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REVIEW ARTICLE

Understanding Pediatric Kidney Transplant Rejection: Its Pathophysiology, Biomarkers, and Management Strategies

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Abstract: End-stage kidney disease requires comprehensive management strategies to ensure patient survival and improve quality of life. Kidney transplantation remains the preferred treatment option, offering superior long-term outcomes. However, graft rejection remains a significant concern, and pediatric patients often require tailored immunosuppressive regimens due to differences in immune response compared to adults. Although the past decade has seen significant improvements in graft and patient survival among pediatric kidney transplant recipients, many questions remain unanswered. There is an ongoing search for non-invasive biomarkers capable of timely detecting graft rejection and novel treatment regimens, specifically tailored to pediatric practice. This review aims to discuss the current knowledge on kidney transplant rejection in pediatric patients, including epidemiology, pathophysiology, and risk factors. In addition, it seeks to explore the latest advancements in biomarkers for early detection of rejection and evaluate current and emerging immunosuppressive therapies. The possible outcomes of this review include identifying gaps in current research, providing recommendations for future studies, and suggesting strategies to enhance clinical practice. By synthesizing the latest evidence, this review aims to contribute to improved long-term outcomes and quality of life for pediatric kidney transplant recipients.

Keywords: Kidney transplantation, graft rejection, children, biomarkers, immunosuppression.

1. INTRODUCTION

End-stage kidney disease requires comprehensive management strategies that encompass both medical and surgical interventions to ensure patient survival and improve quality of life. Dialysis, either hemodialysis or peritoneal dialysis, is a critical component of treatment, providing essential renal replacement therapy to sustain metabolic and fluid balance [1]. However, kidney transplantation (KTx) remains the preferred treatment option, offering superior long-term outcomes and enhanced quality of life compared to dialysis [2]. The transplantation process involves careful donor-recipient matching and ongoing immunosuppressive therapy to prevent rejection and promote graft survival [3]. Biomarkers play a crucial role in the management of human diseases, including kidney transplantation, guiding therapeutic interventions, and improving patient outcomes.

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Graft rejection remains a significant concern in KTx, posing a threat to graft survival and overall patient outcomes. The immune response to the transplanted organ can lead to inflammation and damage, compromising graft function [4]. This necessitates vigilant monitoring and management to detect early signs of rejection and implement timely interventions. Regular monitoring of kidney function, imaging studies, and biopsies are essential. The development of biomarkers has further enhanced the ability to detect rejection early, allowing for timely intervention [5]. Advances in immunosuppressive therapy have substantially reduced the incidence of rejection, but balancing effective immunosuppression with minimizing adverse effects remains challenging [6].

The complexities of managing end-stage kidney disease in children introduce additional challenges and considerations. Pediatric patients often require tailored immunosuppressive regimens due to differences in metabolism and immune response compared to adults. The heightened activity of the pediatric immune sys-

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tem can lead to more aggressive rejection episodes, necessitating more intensive monitoring and potentially higher doses of immunosuppressive drugs [7]. Advancements in immunosuppressive therapies and personalized medicine hold promise for improving outcomes in pediatric KTx. Ongoing research aims to identify age-appropriate biomarkers and develop immunosuppressive protocols that minimize adverse effects while maintaining graft function [8]. Furthermore, factors, such as growth and development, the potential impact on cognitive and emotional health, and the lifelong requirement for immunosuppression are critical in pediatric transplant care [9].

Although the past decade has seen significant improvements in graft and patient survival among pediatric kidney transplant recipients, many questions remain unanswered. There is an ongoing search for non-invasive biomarkers capable of timely detecting graft rejection and novel treatment regimens, specifically tailored to pediatric practice. Therefore, this review aims to discuss the current knowledge on kidney transplant rejection in pediatric patients, including epidemiology, pathophysiology, and risk factors. It seeks to explore the latest advancements in biomarkers for early detection of rejection and evaluate current and emerging immunosuppression therapies.

2. EPIDEMIOLOGY OF PEDIATRIC KIDNEY TRANSPLANTATION AND GRAFT REJECTION

According to the Global Report on Organ Donation and Transplantation, 80,926 KTx were performed globally in 2020, with pediatric KTx accounting for 4%, or 2,836 procedures. Among the 93 countries that submitted their reports to the Global Observatory on Donation and Transplantation, pediatric KTx was performed in 64 countries [10]. It was estimated that the COVID-19 pandemic had a negative impact on the global rate of KTx, which was estimated to constitute 16% [10]. While the overall survival rate of pediatric kidney transplants is generally high, understanding graft rejection rates provides critical insights for clinical practice.

2.1. Epidemiology of Pediatric Kidney Graft Rejection

A meta-analysis of cohort studies on global graft survival in pediatric KTx revealed that one-year survival rate stood at 92%, decreasing to 83% at two years and 74.40% at five years. For longer terms, the seven-year survival was reported at 67.10% and the ten-year survival at 63.50% [11]. Consequently, it could be inferred that the graft rejection rates at one, three, five, seven, and ten years equaled 8%, 17%, 25.60%, 32.9%, and 36.50%, respectively. The highest rates of graft survival were observed in cohorts operated in Asian countries, followed by those in European and North American countries [11].

Regarding patient survival, it exceeded graft survival rates. In the same cohort of children, one-year survival stood at 99.60%, three-year survival at 97.30%, five-year survival at 95.20%, seven-year survival at 74.60%, and ten-year survival at 97.90%. The highest rates of three-year and five-year survival were achieved in cohorts operated in North America (99.3% and 97.5%, respectively), while the highest one-year survival was demonstrated in cohorts operated in Asia (99.9%). The highest seven-year survival was achieved in cohorts operated in North Africa (84.4%), and the highest ten-year survival was attained in cohorts operated in Europe (91.9%) [11].

In general, graft survival tends to be higher when the organ is sourced from a living donor compared to a deceased donor. This is supported by a typically 10-20% lower five-year graft survival rate observed in kidney transplants from deceased donors. Reports indicate that five-year graft survival for kidney transplants from living donors ranges between 80% and 90% [12], a finding consistent with observations in adult kidney transplant recipients [13]. However, some authors hypothesize that the improved graft survival in pediatric recipients of kidney transplants from living donors may be due to the fact that such donors are typically parents of the child [14].

2.2. Causes of Kidney Graft Loss in Children

Acute and chronic graft rejection are the primary causes of graft loss, contributing to 15% and 21% of graft losses, respectively. Disease recurrence also constitutes a significant cause of graft loss, accounting for 10% of cases [15]. Vascular thrombosis emerges as another prevalent cause of graft failure within the first year of KTx, with an incidence rate ranging from 2% to 3%. The risk of graft thrombosis escalates with previous exposure to peritoneal dialysis, KTx from deceased donors, prolonged cold ischemia time, and re--transplantation [16]. Children weighing under 5 kilograms have a higher incidence of graft thrombosis and poorer graft survival within the first year of KTx [17]. However, the long-term survival of these children is generally higher than that observed in older children and adolescents, suggesting that despite the initial challenges, the prognosis improves over time [18]. Some reports indicate that in children younger than 5 years who received living-donor KTx, the estimated graft

half-life exceeds 26 years, while in adolescents, it is below 10 years. This difference has been attributed to a more vigorous immune response observed in adolescents [18]. However, more recent reports have failed to confirm the observation of improved graft half-life in younger children compared to older children [15, 19].

3. PATHOPHYSIOLOGY AND RISK FACTORS FOR KIDNEY GRAFT REJECTION

Graft rejection refers to an inflammatory response elicited by the recipient's immune system against the non-self antigens present in the graft, resulting in specific pathological changes and potential graft dysfunction [20]. This process involves both innate and adaptive immune system responses, with T lymphocytes playing a central role. Inflammatory molecules, particularly cytokines, also significantly contribute to graft rejection [21]. Kidney transplant rejection reactions are typically categorized into four main types: hyperacute rejection, acute rejection, chronic rejection, and acute rejection superimposed on chronic rejection [22].

Hyperacute rejection can occur within hours after KTx and is commonly triggered by ABO blood group or Human Leukocyte Antigen (HLA) mismatches between the donor and recipient [23]. Acute rejections typically manifest days to weeks after transplantation and may be mediated by circulating donor-specific alloantibodies (DSAs) or T lymphocytes [24]. Chronic rejection, on the other hand, typically develops three or more months after transplantation and can also involve antibody-mediated or T-cell-mediated mechanisms [25]. Acute rejection superimposed on chronic rejection often arises due to exposure to new antigens in a graft already affected by chronic rejection [26].

3.1. Hyperacute Kidney Graft Rejection

Hyperacute kidney graft rejection signifies a rapid and severe immune response directed against the transplanted kidney, often resulting in irreversible damage to the transplanted organ. This response stems from a complex cascade of molecular mechanisms orchestrated by the recipient's innate immune system, targeting the donor organ. Initially, antibodies circulating in the recipient's bloodstream bind to antigens present on the surface of the transplanted kidney, forming immune complexes. These complexes activate the complement cascade, resulting in the production of proinflammatory molecules, such as C3a, C4a, and C5a. Additionally, the formation of the Membrane Attack Complex (MAC) occurs, leading to direct lysis of endothelial cells within the kidney vasculature [27].

Concurrently, endothelial injury and activation ensue as a consequence of antibody and complement protein binding to endothelial cells lining the blood vessels of the transplanted kidney. This endothelial activation prompts the upregulation of adhesion molecules, including selectins, integrins, and vascular cell adhesion molecule-1 (VCAM-1). These molecules facilitate the recruitment and adhesion of immune cells to the vascular endothelium [28].

As the inflammatory response intensifies, immune cells, particularly neutrophils and macrophages, infiltrate the renal tissue, exacerbating tissue damage through the release of proinflammatory cytokines, reactive oxygen species (ROS), and proteases. These inflammatory mediators contribute to the disruption of the kidney's vascular architecture, thrombosis of the renal vasculature, and, ultimately, widespread ischemia and necrosis of the renal parenchyma [29].

Moreover, the adaptive immune response also plays an important role in hyperacute rejection. T lymphocytes, especially CD8+ cytotoxic T cells, recognize and directly attack donor cells expressing foreign antigens [21]. Furthermore, the production of DSAs by B lymphocytes can trigger complement activation and antibody-dependent cellular cytotoxicity (ADCC), further exacerbating tissue injury and graft dysfunction [28].

3.2. Acute Kidney Graft Rejection

Acute rejection of a kidney graft shares similarities with hyperacute rejection and can be induced by both DSAs and T lymphocytes. In kidney transplant recipients, DSAs can be pre-existing or develop after transplantation due to exposure to the donor's antigens. When DSAs bind to their target antigens on the endothelial cells of the kidney graft, the complement system is activated, inducing inflammatory responses that lead to endothelial cell injury, complement deposition, and subsequent graft damage [29].

Acute kidney graft rejection can also be mediated by T lymphocytes, particularly $CD4^+$ and $CD8^+$ T cells. Upon recognition of donor antigens presented by the recipient's antigen-presenting cells (APCs), T cells become activated and differentiate into effector cells. $CD4^+$ T cells release cytokines that recruit and activate macrophages and cytotoxic $CD8^+$ T cells, while $CD8^+$ T cells directly attack and destroy the graft cells, primarily endothelial cells and tubular epithelial cells [30].

Both DSA-mediated and T-cell-mediated pathways trigger an inflammatory cascade within the transplanted kidney, characterized by the release of pro-inflammatory cytokines, chemokines, and adhesion

molecules. This inflammatory milieu promotes the recruitment and activation of additional immune cells, including neutrophils, macrophages, and natural killer cells, exacerbating tissue damage and graft dysfunction [29].

3.3. Chronic Kidney Graft Rejection

Chronic kidney graft rejection involves a sustained and progressive immune response against the transplanted kidney. This prolonged immune response is often triggered by persistent low-grade inflammation, which can be initiated during episodes of acute rejection or due to ongoing exposure to DSAs. In chronic rejection, the immune response is characterized by the infiltration of various immune cells into the graft tissue. T lymphocytes, particularly $CD4^+$ and $CD8^+$ T cells, play a central role in this process. These T cells recognize donor antigens presented by antigen-presenting cells within the graft, leading to their activation and differentiation into effector cells [30].

Activated CD4+ T cells release pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). These cytokines promote the recruitment and activation of other immune cells, including macrophages and B cells. Macrophages contribute to chronic inflammation by releasing additional cytokines and phagocytosing damaged tissues. B cells may differentiate into plasma cells and DSAs, further perpetuating the immune response [21].

CD8+ cytotoxic T cells directly target and destroy graft cells, particularly endothelial cells and tubular epithelial cells. This cell-mediated cytotoxicity contributes to tissue damage and fibrosis within the graft [30]. The chronic inflammatory process within the graft leads to the activation of fibroblasts and myofibroblasts, which promote the deposition of extracellular matrix proteins, such as collagen. This results in progressive fibrosis and tissue remodeling within the renal parenchyma. As fibrosis progresses, the normal architecture of the kidney is disrupted, impairing its function. This progressive scarring of the renal parenchyma ultimately leads to the loss of renal function and eventual graft failure [31].

3.4. Acute Rejection Superimposed on Chronic Rejection

In acute rejection superimposed on chronic rejection, the acute inflammatory response of acute rejection occurs within the context of ongoing chronic inflammation and fibrosis. Acutely activated T cells and inflammatory cytokines exacerbate the chronic inflammatory process. In addition to T cell-derived cytokines, other inflammatory molecules, such as chemokines and adhesion molecules, also play a role. The combination of acute and chronic inflammatory processes results in rapid deterioration of graft function and may increase the risk of irreversible graft failure [30].

Fig. (**1**). below provides an overview of pathophysiological mechanisms involved in kidney graft rejection and their possible outcomes.

3.5. Risk Factors for Kidney Graft Rejection in Pediatric Patients

Epidemiological evidence sheds light on the factors associated with kidney graft rejection in pediatric kidney transplant recipients. Apart from transplantation from a deceased donor and HLA and ABO mismatch, several other factors contribute to renal graft rejection. Studies have reported that the donor's advanced age [18] and recipient exposure to dialysis, as well as its duration, increase the risk of chronic graft rejection [32]. Additionally, re-transplantation and pre-existing diseases leading to end-stage renal failure, along with genetic factors, have been identified as contributors to graft loss [32]. Furthermore, previous acute graft rejection has been strongly correlated with chronic rejection [18]. Concurrently, pre-emptive kidney transplantation has been associated with enhanced graft survival [15, 32]. It is important to note that compared to adult KTx, there is relatively limited published evidence on the causes of graft rejection in pediatric populations.

4. BIOMARKERS OF KIDNEY GRAFT REJECTION

The half-life of kidney graft survival in the pediatric population is generally estimated to be between 12 to 15 years. This estimation suggests that children with end-stage kidney disease often require more than one kidney transplant in their lifetime [33]. In pediatric populations, the rate of late acute rejection is elevated, and some evidence indicates that it has been on a growing trend over the past decade [34]. Consequently, pediatric recipients of kidney grafts require different follow-up approaches compared to adult recipients.

Kidney graft biopsy serves as the standard method for detecting graft rejection. Several laboratory tests can be employed to evaluate kidney function and identify kidney graft rejection. Additionally, imaging studies can provide valuable guidance in assessing the status of the graft.

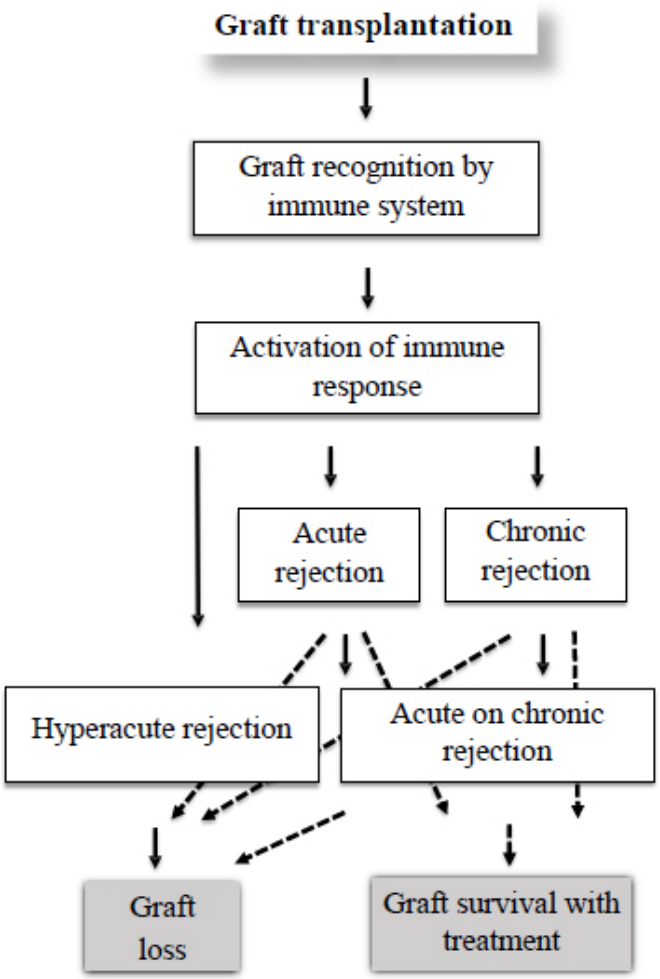

Fig. (1). Pathophysiological mechanisms involved in kidney graft rejection and their possible outcomes. While hyperacute graft rejection typically results in graft loss, acute rejection, chronic rejection, and acute rejection superimposed on chronic rejection may lead to either graft loss or graft survival, depending on the treatment provided. However, with adequate and timely treatment, graft survival is more likely to be achieved. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4.1. Kidney Graft Biopsy

Kidney graft biopsy plays a central role in assessing the severity of rejection, distinguishing between its various types, and providing guidance for treatment. The Banff classification system is utilized to standardize the histopathological findings of kidney graft biopsy. To ensure accurate conclusions, the biopsy section should ideally have a thickness ranging from 3 to 4 microns and should contain a minimum of ten glomeruli and two arteries [35].

According to the Banff system, Category 1 is diagnosed when biopsy findings are either normal or exhibit nonspecific changes. Category 2 indicates the presence of antibody-mediated rejection, which can be further categorized as acute, chronic, or active chronic. Category 3 suggests suspicion of acute T cell-mediated rejection, while Category 4 confirms the presence of T cell-mediated rejection, further subcategorized as acute, chronic, or acute chronic. Category 5 denotes the presence of interstitial fibrosis and tubular atrophy, whereas Category 6 is assigned when other changes are observed that do not stem from acute or chronic rejection of the kidney graft [36].

It is imperative to consider that biopsy is an invasive procedure that carries additional risks for pediatric patients, including the potential for complications, such as bleeding and the formation of arteriovenous fistula [37]. As a result, surveillance biopsies (sampling of the kidney graft at predetermined time intervals) are

implemented in 46% of pediatric kidney transplant centers in the USA [38], while many centers refrain from establishing them due to uncertainties regarding their contribution to long-term graft survival.

On one hand, evidence suggests that subclinical T cell-mediated rejection is identified in a remarkably unexpected proportion of pediatric kidney graft recipients, implying that surveillance biopsies are beneficial for detecting early signs of graft rejection and initiating timely therapy [39]. On the other hand, studies have reported that children with Banff lesions ranging from borderline to Ia, Ib, or IIa at 6 months, along with stable serum creatinine levels, were spared from treatment, and their glomerular filtration rate (GFR) at 24 months post-KTx remained stable. This finding suggests that stable low-risk children may not require surveillance biopsy at 6 months [40].

Certainly, there exists a critical necessity to determine the most suitable timing for surveillance biopsies in pediatric patients. Moreover, it is important to develop and assess alternative diagnostic modalities that are noninvasive or minimally invasive, easy to execute, and appropriate for routine monitoring of kidney graft rejection in pediatric recipients, with the aim of integrating them into clinical practice.

4.2. Laboratory Tests

Creatinine is a traditional laboratory biomarker of kidney function and is commonly employed to assess graft rejection. However, its diagnostic utility is limited due to low sensitivity and specificity, rendering it a late indicator of subclinical kidney graft rejection [38]. This limitation is emphasized by the results of a large cohort study involving pediatric kidney graft recipients, which revealed that despite histological evidence of subclinical graft rejection on surveillance biopsies, serum creatinine levels often remain within the normal range [41].

Generally, graft rejection is suspected when there is a rise in serum creatinine exceeding 25% of the baseline level. Another indicator that may suggest graft rejection is a failure of creatinine to decline in the early post-KTx phase. Elevated serum creatinine levels in kidney graft recipients indicate the need to employ a diagnostic algorithm similar to acute kidney injury. As a first step, the pre-renal and post-renal causes of hypercreatininemia need to be excluded. Second, blood biochemistry (electrolyte levels), complete blood count, and DSAs need to be assessed. Third, urine tests, including urine culture, should be conducted. Additionally, polyomavirus and cytomegalovirus *via* polymerase chain reaction should be ruled out. Lastly, arterial and venous indices need to be evaluated using renal Doppler ultrasound [42].

While albuminuria and proteinuria are routinely used as biomarkers of kidney function, their effectiveness in detecting graft rejection in pediatric populations remains uncertain. However, a substantial cohort study involving adult kidney graft recipients illustrated that proteinuria demonstrates high sensitivity but low specificity for detecting kidney graft rejection [43]. Clinically, any instance of new-onset or worsening proteinuria should be regarded as a potential sign of graft rejection. Regarding the predictive value of the protein/creatinine ratio, its applicability to pediatric patients remains inadequately understood [37].

De novo DSAs have been identified as biomarkers of graft loss in pediatric populations, being associated with both acute and chronic antibody-mediated rejection, as well as transplant glomerulopathy [44]. Their formation has been reported to lead to decreased 10-year kidney graft survival [45]. While pre-transplant non-donor-specific antibodies (NDSAs) have been linked with kidney graft rejection in adult recipients [46], their role in pediatric patients remains unclear. Additionally, angiotensin II type 1 receptor antibodies have been associated with the formation of inflammatory cytokines and worsened clinical outcomes in children who undergo KTx [47].

Several innovative diagnostic biomarkers of kidney graft rejection are currently under investigation for potential clinical use. For instance, analysis of mRNA transcripts in graft specimens has been shown to identify antibody-mediated rejection in histologically negative biopsies [48].

Furthermore, high levels of donor-derived cell-free DNA in the blood of pediatric kidney graft recipients have shown promise in reliably identifying T-cell-mediated rejection [49]. A set of 17 genes has demonstrated the ability to predict both antibody-mediated and T--cell-mediated rejection with a 93% positive predictive value in a cohort that included pediatric kidney graft recipients [50]. Moreover, a “protein signature” of kidney graft rejection has been identified in peripheral blood, with some proteins showing low expression while others exhibit high expression [51].

Urinalysis represents another area of ongoing research for molecules (proteins, lipids, mRNAs, genomes) capable of identifying kidney graft rejection at an early stage. Urinary extracellular vesicle protein biomarkers have been identified as having the potential to differentiate between acute and chronic active graft rejections [52, 53]. Additionally, specific mRNA multi-

gene signatures in urine have been shown to discriminate between antibody-mediated and T-cell-mediated rejection [54]. Moreover, urinary chemokines have been identified as potential biomarkers of subclinical and clinical T-cell-mediated rejection in pediatric patients [55, 56]. Various metabolites tested in the urine of pediatric kidney graft recipients have shown potential in detecting borderline and acute T-cell-mediated graft rejection [57]. However, the integration of these innovative biomarkers into current clinical practice is hindered by a small number of observations, lack of standardization, and elevated costs, necessitating further research and investments before these tests become routine [37].

4.3. Imaging Studies

Imaging studies offer a non-invasive approach to detecting kidney graft rejection, showing significant advancements over the past decade, with some holding the potential to replace graft biopsies in the future. Ultrasound, as a cost-effective diagnostic modality routinely used in clinical practice, plays an important role in this regard. In cases of hyperacute and acute kidney graft rejection, ultrasound reveals an increase in kidney graft volume compared to baseline measurements. Doppler ultrasound may indicate a resistive index exceeding 0.8 due to graft swelling, with the possibility of reversed diastolic flow in severe cases. In addition, severe cases of hyperacute and acute rejection may exhibit signs of graft rupture and bleeding [58]. Conversely, in chronic rejection, Doppler ultrasound assists in identifying a reduction in overall vascularity, while B-mode ultrasound reveals an increase in graft echogenicity, reduction in corticomedullary differentiation, and cortical thinning in the presence of interstitial fibrosis and sclerosing vasculitis [59].

Several advances in renal ultrasonography, notably contrast-enhanced ultrasound (CEUS) and sonoelastography, show promise for detecting kidney graft rejection in pediatric settings. CEUS enhances the early identification of anatomical and vascular abnormalities potentially associated with graft rejection [60], while sonoelastography evaluates the stiffness of graft parenchyma, serving as a non-invasive method to assess the degree of graft fibrosis linked to chronic rejection [61].

Magnetic Resonance Imaging (MRI) boasts high-resolution properties, enabling both the visualization of anatomical structures and the assessment of graft functioning. A range of MRI approaches, including magnetic resonance angiography, MRI diffusion-weighted imaging, magnetic resonance urography, and functional magnetic resonance urography, facilitate the evaluation of kidney grafts in both the early and late postoperative periods. These methods aid in differential diagnosis and treatment planning. In emergency situations where MRI is unavailable, computed tomography can be utilized, albeit requiring age- and weight-adapted protocols. Conversely, excretory urography is no longer employed in pediatric practice due to its association with ionizing radiation [62]. Positron emission tomography and single-photon emission computed tomography have demonstrated efficacy in identifying kidney graft rejection and facilitating differential diagnosis from other kidney pathologies [63]. However, there are currently no reports evaluating their use in pediatric populations.

Fig. (**2**) presents an overview of traditional and novel biomarkers available for evaluating graft rejection in pediatric patients.

5. TREATMENT STRATEGIES IN PEDIATRIC KIDNEY TRANSPLANT REJECTION

Treatment of kidney graft rejection includes three primary strategies: induction therapy, maintenance therapy, and the management of acute rejection episodes. Immunosuppression forms the foundation of these therapeutic modalities. However, in pediatric populations, these strategies exhibit distinctive characteristics. Notably, there is a paucity of robust evidence supporting these approaches, particularly in the form of randomized controlled trials (RCTs). Ethical considerations pose a significant barrier to conducting such trials, as the involvement of pediatric patients in research studies necessitates stringent ethical scrutiny. Nevertheless, despite these challenges, clinicians rely on a combination of empirical evidence, expert consensus, and clinical experience to guide the management of kidney graft rejection in pediatric patients [64].

5.1. Induction Therapy

Induction therapy aims to provide potent immunosuppression early post-KTx to prevent acute rejection and facilitate long-term graft survival. This is largely achieved by depleting or modifying T cells before donor antigens are presented to them. Currently, available induction agents include polyclonal antibodies (antithymocyte globulin rabbit and antithymocyte globulin equine) and monoclonal antibodies (alemtuzumab and basiliximab). Rabbit antithymocyte globulin (ATG), equine ATG, and alemtuzumab are lymphocyte-depleting antibodies, while basiliximab is an IL-2 receptor antagonist [64]. Additionally, corticosteroids play an important role in immunosuppression during the early postoperative phase [64].

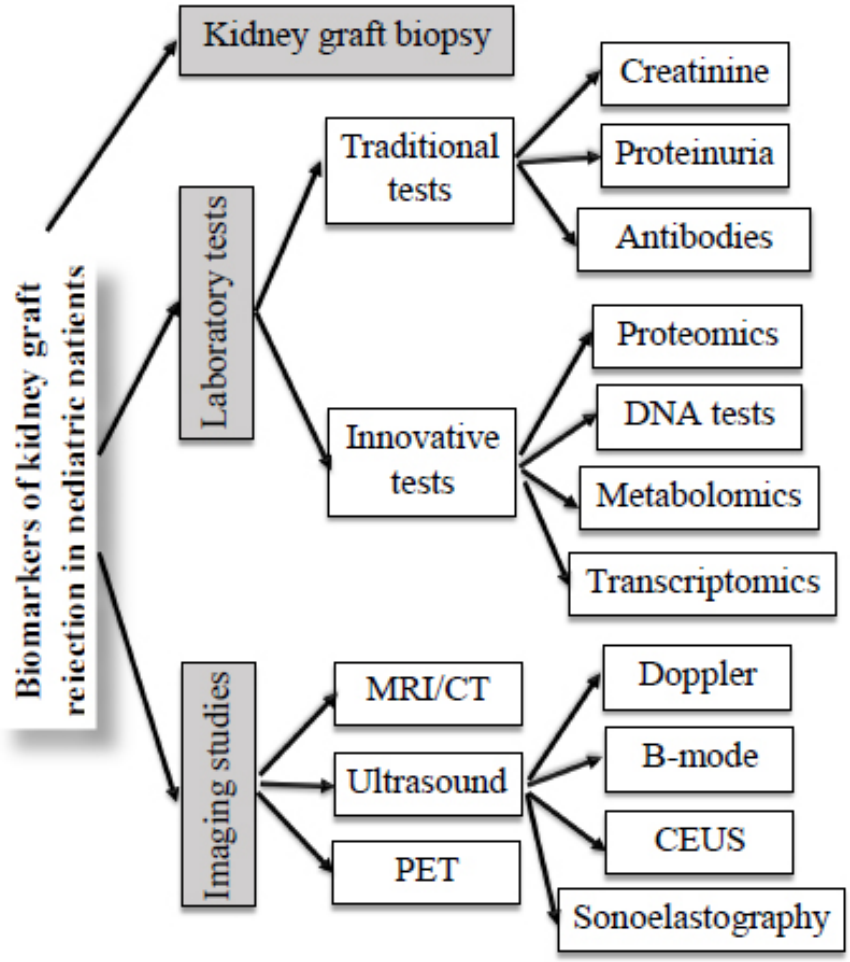

Fig. (2). Biomarkers of kidney graft rejection in pediatric patients. While kidney graft biopsy remains the gold standard for diagnosing graft rejection, a variety of other biomarkers enable timely identification of rejection and facilitate differential diagnosis with other kidney pathologies. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ATGs are the most commonly used induction agents in pediatric practice. Derived from rabbits and horses, ATGs from rabbits are reported to be more effective and safer [65-67]. They are commonly initiated when high rejection risks are present and/or when steroids are discontinued. Immunosuppression is achieved through the targeting of multiple T-cell surface and B-cell surface antigens, as well as natural killer cell antigens, chemokine receptors, and adhesion molecules [68]. ATGs are also capable of downregulating T-cell proliferation and inhibiting T-cell surface receptors [69]. The lymphocyte-depleting effects of ATGs last for 9-12 months [64].

There is a lack of studies investigating the effects of ATGs on pediatric kidney recipients, the majority of which belong to single-center reports. It was found that simultaneous ATG induction and steroid minimization resulted in 5-year graft survival equal to 95%, with only 5 out of 44 patients developing acute rejection episodes during 10 years of observation [70]. ATG induction or alemtuzumab decreased the risk of acute graft rejection compared with pediatric patients receiving anti-IL-2 receptor antibody induction [71]. A low dose of ATG (1.5 mg/kg for 3 days) resulted in a graft survival rate of 90.9% at 6 months and 81.8% at 1 year [72], while a dose of 1.5 mg/kg for 4 days resulted in a graft survival rate of 94.9% at 1 year, 97.3% at 3 years, and 94.6% at 5 years [73]. A report from the Pediatric Nephrology Research Consortium has confirmed the observation that low-dose ATG ($\leq$ 4.5 mg/kg) has no disadvantages compared to the standard higher dose (>4.5 mg/kg) in terms of graft survival and acute rejec-

tion episodes [74]. Given the non-inferiority of the low ATG dosage regimen, it might be considered useful to switch to it from the traditional higher dose regimen [75].

The mechanism of action of alemtuzumab involves binding to the CD-52 antigen present on the surface of T cells, B cells, macrophages, monocytes, and natural killer cells, resulting in antibody-dependent cell lysis [76]. Cell depletion induced by alemtuzumab is typically rapid and can last several months for B cells, and one year or longer for other types of cells [77]. However, similar to ATGs, there is a paucity of studies reporting on the effectiveness of alemtuzumab administered as an induction therapy to pediatric kidney recipients. Early reports [78-81] lacked a control group, making it challenging to draw conclusions regarding the comparability of alemtuzumab with other induction agents. Comparisons of alemtuzumab with other induction agents facilitate understanding of its effectiveness.

An early study by Ellis *et al.* reported on the effectiveness of ATG compared to alemtuzumab in a group of 34 children. Although the number of children receiving ATG or alemtuzumab was not reported, three out of 34 children developed acute rejection episodes, all of whom belonged to the alemtuzumab group [75]. Two subsequent reports by Riad *et al.* examined the rejection rates in children receiving kidney grafts from living and deceased donors. Among children receiving living donor transplants, the rejection rate at 6 months post-KTx was 9.5% in the alemtuzumab group versus 5.7% in the ATG group. At 12 months, the rejection rate was 14.5% in the alemtuzumab group versus 10.8% in the ATG group, which was statistically significant [82]. However, for transplants from deceased donors, this difference was not significant; at 6 months, the rejection rates were 8.6% in the alemtuzumab group and 7.8% in the ATG group, and at 12 months, they were 17.2% in the alemtuzumab group and 15.7% in the ATG group [83]. A recent small-scale study confirmed a higher rejection rate in children receiving alemtuzumab compared to ATG, although this difference was not statistically significant [84]. Another small-group comparison study indicated that graft survival was not significantly different between groups receiving alemtuzumab versus the interleukin-2 receptor antagonist (IL-2RA) [85].

Basiliximab, an IL-2RA, has been a subject of debate regarding its usage in pediatric KTx. Its mechanism of action involves binding to the IL-2 receptor on T-cells, thereby reducing IL-2-induced proliferation of these cells [86]. Additionally, basiliximab can mitigate IL-15-mediated T-cell proliferation [87].

An RCT evaluated the efficacy of basiliximab compared to placebo in pediatric kidney transplant recipients. At 6 months post-transplantation, the rate of acute rejection was comparable between the two groups (20.4% for placebo vs. 19.2% for basiliximab) [88]. Subsequent follow-up at 2 years yielded similar results, with acute rejection rates of 8.6% for the placebo arm and 4.0% for the basiliximab arm, although these differences were not statistically significant [89]. Another RCT also failed to demonstrate a significant difference in acute rejection rates between basiliximab and placebo groups at 6 months (20.4% vs. 19.2%, respectively) [90]. However, a registry-based study with a follow-up duration exceeding 10 years suggested that basiliximab induction therapy was superior to no induction therapy, with a lower incidence of rejection over the entire follow-up period (39.6% in the no induction group vs. 25.6% in the basiliximab group) [91]. In comparison to other induction agents, basiliximab was found to be less effective than alemtuzumab in preventing rejections at 1 year [85] (Table **1**).

Table **1** summarizes the key findings of studies examining graft survival and/or rejection in pediatric kidney transplant recipients undergoing induction therapy.

5.2. Maintenance Therapy

Maintenance immunosuppression is a critical component in the care of pediatric kidney transplant recipients, ensuring the delicate balance between preventing organ rejection and minimizing adverse effects. In the realm of pediatric transplantation, the goal extends beyond mere preservation of the graft to nurturing the child's growth, development, and overall well-being. Commonly used immunosuppressive agents include calcineurin inhibitors (such as tacrolimus or cyclosporine), antimetabolites (like mycophenolate mofetil or azathioprine), mammalian target of rapamycin (mTOR) inhibitors (everolimus and sirolimus), fusion proteins (betacept), and corticosteroids [64]. These drugs act synergistically to suppress the immune response against the transplanted organ.

Calcineurin inhibitors represent the cornerstone of maintenance immunosuppression in transplant recipients. Their mechanism of action revolves around the inhibition of calcineurin, an important enzyme responsible for T-cell activation [92]. Specifically, calcineurin inhibitors, such as tacrolimus and cyclosporine, impede calcineurin activity by forming complexes with intracellular proteins termed immunophilins. These complexes disrupt the dephosphorylation process of the nuclear factor of activated T cells (NFAT), hindering its translocation into the nucleus. Consequently, the activa-

tion of genes crucial for T cell activation, proliferation, and cytokine production is hampered, thereby attenuating the immune response and preventing rejection in organ transplant recipients [93].

Table 1. Studies reporting on graft survival/rejection in pediatric kidney graft recipients receiving induction therapy.

First Author, Year of Publication [Reference]	Study Group	Type of Induction Therapy	Dose and Duration of Therapy	Effects
Ault, 2002 [66]	17 children aged <18 years	Rabbit ATG, steroids	ATG dose: 1.5 mg/kg intra-operatively and daily over the following 4-6 post-operative days. Methylprednisolone dose: 15 mg/kg intra-operatively, 10 mg/kg on post--operative day 1, 5 mg/kg on post-operative day 2, 4 mg/kg on post-operative day 3, 3 mg/kg on post-operative day 4, 2 mg/kg on post-operative day 5, 1 mg/kg on post-operative day 6, and 0.5 mg/kg on post-operative day 7.	The one-year graft survival rate was 93%. No acute rejection episodes were reported.
Khositseth, 2005 [67]	71 children aged <19 years	ATG, steroids	ATG dose: 1.5 mg/kg per dose for 10 doses Prednisolone dose: 2 mg/kg per day, tapered to 0.45 mg/kg per day at 1 month after transplantation.	The one-year graft survival was 93%, followed by 88% at two years, and 83% at three years. During the three-year follow-up period, the total acute rejection rate was 33%.
Warejko, 2014 [70]	44 children aged 13 months to 19 years	ATG, steroids	ATG dose: 1.5 mg/kg immediately prior to reperfusion of the allograft, followed by once-daily administration for an additional 4 days, resulting in a total cumulative dose of 7.5 mg/kg. Methylprednisolone dose: 7 mg/kg initially, then administered as 2 mg/kg before each ATG dose on post-operative day one, transitioning to oral prednisolone or prednisone at 1 mg/kg once daily on days two and three, and 0.5 mg/kg once daily on days four and five.	The five-year graft survival rate was 95%, with only 5 out of 44 patients experiencing an acute rejection episode during the 10-year observation period.
Crowson, 2017 [71]	7884 children aged less than a year to 17 years	IL-2 receptor antagonists (basiliximab or daclizumab) vs. lymphocyte depleting induction (alemtuzumab or ATG)	Not specified	During the one-year follow-up period, lymphocyte-depleting induction was more effective in reducing the risk of acute graft rejection compared to IL-2 receptor antagonists.
Catibog, 2022 [72]	11 children aged <18 years	Rabbit ATG	ATG dose: 1.5 mg/kg once a day for 3 days	Kidney graft survival was 90.9% at 6 months and 81.8% at 1 year of follow-up, with only one child experiencing an episode of acute rejection
Shang, 2014 [73]	39 children aged 4 to 18 years	Rabbit ATG	ATG dose: 1.5 mg/kg once a day for 4 days	Kidney graft survival was 94.9% at 1 year, 97.3% at 3 years, and 94.6% at 5 years of follow-up, with 6 out of the 39 recipients (15.4%) experiencing acute rejection.
Ashoor, 2021 [74]	235 children aged <18 years	Rabbit ATG	ATG dose: ≤ 4.5 mg/kg vs. >4.5 mg/kg	Low-dose ATG (≤ 4.5 mg/kg) has no disadvantages compared to standard higher doses (>4.5 mg/kg) in terms of graft survival and the rates of acute rejection episodes.

(Table 1) contd....

First Author, Year of Publication [Reference]	Study Group	Type of Induction Therapy	Dose and Duration of Therapy	Effects
Ellis, 2007 [75]	34 children aged 1 to 18 years	ATG (n=8) or alemtuzumab (n=26)	ATG dose: 5 mg/kg Alemtuzumab dose: 0.4 -0.5 mg/kg	The rate of acute rejection episodes was 9% (3 of 34). All acute rejection cases were observed in the alemtuzumab group.
Bartosh, 2008 [77]	4 children aged 20 months to 16 years	Alemtuzumab	Alemtuzumab dose: 30 mg given intraoperatively to all children, with one child receiving an additional 30 mg postoperatively.	The rate of acute rejection episodes was 75% (3 of 4 children).
Kaabak, 2013 [79]	101 aged 7 months to 18 years	Alemtuzumab	Alemtuzumab dose: two doses of 30 mg each, with the first administered 12-29 days prior to transplantation and the second administered at the time of transplantation.	The rate of acute rejection episodes was 26% at 1 year and 35% at two years. No rejection episode was observed after 2 years.
Supe-Markovina, 2014 [80]	21 children aged 1 to 10 years	Alemtuzumab	Alemtuzumab dose: 0.6 mg/kg (max 30 mg), administered intraoperatively.	The rate of acute rejection episodes was 14.3% (3 of 21 patients).
Tan, 2008 [81]	42 children (ages not specified)	Alemtuzumab	Alemtuzumab dose: 0.4-0.5 mg/kg administered as a single dose in the evening before transplantation or intraoperatively.	The rate of acute rejection episodes was 0% at 1 year, 2.4% at 2 years, 4.8% at 3 years, and 4.8 at 4 years.
Riad, 2021 [82]	3111 children aged <18 years	ATG (n=1197) or alemtuzumab (n=289), IL-2RA (n=1625)	Doses are not specified	The rejection rate at 6 months was 9.5% in the alemtuzumab group, 5.7% in the ATG group, and 5.3% in the IL-2RA group. At 12 months, the rejection rate was 14.5% in the alemtuzumab group, 10.8% in the ATG group, and 9% in the IL-2RA group.
Riad, 2021 [83]	4576 children aged <18 years	ATG (n=2091) or alemtuzumab (n=320) or IL-2RA (n=2165)	Doses are not specified	The rejection rate at 6 months was 8.6% in the alemtuzumab group, 7.8% in the ATG group, and 9.2% in the IL-2RA group. At 12 months, the rejection rate was 17.2% in the alemtuzumab group, 15.7% in the ATG group, and 16.5% in the IL-2RA group.
Puliyanda, 2020 [84]	36 children aged <18 years	ATG (n=13) or alemtuzumab (n=23)	Alemtuzumab dose: 0.3 mg/kg (max 20 mg) ATG dose: four doses of 1.5 mg/kg each	The rejection rate at 1 year was 7.7% in the alemtuzumab group (1 of 13 children) compared to 4.3% in the ATG group (1 of 23 children).
Kim, 2017 [85]	50 children aged <18 years	Alemtuzumab (n=15) or IL-2RA (n=35)	Alemtuzumab dose: 15 to 30 mg administered as a single dose on the day of surgery. IL-2RA dose: basiliximab (2 doses) or daclizumab (5 doses).	The overall rate of rejections at 1 year was 46.7% in the alemtuzumab group compared to 77.1% in the IL-2RA group.
Offner, 2008 [88]	192 children aged 1 to 18 years	Basiliximab (n=100) or placebo (n=92)	Basiliximab dosage: 10 mg for patients weighing less than 35 kg and 20 mg for patients weighing 35 kg or more, administered in two doses: the first within 2 hours before surgery and the second on day 4 after surgery.	The rate of acute rejection at 6 months was 19.2% in the basiliximab group and 20.4% in the placebo group.
Webb, 2009 [89]	192 children aged 1 to 18 years	Basiliximab (n=100) or placebo (n=92)	Basiliximab dosage: 10 mg for patients weighing less than 35 kg and 20 mg for patients weighing 35 kg or more, administered in two doses: the first within 2 hours before surgery and the second on day 4 after surgery.	The rate of acute rejection at 2 years was 8.6% in the placebo group and 4.0% in the basiliximab group.

(Table 1) contd....

First Author, Year of Publication [Reference]	Study Group	Type of Induction Therapy	Dose and Duration of Therapy	Effects
Grenda, 2006 [90]	192 children aged <18 years	Basiliximab (n=99) or placebo (n=93)	Basiliximab dosage: 20 mg (patients ≥40 kg) or 10 mg (patients <40 kg), administered in two doses: the first within 4 hours before surgery and the second on day 4 after surgery.	The rate of acute rejection at 6 months was 20.4% in the placebo group and 19.2% in the basiliximab group.
Mincham, 2017 [91]	658 children and adolescents aged <21 years	Basiliximab (n=461) or no induction therapy (n=197)	Doses are not specified.	The rate of acute rejection at 6 months was 22.8% in the no-induction group and 11.7% in the basiliximab group. The rate of any rejection during the entire follow-up was 39.6% in the no-induction group vs. 25.6% in the basiliximab group.

Numerous RCTs and clinical investigations have underscored the superiority of tacrolimus over cyclosporine in pediatric KTx practice. For instance, a study involving 18 kidney transplant (KTx) cases from 9 European nations, which enrolled 196 children administered either tacrolimus or cyclosporine alongside azathioprine and corticosteroids, revealed a significantly lower incidence of acute rejection with tacrolimus (36.9%) compared to cyclosporine (59.1%) [94]. Moreover, the four-year extension of this trial demonstrated comparable patient survival rates between tacrolimus and cyclosporine groups (94% vs. 92%), while graft survival was remarkably higher with tacrolimus (86% vs. 69%) [95]. Also, a large retrospective cohort study involving 986 pediatric kidney transplant recipients treated with either tacrolimus or cyclosporine found no disparity in 1-year patient and graft survival rates. However, recipients receiving tacrolimus exhibited significantly better GFR, emphasizing the clinical advantage of tacrolimus in pediatric KTx management [96].

Antimetabolites exert their effects by disrupting nucleic acid synthesis, particularly DNA synthesis, in rapidly proliferating cells, such as activated lymphocytes. Mycophenolate mofetil (MMF) achieves this inhibition by targeting the enzyme inosine monophosphate dehydrogenase (IMPDH), essential for the de novo synthesis of guanosine nucleotides. Through this inhibition, MMF reduces guanosine nucleotide production, consequently curtailing DNA synthesis in lymphocytes, including T and B cells. Consequently, the proliferation of these cells, integral for orchestrating an immune response and potentially rejecting the transplanted organ, is suppressed [97]. In contrast, azathioprine functions as a prodrug, undergoing conversion into mercaptopurine within the body. Mercaptopurine acts as a purine analogue, interfering with DNA and RNA synthesis. By integrating itself into DNA and RNA strands during replication and transcription, respectively, mercaptopurine disrupts nucleic acid metabolism, thereby impeding DNA synthesis and cell proliferation, particularly affecting rapidly dividing cells like activated lymphocytes [98].

A meta-analysis of RCTs comparing the effectiveness of MMF to azathioprine as maintenance therapy in kidney transplant recipients, including pediatric patients, revealed that MMF administration was associated with higher graft survival and a reduced risk of acute rejection [99]. Generally, MMF demonstrates superiority over azathioprine in pediatric KTx practice and has largely supplanted it. Numerous studies corroborate this observation by comparing the effectiveness of MMF to historical treatments with azathioprine [100-102]. However, a large cohort study demonstrated the non-inferiority of azathioprine concerning patient and graft survival, GFR, and acute rejection rates [103].

The mechanism of action of mTOR inhibitors involves the inhibition of mTORC1 signaling, which leads to the suppression of T cell activation and proliferation, as well as the inhibition of vascular smooth muscle cell proliferation. These effects ultimately contribute to immunosuppression and the prevention of allograft rejection [104]. A comparison study involving sirolimus with MMF and basiliximab demonstrated similar effectiveness in a cohort of 34 pediatric kidney graft recipients, with a 31.5% rejection rate [105]. Furthermore, a comparison between a combination of sirolimus, MMF, and corticosteroids and a combination of calcineurin inhibitors, MMF, and corticosteroids did not reveal significant differences in acute rejection rates [106]. In an RCT comparing the effectiveness of maintenance immunosuppression with tacrolimus, MMF, and corticosteroids versus switching to reduced tacrolimus, everolimus, and no steroid regimen starting from the 5th postoperative month, no difference in the rate of acute rejection episodes was observed between the two groups [107]. A subsequent 3-year cont-

inuation of this RCT demonstrated the comparability of both treatment regimens in terms of acute rejection rates, graft loss, GFR, and adverse effects. Consequently, it was concluded that a combination of everolimus with reduced tacrolimus represents a viable alternative to traditional treatment modalities by facilitating steroid withdrawal and reducing the toxicity associated with calcineurin inhibitors in pediatric kidney transplant recipients [108].

Belatacept, a fusion protein consisting of the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the Fc portion of human IgG1, serves as an essential element in maintenance immunosuppression following KTx. Its mechanism of action primarily involves the selective modulation of T cell activation and function by binding with high affinity to CD80 and CD86, costimulatory molecules expressed on antigen-presenting cells. Through competitive inhibition of CD28, an important T cell costimulatory receptor, belatacept disrupts the requisite second signal for complete T cell activation. Consequently, downstream T cell activation pathways, including IL-2 production, cell cycle progression, and effector function, are subdued. This disruption of T cell co-stimulation culminates in the suppression of alloreactive T cell responses directed against the transplanted organ, thereby forestalling rejection [109]. Unlike conventional calcineurin inhibitors, belatacept elicits its immunosuppressive effects without nephrotoxicity and potentially offers a favorable metabolic profile. Nonetheless, its utilization is linked with an elevated risk of post--transplant lymphoproliferative disorder [110].

Studies exploring the efficacy of belatacept in pediatric kidney transplant recipients are limited. However, reports indicate that transitioning six adolescent kidney graft recipients to belatacept resulted in a deceleration of GFR decline [111]. Additionally, a small retrospective study observed 100% adherence and the absence of de novo DSA formation in adolescent kidney transplant recipients maintained on belatacept therapy [112]. The necessity of administering belatacept every four weeks renders it an appealing option for adolescent kidney transplant recipients, enhancing treatment adherence and mitigating the risks of graft loss [110].

Steroids have long been a cornerstone of maintenance immunosuppression in allograft recipients. However, over the past decade, there has been a substantial shift towards evaluating the effects of steroid avoidance in pediatric kidney transplant recipients. In an RCT involving 42 children, no significant differences were observed in the rate of 2-year graft survival or acute rejection episodes between the group receiving steroid therapy and the group undergoing steroid withdrawal. In particular, the steroid withdrawal group exhibited a lower incidence of hypertension and hyperlipidemia [113]. Furthermore, a meta-analysis, including eight studies on pediatric kidney recipients, of which five were RCTs, concluded that steroid avoidance or withdrawal regimens are justified in select pediatric patients. These include prepubertal individuals of Caucasian ethnicity, those with primary diseases unrelated to immunological factors, de novo kidney transplant recipients, and individuals with low panel reactive antibody levels. Such regimens were associated with significant benefits in terms of post-transplant child growth within the first year after withdrawal while posing minimal risks of acute rejection and graft function deterioration. Moreover, these regimens did not impact graft and patient survival within three years post-steroid withdrawal [114]. Thus, the role of steroids in pediatric KTx is evolving, with growing evidence supporting the judicious use of steroid avoidance or withdrawal regimens in selected patient populations.

Fig. (**3**). provides an overview of treatment approaches used for maintenance immunosuppression in pediatric kidney graft recipients.

5.3. Treatment of Acute Rejection Episodes

Advances in the induction and maintenance of immunosuppression have significantly reduced episodes of acute rejection over the past decades [15]. Although rare, acute rejection episodes pose a serious threat to graft survival. The type of rejection, antibody-mediated rejection, T-cell-mediated rejection, or chronic rejection, determines the choice of medications. This decision is also influenced by the severity of the histological lesion (based on the Banff system), the chronicity score, and the presence of coexisting comorbidities [18].

T-cell mediated rejection is treated with intravenous methylprednisolone at a dose of 10-30 mg/kg, administered 3-5 times a day. This dose is maintained for 3 to 5 days, followed by a gradual tapering of the steroids. Patients with severe (Banff Ib, IIa, IIb, III) or refractory rejection are treated with ATG at a dose of 1.5 mg/kg for 5-7 days [115]. Meanwhile, antibody-mediated rejection is treated with intravenous immunoglobulin at a dose of 100 to 200 mg/kg, alongside plasmapheresis performed 3 to 5 times every other day to remove circulating antibodies [116]. However, the duration of this therapy is not well-defined. In cases where antibody-mediated rejection is refractory to intravenous immunoglobulin and plasmapheresis, rituximab at a dose of 375 mg/m^2 or bortezomib at a dose

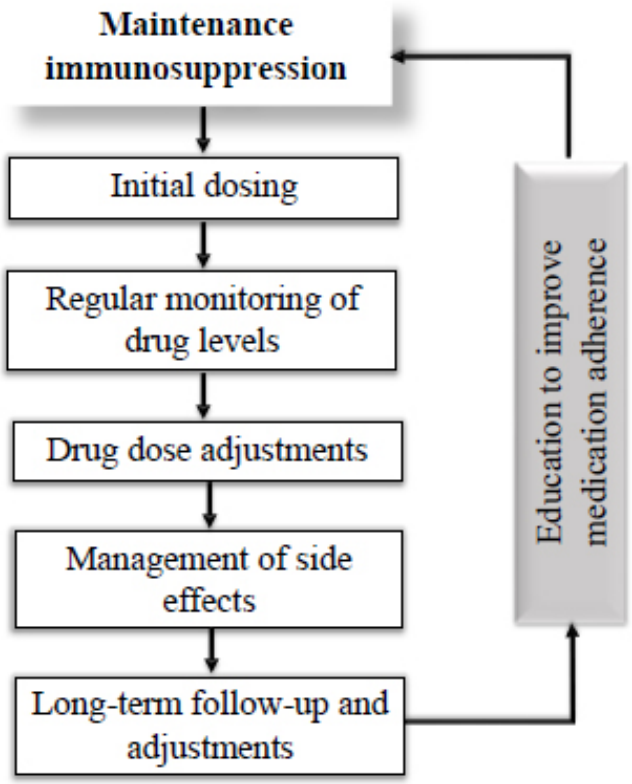

Fig. (3). Maintenance immunotherapy in pediatric recipients of kidney transplants. The present algorithm outlines various steps necessary to achieve optimal immunosuppression while minimizing associated adverse effects. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

of 1.3 mg/m^2 can be administered [116]. For chronic rejection, which is largely mediated by antibodies, the treatment regimen mirrors that used for antibody-mediated rejection [116].

CONCLUSION

Pediatric kidney transplant rejection remains a significant challenge despite advancements in immunosuppressive therapies and surgical techniques. This review highlights the critical importance of understanding and identifying reliable biomarkers for early detection and precise management of rejection episodes. The integration of novel biomarkers with traditional diagnostic tools can significantly improve the accuracy of rejection diagnoses and tailor treatment strategies more effectively.

The beneficial aspects of this review lie in its comprehensive examination of current and emerging biomarkers, which could revolutionize the management of pediatric kidney transplant rejection. By identifying these biomarkers, clinicians can intervene earlier, potentially preventing irreversible damage to the graft. Current treatment strategies, although effective, require further refinement to minimize adverse effects and improve long-term graft survival. This review underlines the necessity of developing individualized immunosuppressive regimens based on the patient's age, immunological profile, the type of rejection, and associated comorbidities. Emerging therapies and approaches, such as the use of biologics and precision medicine, hold promise for improving outcomes in pediatric kidney transplant recipients. Future research should focus on validating new biomarkers, understanding the mechanisms of rejection in pediatric patients, and optimizing treatment protocols to balance efficacy with safety.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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