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## DIAGNOSIS AND TREATMENT OF KIDNEY TRANSPLANT REJECTION: A LITERATURE REVIEW.

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### Abstract

**Introduction.** Kidney transplantation is the only radical method of treating most terminal stages of chronic renal failure. Acute rejection of the transplanted kidney is one of the main and frequently encountered complications in recipients, occurring a few days or months after the transplantation, whether from a living or deceased donor, as a manifestation of the body's immune response to foreign tissue.

**The aim** is to review and analyze the current literature on the diagnosis and treatment of kidney transplant rejection, with a focus on acute and hyperacute rejection

**Search strategy:** Using Pubmed, Google scholar search engine, all articles that included keywords "kidney transplantation" and "rejection", "donor-specific antibodies" were retrieved. In total 50 search results emerged for the 2014-2024 timeline, the last 10 years.

**Results.** Acute rejection of the transplanted kidney results from the immune system recognizing the transplanted organ as foreign and mounting an immune response that leads to the rejection and destruction of the organ's cells. As for hyperacute rejection, it is caused by pre-formed antibodies that trigger a rejection reaction within the first 72 hours after organ transplantation. The manifestations and course of the disease are quite diverse, as are the consequences of developing this complication, so early diagnosis and treatment are crucial.

**Conclusion.** Despite the existing risk prediction algorithms, these complications occur with alarming regularity, including in our country. Combined with imperfect outpatient management practices for recipients and the absence of protocol biopsies, these factors directly impact survival rates.

**Keywords:** Kidney transplantation, rejection, donor-specific antibodies.

### Резюме

## ДИАГНОСТИКА И ЛЕЧЕНИЕ ОТТОРЖЕНИЯ ТРАНСПЛАНТАТА ПОЧКИ: ОБЗОР ЛИТЕРАТУРЫ

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**Введение.** Трансплантация почки является единственным радикальным методом лечения большинства терминальных стадий хронической почечной недостаточности. Острая реакция отторжения трансплантированной почки является одной из основных и часто встречающихся осложнений у реципиентов, возникающих через несколько дней или месяцев после трансплантации, будь то от живого или умершего донора, как проявление иммунного ответа организма на чуждую ткань.

**Цель.** Обзор и анализ современной литературы по диагностике и лечению отторжения трансплантированной почки, с акцентом на острую и сверхострую реакцию отторжения.

**Стратегия поиска.** С использованием PubMed и Google Scholar были найдены все статьи, содержащие ключевые слова «трансплантация почки» и «отторжение», «специфические антитела к донору». В результате поиска за период с 2014 по 2024 годы было получено 50 статьи.

**Результаты.** Острая реакция отторжения трансплантированной почки возникает из-за того, что иммунная система распознает трансплантированный орган как чуждый и инициирует иммунный ответ, который приводит к отторжению и разрушению клеток органа. Сверхострое отторжение вызывается преобразованными антителами, которые запускают реакцию отторжения в течение первых 72 часов после трансплантации органа. Проявления и течение заболевания довольно разнообразны, как и последствия развития этого осложнения, поэтому ранняя диагностика и лечение имеют решающее значение.

**Заключение.** Несмотря на существующие алгоритмы прогнозирования рисков, эти осложнения возникают с тревожной регулярностью, включая нашу страну. В сочетании с несовершенными практиками амбулаторного наблюдения за реципиентами и отсутствием протокольных биопсий эти факторы напрямую влияют на показатели выживаемости.

**Ключевые слова:** Трансплантация почки, отторжение, специфические антитела к донору.

Түйіндеме

## **БҮЙРЕК ТРАНСПЛАНТАТЫН ҚАБЫЛДАМАУДЫ ДИАГНОСТИКАЛАУ ЖӘНЕ ЕМДЕУ: ӘДЕБИЕТТЕРГЕ ШОЛУ.**

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**Кіріспе.** Бүйректі трансплантациялау созылмалы бүйрек жеткіліксіздігінің терминалды сатыларын емдеудің жалғыз радикалды әдісі болып табылады. Трансплантацияланған бүйректің жедел қабылдамау реакциясы реципиенттерде жиі кездесетін негізгі асқынулардың бірі болып саналады, ол тірі немесе қайтыс болған донордан кейін трансплантациядан бірнеше күн немесе айлар өткеннен кейін пайда болады және ағзаның бөгде тінге иммундық жауабы ретінде көрінеді.

**Мақсаты.** Жедел және өте жедел бас тарту қабылдамау реакциясына баса назар аударатын, трансплантацияланған бүйректі қабылдамауды диагностикалау және емдеу бойынша қазіргі әдебиеттерді шолу және талдау.

**Іздестіру стратегиясы.** PubMed және Google Scholar пайдаланып, «бүйректі трансплантациялау» және «қабылдамау» деген кілт сөздерді қамтитын барлық мақалалар табылды. Іздеу нәтижесінде 2014-2024 жылдар аралығында 50 нәтиже алынды.

**Нәтижелер.** Трансплантацияланған бүйректің жедел қабылдамау реакциясы иммундық жүйенің трансплантацияланған органды бөгде ретінде танып, иммундық жауап тудырып, орган жасушаларының қабылданбауы мен жойылуына әкелуімен туындайды. Өте жедел бас тарту, қабылдамау алдын ала қалыптасқан антиденелермен туындайды, олар орган трансплантациясынан кейін алғашқы 72 сағат ішінде қабылдамау реакциясын қоздырады. Аурудың көріністері мен ағымы әр түрлі болғандықтан, бұл асқынудың салдары да әртүрлі болады, сондықтан ерте диагностика және емдеу өте маңызды.

**Қорытынды.** Қауіпті болжау алгоритмдері болғанына қарамастан, бұл асқынулар, соның ішінде біздің елде де, алаңдатарлық тұрақтылықпен орын алады. Реципиенттерді амбулаторлық бақылаудың жетілмеген тәжірибелерімен және хаттамалық биопсиялардың болмауымен бірге бұл факторлар тіршілік деңгейіне тікелей әсер етеді.

**Түйінді сөздер:** Бүйректі трансплантациялау, қабылдамау, донорға тән антиденелер.

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**Relevance**

The relevance of the topic of diagnosis and treatment of kidney allograft rejection is due to the high rate of organ transplantation in modern medical practice and the increasing number of patients requiring kidney transplantation due to chronic kidney disease. Graft rejection remains one of the major causes of post-transplant failure, requiring the attention of researchers and clinicians.

According to recent data, more than 10% of all transplanted kidneys experience acute rejection in the first few months after surgery, which can significantly reduce graft and patient survival. Early diagnosis of rejection is therefore essential to improve outcomes.

Clinical approaches to diagnosing rejection include both invasive methods, such as graft biopsy, and non-invasive methods, such as blood tests for specific markers. The development of new diagnostic technologies, such as liquid biopsy and molecular testing, is opening new horizons in the early detection of rejection and monitoring of graft status.

Treatment of rejection depends on its type (acute or chronic) and requires an individualised approach for each patient. Immunosuppressive therapy is usually the mainstay of treatment, but the choice of drugs and their dosage should be carefully considered, taking into account possible side effects and interactions.

Therefore, the necessity for further investigation into this topic is highlighted by the requirement for an improvement in the efficacy of the diagnosis and treatment of renal allograft rejection. This, in turn, will facilitate an enhancement in the quality of life for patients and a reduction in the prevalence and mortality rates among this particular group.

**Introduction**

The overall incidence and prevalence of acute kidney allograft rejection have decreased over time, and the survival of transplanted kidneys has improved due to the use of more modern immunosuppressive drugs for induction and maintenance immunosuppressive therapy. The incidence of acute rejection within the first year is approximately 5 to 8%. Overall, the frequency of acute rejection is lower with kidney transplants from living donors than from deceased donors, which is associated with better compatibility and shorter cold ischemia time [15].

The etiology of acute rejection is based on an immune response against donor tissue, causing irreversible changes in the transplanted organ. It can be T-cell-mediated or antibody-mediated. Matching for class II major histocompatibility complex antigens is preferable to matching for class I antigens. In the absence of genetic compatibility, the immune system identifies non-matching classes of antigens as foreign, CD4+ T cells react to donor antigens presented by antigen-presenting cells with cytokine stimulation, leading to an immune response and subsequent destruction of the organ's cells [4].

**Search strategy.** Using Pubmed, Google scholar search engine, all articles that included keywords “kidney transplantation” and “rejection” were retrieved. In total 50 search results emerged for the 2014-2024 timeline, the last 10 years (Figure 1). Inclusion criteria were: original studies on the survival of transplanted kidneys, frequency of acute rejection. Exclusion criteria were studies that did not include human subjects (animal studies); review articles, meta-analysis, letters, abstracts, and articles that did report statistical results on effect estimate of OR and 95% CI.

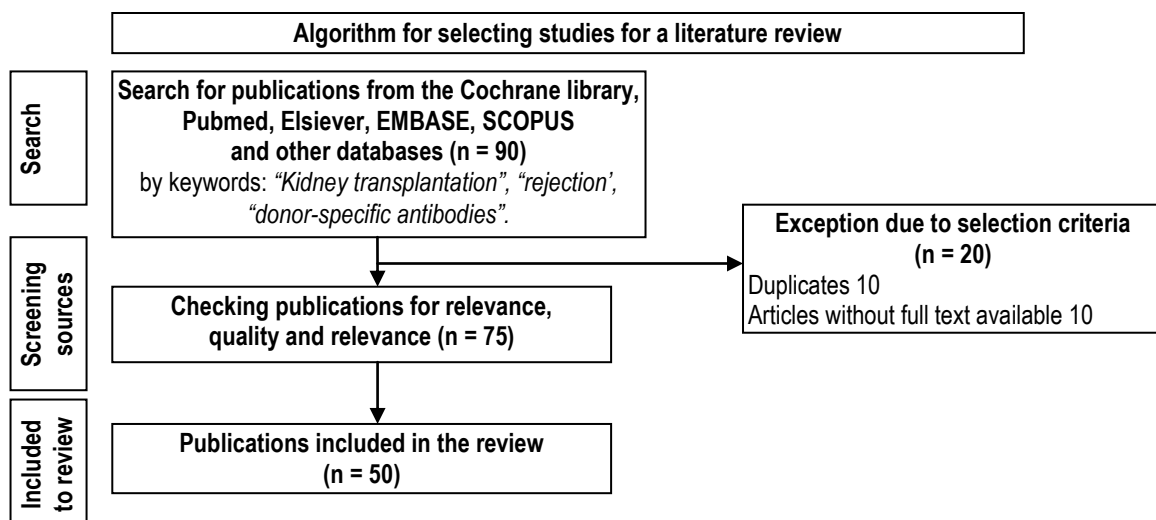


Figure 1. Algorithm for selecting publications for a literature review.

**Results**

**Pathophysiology of Kidney Transplant Rejection**

The rejection of a transplanted kidney involves several key mechanisms rooted in the immune system's response to foreign tissues. This response is underpinned by specific pathophysiological processes and unfolds in distinct stages. Depending on the timing, mechanisms, and severity, kidney rejection is classified into the following types:

**1. Acute Rejection**

Acute rejection is the most common type, developing within weeks or months after transplantation. It includes:

*Acute T-cell-mediated Rejection (Cellular Rejection):*

This is an immune response where T-lymphocytes are activated against the transplanted organ or tissue. It progresses through several stages:

*Antigen Presentation:* Donor cells, such as endothelial or epithelial cells, carry foreign antigens unfamiliar to the recipient's immune system. These antigens are recognized by the recipient's T-lymphocytes.

*T-cell Activation:* T-cells identify foreign antigens via the major histocompatibility complex (MHC, or human leukocyte antigen, HLA, in humans). This recognition activates T-cells, triggering their proliferation and differentiation into effector cells.

*Cytotoxic T-lymphocyte Activation:* CD8+ cytotoxic T-cells attack donor cells, leading to tissue damage, inflammation, and rejection.

*Inflammation and Tissue Damage:* Pro-inflammatory cytokines are released, causing vascular injury, edema, necrosis, and gradual graft rejection.

*Acute Antibody-mediated Rejection (Humoral Rejection):*

This form is driven by antibodies produced by the recipient's immune system, targeting antigens on the transplanted organ. Unlike T-cell-mediated rejection, humoral rejection is characterized by:

*Mechanism:* Recipient antibodies bind to antigens on the graft, initiating inflammation and vascular injury.

*Outcome:* Antibodies cause vascular damage, inflammation, and graft cell destruction. This type of rejection can occur acutely or progress to chronic rejection, with potentially severe consequences, including graft loss.

**2. Hyperacute Rejection**

Hyperacute rejection occurs rapidly, within hours or days after transplantation. It results from pre-existing recipient antibodies against donor antigens formed before the transplant.

*Mechanism:* Preformed antibodies attack the graft immediately, leading to severe vascular damage and rapid graft failure.

*Outcome:* This condition is life-threatening and often results in graft loss unless urgent measures are taken.

**3. Chronic Rejection**

Chronic rejection develops gradually over months or years and often follows repeated acute rejection episodes or a persistent, low-level immune response.

*Features:* It is marked by progressive graft dysfunction, fibrosis (scar tissue formation), and changes in small blood vessels (e.g., arteriosclerosis).

*Challenges:* Chronic rejection is difficult to treat and may eventually lead to graft failure.

**4. Subacute Rejection**

Subacute rejection develops at an intermediate pace, typically between acute and chronic rejection.

*Timing:* It evolves over weeks or months and is often associated with antibodies targeting the graft.

*Features:* Inflammation and tissue damage occur, but less aggressively than in acute rejection. It can still lead to progressive graft dysfunction.

*Immunosuppressive Therapy*

Immunosuppressive therapy is essential for preventing kidney transplant rejection. However, while it reduces rejection risk, it increases the susceptibility to infections and malignancies. Therapy regimens must be individualized based on numerous factors.

*Common Drugs in Maintenance Therapy:*

*Corticosteroids (Prednisolone, Methylprednisolone):* These reduce inflammation and suppress T-lymphocyte activity, but long-term use may cause side effects like osteoporosis, hyperglycemia, and hypertension.

*Calcineurin Inhibitors (Cyclosporine, Tacrolimus):* These inhibit calcineurin, blocking T-cell activation by reducing IL-2 production. Side effects include nephrotoxicity, hypertension, and gum hyperplasia.

*Antiproliferative Agents (Mycophenolate Mofetil, Mycophenolic Acid):* These inhibit lymphocyte proliferation by disrupting purine synthesis, essential for cellular immunity. Side effects include bone marrow suppression, anemia, leukopenia, and thrombocytopenia.

**Factors Affecting Rejection Risk**

*Despite proper immunosuppressive therapy, rejection risk persists due to:*

*Genetic Mismatch:* Greater HLA mismatches increase rejection likelihood.

*Recipient's Immune System State:* Conditions that weaken immunity may predispose patients to rejection.

*Infections and Comorbidities:* These can accelerate rejection or trigger immune responses despite optimal therapy.

*Donor Organ Quality:* Older donor age or pre-existing organ conditions elevate rejection risk.

*Rejection Statistics:*

Acute rejection occurs in approximately 10–20% of cases within the first year post-transplant with proper immunosuppression.

Chronic rejection develops in subsequent years and is more likely with suboptimal immunosuppression.

Effective management of kidney transplant patients requires balancing rejection prevention with minimizing therapy-related complications.

**Rejection and Its Risks:**

Preoperative risks of acute rejection are traditionally associated with factors such as the level of HLA sensitization (PRA level), compatibility with the HLA major histocompatibility complex, the age of the recipient and donor, repeated organ transplantation, and adequately selected immunosuppressive therapy. Donor-specific antibodies (DSA) before transplantation and the lack of compatibility with HLA A/B/DR are the main predictors of antibody-mediated rejection and T-cell-mediated rejection, respectively [19, 50]. About half of the patients with pre-transplantation DSA in titers capable of causing rejection will definitely experience antibody-mediated rejection, whereas low antibody titers independently do not increase

the risk of rejection [32, 2]. The selection of immunosuppression after kidney transplantation also affects the risk of acute rejection, including the induction therapy administered and the immunosuppressive regimens used post-transplantation. Strategies to reduce the impact of calcineurin inhibitors by using mTOR inhibitors were generally associated with higher rates of acute rejection and side effects [36]. Maintenance therapy without calcineurin inhibitors using belatacept, according to published data, led to more favorable long-term outcomes but with higher rates of T-cell-mediated rejection. However, it is worth noting that the use of belatacept resulted in lower rates of DSA development compared to calcineurin inhibitors [49, 6].

There is also a regimen of combined use of belatacept with calcineurin inhibitors, which has shown a lower incidence of acute T-cell-mediated rejection compared to the isolated use of belatacept - 51% with isolated belatacept use versus 16% with combined use with calcineurin inhibitors [1].

#### Clinical Presentation and Differential Diagnosis:

Rejection of a transplanted kidney may have no clinical manifestations, but in most cases, the first prognostic sign observed is an increase in serum creatinine levels, which prompts us to consider possible transplant dysfunction due to rejection [33, 3].

During examination, the most common pre-renal causes related to insufficient blood flow to the kidney and post-renal causes related to urinary tract obstruction, including infections, thrombotic microangiopathy, recurrence of de novo disease leading to damage to native kidneys, or newly developed glomerular disease, should be excluded. Viral infections such as polyomavirus (BK) and cytomegalovirus (CMV) should also be considered [37].

In addition to serum creatinine levels, the main diagnostic methods include a complete blood count, a urinalysis, ultrasound examination of the transplanted kidney, including Doppler imaging, blood tests for BK and CMV viruses using PCR, and antibody testing, including donor-specific antibodies (DSA). Many transplantation centers also use recipient blood testing to detect donor

DNA. This test can be positive even before an actual increase in serum creatinine levels, which may indicate possible rejection.

The gold standard in differential diagnosis when acute rejection is suspected remains biopsy, which not only accurately identifies its presence but also determines its type - cellular, humoral, or mixed. Protocol biopsies in individuals with high immunological risk can detect acute rejection before an increase in serum creatinine levels occurs. In this context, the detection of donor DNA in the recipient's blood could potentially serve as a method for selecting those who truly need a biopsy of the transplanted kidney. [5]

When describing histopathological changes in biopsy material from a transplanted kidney, the Banff classification system is used, which includes six main categories. [27, 22]

- Category 1: Normal biopsy or non-specific changes.

- Category 2: Antibody-mediated rejection (AMR), which is further divided into acute AMR and chronic AMR, including active AMR, depending on the characteristics of the damage.

- Category 3: Suspicion of acute T-cell-mediated rejection (TCMR) with borderline signs.

- Category 4: Acute T-cell-mediated rejection. Depending on the assessment of damage, it is classified as acute TCMR, chronic TCMR, or mixed TCMR.

- Category 5: Interstitial fibrosis and tubular atrophy.
- Category 6: Other changes not resulting from acute or chronic rejection.

#### Treatment:

The treatment of acute rejection generally depends on the type of rejection, the severity of the condition, and the presence of any coexisting diseases, requiring an individualized approach in each specific case [19]. It is important to note that untreated acute rejection leads to early loss of the transplanted organ and, consequently, a decrease in patient survival [11, 20].

Below are the treatment options for acute rejection depending on the type (Table 1) [31, 9, 13, 21].

Table 1.

Treatment options for acute rejection depending on the type.

Drug/procedure	Purpose in treatment	Mechanism
Methylprednisolone	T-cell rejection, Banff Ia, Ib	Multiple effects, affecting T cells, B cells and macrophages.
Antithymocyte immunoglobulin	T-cell rejection, Banff Ib, IIa, IIb,III	T cell depletion
Cascade plasmapheresis	Antibody-mediated rejection	Antibody Removal
Intravenous human immunoglobulin	Antibody-mediated rejection	Multiple immunomodulatory effects including antibody clearance, neutralization and suppression of production, Fc receptor saturation, complement inhibition
Rituximab	Antibody-mediated rejection	Anti-CD20 B cell depletion
Bortezomib	Antibody-mediated rejection	Plasma cell apoptosis through proteasome inhibition.
Eculizumab (soliris)	Antibody-mediated rejection	Inhibition of terminal complement C5.
C1-esterase inhibitor	Antibody-mediated rejection	Inhibition of the classical complement pathway.

**Acute T-cell-mediated Rejection:**

Over time, high-dose methylprednisolone (500 mg for 3-5 days) remains the first-line therapy for acute T-cell-mediated rejection, as previously recommended by KDIGO (23). If steroid therapy is ineffective or if the biopsy results show Banff II or III, T-cell-depleting therapy is added at a dosage of 1.5 mg/kg for 3-7 days [8]. Rabbit antithymocyte globulin has shown more effective results in treating acute T-cell-mediated rejection compared to horse-derived antithymocyte globulin, with efficacy rates of 88% versus 76% [12, 35, 31].

**Acute Antibody-Mediated Rejection:**

The situation with treating antibody-mediated rejection is significantly more complex than with T-cell-mediated rejection and involves a much greater number of regimens, medications, and plasma exchange procedures, as well as comparatively lower survival rates for the transplanted organ. The main treatment focus is on removing antibody-producing B cells or plasma cells and eliminating donor-specific antibodies. Currently, plasma exchange, intravenous human immunoglobulin, and rituximab have become the most widely used treatments for acute antibody-mediated rejection [8, 31, 37, 39]. Plasma exchange is most often performed every other day, followed by intravenous human immunoglobulin administration at a dose of 100–200 mg/kg, with the possible additional intravenous administration of rituximab at 3.75 mg/m<sup>2</sup>. There are also regimens involving high-dose monotherapy with intravenous human immunoglobulin at a dose of 2 g/kg, which has been compared with current regimens involving additional doses of rituximab and plasma exchange sessions. Patients receiving high-dose monotherapy with intravenous human immunoglobulin showed significantly lower 3-year survival rates - 50% - compared to those who additionally received plasma exchange sessions and rituximab, who had a survival rate of 92% [30, 37, 34, 35, 18].

Proteasome inhibitors have relatively recently entered the field of treatment for antibody-mediated rejection, with their main mechanism being the suppression of antibody-producing plasma cells through apoptosis. The detection of a large number of plasma cells in biopsy material during acute rejection is a rare diagnostic finding, and in such cases, research suggests the need for the use of bortezomib [40, 47].

Several studies on the isolated use of bortezomib have shown low efficacy in reducing anti-HLA antibodies and influencing the cross-match test [21, 24, 25]. When combined with standard therapy, including rituximab, plasma exchange, and human immunoglobulin, it shows better survival outcomes [28, 16, 30]. However, most studies involve small patient samples or were conducted in combination with standard procedures, and there is currently no clear understanding of the effectiveness of proteasome inhibitors in treating humoral rejection and reducing donor-specific antibody titers.

The use of C1-esterase inhibitors (C1-INH) is poorly studied. C1-INH inhibits proximal enzymes in the classical complement pathway, including C1q, which provides a basis for its investigation. *Viglietti D. et al.* [42, 43, 44] reported on the use of C1-esterase inhibitors in six patients with antibody-mediated rejection who were unresponsive to

traditional treatments. All patients showed improvement in kidney function (GFR) after 6 months and a reduction in C4d from baseline in five out of six patients by the 6-month mark. Currently, the experience with C1-INH is limited, and more data are needed to assess its effectiveness based on randomized studies. [37]

**Subclinical Rejection:**

Detecting immune responses to the transplanted organ before clinical manifestations begin allows for more effective management of chronic rejection and can improve graft survival. Protocol biopsies, the identification of DSA markers, and donor DNA testing are key diagnostic approaches. However, protocol biopsies within the first year after transplantation do not have a significant impact on transplant rejection and are more appropriately used in patients with high immunological risk [26]. In contrast, the detection of de novo DSA in recipients often leads to the identification of subclinical rejection in about half of the cases, according to biopsy data [48, 45, 43].

The idea of detecting subclinical rejection in patients before clinical signs appear is promising, but there is currently insufficient evidence to accurately assess the effectiveness of treatment and improvement in survival.

**Discussion**

Kidney transplant rejection remains a significant challenge, despite advances in immunosuppressive therapies. This review highlights key factors influencing rejection risk, diagnostic approaches, and treatment strategies, aligning with findings from previous research.

Preoperative factors, including HLA sensitization, donor-specific antibodies (DSA), and donor-recipient HLA compatibility, are major contributors to rejection risk. The review confirms that patients with high levels of DSA are at greater risk for antibody-mediated rejection (ABMR), as previously reported by *Wiebe et al.* (2019) [47]. HLA incompatibility similarly increases the likelihood of T-cell-mediated rejection (TCMR), a finding that is consistent with studies focusing on immunological matching. Moreover, emerging data suggest that expanded use of virtual crossmatching and single-antigen bead assays may allow for a more precise assessment of DSA levels and immunological risk, further refining preoperative stratification.

Low DSA titers, however, do not independently increase rejection risk, supporting *Loupy et al.* (2020) [20, 22, 23], who suggested close monitoring but not necessarily heightened concern. In contrast, patients with a history of sensitizing events (e.g., pregnancy, previous transplants, or blood transfusions) may experience heightened immunological reactivity even in the presence of low DSA titers. Additional investigation into memory B-cell populations could provide further insight into this phenomenon. Immunosuppressive regimens also play a crucial role, with calcineurin inhibitor (CNI)-free protocols being associated with higher TCMR rates, a point reiterated by *Vincenti F. et al.* (2020) [50]. Balancing the nephrotoxicity of CNIs with their immunosuppressive efficacy remains a clinical challenge, prompting the exploration of alternative regimens, such as the use of belatacept in CNI-minimization strategies.

An increase in serum creatinine remains a common indicator of kidney transplant rejection, aligning with earlier

studies, though its specificity is limited. New diagnostic tools like donor-derived cell-free DNA (dd-cfDNA) testing show promise in detecting immune activation before clinical signs appear, as noted by *Halloran et al.* (2019) [17]. Additionally, urinary biomarkers such as CXCL9 and CXCL10 are gaining traction as non-invasive diagnostic tools for monitoring rejection risk. Nonetheless, biopsy remains the gold standard for diagnosing rejection, particularly when histological classification through the Banff system is required. Notably, advancements in molecular microscopy diagnostic systems (MMDx) are enhancing biopsy interpretation, providing a more nuanced understanding of underlying rejection mechanisms.

Treatment varies depending on whether the rejection is TCMR or ABMR. High-dose corticosteroids remain the first-line therapy for TCMR, and when steroids fail, T-cell depleting agents like antithymocyte globulin (ATG) are effective, as confirmed by *Chadban S.J. et al.* (2021) [8]. In contrast, ABMR treatment is more complex, often involving plasmapheresis, intravenous immunoglobulin (IVIg), and rituximab. Recent trials exploring the efficacy of complement inhibitors, such as eculizumab and C1-inhibitors, have shown promise in mitigating the inflammatory cascade associated with ABMR. While proteasome inhibitors such as bortezomib are emerging as potential treatments, their efficacy remains unclear, particularly in reducing DSA levels, as noted in early studies. Strategies to modulate the innate immune system, including the use of IL-6 inhibitors like tocilizumab, are also being evaluated and may offer additional avenues for managing refractory ABMR.

Long-term management and prevention of chronic rejection continue to rely on minimizing immune activation while preserving graft function. The integration of precision medicine tools, such as pharmacogenomics-guided immunosuppressive dosing and individualized risk assessments based on immune profiling, is anticipated to transform clinical practice. Future research should prioritize multicenter trials investigating novel therapeutic agents, combination regimens, and long-term outcomes to address the unmet needs in kidney transplant rejection management.

**Conclusion:** The use of effective immunosuppressive drugs and the identification of high-risk groups for rejection have significantly reduced episodes of acute rejection. However, despite this, acute rejection remains one of the major problems affecting the survival of transplanted organs. A large number of studies in this area in the future will help develop the most effective model for diagnosing and treating this group of patients.

#### Limitation

Most of the studies cited in this article are not randomized, and the proposed treatment algorithms are not universally accepted or approved.

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We declare that this material has not been previously published and is not under consideration by other publishers.

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