



HLA Type and the Effect of HLA Antibodies in Kidney, Liver, and Pancreas Transplantation: A Review

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Abstract

Solid Organ Transplantation (SOT) has evolved from being an experimental procedure to a well-established therapeutic option for patients with end-stage organ failure. Among the most prevalent types of transplantation are liver, kidney, and pancreas transplants. Progress in surgical techniques and organ procurement has led to a decrease in complications, such as ischemic injury. Nevertheless, immune-mediated graft rejection continues to pose a significant challenge. The purpose of this review is to underscore the significance of Human Leukocyte Antigen (HLA) in the outcomes of SOT, particularly its critical role in donor–recipient matching, the risk of rejection, and the long-term survival of grafts. A comprehensive review of the relevant literature concerning the relationship between HLA and SOT was conducted, focusing on the function of Major Histocompatibility Complex (MHC) molecules, HLA typing, and the effects of HLA diversity on organ matching and clinical results. HLA typing serves as a fundamental element in assessing donor–recipient compatibility and minimizing the chances of graft rejection. The extensive polymorphism of HLA alleles, along with the existence of donor-specific antibodies, complicates the matching process, influences waiting periods, and impacts graft prognosis. Modulating HLA-mediated immune responses has the potential to enhance graft stability in liver, kidney, and pancreas transplantation. HLA molecules are crucial to the success of SOT. Ongoing clinical trials investigating novel immunosuppressive agents and HLA-targeted strategies may improve rejection management and long-term transplant outcomes. This review highlights the critical importance of HLA in liver, kidney, and pancreas transplantation.

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Received: 14 May 2025

Accepted: 29 Sept 2025

Keywords: Antigens, Kidney, Liver, Pancreas, Solid organ transplantation

To cite this article: Zarei E, Roozbeh J, Nikoupour Deylami H, Nikeghbalian S, Ahrami M, Nasrollozoda F, et al. HLA Type and the Effect of HLA Antibodies in Kidney, Liver, and Pancreas Transplantation: A Review. *Avicenna J Med Biotech* 2026;18(1):16-31.

Introduction

Human Leukocyte Antigen (HLA) system is a complex of genes found in Major Histocompatibility Complex (MHC) that encode surface cell proteins, and has a pivotal role in regulation of the human immune system ¹⁻³. MHC has 3 classifications; namely MHC-I (A, B, and C), MHC-II (DP, DM, DO, DQ, and DR) and the MHC-III region that encode components of the complement system ⁴⁻⁶. The function of MHC is to bind peptide fragments determined from pathogens and pre-

sent them on the cell surface for recognition by the appropriate T cells ^{7,8}.

Solid Organ Transplantation (SOT) between different individuals have led to fast rejection of the transplanted allograft because for this reason, HLA typing methods are crucial for determining the compatibility between donors and recipients. These methods such as serological methods, Sequence-Specific Priming (SSP), Sequence-Specific Oligonucleotide Probing (SSOP),

Reference Strand-based Conformation Analysis (RSCA), and Sequence-Based Typing (SBT), help identify the specific HLA types of both the recipient and donor and aid in successful transplantation procedures and decrease the risk of graft rejection^{9,10}. However, the diversity of HLA alleles and haplotypes across different populations poses an important obstacle to organ and hematopoietic stem cell transplantation. This challenge stems from the discovery of HLA incompatibilities by T and B lymphocytes^{11,12}. While selecting organs for transplant recipients, it is crucial to consider the existence of anti-HLA antibodies that may be now beforehand. Despite the use of immunosuppressive drugs, the synthesis of new anti-HLA antibodies remains a significant reason for graft rejection¹³. However, factors like donor type, donor age, and the specific immunosuppressive treatment can affect the benefits of HLA matching^{14,15}.

Successful transplantation with an identical HLA profile has been achieved between monozygotic twins, as within to begin with successful living-related kidney transplant between identical twins in 1954, performed by Joseph E. Murray^{16,17}. The immune response triggered against transplanted organs or tissues by specific cell surface molecules can potentially lead to graft rejection^{18,19}. Various types of transplantation antigens have been identified. They consist of little histocompatibility antigens, ABO blood group antigens main histocompatibility molecules, and endothelial cell antigens. These antigens play an essential role in the immune recognition process and can lead to the development of graft rejection^{20,21}.

It is important to state that only a subset of patients may find an adequately matched donor, resulting in longer waiting times²². To provide a comprehensive understanding of the topic, a detailed review was conducted of a wide range of studies that investigate the relationship between HLA and solid organ transplantation, shedding light on the complexities and advancements of this field²³.

HLA

In 1958, a significant breakthrough occurred when a research team successfully identified an alloantigen (an antigen that is found exclusively in certain individuals) on human leukocytes, thus establishing it as the pioneering HLA¹¹. This discovery catalyzed the advancement of the HLA field, which has since expanded beyond its initial focus on histocompatibility and gained prominence in both basic and clinical immunology²⁴. HLA refers to a group of cell surface proteins encoded by genes located within the MHC in humans^{9,11}. In mice, these proteins are referred to as H-2^{25,26}. These genes are located on the short arm of chromosome 6 at the 6p21 position with approximately 4,000 kilobases (kb) of DNA and encode three main classes of proteins²⁷. Biologically, HLA molecules play a main role in immune responses. HLA class I (HLA-A,

HLA-B, and HLA-C), all of which present peptides from inside the cell and stimulate T-lymphocytes called cytotoxic T cells (also referred to as CD8⁺ T-cells), class II (HLA-DP, HLA-DQ, and HLA-DR), present antigens from outside of the cell to T-lymphocytes²⁸. These particular antigens presented to T-helper cells (also called CD4-positive T cells), which are triggers for antibody-producing B-cells and class III that are not directly involved in antigen binding and have a role as signaling molecules in cell communications include components complement (C2,C4), steroid 21- hydroxylase (CYP21), Heat Shock Protein (HSP) and Tumor Necrosis Factors (TNF)^{29,30}.

HLA is found on the top of almost all nucleated cells. They have a crucial role in initiating graft rejection, which is the immune response triggered when foreign tissue is introduced during transplantation. By recognizing and presenting antigens to immune cells, HLA molecules help to distinguish between "self" and "non-self" cells, enabling the immune system to mount an appropriate response. Clinically the study of HLA has provided valuable insights into immune function, transplantation, and various diseases associated with immunogenetics, contributing significantly to our understanding of these fields (Figure 1)^{9,23,29}.

Recent insights have clarified the function of antibodies and B cells in regulating the function and survival of transplanted organs³¹. Significant improvements in diagnostic techniques, such as immunohistochemistry and serology, have led to the monitoring of

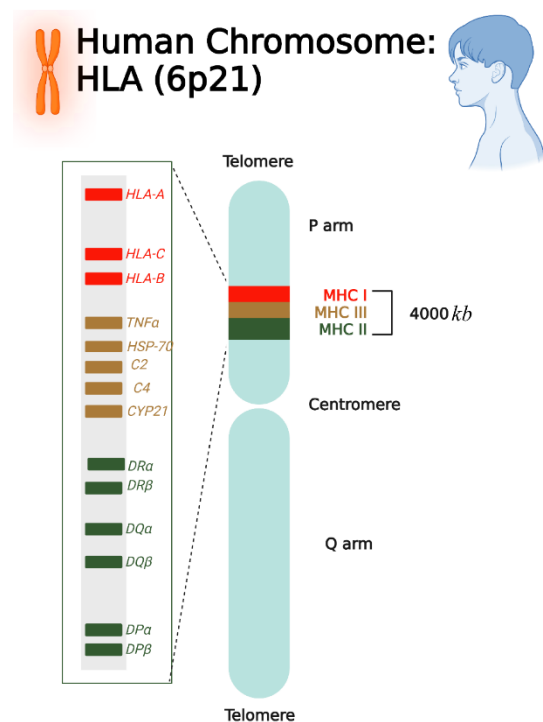


Figure 1. Genomic Map of the Human HLA Complex: Located at chromosome 6p21, encompassing ~4,000 kb and encoding HLA Class I (HLA-A, -B, -C), Class II (HLA-DP, -DQ, -DR), and Class III genes (TNF, HSP, complement C2/C4, CYP21) (29, 30). Non-HLA.

antibody responses against HLA antigens³². It is significant to note that even organ transplantation between HLA-identical donor and recipient, acute and chronic rejection can still occur, accentuating the significance of diversity in any other protein apart from leukocyte antigens that could elicit immune responses versus non-HLA targets. It is now understood that alloimmunity and autoimmunity work together to produce non-HLA antibodies but autoantibodies appear to play a more dominant role^{32,33}.

Non-HLA antibodies can be categorized into two primary groups: I. alloantibodies that attack polymorphic antigens found in the donor but not in the recipient, II. autoantibodies that target self-antigens.

Non-HLA antibodies can target a variety of antigens, including vascular receptors, minor histocompatibility antigens, intermediate filaments, and adhesion molecules³⁴. These antibodies can function both complementarily and non-complementarily, resulting in a range of acute and chronic pathogenesis³⁵. Developing methods that³⁶ consider the intricate mechanistic variations in specific antibody responses, focused against non-HLA antigens, could aid in recognizing patients more susceptible to irreversible chronic or acute allograft injuries, ultimately leading to better transplant surgery outcomes^{32,37}. Advancements in genome-wide and transcriptomics assessment have provided valuable insights into the underlying mechanisms involved^{35,38,39}.

Non-HLA antibodies mainly focus on vascular endothelial antigens that are available for immune detection³⁶. Some of these antibodies are autoantibodies, which develop against self-proteins found in both the recipient and the graft, and are frequently observed in autoimmune disorders. These antibodies may arise following tissue damage due to the exposure of hidden self-epitopes or as a result of post-translational modifications⁴⁰. Notable examples include antibodies targeting alpha-enolase 1 (ENO1) and Vimentin (VIM), which can be identified using Luminex non-HLA panels. Furthermore, genetic differences between the donor and recipient that exist outside the HLA system can provoke alloimmune responses, as illustrated by antibodies directed against Glutathione S-Transferase Theta 1 (GSTT1)^{40,41}.

Anti HLA

A key issue in the first days after transplantation, following Brent's discovery that the reaction to allografts is immunological, was the debate over whether graft rejection primarily occurs through humoral (antibody-mediated) or cellular mechanisms⁴². Presently, the cellular theory of graft rejection is widely accepted as the prevailing explanation. However, despite numerous efforts to identify pretransplant immunization through tests measuring T lymphocyte function, only the anti-HLA Panel-Reactive Antibody (PRA) test, assessing humoral alloimmunization, has been success-

ful. The clinical importance of the humoral immune response was dramatically shown in 1969 when an entire transplanted kidney was instantaneously destroyed by HLA antibodies⁴²⁻⁴⁴. Recent reviews have emphasized the raised risk of graft rejection in patients with pretransplant anti-HLA PRA, prompting the routine level of anti-HLA antibodies before transplantation¹³. However, post-transplant screening of the mentioned antibodies is not consistently performed. Encouragingly, recent advancements in techniques for diagnosis anti-HLA antibodies, paired with numerous studies demonstrating the link between post-transplant anti-HLA antibodies and adverse events, suggest the potential clinical utility of such testing in gaining valuable insights into the mechanisms behind graft rejection⁴².

Solid-organ transplantation

As mentioned in the introduction, in the current era, SOT are carried out globally, increasing the length and quality of life in patients. The most important SOTs are the kidney, liver, lung, heart, intestine, and pancreas.

Kidney

Kidney transplantation, an ideal choice for end-stage kidney disease, has many advantages, including better quality of life and longer life expectancy in comparison to dialysis. Nevertheless, a significant number of patients face complications in finding a suitable kidney due to broad sensitization compared to HLA antigens, limiting the availability of HLA-compatible organs³⁴.

To overcome this challenge, certain highly sensitized individuals may undergo pretransplant desensitization. These programs involve techniques such as plasmapheresis combined with high doses of rituximab plus IVIg, intravenous polyvalent immunoglobulins (IVIg), semi-specific immunoadsorption plus imlifidase, a recombinant cysteine protease capable of cleaving human IgGs, rituximab or tocilizumab⁴⁵. This table provides a summary of 24 clinical trials concerning kidney transplantation and HLA immunology. It encompasses the titles of the studies, NCT registration numbers (each trial is recognized by its official title along with its ClinicalTrials.gov registration number), the status of the trials, the conditions examined, interventions (including immunosuppressive drugs, biologics, or procedures), and the phases of the clinical trials. The focus of these trials includes areas such as desensitization, immune tolerance, prevention of transplant rejection, and the impact of various immunosuppressive therapies (Table 1).

In spite of pretransplant desensitization, many patients underwent renal transplantation despite the presence of donor-specific anti-HLA alloantibodies, resulting in what we refer to as HLA-incompatible (HLAi) renal transplantation⁴⁶.

Lymphocytotoxicity: Three decades ago, Terasaki and colleagues were the first to report that renal transplant

Table 1. Clinical trials evaluating HLA-mediated immune responses, desensitization, and tolerance induction in renal transplant recipients

Study title	NCT number	Conditions	Interventions
Impact of Proteasome Inhibition on Anti-Donor HLA Antibody Production After Kidney Transplantation	NCT01349595/Phase 2/Terminated	Disorder of transplanted kidney	Drug: Bortezomib
Pilot Study for HLA Identical Living Donor Renal Transplant Recipients	NCT00352092/Phase 4/Completed	Renal transplant	Drug: Calcineurin inhibitor Drug: Sirolimus Drug: Mycophenolate mofetil
Certican (Everolimus) for Recipients of Kidney From HLA-identical Living Donors	NCT01653041/Phase 4/Completed	Kidney transplantation	Drug: Everolimus
Cellular Immunotherapy in Recipients of HLA Mismatched, Living Donor Kidney Transplants	NCT03605654/Phase 2/3/Not yet recruiting	Kidney transplant rejection	Biological: MDR-102 Drug: Immunosuppressive agents
rATG Versus rATG Combined with Intravenous Immunglobulin (IVIg) Induction Immunosuppression in HLA Incompatible Transplantation (INHIBIT)	NCT04302805/Phase 3/Recruiting	Kidney transplantation	Drug: Privigen Drug: Thymoglobulin Other: Plasma Exchange
Efficacy of Belatacept in Reducing Donor HLA-Specific Antibodies (DSA)	NCT02078193/Phase 4/Completed	Kidney transplantation	Drug: Belatacept
Mycophenolic Acid Monotherapy in Recipients of HLA-identical Living-Related Transplantation	NCT01053221/Phase 2/Terminated	Kidney transplantation	Drug: Mycophenolic acid Drug: Standard of Care: CNI and MPA Drug: Mycophenolate mofetil 500 mg Tab. or 250 mg Cap. Drug: Tacrolimus Drug: Methylprednisolone/prednisolone
Impact of Lymphocyte Anti-metabolite Immunosuppressions on Donor-Specific Anti-HLA Antibody and Kidney Graft Outcome	NCT03794492/Phase 4/Unknown status	Kidney transplant	
Cellular Immunotherapy in Recipients of HLA-matched, Living Donor Kidney Transplants	NCT03363945/Phase 3/Active, not recruiting	Kidney transplant rejection	Biological: MDR-101
Clazakizumab in Highly-HLA Sensitized Patients Awaiting Renal Transplant	NCT03380962/Phase 1/2/Active, not recruiting	Kidney failure, Chronic end-stage renal disease transplant glomerulopathy	Drug: Clazakizumab
Effects of the Quadruple Immunosuppression on Peripheral Blood Lymphocytes and Development of Anti-HLA Antibodies in Kidney Transplant	NCT02208791/Phase 4/Unknown status	Kidney transplantation	Drug: Sirolimus Drug: No intervention
Desensitization in Kidney Transplantation	NCT00908583/Phase 4/Completed	HLA sensitization	Drug: Plasmapheresis Drug: Bortezomib Drug: Rituximab
Cellular Immunotherapy for Immune Tolerance in Past Recipients of HLA Zero-mismatch, Living Donor Kidney Transplants	NCT03606746/Phase 2/Not yet recruiting	Kidney transplant rejection	Biological: MDR-103
Comparison of Tacrolimus Extended-Release (Envarsus XR) to Tacrolimus Immediate-Release in HLA Sensitized Kidney Transplant Recipients	NCT04225988/Phase 4/Active, not recruiting	Kidney transplant rejection	Drug: Extended-release tacrolimus Drug: Immediate-release tacrolimus
Rituximab in Renal Allograft Recipients Who Develop Early De Novo Anti-HLA Alloantibodies	NCT00307125/Phase 2/Completed	Kidney transplant kidney transplant recipient graft function/survival	Drug: Rituximab plus immunosuppression Drug: Placebo plus immunosuppression
Steroid Withdrawal and Donor-specific Anti-HLA Antibodies in Renal Transplant Patients	NCT02284464/Phase 4/Completed	Other complication of kidney transplant renal transplant rejection	Drug: Prednisone withdrawal Drug: Prednisone continuation
Carfilzomib and Belatacept for Desensitization	NCT05017545/Phase 1/2/Recruiting	Highly sensitized prospective kidney transplant recipients	Biological: Carfilzomib Biological: Belatacept Procedure: Bone marrow aspiration
Retro-active Immunological Tolerance in Patients with Well-functioning Pre-existing HLA-identical Kidney Transplants	NCT05525507/Phase 1/Recruiting	End stage kidney disease immunological tolerance kidney transplant failure and rejection	Combination product: Conditioning and stem cell infusion
Effects of Mycophenolate Mofetil (MMF) On Anti-HLA (Human Leukocyte Antigen) Antibody Levels in Patients Awaiting Cadaveric Renal Transplant.	NCT00446459/Phase 2/Completed	Kidney failure, Chronic diabetic nephropathies glomerulonephritis, IGA	Drug: Mycophenolate mofetil (CellCept)
Inducing Graft Tolerance in HLA Haplotype Matched Related and 3 Ag Matched Unrelated Living Donor Kidney Transplantation	NCT03292445/Early Phase 1/Recruiting	Immune tolerance	Procedure: Immune tolerance after kidney transplant Drug: Donor blood stem cells and T cells
Trial to Evaluate Safety and Tolerability of Tacrolimus Extended-Release (Astagraf XL) in HLA Sensitized Kidney Transplant Recipients	NCT03194321/Phase 4/Completed	End stage renal disease	Drug: Tacrolimus extended-release oral capsule
To Compare the Effects of Immediate-release Tacrolimus and Astagraf XL on DSA Formation and the Development of Immune Activation (IA) in De Novo Kidney Transplant Recipients	NCT02723591/Phase 4/Completed	Kidney transplantation	Drug: Tacrolimus Drug: Tacrolimus immediate release
Use of Immune Globulin Plus Rituximab for Desensitization in Highly HLA Sensitized Patients Awaiting Deceased Donor Kidney Transplantation	NCT01178216/Phase 1/2/Completed	End stage renal disease	Biological: Rituxan
Delayed Blood Stem Transplantation in HLA Matched Kidney Transplant Recipients to Eliminate Immunosuppressive Drugs	NCT03591302/Phase 1/Recruiting	Immune tolerance	Biological: Hematopoietic cell transplantation Radiation: Total Lymphoid irradiation

recipients with lymphocytotoxic antibodies in their serum previously transplantation were at a higher hazard of graft failure^{47,48}. This discovery has been accepted by numerous subsequent researches. As a result,

it is now routine practice to test patients awaiting kidney transplantation for lymphocytotoxic Panel-Reactive Antibodies (PRA) as part of the evaluation process⁴⁹. Patients who are awaiting kidney transplantation

undergo regular testing for lymphocytotoxic PRA, and the allocation of grafts is dependent on the results of the T- and B-cell Complement-Dependent Cytotoxicity (CDC) crossmatches. Additionally, new techniques utilizing extremely sensitive and severely HLA-specific ELISAs have been developed for pretransplant antibody testing^{50,51}.

While the outcome of renal transplantation can be influenced by various factors, HLA-identical siblings' donors are considered as a distinct group. They have meaningfully higher success rates compared to transplants of HLA-mismatched donors and serve as the standard for comparison with other donor sources. However, grafts from HLA-identical sibling donors are less likely to be rejected without immunosuppression; recipients still receive lower doses of immunosuppressive regimens compared to recipients of grafts from deceased donors. The necessity for an immunosuppressive regimen indicates that aside from HLA, it is very probable that some other antigen systems are responsible for graft failure. HLA-identical sisters and brothers transplants do not present an aim for anti-HLA antibodies, and the intensity of PRA prior to transplantation may not affect their success rate^{52,53}.

HLA desensitization: IL-6 presents an appealing goal in HLA desensitization procedures^{54,55}. This cytokine possesses multiple functions and influences the activities of B and T cells. This is generated by different cells in the essential immune system, B cells, and to some breadth CD4 T helper (Th) cells^{56,57}. IL-6 also plays a role as a delayed factor in B cell separation, promoting the transformation of B cells to antibody-producing cells and facilitating germinal-center responses. Additionally, it adjusts the acute phase repercussion during inflammation interferes with plasma blasts and decreases the amount of mixing T follicular helper cells and IL-21 production⁵⁷.

HLA Matchmaker: This approach identifies HLA Matchmaker, a computer algorithm analyzing HLA antigen as a sequence of multiform amino acid triplets located in regions available to antibodies on the HLA molecules at the structural level. Interestingly, this algorithm can recognize HLA antigens that would be considered inconsistent using customary indicators. However, if these antigens contribute all their triplets to the patient, they are deemed completely suitable at the epitope level. This plan has proven especially valuable in identifying suitable donors used for very sensitized patients⁵⁸.

HLA-A, -B, G, and -DR antigens and the degree of donor: In renal transplantation, level of HLA-A, HLA -B, and HLA-DR antigen mismatch between the donor and recipient is commonly used to assess donor-recipient compatibility⁵⁹. Researches consistently show that transplants with zero HLA antigen mismatches have the maximum accomplishment rates. This led to the adoption of an allocation policy in which zero-mis-

matched cadaver kidneys are allocated through mandatory sharing. However, only a few percentages (9%) of all renal transplants recorded by the United Network for Organ Sharing (UNOS) fall into this zero-mismatch category. Furthermore, using HLA matching for organ allocation system can put certain groups at a disadvantage, as they have diverse HLA antigen frequencies^{60,61}.

A method of evaluating donor-recipient adaptability takes into account public epitopes shared by HLA antigens in Cross-Reactive antigen Groups (CREGs). These epitopes are mainly defined by alloantibodies and characterized by class I antigens encoded by the HLA-A and HLA-B loci. CREG matching takes into account wider groups of HLA-A and HLA-B antigens that share public epitopes, partly than focusing on exclusive HLA antigens. This substitute HLA-based organ assign system aims to profit a larger number of transplant recipients and offer better availability to well-matched organs for minority populations^{62,63}.

Advancements in immunosuppressive strategies in the late 1980s and 1990s^{64,65} were highly effective in controlling T-cell alloimmunity and occasioned an important decrease in instances of acute rejection caused by T-cell-mediated responses. Nowadays our ability to manage Antibody-Mediated Rejection (AMR) has been exposed as a challenge, and the significance of chronic AMR came to light⁶⁴. Two key advancements greatly contributed to our comprehension of antibody-mediated allograft injury. Firstly, it was recognized that the presence of the supplement gap invention C4d, exclusively in the peritubular capillaries of kidney allografts, can specify antibody-mediated injury to the graft. Secondly, the union between the detection of Donor HLA-Specific Antibodies (DSA) using extremely sensitive techniques and poorer outcomes in kidney transplantation became evident⁶⁰.

These advances have greatly enhanced our comprehension of the character antibodies play in the rejection of transplanted organs, presenting new opportunities for specific strategies to address AMR in transplantation. Recent studies have indicated that more than 60% of cases involving the loss of kidney grafts later on, can be attributed to antibody-mediated damage to the tissue. Additionally, mounting evidence suggests that HLA antibodies are accountable for graft fatality in kidney transplantation and other SOTs^{60,66}.

To achieve successful graft outcomes, it is necessary to monitor HLA class I and II antibodies and the deprivation of alloantibodies mismatches in susceptible kidney recipients. Currently, the CDC test is commonly used to assess PRA in the serum of recipients, which helps identify potential Donor-Reactive Antibodies (DRA) during cross matching. Furthermore, CDC or Flow Cytometry (FC) methods are employed for early investigation of DRA after transplantation, aiding for the monitoring of rejection^{49,60}. The arrival of DRA signals the beginning of vascular rejection, prompting

rejection therapy utilizing polyclonal or monoclonal antibodies. Nevertheless, there are several limitations to using the CDC test for monitoring the HLA-specific antibody condition of transplant patients before and after transplantation⁶⁰.

These drawbacks include (a) CDC's inability to diagnose non-complement-fixing antibodies: The CDC test primarily focuses on detecting complement-fixing antibodies, which means it may miss non-complement-fixing antibodies that can still contribute to graft rejection^{61,67,68}. (b) Impracticality during antibody rejection therapy: When patients undergo antibody rejection therapy using medications such as OKT3 or antithymocyte globulin antibodies, the presence of these antibodies can interfere with the CDC test results^{68,69}. To overcome this, additional steps, such as affinity chromatography, may be required to remove these medications from the patient's serum before conducting the CDC test^{68,70}. (c) Limited sensitivity and lack of HLA specificity: the CDC test may have limited sensitivity, potentially leading to false-negative results. Furthermore, it does not always provide HLA-specific information, meaning that it may not accurately identify the specific HLA antibodies involved in the rejection process^{68,71}.

A higher risk of antibody-mediated injury and initial loss of the transplanted kidney is seen in patients with antibodies against donor HLA class I. However, the significance of having antibodies against HLA Class II is not as well understood⁷².

HLA-G is produced in the cytotrophoblast throughout the process of planting and is believed to enable endurance and support the growth of a partially genetically distinct embryo. In laboratory settings, HLA-G hinders the destructive action of Natural Killer (NK) cells and CD8 T-cells. Additionally, HLA-G reduces the proliferation of CD4 T-cells. These findings represent that HLA-G has a function in facilitating the acceptance of organ transplants from genetically different donors in humans⁷³.

HLA epitope: By examining antibody recognition and its impact on HLA antigen matching, we can gain insights into preventing the severe effects of de-novo donor-specific antibody (dn-DSA) establishment and reducing the dangers associated with transplantation when pre-existing anti-HLA antibodies are present. Epitopes, which are characterized by their potency to bind antibodies, offer a means of addressing the alloantibody response through an epitope-based matching system. Considerable advancements have been made in defining HLA epitopes, particularly with the popularization of the eplet system. This system is favored due to its strong theoretical foundation, validation through the identification of eplet-particular antibodies, user-friendliness, and correlation with clinical outcomes. However, large-scale based on cooperation research is necessary to corroborate the possible benefits of HLA

epitope-based matching previously recommending its widespread implementation in clinical practice⁷⁴⁻⁷⁶.

HLA in young recipients than older recipients: The result of HLA matching on maintaining graft performance and the potential for obtaining a subsequent graft after graft loss may hold greater significance for younger recipients than older recipients⁷⁷. Young adult and pediatric renal transplant recipients face a significantly better danger of graft failure leading to death than other age groups. The graft failure rates reach their top as young recipient's transition between the ages of 17 and 24^{77,78}. Furthermore, young recipients have an extended expected lifetime due to their young age, necessitating an effective graft for several decades. These aspects contribute to the significantly higher likelihood that youthful recipients will want a second graft at several points in their lives. Hence, it is crucial to propound the role of HLA matching on the existence of the initial graft, the expected time for a second transplant, and the total duration of graft occupation throughout their lifetime^{77,78}.

Non-HLA antibody in kidney grafts: While the polymorphic HLA has long been the key target for alloimmunity, recent findings have revealed the significance of antibodies targeting antigens beyond the major histocompatibility complex³⁵. In particular, non-HLA antibodies, including anti-HLA donor-particular antibodies, have emerged as a critical aspect in AMR and are a focus of research in graft pathology^{35,79}. Various non-HLA antibodies have been discovered against endothelial, epithelial, and other proteins, with their presence linked to negative outcomes for kidney grafts. Of these, AT1R-Ab (angiotensin II type 1 receptor antibodies) have garnered considerable attention in the kidney transplantation field. As the vasculature serves as the interface between the transplanted organ and the immune system of recipients, a substantial percentage of non-HLA antibodies linked to the kidney rejection target autoantigens present in endothelial cells^{35,38,39}.

Pregnancy: Pregnancy is an inevitable event that sensitizes women to HLA⁸⁰. This sensitization has an important impact on the growth of HLA class I and class II antibodies. Compared to sensitization after transfusion, the rate of HLA-B antibody development is higher in patients sensitized by pregnancy⁸¹. Studies have demonstrated that the probability of a substantial increase in DSAs is highest when the antibodies were initially incited by gestation rather than transplant antigens⁸². Additionally, the abundance of anti-HLA antibodies is better in pregnant women compared to cases involving transplantation or transfusion events⁸¹.

During pregnancy, a baby inherits HLA types from both parents, exposing the mother to antigens spoken in the cells of the emerging baby, which are foreign to her immune system. However, these HLA antibodies produced through pregnancy do not pass through the harm and placenta of the baby. Antibodies targeting

HLA I are more frequent than those targeting class II⁸³. The expression of anti-HLA antibodies during pregnancy is probably related to the development of specific HLA alleles⁸⁴. In female patients, several pregnancies increase the likelihood of developing anti-HLA antibodies versus embryonic antigens arrested from the father, which can render them unsuitable as potential blood recipients⁸⁵. The outbreak of HLA antibodies rises with the increasing count of pregnancies⁸⁶. Direct sensitization of a female human being compared to her partner and/or offspring also causes them to be inappropriate possible donors for the mother⁸⁷. In the same way, research has shown that female patients getting kidney transplants due to their male partners or offspring involvement developed rates of graft failure⁸⁸.

Transfusion: The ABO (blood group) system antigens are crucial in transfusions. Even with appropriate ABO antigen matching, patients may still experience transfusion reactions after they collect multiple blood supplies. Organ transplants that are ABO-incompatible can lead to hyperacute rejection as an effect of pre-made antibodies, such as hemagglutinin A and/or B, reacting to non-self A or B antigens⁸⁹.

In the context of blood transfusion, severe lung injury is the primary cause of mortality^{90,91}. Antibodies present in the donor's blood can act on the recipient's pulmonary neutrophils, resulting in pulmonary edema⁹². The transfusion itself has low immunogenicity⁸⁸, and repeated transfusions are necessary to encourage persistent HLA allosensitization⁹³. The utilization of blood transfusions corresponding to HLA-DR antigens served as the initial approach in transfusion⁹⁴. Platelets express HLA antigens, whereas red blood cells do not. The utilization of HLA-matched blood⁹⁵ and leukocyte-depleted blood products reduces the risk of HLA sensitization⁹³.

Pancreas

Survival of pancreas grafts is not as successful as that of additional SOT, and the underlying explanations for this disparity remain obscure⁹⁶. Various studies have established an important relationship between lower graft survival and the attendance of DSA and/or non-DSA after lung, kidney, and heart transplantation⁹⁷. Unlike other SOTs, HLA matching is not routinely performed during pancreas transplantation, primarily due to logistical reasons. Since pancreas transplantation involves the endocrine and exocrine pancreatic tissues, also a sizable portion of the donor's duodenum, it is possible to be further immunogenic. This assumption is partially reinforced via the development of powerful anti-HLA sensitization following key transplantation rejection⁹⁸. The assessment of anti-HLA can now be conducted using new and further drugs in clinical trial studies⁹⁹.

HLA-G and HLA-E in pancreatic disorders: Immune system cell typically exhibits pathogenic features in autoimmune and chronic inflammatory pancreatic dis-

orders, and the pancreas is one of the few organs that express the immune checkpoint HLA-G¹⁰⁰. HLA-G and HLA-E are non-classical class I molecules that can be described both as membrane-bound and soluble isoforms¹⁰¹. The reduced expression of HLA-G and -E in islets and acini, along with the presence of these molecules in the inflammatory infiltrating cells, is a common characteristic observed in chronic inflammatory and autoimmune pancreatic disorders¹⁰⁰.

Immunoassays: Extremely sensitive solid phase immunoassays have been effectively implemented in scientific practice to monitor donor-specific HLA antibodies, particularly in sick collections for example already sensitive kidney recipients. Nevertheless, dissimilar to kidney transplantation, there is a lack of specific recommendations for monitoring DSA in Simultaneous Pancreas-Kidney Transplant (SPKT) recipients due to limited research conducted in this area. Additionally, the Banff guidelines for diagnosing AMR in the pancreas graft do not require the existence of DSA. A diagnosis of "consistent with acute AMR" can be made based solely on histological findings of the pancreas¹⁰².

CD4⁺ T: Autoreactive CD4⁺ T cells in the peripheral immune system play a significant role in the development of autoimmune diseases. Moreover, these cells have the potential to serve as valuable biomarkers for evaluating individuals at different levels of disease development or undergoing development. The use of HLA class II tetramers, allows to identification of antigen-specific CD4⁺ T cells recognizing a wide range of both exogenous and endogenous antigens. This is possible when the MHC limitation element and the related peptide epitope are identified^{103,104}. One example of such a disease is Type 1 Diabetes (T1D), where the association between the disease and the HLA-DR4 haplotype is well-established. Additionally, the immunodominant epitopes derived since Glutamic Acid Decarboxylase (GAD), proinsulin, IA-2, and IGRP, important in T1D, have been extensively characterized¹⁰⁵.

HLA in pancreas-kidney transplantation: In Simultaneous Pancreas-Kidney (SPK) transplantation, the matching of HLA between the donor and recipient is crucial for minimizing the risk of acute rejection and enhancing long-term graft survival. While some research indicates that overall HLA matching may not have a significant effect on the survival of pancreas or kidney grafts, greater degrees of mismatch—especially within the 4–6 antigen mismatch range—are linked to a higher occurrence of acute rejection. For example, in recipients with poor matching (4–6 antigens), the 3-year rejection-free survival rate was around 41%, in contrast to 66% for those with better matching (0–3 antigens)¹⁰⁶.

Recently, molecular techniques such as the Predicted Indirectly Recognizable HLA Epitopes algorithm

(PIRCHE-II) have been developed to evaluate epitope mismatch load as a predictor for the emergence of *De Novo* donor-specific antibodies (dnDSA) following SPK transplantation. A cohort study involving 72 SPK recipients revealed that elevated PIRCHE-II scores for HLA-DQ were independently correlated with a heightened risk of dnDSA formation ¹⁰⁷.

HLA in langerhans islet transplant: HLA is crucial for the immune system's ability to recognize transplanted Langerhans islets. The diverse characteristics of HLA molecules, especially class II alleles like HLA-DR and HLA-DQ, significantly affect the likelihood of graft rejection during islet transplantation.

Among the HLA class II molecules, the HLA-DR3 and HLA-DR4 alleles have been significantly linked to an increased susceptibility to type 1 diabetes as well as a heightened risk of islet graft rejection. These alleles are proficient in presenting pancreatic islet autoantigens, including insulin and GAD, to CD4⁺ T helper cells, thereby promoting the activation of autoreactive T cells. This mechanism triggers a series of immune responses, which encompass the clonal expansion of Cytotoxic T Lymphocytes (CTLs), the recruitment of macrophages, and the secretion of pro-inflammatory cytokines (such as IFN- γ and TNF- α), ultimately resulting in the destruction of β -cells ¹⁰⁸.

Simultaneously, HLA class I molecules (HLA-A, HLA-B, and HLA-C) found on donor islet cells present endogenous peptides to CD8⁺ cytotoxic T cells. These CTLs facilitate direct cell destruction through perforin/granzyme pathways or Fas-FasL interactions, thereby further promoting graft rejection ¹⁰⁹.

Liver

The harmful impact of alloantibodies versus donor HLA is an uncertain issue in liver transplantation. It is widely recognized that the appearance of dn-DSA plays a destructive role in various solid organ allografts, including intestine, pancreas, heart, lung, and kidney. dn-DSAs are related to delayed acute AMR and chronic AMR and negatively impress long-term graft survival. Liver is a resistant organ to rejection following transplantation because of its remarkable capacity to attract alloantibodies targeting HLA antigens. In liver transplant recipients, initial records did not demonstrate a relationship between dn-DSAs and failure or survival. However, with advancements in understanding the humoral immunity response in transplants, facilitated by sensitive, high-throughput antibody detection techniques, there has been an improved comprehension of these processes ¹¹⁰⁻¹¹⁵.

The liver is known to express together HLA class I and II antigens, believed to absorb alloantibodies and also conceals HLA class I antigens that can aid in the renovator of DSAs ¹¹¹. The liver's renovator capacity and the presence of Kupffer Cells (KCs) further contribute to the potential clearance of DSAs that bind to soluble HLA class I antigens ^{111,116}. As a result, the liver might possess inherent resistance to injury caused

by antibody-mediated responses. In the field of initial liver transplantation (excluding re-transplantation), previous evidence indicates that assembled DSAs do not affect graft survival ¹¹⁷. However, recent researches have shown that the presence of DSA, as detected by Luminex single-antigen bead analyses, is related to poor results in deceased donor liver transplants. These findings contrast with prior reports but highlight the potential influence of DSA status on transplantation outcomes in specific situations ^{118,119}.

To date, assembled DSAs have been linked to a poorer anticipate in recipients of deceased donors compared to those receiving from living donors ¹²⁰. A study comparing results of deceased and living donors showed an important correlation between performed DSAs and increased graft loss, but practically this finding can't be certified in living donors. Although the shorter cold ischemia time in living donors might show an important role in promoting antibody-mediated graft damage, prolonged cold ischemia time can be linked to vascular arteriosclerosis in combined with the attendance of HLA antibodies. So, as a conclusion, it can be implied that the shorter cold ischemia time, the higher success rate in transplantation ^{120,121}. In transplantation from living donors the condition can result in paternal antigen sensitization because donors are often one of family members, and the lower volume of graft tissue is presumed to be harmful in comparison to deceased whole-organ donor. Whole-liver transplants can include an adequate vascular bed that assistances in the absorption of antibodies, which may not be as effective in smaller grafts ¹¹⁶.

HLA-specific antibodies: The exact effect of HLA-specific antibodies in liver transplantation is still not well comprehended. However, there is evidence proposing that these antibodies hurt graft survival. Several researches confirmed that an increased risk of graft damage in patients who have assembled HLA-specific antibodies or developed antibodies during the first year after transplantation ^{122,123}. Additionally, an examination has indicated a relation between HLA-specific antibodies and primitive AR within the first month following liver transplantation. These findings point to a potential negative effect of HLA-specific antibodies on liver transplant results, but further research is needed to fully comprehend their significance and underlying mechanisms ¹²².

Another analysis has found a relationship among HLA-specific antibodies and AR within the first month after transplantation. Current retrospective studies have also demonstrated a relationship among HLA-specific antibodies and CR ¹²³. In one of these studies, it was found that 92% of patients with CR had identifiable HLA-specific antibodies previously the occurrence of CR-induced graft damage, while just 61% of non-CR patients had antibodies ¹²⁴. Additionally, a similar research group has categorized the successful treatment

of AMR in liver transplant recipients using bortezomib¹²⁵. Lastly, it has been reported that assembled class I donor-specific HLA antibodies significantly reduced organ survival following liver retransplantation¹²⁶. These results propose that HLA-specific antibodies have a significant effect on acute and chronic rejection in liver transplantation, and their presence can affect graft outcomes.

In addition to the aforementioned findings, there have been reports linking Operational Tolerance (OT) with HLA-specific antibodies related to graft rejection^{127,128}. Patients with high levels of circulating HLA-specific antibodies have shown a better rate of steroid-resistant rejection compared to patients with low concentrations¹²⁹. In a retrospective study, recipients with effective weaning off immunosuppression were found to be negative for HLA-specific antibodies¹²⁷.

However, no training has specifically studied the potential negative impact of different types of HLA-specific antibodies (HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP) on achieving liver allograft OT and the importance of Mean Fluorescence Intensity (MFI) in combination with these antibodies has not been addressed in any study¹²³. These research gaps highlight the need for further investigation to understand the specific characteristics and implications of different HLA-specific antibodies and their relationship with achieving operational tolerance in liver transplantation.

Humoral immune response: Some studies showed that antibodies targeting liver tissue, rather than donor-specific anti-human HLA antibodies have a significant effect on the evolution of identified hepatitis in children after transplantation. This finding provides a basis for developing therapeutic approaches to address this condition¹³⁰. Several mechanisms are purposed to explain the etiology of late graft dysfunction in post transplantation phase. One potential mechanism that has been identified is the humoral immune response, which has been associated with graft liver fibrosis primarily observed in the centrilobular area¹³¹.

Idiopathic Post-Transplantation Hepatitis (IPTH) is a form of late-phase graft damage that can result in graft inefficiency¹³². The initial characteristic pathological attributes of IPTH are connector hepatitis¹³³. New connector hepatitis after liver transplantation was primarily reported in 1998, and many patients with this condition had elevated levels of Anti-Nuclear Antibodies (ANA)¹³⁰. Subsequently, there have been numerous information of new interface hepatitis following liver transplantation¹³⁴⁻¹³⁸. Furthermore, an association among autoantibodies and interface hepatitis has been observed¹³³.

However, some patients with interface hepatitis do not exhibit elevated levels of autoantibodies, leading to the proposal of the idea of IPTH to describe this difference¹³². Given that the pathological results of IPTH resemble those of Autoimmune Hepatitis (AIH), hu-

moral immunity has been suggested to be involved in the etiology of IPTH¹³³. In this context, the authors of the study encountered patients who had resistant connector hepatitis without height of autoantibodies.

DSAs in adult and pediatric: In adult liver transplantation, the effect of DSAs on long-term success is a subject of debate, but there is evidence to suggest that DSAs might be a risk factor for poorer survival^{139,140}. Patients who undergo liver transplantation by prefabricated DSAs are at a higher danger of hyper acute rejection¹¹⁸ and AMR during the initial weeks after transplantation¹⁴⁰. Additionally, DSAs have been related to CR^{113,141}, accelerated fibrosis¹⁴³, and anastomotic biliary strictures¹⁴³.

In the case of pediatric recipients, the incidence of DSAs next transplantation appears to be higher compared to adult recipients. Reports indicate that the positive rate of DSAs in children liver transplant recipients can be as high as 54%¹⁴⁴. Nevertheless, the association among the existence of AMR and DSAs in pediatric liver transplantation, as well as its impact on the survival of allogeneic liver transplant recipients, is not yet obvious. More investigation is required to understand the specific implications of DSAs in pediatric liver transplantation.

IgG: The present single antigen bead assay used in HLA antibody testing employs a detection method for antibody that identifies all human IgG bound to HLA antigens. Nevertheless, various IgG subdivisions possess incomparable features that can distinguish their possible pathogenicity, with their interactions with Fc Receptors (FcR) on cells and their ability to activate complement fixation. Each IgG subclass has distinct properties in terms of complement activation and cellular binding. Among them, IgG3 is the more potent activator of the supplement, followed by IgG1 and IgG2, while IgG4 cannot activate the supplement. Furthermore, various IgG subclasses exhibit varying measurements to tie to NK cells, macrophages, neutrophils, monocytes, and B cells through their Fc receptors. IgG3 and IgG1 can bind to all three classes of Fc receptors (FcRI, FcRII, and FcRIII), while IgG4 can bind to two (FcRII and FcRIII), and IgG2 capable only bind to FcRII^{145,146}.

The binding efficiencies of IgG subgroups to Fc receptors allow them to trigger various immune responses, include Antibody-Dependent Cell-mediated Cytotoxicity (ADCC), degranulation of inflammatory cells, cytokine creation, intracellular signaling, and cell recruitment¹⁴⁶. These variations in IgG subclasses underscore their diverse useful capabilities and suggestion that various subclasses might have varying impacts on immune responses and disease pathology. Understanding the detailed characteristics and activities of IgG subclasses is crucial for comprehending the potential pathogenicity of HLA antibodies and their interference in immune-mediated processes^{146,147}.

HLA matchmaker and PIRCHE-II algorithms: In liver transplantation, the production of dn-DSA is related to an extended chance of antibody-mediated rejection. These antibodies can identify the whole HLA antigen, as well as be able to bind to detailed, useful epitopes on the surface of the HLA molecules ¹⁴⁸. To predict and assess the likelihood of dn-DSA synthesis based on alloreactive epitopes, two algorithms, PIRCHE-II and HLA Matchmaker, have been developed ¹⁴⁹.

Research planned to evaluate the complementarity between these two algorithms in the context of liver transplantation of adults and pediatrics who had not undergone DSA utilizing the PIRCHE-II and HLA Matchmaker algorithms to identify predictive epitope mismatch scores and assess the likelihood of dn-DSA synthesis according to alloreactive eplet recognition ^{149,150}. In conclusion, the study highlights that the PIRCHE-II and HLA Matchmaker algorithms are valuable tools in identifying the risk of anti-HLA immunization and predicting the formation of new DSA after liver transplantation. These algorithms provide important information for risk stratification and may assist clinicians in tailoring immunosuppressive strategies in liver transplant recipients ¹⁴⁹.

Histological features of acute rejection: Liver-specific cells, including Liver Sinusoidal Epithelial Cells (LSECs), KCs, and Hepatic Stellate Cells (HSCs), are thought to contribute to the tolerogenic properties of the liver. Other mechanisms, such as microchimerism, soluble MHC molecules, the donor HLA-C genotype, and regulatory T cells may affect the acceptance ¹⁵¹. The relatively little development of hyperacute or AMR in liver transplantation may be related to the rarity of chronic failure in liver transplants ¹⁵². Answering the challenging questions underlying liver transplant failure and acceptance, as well as improving immune monitoring techniques, could aid in the expansion of approaches to identify tolerance and reduce rejection in patients receiving a transplant ¹⁵³. Further research is needed to gain a comprehensive understanding of these mechanisms and their clinical implications.

HLA-C: In various species, liver allografts have been spontaneously accepted without the need for immunosuppression. However, achieving tolerance in human transplant patients is relatively rare, even though the reversal of failure is often achievable. The histological attributes of acute failure in liver transplantation are similar to cases observed in other solid organs ¹⁵¹. However, the methods underlying liver transplant rejection might change in terms of the extent of involvement and the specific cell types implicated. HLA-C is the main inhibitory ligand for Killer Immunoglobulin-like Receptors (KIRs), which sets up the cytotoxic activity of NK cells. HLA-C alleles can be assigned into two parts, named HLA-C1 and HLA-C2, based on their KIR exclusivity. HLA-C2 mutual effects are over-inhibiting in NK cell activation ¹⁵⁴.

HLA-DR and HLA-DQ

The impact of mismatches in HLA class II—especially at the DRB1 (DR) and DQB1 (DQ) loci—on liver transplant rejection varies across different studies. A cohort study conducted in China indicated that a greater number of mismatches at the DQB1 and the combined DRB1+DQB1 loci were more frequently observed in recipients who underwent acute rejection. Nevertheless, when controlling for variables such as HBV infection and immunosuppression, these mismatches did not emerge as statistically significant independent risk factors ¹⁵⁵. In contrast, another study found that mismatches involving one or two alleles of DRB1 and DQB1 were associated with the occurrence of donor microchimerism in the absence of rejection ($p < 0.05$), implying a possible tolerogenic effect of these mismatches. These results underscore the intricate and context-sensitive influence of HLA-DR and HLA-DQ mismatching on the outcomes of liver transplantation.

Conclusion

The HLA molecule is the primary antigen responsible for humoral and cellular alloreactivities. Over the last thirty years, significant advancements in immunogenetics have greatly enhanced the safety of transplantation and fostered the creation of novel approaches that allow sensitized patients with anti-HLA antibodies to receive transplants. Promising new medications are currently being evaluated alongside standard therapies for desensitization and the management of AMR. The most effective treatment regimens are expected to involve a combination of various agents that operate through different mechanisms. The impact of HLA in SOT patients is undeniable, and HLA inhibition enhances stability in liver, kidney, and pancreas transplants. Each of these conditions, along with different drugs and agents, is in various phases of clinical trials, which can help to understand and control rejection. In spite of considerable progress in SOT and advancements in HLA typing methods, graft rejection continues to pose a significant challenge. Future investigations are anticipated to concentrate on personalized donor–recipient matching through genomic profiling and artificial intelligence to more accurately forecast rejection risk. Innovative immunomodulatory strategies, such as targeted biologics and cell-based therapies, may further improve graft longevity and minimize long-term complications. Furthermore, the amalgamation of global transplant databases and multicenter clinical trials will enhance our comprehension of HLA diversity and its effects on outcomes. The integration of genetic, immunologic, and computational advancements presents a promising avenue for optimizing the success of liver, kidney, and pancreas transplantation.

Acknowledgement

This study was approved and supported by the Research Council of Shiraz University of Medical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.

Funding: No funding was used for this review.

Conflict of Interest

Authors declare no conflict of interest.

References

- Mosaad YM. Clinical Role of Human Leukocyte Antigen in Health and Disease. *Scand J Immunol*. 2015 Oct;82(4):283-306.
- Crux NB, Elahi S. Human Leukocyte Antigen (HLA) and Immune Regulation: How Do Classical and Non-Classical HLA Alleles Modulate Immune Response to Human Immunodeficiency Virus and Hepatitis C Virus Infections? *Front Immunol*. 2017 Jul 18;8:832.
- Beri S, Garg N. Major Histocompatibility Complex and Antigen Presentation. In *An Interplay of Cellular and Molecular Components of Immunology* 2022 Dec 19 (pp. 151-171). CRC Press.
- Fan S, Wang Y, Wang S, Wang X, Wu Y, Li Z, Zhang N, Xia C. Polymorphism and peptide-binding specificities of porcine major histocompatibility complex (MHC) class I molecules. *Mol Immunol*. 2018 Jan;93:236-245.
- Liu Y, Ouyang XH, Xiao ZX, Zhang L, Cao Y. A review on the methods of peptide-MHC binding prediction. *Current Bioinformatics*. 2020 Oct 1;15(8):878-88.
- Xu T, Liu J, Sun Y, Zhu Z, Liu T. Characterization of 40 full-length MHC class IIA functional alleles in miiuy croaker: Polymorphism and positive selection. *Dev Comp Immunol*. 2016 Feb;55:138-43.
- Rossjohn J, Gras S, Miles JJ, Turner SJ, Godfrey DI, McCluskey J. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol*. 2015;33:169-
- van der Merwe PA, Davis SJ. Molecular interactions mediating T cell antigen recognition. *Annu Rev Immunol*. 2003;21:659-84.
- Mahdi BM. A glow of HLA typing in organ transplantation. *Clin Transl Med*. 2013 Feb 23;2(1):6.
- Sivakumar N, Brundha MP, Ganapathy D. HLA Typing And Its Influence On Organ Transplantation. *Int J Dentistry Oral Sci*. 2021 Feb 25;8(2):1698-700.
- Thorsby E. A short history of HLA. *Tissue Antigens*. 2009 Aug;74(2):101-16.
- Cano RL, Lopera HD. Introduction to T and B lymphocytes. In *Autoimmunity: from bench to bedside* [Internet] 2013 Jul 18. El Rosario University Press.
- Betjes MGH, Sablik KS, Otten HG, Roelen DL, Claas FH, de Weerd A. Pretransplant Donor-Specific Anti-HLA Antibodies and the Risk for Rejection-Related Graft Failure of Kidney Allografts. *J Transplant*. 2020 Jan 29; 2020:5694670.
- Milner J, Melcher ML, Lee B, Veale J, Ronin M, D'Alessandro T, Hil G, Fry PC, Shannon PW. HLA Matching Trumps Donor Age: Donor-Recipient Pairing Characteristics That Impact Long-Term Success in Living Donor Kidney Transplantation in the Era of Paired Kidney Exchange. *Transplant Direct*. 2016 Jun 6;2(7):e85.
- Takemoto S, Port FK, Claas FH, Duquesnoy RJ. HLA matching for kidney transplantation. *Hum Immunol*. 2004 Dec;65(12):1489-505.
- Hodges CY, Pickering DE, Murray JE, Goodwin WE. Kidney transplant between identical twins. *The J Urol* 1963 Feb;89(2):115-21.
- Barr J, Bradley JA, Hamilton D. Organ transplantation: a historical perspective. In *Transplantation Surgery* 2020 Dec 22 (pp. 1-29). Cham: Springer International Publishing.
- Rocha PN, Plumb TJ, Crowley SD, Coffman TM. Effector mechanisms in transplant rejection. *Immunol Rev*. 2003 Dec;196:51-64.
- Wood KJ, Goto R. Mechanisms of rejection: current perspectives. *Transplantation*. 2012 Jan 15;93(1):1-10.
- Barker CF, Markmann JF. Historical overview of transplantation. *Cold Spring Harb Perspect Med*. 2013 Apr 1;3(4):a014977.
- Zhang X, Reinsmoen N, Kobashigawa J. Overview of Transplantation Immunobiology. *Clinical Guide to Heart Transplantation* 2017:47-56.
- Koo TY, Lee JH, Min SI, Lee Y, Kim MS, Ha J, Kim SI, Ahn C, Kim YS, Kim J, Huh KH, Yang J. Presence of a survival benefit of HLA-incompatible living donor kidney transplantation compared to waiting or HLA-compatible deceased donor kidney transplantation with a long waiting time. *Kidney Int*. 2021 Jul;100(1):206-214.
- Sheldon S, Poulton K. HLA typing and its influence on organ transplantation. *Methods Mol Biol*. 2006;333:157-74.
- Lee J, editor. *The HLA system: a new approach*. Springer Science & Business Media; 2012 Dec 6.
- Pajot A, Michel ML, Fazilleau N, Pancré V, Auriault C, Ojcius DM, Lemonnier FA, Lone YC. A mouse model of human adaptive immune functions: HLA-A2.1/HLA-DR1-transgenic H-2 class I/class II-knockout mice. *Eur J Immunol* 2004 Nov;34(11):3060-9.
- Kong YC, Flynn JC, Wan Q, David CS. HLA and H2 class II transgenic mouse models to study susceptibility and protection in autoimmune thyroid disease. *Autoimmunity*. 2003 Sep-Nov;36(6-7):397-404.
- Mostafa AA, Petrosenko M, Stamm L, Khan F, Berka N. The novel HLA-B*08:183 allele identified by sequence-based typing in a Caucasian leukemia patient. *HLA*. 2017 Dec;90(6):367-368.
- Jaramillo A, Hacke K. The human leukocyte antigen system: nomenclature and DNA-based typing for transplantation. In *Human Leukocyte Antigens-Updates and Advances* 2023 Feb 27. IntechOpen.
- Medhasi S, Chantratita N. Human Leukocyte Antigen (HLA) System: Genetics and Association with Bacterial and Viral Infections. *J Immunol Res*. 2022 May 26;2022: 9710376.

30. Couture A, Garnier A, Docagne F, Boyer O, Vivien D, Le-Mauff B, Latouche JB, Toutirais O. HLA-Class II Artificial Antigen Presenting Cells in CD4⁺ T Cell-Based Immunotherapy. *Front Immunol*. 2019 May 17;10:1081.
31. Chong AS. Mechanisms of organ transplant injury mediated by B cells and antibodies: Implications for antibody-mediated rejection. *Am J Transplant*. 2020 Jun;20 Suppl 4(Suppl 4):23-32.
32. Dragun D, Hegner B. Non-HLA antibodies post-transplantation: clinical relevance and treatment in solid organ transplantation. *Contrib Nephrol*. 2009;162:129-39.
33. Reindl-Schwaighofer R, Heinzl A, Gualdoni GA, Mesnard L, Claas FHJ, Oberbauer R. Novel insights into non-HLA alloimmunity in kidney transplantation. *Transpl Int*. 2020 Jan;33(1):5-17.
34. Alelign T, Ahmed MM, Bobosha K, Tadesse Y, Howe R, Petros B. Kidney Transplantation: The Challenge of Human Leukocyte Antigen and Its Therapeutic Strategies. *J Immunol Res*. 2018 Mar 5;2018:5986740.
35. Sorohan BM, Baston C, Tacu D, Bucşa C, Țincu C, Vizireanu P, Sinescu I, Constantinescu I. Non-HLA Antibodies in Kidney Transplantation: Immunity and Genetic Insights. *Biomedicines*. 2022 Jun 25;10(7):1506.
36. Panicker AJ, Prokop LJ, Hacke K, Jaramillo A, Griffiths LG. Outcome-based Risk Assessment of Non-HLA Antibodies in Heart Transplantation: A Systematic Review. *J Heart Lung Transplant*. 2024 Sep;43(9):1450-1467.
37. Stegall MD, Gaston RS, Cosio FG, Matas A. Through a glass darkly: seeking clarity in preventing late kidney transplant failure. *J Am Soc Nephrol*. 2015 Jan;26(1):20-9.
38. Sorohan BM, Ismail G, Leca N, Tacu D, Obrișcă B, Constantinescu I, Baston C, Sinescu I. Angiotensin II type 1 receptor antibodies in kidney transplantation: An evidence-based comprehensive review. *Transplant Rev (Orlando)*. 2020 Oct;34(4):100573.
39. Pearl MH, Zhang Q, Palma Diaz MF, Grotts J, Rossetti M, Elashoff D, Gjertson DW, Weng P, Reed EF, Tsai Chambers E. Angiotensin II Type 1 receptor antibodies are associated with inflammatory cytokines and poor clinical outcomes in pediatric kidney transplantation. *Kidney Int*. 2018 Jan;93(1):260-269.
40. Philogene MC, Tchoukina I, Gimferrer I. Challenges and opportunities in bringing non-HLA antibody testing for post-transplant monitoring. *Front Transplant*. 2025 Jun 5;4:1594241.
41. Jethwani P, Rao A, Bow L, Menon MC. Donor-Recipient Non-HLA Variants, Mismatches and Renal Allograft Outcomes: Evolving Paradigms. *Front Immunol*. 2022 Apr 1;13:822353.
42. McKenna RM, Takemoto SK, Terasaki PI. Anti-HLA antibodies after solid organ transplantation. *Transplantation*. 2000 Feb 15;69(3):319-26.
43. Hajeer AH. Panel Reactive Antibody test (PRA) in renal transplantation. *Saudi J Kidney Dis Transpl*. 2006 Mar; 17(1):1-4.
44. Ciftci HS, Oguz FS, Cinar CK, Izgi DK. The correlation of results of panel reactive antibody, identification, and single antigen beads in detection of anti-HLA antibodies: Istanbul Faculty of Medicine, tissue typing laboratory experience. *Transpl Immunol*. 2023 Oct;80:101891.
45. Daligault M, Bardy B, Noble J, Bourdin A, Masson D, Naciri Bennani H, Bugnazet M, Malvezzi P, Rostaing L, Jouve T. Marginal Impact of Tocilizumab Monotherapy on Anti-HLA Alloantibodies in Highly Sensitized Kidney Transplant Candidates. *Transplant Direct*. 2021 Apr 22;7 (5):e690.
46. Park Y, Ko EJ, Chung BH, Yang CW. Kidney transplantation in highly sensitized recipients. *Kidney Res Clin Pract*. 2021 Sep;40(3):355-370.
47. Lee KW, Kim SJ, Lee DS, Lee HH, Joh JW, Lee SK, Oh HY, Kim DJ, Kim YG, Huh WS, Oh WI, Lee BB. Effect of panel-reactive antibody positivity on graft rejection before or after kidney transplantation. *Transplant Proc*. 2004 Sep;36(7):2009-10.
48. Terasaki PI. A personal perspective: 100-year history of the humoral theory of transplantation. *Transplantation*. 2012 Apr 27;93(8):751-6.
49. Gebel HM, Bray RA, Nickerson P. Pre-transplant assessment of donor-reactive, HLA-specific antibodies in renal transplantation: contraindication vs. risk. *Am J Transplant*. 2003 Dec;3(12):1488-500.
50. Hwang HS, Yoon HE, Choi BS, Oh EJ, Kim JI, Moon IS, Kim YS, Yang CW. B-cell complement dependent cytotoxic crossmatch positivity is an independent risk factor for long-term renal allograft survival. *J Korean Med Sci*. 2011 Apr;26(4):528-33.
51. Lefaucheur C, Suberbielle-Boissel C, Hill GS, Nochy D, Andrade J, Antoine C, Gautreau C, Charron D, Glotz D. Clinical relevance of preformed HLA donor-specific antibodies in kidney transplantation. *Am J Transplant*. 2008 Feb;8(2):324-31.
52. de Mattos AM, Bennett WM, Barry JM, Norman DJ. HLA-identical sibling renal transplantation--a 21-yr single-center experience. *Clin Transplant*. 1999 Apr;13 (2):158-67.
53. Pérez-Sáez MJ, Montero N, Oliveras L, Redondo-Pachón D, Martínez-Simón D, Abramovicz D, Maggiore U, Mariat C, Mjoen G, Oniscu GC, Peruzzi L, Sever MS, Watschinger B, Velioglu A, Demir E, Gandolfini I, Hellemans R, Hilbrands L, Pascual J, Crespo M; ERA-EDTA-Descartes working group. Immunosuppression of HLA identical living-donor kidney transplant recipients: A systematic review. *Transplant Rev (Orlando)*. 2023 Dec;37(4):100787.
54. Vo A, Ammerman N, Jordan SC. Advances in desensitization for human leukocyte antigen incompatible kidney transplantation. *Curr Opin Organ Transplant*. 2024 Apr 1;29(2):104-120.
55. Jordan SC, Ammerman N, Huang E, Vo A. Importance of IL-6 inhibition in prevention and treatment of antibody-mediated rejection in kidney allografts. *Am J Transplant*. 2022 Dec;22 Suppl 4:28-37.
56. Sahakian SK. The alloimmune response of T-cells in a single MHC-mismatch murine model of allosensitization. McGill University (Canada); 2014.

57. J Jouve T, Laheurte C, Noble J, Weinhard J, Daligault M, Renaudin A, Naciri Bennani H, Masson D, Gravelin E, Bugnazet M, Bardy B, Malvezzi P, Saas P, Rostaing L. Immune responses following tocilizumab therapy to desensitize HLA-sensitized kidney transplant candidates. *Am J Transplant* 2022 Jan;22(1):71-84.
58. Claas FH, Dankers MK, Oudshoorn M, van Rood JJ, Mulder A, Roelen DL, Duquesnoy RJ, Doxiadis II. Differential immunogenicity of HLA mismatches in clinical transplantation. *Transpl Immunol*. 2005 Aug;14 (3-4):187-91.
59. Larkins NG, Wong G, Taverniti A, Lim WH. Epitope matching in kidney transplantation: recent advances and current limitations. *Curr Opin Organ Transplant*. 2019 Aug;24(4):370-377.
60. Duquesnoy RJ, Takemoto S, de Lange P, Doxiadis II, Schreuder GM, Persijn GG, Claas FH. HLAmatchmaker: a molecularly based algorithm for histocompatibility determination. III. Effect of matching at the HLA-A,B amino acid triplet level on kidney transplant survival. *Transplantation*. 2003 Mar 27;75(6):884-9.
61. Simpson N, Cho YW, Cicciarelli JC, Selby RR, Fong TL. Comparison of renal allograft outcomes in combined liver-kidney transplantation versus subsequent kidney transplantation in liver transplant recipients: Analysis of UNOS Database. *Transplantation*. 2006 Nov 27;82(10): 1298-303.
62. Wade JA, Hurley CK, Takemoto SK, Thompson J, Davies SM, Fuller TC, Rodey G, Confer DL, Noreen H, Haagensohn M, Kan F, Klein J, Eapen M, Spellman S, Kollman C. HLA mismatching within or outside of cross-reactive groups (CREGs) is associated with similar outcomes after unrelated hematopoietic stem cell transplantation. *Blood*. 2007 May 1;109(9):4064-70.
63. Hwang SH, Oh HB, Shin ES, Yew M, Kim SC, Han DJ. Influence of mismatching of HLA cross-reactive groups on cadaveric kidney transplantation. *Transplant Proc*. 2005 Dec;37(10):4194-8.
64. Pilch NA, Bowman LJ, Taber DJ. Immunosuppression trends in solid organ transplantation: The future of individualization, monitoring, and management. *Pharmacotherapy*. 2021 Jan;41(1):119-131.
65. Shapiro R, Young JB, Milford EL, Trotter JF, Bustami RT, Leichtman AB. Immunosuppression: evolution in practice and trends, 1993-2003. *Am J Transplant*. 2005 Apr;5(4 Pt 2):874-86.
66. Stegall MD, Chedid MF, Cornell LD. The role of complement in antibody-mediated rejection in kidney transplantation. *Nat Rev Nephrol*. 2012 Nov;8(11):670-8.
67. Schlaf G, Mauz-Körholz C, Ott U, Leike S, Altermann W. General insufficiency of the classical CDC-based crossmatch to detect donor-specific anti-HLA antibodies leading to invalid results under recipients' medical treatment or underlying diseases. *Histol Histopathol*. 2012 Jan;27(1):31-8.
68. Schönemann C, Groth J, Leverenz S, May G. HLA class I and class II antibodies: monitoring before and after kidney transplantation and their clinical relevance. *Transplantation*. 1998 Jun 15;65(11):1519-23.
69. Bearden CM, Book BK, Sidner RA, Pescovitz MD. Removal of therapeutic anti-lymphocyte antibodies from human sera prior to anti-human leukocyte antibody testing. *J Immunol Methods* 2005 May;300(1-2):192-9.
70. Fuller TC, Fuller AA, Golden M, Rodey GE. HLA alloantibodies and the mechanism of the antiglobulin-augmented lymphocytotoxicity procedure. *Hum Immunol* 1997 Aug-Sep;56(1-2):94-105.
71. Kim B, Kim S, Park Y, Kim HS. False-positive reactivity of anti-human leukocyte antigen antibodies detected using the single-antigen bead assay. *Hum Immunol* 2021 Jun;82(6):409-413.
72. Montgomery RA, Tatapudi VS, Leffell MS, Zachary AA. HLA in transplantation. *Nat Rev Nephrol*. 2018 Sep;14 (9):558-570.
73. Rebmann V, da Silva Nardi F, Wagner B, Horn PA. HLA-G as a tolerogenic molecule in transplantation and pregnancy. *J Immunol Res*. 2014;2014:297073.
74. Duquesnoy RJ. Are We Ready for Epitope-Based HLA Matching in Clinical Organ Transplantation? *Transplantation*. 2017 Aug;101(8):1755-1765.
75. Kubal CA, Mangus R, Ekser B, Mihaylov P, Ceballos B, Higgins N, et al. Class II Human Leukocyte Antigen Epitope Mismatch Predicts De Novo Donor-Specific Antibody Formation After Liver Transplantation. *Liver Transpl*. 2018 Aug;24(8):1101-1108.
76. Geneugelijk K, Wissing J, Koppenaal D, Niemann M, Spierings E. Computational Approaches to Facilitate Epitope-Based HLA Matching in Solid Organ Transplantation. *J Immunol Res*. 2017;2017:9130879.
77. Foster BJ, Dahhou M, Zhang X, Platt RW, Smith JM, Hanley JA. Impact of HLA mismatch at first kidney transplant on lifetime with graft function in young recipients. *Am J Transplant*. 2014 Apr;14(4):876-85.
78. Foster BJ, Dahhou M, Zhang X, Platt RW, Samuel SM, Hanley JA. Association between age and graft failure rates in young kidney transplant recipients. *Transplantation*. 2011 Dec 15;92(11):1237-43.
79. Senev A, Ray B, Lerut E, Hariharan J, Heylen C, Kuypers D, Sprangers B, Emonds MP, Naesens M. The Pre-Transplant Non-HLA Antibody Burden Associates With the Development of Histology of Antibody-Mediated Rejection After Kidney Transplantation. *Front Immunol*. 2022 Feb 16;13:809059.
80. Scornik JC, Kriesche HU. Human leukocyte antigen sensitization after transplant loss: timing of antibody detection and implications for prevention. *Hum Immunol*. 2011 May;72(5):398-401.
81. Akgul SU, Ciftci HS, Temurhan S, Caliskan Y, Bayraktar A, Tefik T, et al. Association Between HLA Antibodies and Different Sensitization Events in Renal Transplant Candidates. *Transplant Proc*. 2017 Apr;49(3):425-429.
82. Higgins R, Lowe D, Daga S, Hathaway M, Williams C, Lam FT, et al. Pregnancy-induced HLA antibodies respond more vigorously after renal transplantation than antibodies induced by prior transplantation. *Hum Immunol*. 2015 Aug;76(8):546-52.

83. Hickey MJ, Valenzuela NM, Reed EF. Alloantibody Generation and Effector Function Following Sensitization to Human Leukocyte Antigen. *Front Immunol*. 2016 Feb 4;7:30.
84. Picascia A, Grimaldi V, Sabia C, Napoli C. Comprehensive assessment of sensitizing events and anti-HLA antibody development in women awaiting kidney transplantation. *Transpl Immunol*. 2016 May;36:14-9.
85. Boehlen F, Bulla O, Michel M, Reber G, de Moerloose P. HPA-genotyping and antiplatelet antibodies in female blood donors. *Hematol J*. 2003;4(6):441-4.
86. Triulzi DJ, Kleinman S, Kakaiya RM, Busch MP, Norris PJ, Steele WR, et al. The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. *Transfusion*. 2009 Sep;49(9):1825-35.
87. Kumbala D, Zhang R. Essential concept of transplant immunology for clinical practice. *World J Transplant*. 2013 Dec 24;3(4):113-8.
88. Higgins R, Lowe D, Hathaway M, Williams C, Lam FT, Kashi H, et al. Human leukocyte antigen antibody-incompatible renal transplantation: excellent medium-term outcomes with negative cytotoxic crossmatch. *Transplantation*. 2011 Oct 27;92(8):900-6.
89. Rydberg L. ABO-incompatibility in solid organ transplantation. *Transfus Med*. 2001 Aug;11(4):325-42.
90. Clifford L, Jia Q, Subramanian A, Yadav H, Wilson GA, Murphy SP, et al. Characterizing the epidemiology of postoperative transfusion-related acute lung injury. *Anesthesiology* 2015 Jan;122(1):12-20.
91. Kim J, Na S. Transfusion-related acute lung injury; clinical perspectives. *Korean J Anesthesiol* 2015 Apr;68(2):101-5.
92. Middelburg RA, van Stein D, Briët E, van der Bom JG. The role of donor antibodies in the pathogenesis of transfusion-related acute lung injury: a systematic review. *Transfusion* 2008 Oct;48(10):2167-76.
93. Scornik JC, Meier-Kriesche HU. Blood transfusions in organ transplant patients: mechanisms of sensitization and implications for prevention. *Am J Transplant* 2011 Sep;11(9):1785-91.
94. Hiesse C, Busson M, Buisson C, Farahmand H, Bierling P, Benbunan M, et al. Multicenter trial of one HLA-DR-matched or mismatched blood transfusion prior to cadaveric renal transplantation. *Kidney Int* 2001 Jul;60(1):341-9.
95. Morath C, Opelz G, Zeier M, Süsal C. Prevention of antibody-mediated kidney transplant rejection. *Transpl Int* 2012 Jun;25(6):633-45.
96. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet* 2009 May 23;373(9677):1808-17.
97. Cantarovich D, De Amicis S, Akl A, Devys A, Vistoli F, Karam G, et al. Posttransplant donor-specific anti-HLA antibodies negatively impact pancreas transplantation outcome. *Am J Transplant* 2011 Dec;11(12):2737-46.
98. Campbell PM, Senior PA, Salam A, Labranche K, Bigam DL, Kneteman NM, et al. High risk of sensitization after failed islet transplantation. *Am J Transplant* 2007 Oct;7(10):2311-7.
99. Colombo MB, Haworth SE, Poli F, Nocco A, Puglisi G, Innocente A, et al. Luminex technology for anti-HLA antibody screening: evaluation of performance and of impact on laboratory routine. *Cytometry B Clin Cytom* 2007 Nov;72(6):465-71.
100. Bertol BC, Dias FC, da Silva DM, Zambelli Ramalho LN, Donadi EA. Human Antigen Leucocyte (HLA)-G and HLA-E are differentially expressed in pancreatic disorders. *Hum Immunol* 2019 Nov;80(11):948-954.
101. Costa Arantes DA, Gonçalves AS, Jham BC, Duarte ECB, de Paula ÉC, de Paula HM, et al. Evaluation of HLA-G, HLA-E, and PD-L1 proteins in oral osteosarcomas. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2017 Jun;123(6):e188-e196.
102. Becker LE, Hallscheidt P, Schaefer SM, Klein K, Grenacher L, Waldherr R, et al. A Single-center Experience on the Value of Pancreas Graft Biopsies and HLA Antibody Monitoring After Simultaneous Pancreas-Kidney Transplantation. *Transplant Proc* 2015 Oct;47(8):2504-12.
103. Oling V, Marttila J, Ilonen J, Kwok WW, Nepom G, Knip M, et al. GAD65- and proinsulin-specific CD4+ T-cells detected by MHC class II tetramers in peripheral blood of type 1 diabetes patients and at-risk subjects. *J Autoimmun* 2005 Nov;25(3):235-43.
104. Danke NA, Yang J, Greenbaum C, Kwok WW. Comparative study of GAD65-specific CD4+ T cells in healthy and type 1 diabetic subjects. *J Autoimmun* 2005 Dec;25(4):303-11.
105. Veldman C, Eming R, Wolff-Franke S, Sonderstrup G, Kwok WW, Hertl M. Detection of low avidity desmoglein 3-reactive T cells in pemphigus vulgaris using HLA-DR beta 1*0402 tetramers. *Clin Immunol* 2007 Mar;122(3):330-7.
106. Berney T, Malaise J, Morel P, Toso C, Demuylder-Mischler S, Majno P, et al. Impact of HLA matching on the outcome of simultaneous pancreas-kidney transplantation. *Nephrol Dial Transplant* 2005 May;20 Suppl 2:ii48-53, ii62.
107. Raineri F, Frischknecht L, Nilsson J, Rössler F, Cavelti-Weder C, von Moos S, et al. Assessing the Predictive Power of PIRCHE-II Scores for the Development of De Novo Donor-Specific Antibodies After Simultaneous Pancreas-Kidney Transplantation. *Transpl Int* 2024 Dec 18;37:13720.
108. van Belle TL, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. *Physiol Rev* 2011 Jan;91(1):79-118.
109. Roep BO, Tree TI. Immune modulation in humans: implications for type 1 diabetes mellitus. *Nat Rev Endocrinol* 2014 Apr;10(4):229-42.
110. Platt JL, Cascalho M. Donor specific antibodies after transplantation. *Pediatr Transplant* 2011 Nov;15(7):686-90.
111. O'Leary JG, Demetris AJ, Friedman LS, Gebel HM, Halloran PF, Kirk AD, et al. The role of donor-specific

- HLA alloantibodies in liver transplantation. *Am J Transplant* 2014 Apr;14(4):779-87.
112. Ali S, Ormsby A, Shah V, Segovia MC, Kantz KL, Skorupski S, et al. Significance of complement split product C4d in ABO-compatible liver allograft: diagnosing utility in acute antibody mediated rejection. *Transpl Immunol* 2012 Jan;26(1):62-9.
 113. Musat AI, Pigott CM, Ellis TM, Agni RM, Levenson GE, Powell AJ, et al. Pretransplant donor-specific anti-HLA antibodies as predictors of early allograft rejection in ABO-compatible liver transplantation. *Liver Transpl* 2013 Oct;19(10):1132-41.
 114. Chan KM, Lee CS, Wu TJ, Lee CF, Chen TC, Lee WC. Clinical perspective of acute humoral rejection after blood type-compatible liver transplantation. *Transplantation* 2011 Mar 15;91(5):e29-30.
 115. Beyzaei Z, Geramizadeh B, Bagheri Z, Karimzadeh S, Shojazadeh A. De Novo Donor Specific Antibody and Long-Term Outcome After Liver Transplantation: A Systematic Review and Meta-Analysis. *Front Immunol* 2020 Dec 23;11:613128.
 116. Goto R, Ito M, Kawamura N, Watanabe M, Ganchiku Y, Kamiyama T, et al. The impact of preformed donor-specific antibodies in living donor liver transplantation according to graft volume. *Immun Inflamm Dis* 2022 Mar;10(3):e586.
 117. Koch M, Marget M, Sterneck M, Fischer L, Thude H, Nashan B. Limited impact of pre-existing donor specific HLA-antibodies (DSA) on long term allograft survival after first adult liver transplantation. *Hum Immunol* 2018 Jul;79(7):545-549.
 118. Taner T, Gandhi MJ, Sanderson SO, Poterucha CR, De Goey SR, Stegall MD, et al. Prevalence, course and impact of HLA donor-specific antibodies in liver transplantation in the first year. *Am J Transplant* 2012 Jun;12(6):1504-10.
 119. Yoshizawa A, Egawa H, Yurugi K, Hishida R, Tsuji H, Ashihara E, et al. Significance of semiquantitative assessment of preformed donor-specific antibody using luminex single bead assay in living related liver transplantation. *Clin Dev Immunol* 2013;2013:972705.
 120. Levitsky J, Kaneku H, Jie C, Walsh RC, Abecassis M, Tambur AR. Donor-Specific HLA Antibodies in Living Versus Deceased Donor Liver Transplant Recipients. *Am J Transplant* 2016 Aug;16(8):2437-44.
 121. Reichman TW, Katchman H, Tanaka T, Greig PD, McGilvray ID, Cattral MS, et al. Living donor versus deceased donor liver transplantation: a surgeon-matched comparison of recipient morbidity and outcomes. *Transpl Int* 2013 Aug;26(8):780-7.
 122. Castillo-Rama M, Castro MJ, Bernardo I, Meneu-Diaz JC, Elola-Olaso AM, Calleja-Antolin SM, et al. Preformed antibodies detected by cytotoxic assay or multi-bead array decrease liver allograft survival: role of human leukocyte antigen compatibility. *Liver Transpl* 2008 Apr;14(4):554-62.
 123. Waki K, Sugawara Y, Mizuta K, Taniguchi M, Ozawa M, Hirata M, et al. Predicting operational tolerance in pediatric living-donor liver transplantation by absence of HLA antibodies. *Transplantation* 2013 Jan 15;95(1):177-83.
 124. O'Leary JG, Kaneku H, Susskind BM, Jennings LW, Neri MA, Davis GL, et al. High mean fluorescence intensity donor-specific anti-HLA antibodies associated with chronic rejection postliver transplant. *Am J Transplant* 2011 Sep;11(9):1868-76.
 125. Paterno F, Shiller M, Tillery G, O'Leary JG, Susskind B, Trotter J, Klintmalm GB. Bortezomib for acute antibody-mediated rejection in liver transplantation. *Am J Transplant* 2012 Sep;12(9):2526-31.
 126. Goh A, Scalapogna M, De Feo T, Poli F, Terasaki PI. Human leukocyte antigen crossmatch testing is important for liver retransplantation. *Liver Transpl* 2010 Mar;16(3):308-13.
 127. Girnita A, Mazariegos GV, Castellaneta A, Reyes J, Bentlejewski C, Thomson AW, et al. Liver transplant recipients weaned off immunosuppression lack circulating donor-specific antibodies. *Hum Immunol*. 2010 Mar;71(3):274-6.
 128. Feng S, Ekong UD, Lobritto SJ, Demetris AJ, Roberts JP, Rosenthal P, et al. Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of parental living donor liver transplants. *JAMA* 2012 Jan 18;307(3):283-93.
 129. Scornik JC, Soldevilla-Pico C, Van der Werf WJ, Hemming AW, Reed AI, Langham MR Jr, et al. Susceptibility of liver allografts to high or low concentrations of preformed antibodies as measured by flow cytometry. *Am J Transplant* 2001 Jul;1(2):152-6.
 130. Hirata Y, Yoshizawa A, Egawa H, Ueda D, Okamoto S, Okajima H, et al. Impact of Antibodies That React With Liver Tissue and Donor-Specific Anti-HLA Antibodies in Pediatric Idiopathic Posttransplantation Hepatitis. *Transplantation* 2017 May;101(5):1074-1083.
 131. Vij M, Rammohan A, Rela M. Long-term liver allograft fibrosis: A review with emphasis on idiopathic post-transplant hepatitis and chronic antibody mediated rejection. *World J Hepatol* 2022 Aug 27;14(8):1541-1549.
 132. Banff Working Group; Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. *Hepatology* 2006 Aug;44(2):489-501.
 133. Miyagawa-Hayashino A, Haga H, Egawa H, Hayashino Y, Uemoto S, Manabe T. Idiopathic post-transplantation hepatitis following living donor liver transplantation, and significance of autoantibody titre for outcome. *Transpl Int* 2009 Mar;22(3):303-12.
 134. Hernandez HM, Kovarik P, Whittington PF, Alonso EM. Autoimmune hepatitis as a late complication of liver transplantation. *J Pediatr Gastroenterol Nutr* 2001 Feb;32(2):131-6.
 135. Miyagawa-Hayashino A, Haga H, Sakurai T, Shirase T, Manabe T, Egawa H. De Novo autoimmune hepatitis affecting allograft but not the native liver in auxiliary partial orthotopic liver transplantation. *Transplantation* 2003 Jul 15;76(1):271-2.

136. Miyagawa-Hayashino A, Haga H, Egawa H, Hayashino Y, Sakurai T, Minamiguchi S, Tanaka K, et al. Outcome and risk factors of De Novo autoimmune hepatitis in living-donor liver transplantation. *Transplantation* 2004 Jul 15;78(1):128-35.
137. Venick RS, McDiarmid SV, Farmer DG, Gornbein J, Martin MG, Vargas JH, et al. Rejection and steroid dependence: unique risk factors in the development of pediatric posttransplant De Novo autoimmune hepatitis. *Am J Transplant* 2007 Apr;7(4):955-63.
138. Andries S, Casamayou L, Sempoux C, Burlet M, Reding R, Bernard Otte J, Buts JP, Sokal E. Posttransplant immune hepatitis in pediatric liver transplant recipients: incidence and maintenance therapy with azathioprine. *Transplantation* 2001 Jul 27;72(2):267-72.
139. Muro M, López-Álvarez MR, Campillo JA, Marin L, Moya-Quiles MR, Bolarín JM, et al. Influence of human leukocyte antigen mismatching on rejection development and allograft survival in liver transplantation: is the relevance of HLA-A locus matching being underestimated? *Transpl Immunol* 2012 Mar;26(2-3):88-93.
140. Liu W, Wang K, Xiao YL, Liu C, Gao W, Li DH. Clinical relevance of donor-specific human leukocyte antigen antibodies after pediatric liver transplantation. *Exp Ther Med* 2021 Aug;22(2):867.
141. Musat AI, Agni RM, Wai PY, Pirsch JD, Lorentzen DF, Powell A, Leverson GE, Bellingham JM, Fernandez LA, Foley DP, Mezrich JD, D'Alessandro AM, Lucey MR. The significance of donor-specific HLA antibodies in rejection and ductopenia development in ABO compatible liver transplantation. *Am J Transplant* 2011 Mar;11(3):500-10.
142. Del Bello A, Congy-Jolivet N, Muscari F, Lavayssière L, Esposito L, Cardeau-Desangles I, et al. Prevalence, incidence and risk factors for donor-specific anti-HLA antibodies in maintenance liver transplant patients. *Am J Transplant* 2014 Apr;14(4):867-75.
143. Miyagawa-Hayashino A, Yoshizawa A, Uchida Y, Egawa H, Yurugi K, Masuda S, et al. Progressive graft fibrosis and donor-specific human leukocyte antigen antibodies in pediatric late liver allografts. *Liver Transpl* 2012 Nov;18(11):1333-42.
144. Wozniak LJ, Hickey MJ, Venick RS, Vargas JH, Farmer DG, Busuttil RW, et al. Donor-specific HLA Antibodies Are Associated With Late Allograft Dysfunction After Pediatric Liver Transplantation. *Transplantation* 2015 Jul;99(7):1416-22.
145. Schroeder HW Jr, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol* 2010 Feb;125(2 Suppl 2):S41-52.
146. O'Leary JG, Kaneku H, Banuelos N, Jennings LW, Klintmalm GB, Terasaki PI. Impact of IgG3 subclass and C1q-fixing donor-specific HLA alloantibodies on rejection and survival in liver transplantation. *Am J Transplant* 2015 Apr;15(4):1003-13.
147. Filippone EJ, Farber JL. The Humoral Theory of Transplantation: Epitope Analysis and the Pathogenicity of HLA Antibodies. *J Immunol Res* 2016;2016: 5197396.
148. O'Leary JG, Samaniego M, Barrio MC, Potena L, Zeevi A, Djamali A, Cozzi E. The Influence of Immunosuppressive Agents on the Risk of De Novo Donor-Specific HLA Antibody Production in Solid Organ Transplant Recipients. *Transplantation* 2016 Jan;100(1): 39-53.
149. Hamada S, Dumortier J, Thévenin C, Pageaux GP, Faure S, Guillaud O, et al. Predictive value of HLA-Matchmaker and PIRCHE-II scores for De Novo donor-specific antibody formation after adult and pediatric liver transplantation. *Transpl Immunol* 2020 Aug;61:101306.
150. Kok G, Verstegen MMA, Houwen RHJ, Nieuwenhuis EES, Metselaar HJ, Polak WG, et al. Assessment of human leukocyte antigen matching algorithm PIRCHE-II on liver transplantation outcomes. *Liver Transpl*. 2022 Aug;28(8):1356-1366.
151. Knechtle SJ, Kwun J. Unique aspects of rejection and tolerance in liver transplantation. *Semin Liver Dis*. 2009 Feb;29(1):91-101.
152. Nakamura T, Shirouzu T. Antibody-mediated rejection and recurrent primary disease: two main obstacles in abdominal kidney, liver, and pancreas transplants. *J Clin Med* 2021 Nov 19;10(22):5417.
153. Sood S, Testro AG. Immune monitoring post liver transplant. *World J Transplant* 2014 Mar 24;4(1):30-9.
154. Hanvesakul R, Spencer N, Cook M, Gunson B, Hathaway M, Brown R, et al. Donor HLA-C genotype has a profound impact on the clinical outcome following liver transplantation. *Am J Transplant* 2008 Sep;8(9): 1931-41.
155. Lu G, Lu Y, He Y, Chen W, Zhu F. Impact of human leukocyte antigen mismatch between donor-recipient on acute rejection in liver transplantation using next-generation sequencing: a single-center study. *Front Immunol* 2025 May 20;16:1576815.