified. Therefore, AASLD suggested corticosteroids should be gradually tapered in following liver transplantation[6]. The latest European Association for the Study of the Liver guidelines regarding autoimmune hepatitis do not provide a clear recommendation on how long corticosteroids should be given after transplantation[20].

Another alternative approach is meticulous selection of patients that are at high risk of recurrence and who may benefit from intensified immunosuppression. This group of patients should receive long-term steroids. Steroids should be tapered gradually with close follow-up, if the risk of recurrence is low and long-term steroid administration would cause additional problems in the patients such in patients with diabetes, hypertension, hyperlipidemia and osteoporosis[21].

Until a specific marker is developed or standardization of the diagnosis of recurrent or *de novo* autoimmune hepatitis is developed, steroids will always be an important part of treatment and duration of steroid use will always be a matter of debate.

## CONCLUSION

*De novo* autoimmune hepatitis and recurrent autoimmune hepatitis are known causes of late graft dysfunction in pediatric and adult liver transplantation. In liver transplant recipients with graft dysfunction, recurrent or *de novo* autoimmune hepatitis should always be considered in differential diagnosis. Early diagnosis and intervention are vital in *de novo* and recurrent autoimmune hepatitis because they cause graft loss and subsequent re-transplantation if they are not treated properly.

## FOOTNOTES

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