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Kidney transplantation in Lupus Nephritis: a comprehensive review of challenges and strategies

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Abstract

Purpose of review Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE), significantly impacting patient outcomes. Despite advances in immunosuppressive therapies, many patients progress to end-stage renal disease (ESRD), and kidney transplantation becomes essential for improving survival. However, the unique characteristics of autoimmune diseases make the timing of kidney transplantation and post-transplant management challenging. This review evaluates authoritative guidelines and recent studies to identify optimal timing for kidney transplantation and effective pre- and post-transplant management measures for patients with LN.

Recent findings Advancements in immunosuppressive therapies, including calcineurin inhibitors, Voclosporin, and biologic agents such as belimumab, have significantly improved LN management. Emerging biomarkers, such as urinary MCP-1 and BAFF, offer promising tools for monitoring LN activity and predicting recurrence risk post-transplantation. Current guidelines emphasize the importance of achieving disease quiescence before transplantation, while new evidence supports the benefits of preemptive transplantation and personalized immunosuppressive regimens in improving patient and graft survival.

Summary This review highlights the latest evidence and strategies for optimizing kidney transplantation outcomes in LN patients, focusing on timing, immunosuppression, and disease monitoring.

Keywords Lupus Nephritis, Kidney transplantation, Immunosuppressive Therapy, Biomarkers, Outcome

Introduction

Lupus nephritis (LN) is a common and serious manifestation of systemic lupus erythematosus (SLE), an autoimmune disorder that affects multiple organs [1]. LN is marked by immune complex deposition in the kidneys, which leads to inflammation and progression to end-stage renal disease (ESRD) if left inadequately managed [1]. Despite advancements in immunosuppressive therapies, many patients still experience poor long-term outcomes, with a significant proportion progressing to ESRD and requiring renal replacement therapy [2, 3].

The variability in LN incidence and progression due to gender, ethnicity, and age underscores the need for personalized treatment approaches [4]. Current guidelines, such as KDIGO 2024 and EULAR/ERA-EDTA 2019, have provided valuable recommendations on the timing and management of kidney transplantation in lupus nephritis patients [5, 6]. The timing of kidney transplantation in lupus nephritis is contingent upon achieving a quiescent phase. However, controversies remain regarding the definition of disease quiescence and the application

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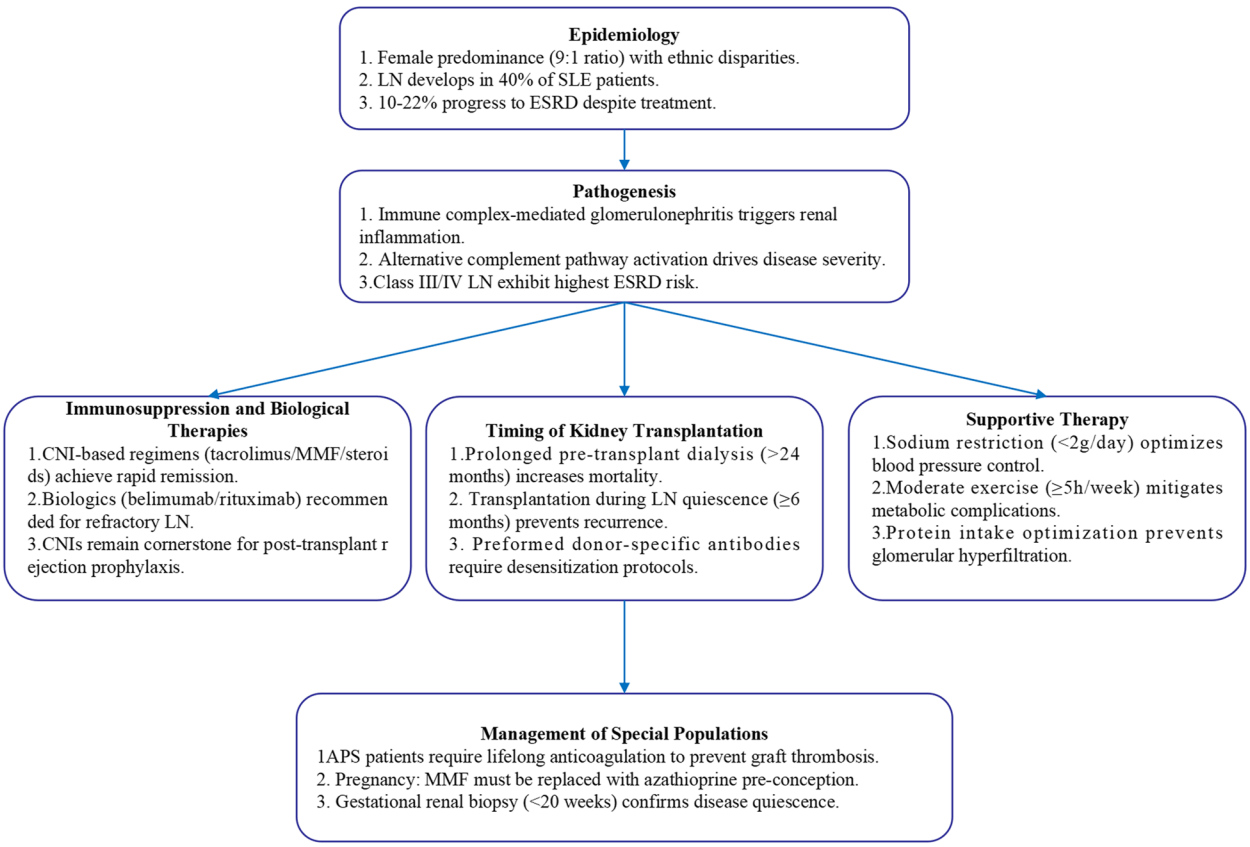

Fig. 1 Overview of Lupus Nephritis (LN) Epidemiology, Pathogenesis, and Management Approaches

This figure summarizes the epidemiology, pathogenesis, and management of LN. It highlights the female predominance, immune complex-mediated inflammation, and the impact of complement activation. Management includes immunosuppressive therapies, kidney transplantation considerations, supportive care, and special population management, such as in pregnancy and antiphospholipid syndrome

of preemptive transplantation, which require further discussion.

Given kidney transplantation's pivotal role in managing advanced LN, this review evaluates recent advancements in immunosuppressive therapies, biomarkers for disease activity monitoring, and the influence of demographic factors on treatment efficacy. Our goal is to offer a comprehensive guide for LN patients requiring kidney transplantation (Fig. 1).

Epidemiology and Renal Impact of Lupus Nephritis

Lupus nephritis (LN) is a significant manifestation of systemic lupus erythematosus (SLE), affecting approximately 40% of adults with SLE during their disease course [7, 8]. LN is characterized by immune complex-induced kidney inflammation. The incidence and prevalence of SLE and LN vary across different populations and gender, with higher rates observed among certain ethnic groups [9]. Notably, while SLE predominantly affects females regardless ethnicity, male patients with LN often experience more severe renal involvement and a higher likelihood of progression to ESRD [10, 11]. Several studies have shown that Hispanic, African American, and Asian patients with SLE are at a higher risk of developing LN and subsequently ESRD [9, 12–14]. Lupus Registry data in USA showed that the incidence rate of ESRD was 13.8 per 1000 patient-years for African Americans with SLE, compared to 3.3 for white patients [13]. A multiethnic cohort of 1,827 SLE patients reported an overall of 31.0% patients developed into LN. Higher LN rates were observed in Hispanic (49.3%), African American (39.9%), and Asian (36.8%) patients, while only 20.3% of Caucasians were affected [12]. In North America, black patients were at a higher risk of progressing to ESRD compared with any other ethnicity (adjusted hazard ratio 1.4) [15]. The differences between ethnic groups are not only reflected in the prevalence and progression risk of LN, but also in their response to treatment medications. The Aspreva Lupus Management Study (ALMS) showed that more Black and Hispanic patients responded to MMF

than to intravenous cyclophosphamide (IVC) [16]. The differences in ESRD caused by LN across various ethnic groups highlight the complex interplay of genetic background and socioeconomic factors.

The pathogenesis of both SLE and LN involved complex interplay of environmental factors, genetic predispositions, and hormonal influences [17]. Environmental triggers such as ultraviolet radiation and infections can initiate autoimmune responses in genetically susceptible individuals. Genetic factors, including gene polymorphisms, contribute to immune system dysregulation. Hormonal influences, particularly estrogen, play a significant role, as evidenced by the higher prevalence of SLE in females. This intricate combination leads to immune system aberrations, resulting in systemic inflammation and organ-specific manifestations like LN [17]. The primary pathogenic mechanism of LN involves an immune complex-mediated response in the kidney, activation of autoreactive B and T cells, and significant contributions from alternative pathways of complement activation [18]. The activation of alternative complement pathways further exacerbates renal injury. LN is classified into six histologic types, with Class III (focal) and Class IV (diffuse) being the most likely to progress to ESRD, necessitating consideration of kidney transplantation [19]. Class V (membranous) LN can also lead to significant renal impairment, though typically at a slower progression rate compared to Classes III and IV [19]. While Class VI (advanced sclerosing LN), is characterized by global sclerosis of more than 90% of glomeruli. It represents chronic, irreversible damage resulting from prior inflammatory injury and is generally at the ESRD stage [4].

Despite significant advances in immunosuppressive therapies for patients with LN, the prognosis of LN has still not improved since 2000 [20]. The progression from LN to ESRD is a critical concern, as ESRD necessitates renal replacement therapies such as dialysis or kidney transplantation. It has been reported that 10% to 22% of LN patients may advance to ESRD despite advancements in treatment [21]. Once progression from LN to ESRD occurs, the best approach is dialysis followed by kidney transplantation. Compared to dialysis alone, patients who undergo kidney transplantation experience significantly improved prognosis and survival rates [22, 23]. However, determining the optimal timing for transplantation is complex and requires careful consideration of the disease's natural course and the patient's overall condition.

Optimal Timing of Kidney Transplantation in LN patients

Impact of Pre-Transplant Dialysis Duration in LN

Extended periods on dialysis before transplantation have been associated with increased mortality in LN patients. A retrospective study analyzing LN patients over a 40-year period found that each additional month on dialysis prior to renal transplantation increased the risk of mortality [24]. This study also showed that dialysis more than 24 months affected survival rates [24]. According to the current guidelines, preemptive transplantation was strongly encouraged to avoid the long-term complications of dialysis [6]. The KDIGO 2024 Guideline conditionally recommends preemptive kidney transplantation over initiating dialysis or non-preemptive transplant for patients with LN approaching ESRD [5]. This approach aims to reduce dialysis-related complications and improve long-term outcomes [5]. Delayed transplantation, especially with dialysis exceeding 24 months, significantly increases mortality risks and complications [25]. Recent studies have shown that earlier transplantation leads to higher survival rate of both the patient and the graft, while the application of immunosuppressive drugs further reduces the chances of disease recurrence after surgery [26–29]..

While preemptive transplantation can offer better prognosis in LN, it's essential to evaluate disease activity, overall health status, and potential risks. Collaborative decision-making involving nephrologists and rheumatologists is vital to determine the optimal timing for transplantation, balancing the benefits of reduced dialysis exposure against the risks associated with active disease. Additionally, it is important to recognize that preemptive kidney transplantation may not always be acceptable to patients due to concerns about surgery, the potential risks of immunosuppression, or cultural and psychological factors.

Monitoring Disease Activity Levels in LN

Quiescent phase, or disease remission, is crucial in determining the optimal timing for kidney transplantation in LN patients. However, there is no universally accepted definition of quiescence, and criteria vary across studies and guidelines. Both KDIGO 2024 and EULAR/ERA-EDTA 2019 guidelines highlighted the importance of achieving quiescence before kidney transplantation to minimize the risk of recurrence. Quiescence is generally defined as a state where serological and clinical markers indicate disease stability for at least six months, including the normalization or stabilization of anti-dsDNA antibody levels and complement (C3/C4) levels, proteinuria below 0.5 g/24 h or below 300 mg/m^2/d, and the absence of active inflammation on renal biopsy, characterized by minimal immune deposits and quiescent glomerular changes [5, 6].

Commonly used serologic markers include anti-double-stranded DNA (ds-DNA) antibodies, serum creatinine and complement activation markers C3 and C4 [30]. Elevated ds-DNA antibodies and decreased levels of C3

and C4 typically indicate active LN, but these markers have limitations in both specificity and sensitivity, especially following immunosuppressive therapy [30]. Recognizing these limitations, recent studies have investigated additional markers that could provide more precise monitoring of LN activity and recurrence. Autoantibodies such as anti-C1q, anti-chromatin, anti-Smith antibody (anti-Sm), and anti-ribosomal P [31] have been linked to disease activity, with significant reductions observed in patients achieving remission. Furthermore, elevated serum type I interferon (IFN-I) levels and transcriptomic changes in renal biopsies particularly among patients resistant to conventional therapies, have been associated with more severe disease course [32].

In addition to traditional serum markers, urine biomarkers, beyond proteinuria, are increasingly valued for their ability to provide a more comprehensive reflection of LN activity. More specific urinary markers, such as monocyte chemoattractant protein-1 (MCP-1) [33–36], B-cell activating factor (BAFF) [37] and matrix metalloproteinase-7 (MMP-7) [38, 39], have shown strong correlation with disease activity and renal function, offering better predictive value than traditional markers. MCP-1 recruits monocytes to inflammation sites. Elevated urinary MCP-1 levels have been associated with active LN and correlate with histological findings of renal inflammation [33]. Studies have demonstrated that higher urinary MCP-1 levels can differentiate between active and chronic LN, and their reduction over time is linked to effective therapeutic responses and stable kidney function [40, 41]. BAFF functions in B-cell activation and survival and elevated urinary BAFF levels have been observed in patients with active LN [42]. Studies also indicated that urinary BAFF levels decrease following effective treatment [42, 43]. Increased urinary MMP-7 levels have been associated with renal inflammation and fibrosis in LN. Research suggested that urinary MMP-7 could serve as a biomarker for kidney injury, aiding in the assessment of disease severity and progression [39].

However, these markers alone may not reliably reflect subclinical disease activity. For example, recent studies have demonstrated that some patients who achieve clinical remission may still exhibit active renal inflammation on histological evaluation, increasing the risk of post-transplant recurrence [44, 45]. Renal biopsy remains the gold standard for confirming histological quiescence, especially in cases where clinical or serological markers are inconclusive [46]. Common indicators of activity in patients with LN are IgG, IgA, IgM, C1q, C3, and tissue anti-nuclear antibodies (ANA), extraglomerular immune deposits, and endothelial tubular reticulum inclusion bodies. Among these markers, ANA demonstrates the highest specificity but low sensitivity, whereas IgG exhibits the opposite pattern. Therefore, a combined testing approach involving both indicators is recommended [47].. However, renal biopsy is an invasive procedure and may not be feasible for all patients. Therefore, combining serological markers with histological findings provides the most comprehensive assessment of LN activity and reduces the likelihood of disease recurrence following transplantation.

Key Indicators for Transplant Matching in LN

Effective transplant matching is crucial to improving graft survival in LN patients. High titers of circulating HLA antibodies, particularly donor-specific HLA antibodies (DSA), are associated with a higher risk of graft rejection, including hyperacute rejection [48]. HLA mismatches, especially at the HLA-DR and HLA-C loci, significant impact graft survival and should be carefully considered [49–52]. The traditional complement-dependent cytotoxicity crossmatch (CDC-XM) may yield false-positive results, particularly in patients with autoimmune diseases, which can be attributed to non-specific binding of donor lymphocytes, prozone effect, incomplete donor typing, and the presence of non-HLA antibodies [53]. Flow cytometry crossmatch (FCXM) is a more sensitive method than CDC and is used to detect pre-formed antibodies in the recipient's serum against the donor's lymphocytes [54]. This method combines the advantages of CDC-XM, which identifies both HLA and non-HLA antibodies, with the ability to simultaneously detect antibodies that mediate tissue damage through both complement activation and antibody-dependent cell-mediated cytotoxicity. To further improve specificity and sensitivity, pronase digestion is often employed in FCXM. This technique removes Fc receptors on the cell surface for enhancing the accuracy of B-cell crossmatching [55, 56]. LN patients generally manifest heightened immune activity, increasing the risk of sensitization to HLA. Therefore, transplant matching for LN patients requires careful consideration of immunological factors, including HLA compatibility and the presence of DSAs, to minimize the risk of graft rejection [57]. It is currently clinically accepted that the risk of the presence of DSA can be minimized with pre-transplant interventions such as plasma exchange, IVIG, rituximab, or the proteasome inhibitor [58]. High-resolution sequencing-based typing technology can obtain high-resolution HLA typing results, providing accurate evidence for identifying donor-specific HLA antibodies in recipients [59]. However, some of these approaches are generally not feasible prior to deceased donor transplantation due to the limited time and may instead be employed in the early post-transplant period to reduce associated risks.

Non-HLA antibodies have been recognized as important factors in kidney transplantation. It was reported that 38% of kidney allograft losses could be due to non-HLA-related immunological factors, compared to only 18% due to HLA mismatches [60]. These antibodies included major histocompatibility complex class I chain-associated molecule A (MICA), poikilodulin, myocardin, angiotensin II type 1 receptor (AT1R), microtubulin, and collagen, in influencing graft outcomes, potentially through mechanisms involving fibrosis and immune modulation [61–63]. Living donor kidney transplantation is generally associated with better prognosis compared to deceased donor transplantation, a trend also observed in LN patients [3]. These findings suggest a comprehensive evaluation should be conducted prior to kidney transplantation in LN patients to optimize the surgical outcome.

Standard Pre- and Post-Transplant Management for LN patients

Pre-Transplantation Medication

Immunosuppressive and Antimetabolic Drugs

Pre-transplantation management of LN patients necessitates achieving a quiescent disease state through optimized immunosuppressive therapy to minimize the risk of post-transplant complications. Cyclophosphamide (CYC) and corticosteroids, such as Prednisolone, are commonly used in combination as immunosuppressive agents to induced remission. However, these drugs are associated with relatively high adverse effects including amenorrhea and alopecia [64]. To mitigate the side effects, lower-dose CYC regimens, such as the Euro-Lupus protocol, have been developed. This protocol administers 500 mg of cyclophosphamide intravenously every two weeks for a total of six doses, followed by maintenance therapy with azathioprine [65]. Meanwhile, MMF, an antimetabolic drug, is often preferred for maintenance therapy due to its comparable efficacy to CYC with fewer side effects, and is increasingly used for induction therapy at doses adjusted according to disease activity [6]. Immunosuppressive agents, including calcineurin inhibitors (CNIs) such as cyclosporine A, tacrolimus, and voclosporin, are commonly used to control disease activity and induce remission prior to transplantation, often in combination with mycophenolate mofetil (MMF) or glucocorticoids. Voclosporin is a novel calcineurin inhibitor, which has been tested in pivotal trials in patients with LN [66, 67]. Clinical trials showed that adding voclosporin to MMF and low-dose steroids resulted in a clinically and statistically superior complete renal response rate compared to MMF and low-dose steroids alone, while maintaining a comparable safety profile [66, 68, 69]. Notably, clinical trials indicated that adding voclosporin to MMF and low-dose steroids resulted in significantly more patients achieving urine protein creatinine ratio (UPCR) reductions of ≥ 50% from baseline at 6 months [70]. In a phase 2 study comparing voclosporin to tacrolimus in kidney transplant recipients, voclosporin demonstrated similar efficacy in reducing acute rejection rates. Notably, the incidence of new-onset diabetes after transplantation was significantly lower in the voclosporin group (1.6%) compared to the tacrolimus group (16.4%) [67]. The combination of immunosuppressive drugs not only enhances therapeutic efficacy but also minimizes the adverse effects associated with higher doses of a single drug, making it a preferred strategy in preparing LN patients for transplantation.

Hydroxychloroquine (HCQ) is a cornerstone in the management of SLE) LN, owing to its immunomodulatory, anti-inflammatory, and antithrombotic properties [71]. The optimal dosing of HCQ in patients with advanced LN, particularly those with renal impairment, remains a topic of debate. Current guidelines suggest a reduction of 50% in HCQ dose for patients with a glomerular filtration rate (GFR) less than 30 mL/min to mitigate potential toxicity [6]. Nonetheless, some studies advocate for maintaining standard dosing, emphasizing the drug's protective effects against disease progression [72, 73].

Biologic Agents

The use of biologic agents has significantly enhanced LN management by targeting specific immune pathways involved in disease pathogenesis and reduce side effects. Interleukin-2 (IL-2) plays a crucial role in maintaining immune tolerance by promoting the proliferation and function of regulatory T-cells. Recent studies have shown that low-dose IL-2 therapy can restore Treg function and ameliorate disease activity in SLE patients [74, 75].

On the other hand, biologic agents modulating B-cell activity, such as belimumab, rituximab, and Obinutuzumab, also have been proved effective in RN. Belimumab, a monoclonal antibody against B-lymphocyte stimulator (BLyS), can reduce B-cell activation and autoantibody production [76]. The BLISS-LN trial demonstrated that adding belimumab to standard therapy improved renal response rates in patients with active LN [77]. Other trials proved that belimumab could reduce the risk of LN flare and decrease the eGFR decline in a broad spectrum of patients with LN [78, 79]. Consequently, the KDIGO 2024 guidelines recommend belimumab as an adjunct to standard immunosuppressive therapy for patients with active

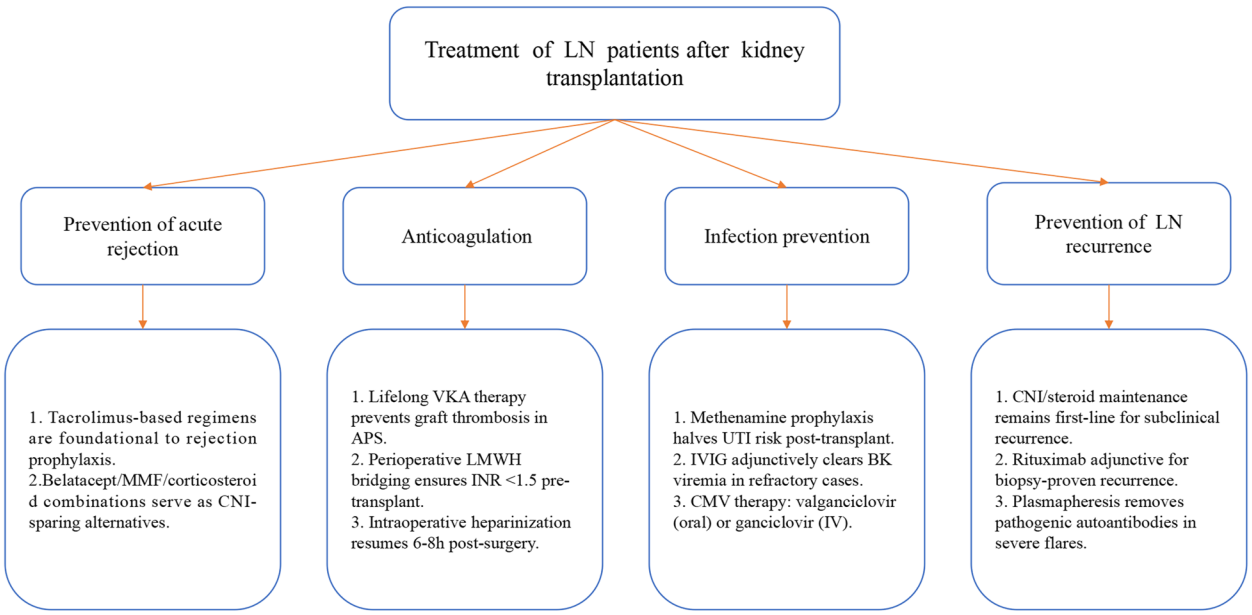

Fig. 2 Outline of medication management after renal transplantation in patients with Lupus Nephritis

This figure summarizes the key strategies for managing Lupus Nephritis after kidney transplantation. It includes prevention of acute rejection with tacrolimus-based regimens, anticoagulation with VKA, infection prevention through methenamine and CMV therapy, and prevention of LN recurrence with CNI/steroid maintenance, rituximab, and plasmapheresis for severe flares

LN [5]. Rituximab targets CD20-positive B cells, leading to their depletion. While a clinical trial did not show a significant benefit of rituximab over placebo in achieving renal response, subsequent studies suggest potential efficacy in refractory LN cases [80, 81]. The KDIGO 2024 guidelines suggest considering rituximab for patients who do not respond adequately to initial therapy [5]. Meanwhile, Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody engineered for enhanced B-cell depletion. The Phase II NOBILITY trial demonstrated that Obinutuzumab, in combination with standard therapy, led to higher renal response rates in LN patients [82]. While not yet included in the KDIGO 2024 guidelines, Obinutuzumab represents a promising therapeutic option pending further evidence.

Post-Transplant Medications (Fig. 2)

The immunosuppressive regimen for LN patients after kidney transplantation is similar to that for patients receiving kidney transplants for other causes. Commonly used immunosuppressive regimens include the combination of CNIs, MMF, and glucocorticoids [83, 84]. In addition to immunosuppression, LN patients require particular attention to the control of lupus activity to prevent recurrence after transplantation. Tacrolimus or cyclosporine are the mainstay CNI agents and can be used as maintenance immunosuppressants in LN patients after kidney transplantation to prevent graft rejection and manage residual SLE disease activity [5]. MMF and MPA are recommended for the maintenance treatment of LN patients, including those who have undergone kidney transplantation, as they have significant effects in reducing proteinuria and preventing disease relapse [5]. For patients who are unable to tolerate or cannot access MPA, azathioprine is an alternative choice for maintenance immunosuppressive therapy. In cases of LN patients with TMA, the use of complement inhibitors (such as eculizumab) should be considered, especially in situations of atypical hemolytic uremic syndrome or catastrophic APS [85]. For LN patients with childbearing needs, hydroxychloroquine is recommended, and low-dose aspirin should be started before 16 weeks of gestation to reduce the risk of preeclampsia and intrauterine growth restriction [5]. Belatacept, a selective T-cell co-stimulation blocker, has been explored as an alternative to CNIs in kidney transplantation. However, studies such as the BENEFIT trial have shown that belatacept is associated with higher rates and increased severity of acute rejection episodes compared to cyclosporine [86]. An alternative approach is the combination of belatacept with mycophenolate mofetil and corticosteroids, which has been approved by the U.S. Food and Drug Administration (FDA) for use in adult kidney transplant recipients [87–89]. Study showed that switching from a CNI-based regimen to everolimus can improve and

stabilize graft function without a significant increase in the risk of biopsy-proven acute rejection [90]. Another alternative is the use of anti-CD25 monoclonal antibodies, such as basiliximab and daclizumab, which have been shown to reduce the incidence of acute rejection in solid-organ transplant recipients [91]. The choice of alternative CNIs options should be based on the patients' specific condition and the availability of these agents in the regions.

Anticoagulation Therapy

The presence of antiphospholipid syndrome (APS) in LN patients elevates the risk of thrombotic events post-transplantation [92]. If APS affects the kidneys, it can lead to antiphospholipid syndrome nephropathy (APSN), characterized by renal vascular lesions and thrombotic microangiopathy (TMA) [93]. APS may occur concurrently with or independently from LN. The diagnosis of APS relies on the detection of antiphospholipid antibodies (aPL), including anticardiolipin antibodies (aCL), lupus anticoagulant (LA), and anti-β2 glycoprotein I antibodies (aβ2GPI). Notably, these antibodies may also be positive in LN patients, typically during disease active periods. Therefore, the diagnosis of APS in LN patients should be based on the occurrence of thrombotic events and the repeated testing of aPL at least 12 weeks apart during a period of LN quiescence, with sustained positivity. Positive IgA-aB2GPI antibodies was defined as an independent risk factor for early graft loss (6 months after transplantation) [94]. Patients with APS are more likely to experience graft loss due to thrombotic events, which can occur in almost 100% of APS patients if they do not receive preemptive anticoagulation [95]. A long-term multicenter analysis reported that patients with APS had lower 15-year allograft survival rate compared with patients without APS (73.86% vs. 90.48%) [96].

There are no specific treatments for APS. In renal transplant recipients with concurrent APS and LN, the primary focus post-transplantation should be on thrombosis prevention. For patients with pre-existing APS, anticoagulation therapy should be initiated prior to transplantation [97]. For most patients with end-stage renal disease (ESRD), particularly those awaiting deceased donor transplantation, the use of low molecular weight heparin (LMWH) in therapeutic doses is limited due to the high risk of bleeding and the impracticality of advanced notice. Instead, the preferred approach involves adjusting the international normalized ratio (INR) to below 1.5, followed by unfractionated heparin (UFH) infusion, which allows for better control and rapid reversal if needed. This approach ensures safer anticoagulation management in the perioperative period while minimizing complications. Warfarin is usually reintroduced 24 h after transplantation to continue long-term anticoagulation management [98].

Anti-Microbial Therapy

Infection is a major contributor to post-transplant mortality in patients with LN, making anti-microbial therapy important [98]. Early post-transplant infections commonly include surgical site infections, pneumonia, urinary tract infections (UTIs), bacteremia, fungal infections and C. difficile colitis [99]. Among these, urinary tract infections require particular attention, especially given the limited options for treatment and risk of developing drug-resistant bacteria with prolonged prophylactic antibiotics use. To reduce the rate of UTIs, Methenamine Hippurate is recommended twice daily, which can lower infection rates by up to 50% [100, 101]. Immunosuppressive therapy after renal transplantation also increases the risk of opportunistic infections or reactivation of latent pathogens, such as BK virus, CMV, herpes simplex virus (HSV), varicella zoster virus, hepatitis B virus, hepatitis C virus (HCV), and tuberculosis [102]. For BK virus, which is often linked to the use of immunosuppressive drugs, the primary treatment involves reducing immunosuppression, while intravenous immunoglobulin (IVIG) can provide passive immunity to help clear the infection [103]. CMV infections, often contracted from is seropositive renal donors, are typically treated with valganciclovir (oral) or ganciclovir (intravenous) [104, 105]. For other viral infections, standard antiviral therapies are generally effective.

Supportive therapy

Supportive therapy is crucial for optimizing outcomes in LN patients undergoing kidney transplantation. Given the distinct challenges posed by LN, tailored supportive measures are essential [106]. LN patients generally experience proteinuria and hypoalbuminemia and required dietary planning. A balanced diet with adequate protein intake is recommended to compensate for urinary protein losses while avoiding excessive intake that could exacerbate glomerular hyperfiltration and intraglomerular pressure [107]. Sodium intake should be restricted to manage hypertension, a common complication in LN patients. Additionally, maintaining adequate caloric intake is important to prevent malnutrition and support recovery post-transplantation [108, 109]. Additionally, managing dietary salt intake is important, as elevated systolic blood pressure has been associated with an increased risk of graft loss, specifically, a 32% increase for 20 mmHg rise in blood pressure. Antihypertensive agents such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are often preferred due to their renal protective effects [110, 111].

Given the rising incidence of obesity and insulin resistance post-transplantation, largely due to ongoing glucocorticoid therapy and low physical activity. patients are

encouraged to engage in at least 5 h of moderate exercise per week [112–114]. Chronic corticosteroid use in LN patients can lead to decreased bone mineral density. Bone health should be monitored regularly, and interventions such as calcium and vitamin D supplementation, along with weight-bearing exercises, are advised to mitigate the risk of osteoporosis [115].

Prognosis of Renal Transplantation and Management in Special Populations with LN

Recurrence of LN Following Kidney Transplantation

LN recurrence following kidney transplantation is a significant concern for patients with ESRD due to SLE. The reported recurrence rates of LN post-transplantation vary widely across studies. The overall recurrence rate of post-transplant LN was reported to be 2.44% [116]. The recurrence rates also demonstrated temporal variability: [116] between 1987 and 1995, the recurrence rate was 3.19%, while it decreased to 1.98% during the period from 1996 to 2006, potentially attributed to the increased utilization of MMF. Post-transplant lupus flares were significantly associated with a higher risk of graft failure, with a graft failure incidence of 93.4% in post-transplant LN patients. In comparison, the graft failure incidence was 85.7% in the rejection group and only 19.1% in the group without relapse or rejection. In addition, the overall survival rate of post-transplant LN patients was lower than that of the non-relapse group but comparable to the rejection group. The mortality rate in the post-transplant LN group was 16%, lower than the rejection group (18%) but higher than the no-relapse group (11%) [116]. Another study from 2019 reported a recurrence rate of 8% among renal transplant recipients with LN, noting that recurrence was not associated with graft loss [117]. In contrast, a surveillance biopsy study found a higher recurrence rate of 54% in 41 patients, with most cases being subclinical and classified as class I or II LN [118]. Recent meta-analysis showed that LN patients had lower graft survival rate (HR = 1.15) and patient survival rate (HR = 1.06) when compared with patients underwent transplantation due to other causes [3].

The management of recurrent LN involves a combination of early monitoring, immunosuppressive therapies and supportive treatments [5]. Monitoring should start within 1–2 weeks after the transplantation, including regular assessments of urine protein, serum creatinine, and kidney function. When symptoms such as proteinuria, increased serum creatinine, or hematuria are observed, a kidney biopsy should be promptly performed to confirm the recurrence of LN. Currently, no studies have compared the effects of different immunosuppressive drugs on the recurrence of LN in kidney transplant recipients. The treatment approach for recurrent LN in transplant kidneys is similar to that for conventional LN [5, 119]. High-dose corticosteroids are commonly used to control the immune response, along with cyclophosphamide for induction therapy. If patients experience adverse reactions or are intolerant to conventional CNIs such as cyclosporine or tacrolimus, immunosuppressive regimens can be adjusted to include MMF or azathioprine. For patients who do not respond adequately to conventional immunosuppressive treatments, anti-CD20 monoclonal antibodies can be used to suppress B-cell activity. In cases of more severe recurrent LN, plasmapheresis can be applied as an adjunctive therapy to help remove circulating autoantibodies, thereby reducing immune-mediated damage.

Women of Childbearing Age

Pregnancy in women with LN requires meticulous planning and management to optimize maternal and fetal outcomes. It is important that pregnancy is deferred until the disease has been in remission for at least six months, as active LN at conception is associated with increased risks of adverse outcomes, including preeclampsia, preterm birth, and fetal loss [120]. Kidney transplantation can improve the success rate of pregnancy [121]. It is recommended to avoid pregnancy for at least one year after kidney transplantation, as the risk of acute rejection is highest during this period of maximum immunosuppression [122]. CNIs, such as tacrolimus and cyclosporine, are commonly employed in transplant immunosuppression and are considered safe during pregnancy [123]. These agents should be continued to maintain graft function and prevent disease flare-ups. HCQ is another cornerstone of therapy in pregnant women with LN. Its use has been associated with a reduction in lupus activity and is deemed safe for both mother and fetus. Continuation of HCQ during pregnancy is recommended to decrease the risk of disease exacerbation [124]. MMF is teratogenic and should be replaced with AZA (azathioprine) before conception and throughout pregnancy [125, 126]. Rituximab, which can cross the placenta and depletes fetal B-cells, should also be avoided for at least one year before pregnancy [4]. APS requires special attention due to the increased risk of thrombosis and fetal miscarriage caused by antiphospholipid antibodies [127]. Anticoagulation therapy may be indicated in pregnant women with LN, particularly in the presence of antiphospholipid antibodies or a history of thrombotic events. Low-dose aspirin and prophylactic heparin are commonly used to mitigate the risk of thrombosis and pregnancy complications [128]. Tacrolimus is

preferred over cyclosporine due to its lower impact on blood pressure [129]. Although advancements in pharmacologic therapy improving pregnancy outcomes for women with LN post-transplant, it is still recommended to perform a renal biopsy before the 20th week of gestation to confirm disease quiescent. Regular placental Doppler ultrasounds are essential to monitor fetal health [121, 130].

Conclusion

Kidney transplant outcomes in LN patients are influenced by disease activity, demographics, and treatment history. Advances in biomarkers, immunosuppressive strategies, and transplant matching promise to enhance survival rates and reduce recurrence.

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Authors' contributions
Conceptualization was carried out by Kerong Jiang. Methodology was developed by Kerong Jiang, Yongsheng Pan, and Dan Pu. The original draft was prepared by Kerong Jiang, while the review and editing were performed by Yongsheng Pan, Dan Pu, Lijuan Shi, Xiaoliang Xu, Minfeng Bai, Xiaqiong Gong, Jie Guo, Ming Li, and Kerong Jiang. Supervision was provided by Kerong Jiang and Yongsheng Pan.

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Data availability
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Declarations

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Not applicable.

Consent for publication
Written informed consent for publication was obtained from all participants for the publication of this study and any accompanying materials.

Competing interests
The authors declare no competing interests.

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References

1. Xipell M, Lledó GM, Egan AC, Tamirou F, Del Castillo CS, Rovira J, et al. Quintana LF. From Systemic Lupus Erythematosus to Lupus Nephritis: The Evolving Road to Targeted Therapies. Autoimmun Rev. 2023;22(10):103404.
2. Kostopoulou M, Fanouriakis A, Bertsias G, Boumpas DT. Annals of the Rheumatic Diseases Collection on Lupus Nephritis (2019–2022): Novel Insights and Advances in Therapy. Ann Rheum Dis. 2023;82(6):729–33.
3. Jiang W, Xu Y, Yin Q. Graft Survival and Mortality Outcomes after Kidney Transplant in Patients with Lupus Nephritis: A Systematic Review and Meta-Analysis. Ren Fail. 2024;46(1):2296000.
4. Parikh SV, Almaani S, Brodsky S, Rovin BH. Update on Lupus Nephritis: Core Curriculum 2020. Am J Kidney Dis. 2020;76(2):265–81.
5. Rovin BH, Ayoub IM, Chan TM, Liu ZH, Mejía-Vilet JM, Balk EM, et al. Floege J. Executive Summary of the Kdigo 2024 Clinical Practice Guideline for the Management of Lupus nephritis. Kidney Int. 2024;105(1):31–34.
6. Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al. Boumpas DT. 2019 Update of the Joint European League against Rheumatism and European Renal Association-European Dialysis and Transplant Association (Eular/Era-Edta) Recommendations for the Management of Lupus Nephritis. Ann Rheum Dis. 2020;79(6):713–723.
7. Siegel CH, Sammaritano LR. Systemic Lupus Erythematosus: A Review. JAMA. 2024;331(17):1480–91.
8. Davidson A. What Is Damaging the Kidney in Lupus Nephritis? Nat Rev Rheumatol. 2016;12(3):143–53.
9. Barber MRW, Drenkard C, Falasinnu T, Hoi A, Mak A, Kow NY, et al. Ramsey-Goldman R. Global Epidemiology of Systemic Lupus Erythematosus. Nat Rev Rheumatol. 2021;17(9):515–532.
10. Trentin F, Signorini V, Manca ML, et al. Gender differences in SLE: report from a cohort of 417 Caucasian patients. Lupus Sci Med. 2023;10(1):e000880.
11. Ramírez Sepúlveda JI, Bolin K, Mofors J, Leonard D, Svenungsson E, Jönsen A, et al. Wahren-Herlenius M. Sex Differences in Clinical Presentation of Systemic Lupus Erythematosus. Biol Sex Differ. 2019;10(1):60.
12. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. Farewell V. The Frequency and Outcome of Lupus Nephritis: Results from an International Inception Cohort Study. Rheumatology (Oxford). 2016;55(2):252–62.
13. Plantinga L, Lim SS, Patzer R, McClellan W, Kramer M, Klein M, et al. Drenkard C. Incidence of End-Stage Renal Disease among Newly Diagnosed Systemic Lupus Erythematosus Patients: The Georgia Lupus Registry. Arthritis Care Res (Hoboken). 2016;68(3):357–65.
14. Mahajan A, Amelio J, Gairy K, Kaur G, Levy RA, Roth D, Bass D. Systemic Lupus Erythematosus, Lupus Nephritis and End-Stage Renal Disease: A Pragmatic Review Mapping Disease Severity and Progression. Lupus. 2020;29(9):1011–20.
15. Nee R, Martinez-Osorio J, Yuan CM, Little DJ, Watson MA, Agodoa L, Abbott KC. Survival Disparity of African American Versus Non-African American Patients with Esrd Due to Sle. Am J Kidney Dis. 2015;66(4):630–7.
16. Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, et al. Solomons N. Influence of Race/Ethnicity on Response to Lupus Nephritis Treatment: The Alms Study. Rheumatology (Oxford). 2010;49(1):128–40.
17. Accapezzato D, Caccavale R, Paroli MP, et al. Advances in the Pathogenesis and Treatment of Systemic Lupus Erythematosus. Int J Mol Sci. 2023;24(7):6578.
18. Obrișcă B, Sorohan B, Tuță L, Ismail G. Advances in Lupus Nephritis Pathogenesis: From Bench to Bedside. Int J Mol Sci. 2021;22(7):3766.
19. Bajema IM, Wilhelmus S, Alpers CE, Bruijn JA, Colvin RB, Cook HT, et al. Fogo AB. Revision of the International Society of Nephrology/Renal Pathology Society Classification for Lupus Nephritis: Clarification of Definitions, and Modified National Institutes of Health Activity and Chronicity Indices. Kidney Int. 2018;93(4):789–796.
20. Tektonidou MG, Dasgupta A, Ward MM. Risk of End-Stage Renal Disease in Patients with Lupus Nephritis, 1971–2015: A Systematic Review and Bayesian Meta-Analysis. Arthritis Rheumatol. 2016;68(6):1432–41.
21. Li X, Cao CX, Chen J. Complications Associated with Kidney Transplantation, Causes of Graft Failure and Mortality Following Kidney Transplantation in Patients with Systemic Lupus Erythematosus: A Meta-Analysis. Renal Replacement Therapy. 2024 2024/08/21;10(1):49.
22. Rangoonwala S, Marks SD. Kidney Transplantation Outcomes for Children and Young People with Lupus Nephritis. Pediatr Transplant. 2022;26(1): e14193.
23. Wong T, Goral S. Lupus Nephritis and Kidney Transplantation: Where Are We Today? Adv Chronic Kidney Dis. 2019;26(5):313–22.
24. Ntatsaki E, Velo-Garcia A, Vassiliou VS, Salama AD, Isenberg DA. Impact of Pre-Transplant Time on Dialysis on Survival in Patients with Lupus Nephritis. Clin Rheumatol. 2018;37(9):2399–404.

25. Jorge A, Wallace ZS, Lu N, Zhang Y, Choi HK. Renal Transplantation and Survival among Patients with Lupus Nephritis: A Cohort Study. Ann Intern Med. 2019;170(4):240–7.
26. Naveed A, Nilubol C, Melancon JK, Girlanda R, Johnson L, Javaid B. Preemptive Kidney Transplantation in Systemic Lupus Erythematosus. Transplant Proc. 2011;43(10):3713–4.
27. Goyal N, Weiner DE, Levey AS. Kidney Transplantation in Lupus Nephritis: Can We Do Even Better? Ann Intern Med. 2019;170(4):266–7.
28. Plantinga LC, Patzer RE, Drenkard C, Kramer MR, Klein M, Lim SS, et al. Pastan SO. Association of Time to Kidney Transplantation with Graft Failure among U.S. Patients with End-Stage Renal Disease Due to Lupus Nephritis. Arthritis Care Res (Hoboken). 2015;67(4):571–81.
29. McPherson L, Plantinga LC, Howards PP, Kramer M, Pastan SO, Patzer RE. Referral and Evaluation for Kidney Transplantation among Patients with Lupus Nephritis-Related End-Stage Kidney Disease. Lupus. 2024;33(1):48–57.
30. Yung S, Chan TM. Endothelial Cell Activation and Glycocalyx Shedding - Potential as Biomarkers in Patients with Lupus Nephritis. Front Immunol. 2023;14:1251876.
31. Gómez-Bañuelos E, Fava A, Andrade F. An Update on Autoantibodies in Systemic Lupus Erythematosus. Curr Opin Rheumatol. 2023;35(2):61–7.
32. Postal M, Vivaldo JF, Fernandez-Ruiz R, Paredes JL, Appenzeller S, Niewold TB. Type I Interferon in the Pathogenesis of Systemic Lupus Erythematosus. Curr Opin Immunol. 2020;67:87–94.
33. Liu Y, Xu K, Xiang Y, Ma B, Li H, Li Y, et al. Bai Y. Role of Mcp-1 as an Inflammatory Biomarker in Nephropathy. Front Immunol. 2023 14:1303076.
34. Guimarães JAR, Furtado SDC, Lucas A, Mori B, Barcellos JFM. Diagnostic Test Accuracy of Novel Biomarkers for Lupus Nephritis-an Overview of Systematic Reviews. PLoS ONE. 2022;17(10): e0275016.
35. Lee YH, Song GG. Urinary MCP-1 as a biomarker for lupus nephritis: a meta-analysis. Z Rheumatol. 2017;76(4):357–63.
36. Xia YR, Li QR, Wang JP, Guo HS, Bao YQ, Mao YM, et al. Ye DQ. Diagnostic Value of Urinary Monocyte Chemoattractant Protein-1 in Evaluating the Activity of Lupus Nephritis: A Meta-Analysis. Lupus. 2020;29(6):599–606.
37. Möckel T, Basta F, Weinmann-Menke J, Schwarting A. B Cell Activating Factor (Baff): Structure, Functions, Autoimmunity and Clinical Implications in Systemic Lupus Erythematosus (Sle). Autoimmun Rev. 2021;20(2): 102736.
38. van Heugten MH, Blijdorp CJ, Arjune S, van Willigenburg H, Bezstarosti K, Demmers JAA, et al. Hoorn EJ. Matrix Metalloproteinase-7 in Urinary Extracellular Vesicles Identifies Rapid Disease Progression in Autosomal Dominant Polycystic Kidney Disease. J Am Soc Nephrol. 2024;35(3):321–334.
39. Wang G, Wu L, Su H, Feng X, Shi M, Jin L, et al. Cao W. Association of Urinary Matrix Metalloproteinase 7 Levels with Incident Renal Flare in Lupus Nephritis. Arthritis Rheumatol. 2021;73(2):265–275.
40. Pérez-Arias AA, Méndez-Pérez RA, Cruz C, Zavala-Miranda MF, Romero-Diaz J, Márquez-Macedo SE, et al. Mejía-Vilet JM. The First-Year Course of Urine Mcp-1 and Its Association with Response to Treatment and Long-Term Kidney Prognosis in Lupus Nephritis. Clin Rheumatol. 2023;42(1):83–92.
41. Gupta R, Yadav A, Aggarwal A. Longitudinal Assessment of Monocyte Chemoattractant Protein-1 in Lupus Nephritis as a Biomarker of Disease Activity. Clin Rheumatol. 2016;35(11):2707–14.
42. Phatak S, Chaurasia S, Mishra SK, Gupta R, Agrawal V, Aggarwal A, Misra R. Urinary B Cell Activating Factor (Baff) and a Proliferation-Inducing Ligand (April): Potential Biomarkers of Active Lupus Nephritis. Clin Exp Immunol. 2017;187(3):376–82.
43. Sari S, Cinar S, Yalcinkaya Y, Artim-Esen B, Ozluk Y, Gul A, et al. Inanc M. The Relationship between Serum a Proliferation-Inducing Ligand and B-Cell Activating Factor Levels with Disease Activity and Organ Involvement in Systemic Lupus Erythematosus. Lupus. 2022;31(5):555–564.
44. Das U, Patel R, Guditi S, Taduri G. Correlation between the Clinical Remission and Histological Remission in Repeat Biopsy Findings of Quiescent Proliferative Lupus Nephritis. Lupus. 2021;30(6):876–83.
45. Malvar A, Pirruccio P, Alberton V, Lococo B, Recalde C, Fazini B, et al. Rovin BH. Histologic Versus Clinical Remission in Proliferative Lupus Nephritis. Nephrol Dial Transplant. 2017;32(8):1338–1344.
46. De Rosa M, Azzato F, Toblli JE, De Rosa G, Fuentes F, Nagaraja HN, et al. Rovin BH. A Prospective Observational Cohort Study Highlights Kidney Biopsy Findings of Lupus Nephritis Patients in Remission Who Flare Following Withdrawal of Maintenance Therapy. Kidney Int. 2018;94(4):788–794.
47. Kudose S, Santoriello D, Bomback AS, Stokes MB, D'Agati VD, Markowitz GS. Sensitivity and Specificity of Pathologic Findings to Diagnose Lupus Nephritis. Clin J Am Soc Nephrol. 2019;14(11):1605–15.
48. Lefaucheur C, Louis K, Morris AB, Taupin JL, Nickerson P, Tambur AR, et al. Reed EF. Clinical Recommendations for Posttransplant Assessment of Anti-Hla (Human Leukocyte Antigen) Donor-Specific Antibodies: A Sensitization in Transplantation: Assessment of Risk Consensus Document. Am J Transplant. 2023;23(1):115–132.
49. Hafeez MS, Awais SB, Razvi M, Bangash MH, Hsiou DA, Malik TH, et al. Rana AA. Hla Mismatch Is Important for 20-Year Graft Survival in Kidney Transplant Patients. Transpl Immunol. 2023;80:101861.
50. de Fijter J, Dreyer G, Mallat M, Budde K, Pratschke J, Klempnauer J, et al. Krämer BK. A Paired-Kidney Allocation Study Found Superior Survival with Hla-Dr Compatible Kidney Transplants in the Eurotransplant Senior Program. Kidney Int. 2023;104(3):552–561.
51. Visentin J, Couzi L, Taupin JL. Clinical Relevance of Donor-Specific Antibodies Directed at Hla-C: A Long Road to Acceptance. Hla. 2021;97(1):3–14.
52. Kernig K, Albrecht V, Dräger DL, Führer A, Mitzner S, Kundt G, Hakenberg OW. Predictors of Delayed Graft Function in Renal Transplantation. Urol Int. 2022;106(5):512–7.
53. Tafulo S, Osório E, Mendes C, Liwski R. Complement-Dependent Cytotoxicity Crossmatch in Solid Organ Transplantation: The Gold Standard or Golden History? Hum Immunol. 2024;85(1): 110734.
54. Guillaume N. Improved Flow Cytometry Crossmatching in Kidney Transplantation. Hla. 2018;92(6):375–83.
55. Liwski RS, Greenshields AL, Conrad DM, Murphey C, Bray RA, Neumann J, Gebel HM. Rapid Optimized Flow Cytometric Crossmatch (Fcxm) Assays: The Halifax and Halifaster Protocols. Hum Immunol. 2018;79(1):28–38.
56. Philogene MC, Timofeeva OA, Gimferrer I, Hod-Dvorai R. Assessment of Inter-Laboratory Variability for Flow Cytometric Crossmatch Testing: Lessons Learned from Proficiency Surveys. Hum Immunol. 2025;86(1): 111176.
57. Bouquegneau A, Loheac C, Aubert O, Bouatou Y, Viglietti D, Empana JP, et al. Loupy A. Complement-Activating Donor-Specific Anti-Hla Antibodies and Solid Organ Transplant Survival: A Systematic Review and Meta-Analysis. PLoS Med. 2018;15(5):e1002572.
58. Kim MY, Brennan DC. Therapies for Chronic Allograft Rejection. Front Pharmacol. 2021;12: 651222.
59. Tran JN, Sherwood KR, Mostafa A, Benedicto RV, ElaAlim A, Greenshields A, et al. Lan JH. Novel Alleles in the Era of Next-Generation Sequencing-Based Hla Typing Calls for Standardization and Policy. Front Genet. 2023 14:1282834.
60. Reindl-Schwaighofer R, Heinzel A, Gualdoni GA, Mesnard L, Claas FHJ, Oberbauer R. Novel Insights into Non-Hla Alloimmunity in Kidney Transplantation. Transpl Int. 2020;33(1):5–17.
61. Allison SJ. Mica in Kidney Transplants. Nat Rev Nephrol. 2022;18(5):273.
62. Pearl MH. Clinical Conundrums in Pediatric Kidney Transplantation: What We Know About the Role of Angiotensin Ii Type I Receptor Antibodies in Pediatric Kidney Transplantation and the Path Forward. Pediatr Transplant. 2024;28(3): e14762.
63. Sorohan BM, Baston C, Tacu D, Bucșa C, Țincu C, Vizireanu P, et al. Constantinescu I. Non-Hla Antibodies in Kidney Transplantation: Immunity and Genetic Insights. Biomedicines. 2022;10(7)
64. Mok CC. Con: Cyclophosphamide for the Treatment of Lupus Nephritis. Nephrol Dial Transplant. 2016;31(7):1053–7.
65. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, et al. Cervera R. Immunosuppressive Therapy in Lupus Nephritis: The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide. Arthritis Rheum. 2002;46(8):2121–31.
66. Saxena A, Ginzler EM, Gibson K, Satirapoj B, Santillán AEZ, Levchenko O, et al. Teng YKO. Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 Aurora 2 Clinical Trial. Arthritis Rheumatol. 2024;76(1):59–67.

67. Busque S, Cantarovich M, Mulgaonkar S, Gaston R, Gaber AO, Mayo PR, et al. Meier-Kriesche HU. The Promise Study: A Phase 2b Multicenter Study of Voclosporin (Isa247) Versus Tacrolimus in De Novo Kidney Transplantation. Am J Transplant. 2011;11(12):2675–84.
68. Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, et al. Huizinga RB. Efficacy and Safety of Voclosporin Versus Placebo for Lupus Nephritis (Aurora 1): A Double-Blind, Randomised, Multicentre, Placebo-Controlled, Phase 3 Trial. Lancet. 2021;397(10289):2070–2080.
69. Heo YA. Voclosporin: First Approval. Drugs. 2021;81(5):605–10.
70. Dall'Era M, Kalunian K, Solomons N, Truman M, Hodge LS, Yap E, Askanase AD. Comparison of a Voclosporin-Based Triple Immunosuppressive Therapy to High-Dose Glucocorticoid-Based Immunosuppressive Therapy: A Propensity Analysis of the Aura-Lv and Aurora 1 Studies and Alms. Lupus Sci Med. 2024;11(2).
71. Fanouriakis A, Kostopoulou M, Andersen J, Aringer M, Arnaud L, Bae SC, et al. Boumpas DT. Eular Recommendations for the Management of Systemic Lupus Erythematosus: 2023 Update. Ann Rheum Dis. 2024;83(1):15–29.
72. Jourde-Chiche N, Costedoat-Chalumeau N, Baumstarck K, Loundou A, Bouillet L, Burtey S, et al. Daugas E. Weaning of Maintenance Immunosuppressive Therapy in Lupus Nephritis (Win-Lupus): Results of a Multicentre Randomised Controlled Trial. *Ann Rheum Dis*. 2022 Oct;81(10):1420–1427.
73. Zanetti CB, Pedrosa T, Kupa LVK, Aikawa NE, Borba EF, Vendramini MBG, et al. Bonfa E. Hydroxychloroquine Blood Levels in Stable Lupus Nephritis under Low Dose (2–3 Mg/Kg/Day): 12-Month Prospective Randomized Controlled Trial. *Clin Rheumatol*. 2021 Jul;40(7):2745–2751.
74. Zhang X, Feng R, Shao M, Wang Y, Sun X, He J. Low-Dose Interleukin-2 as an Alternative Therapy for Refractory Lupus Nephritis. Rheumatol Ther. 2021Dec;8(4):1905–14.
75. He J, Zhang R, Shao M, Zhao X, Miao M, Chen J, et al. Li Z. Efficacy and Safety of Low-Dose Il-2 in the Treatment of Systemic Lupus Erythematosus: A Randomised, Double-Blind, Placebo-Controlled Trial. *Ann Rheum Dis*. 2020 Jan;79(1):141–149.
76. Jin X, Ding C. Belimumab–an Anti-Blys Human Monoclonal Antibody for Rheumatoid Arthritis. Expert Opin Biol Ther. 2013Feb;13(2):315–22.
77. Furie R, Rovin BH, Houssiau F, Contreras G, Teng YKO, Curtis P, et al. Roth DA. Safety and Efficacy of Belimumab in Patients with Lupus Nephritis: Open-Label Extension of Bliss-Ln Study. *Clin J Am Soc Nephrol*. 2022 Nov;17(11):1620–1630.
78. Rovin BH, Furie R, Teng YKO, Contreras G, Malvar A, Yu X, et al. Roth DA. A Secondary Analysis of the Belimumab International Study in Lupus Nephritis Trial Examined Effects of Belimumab on Kidney Outcomes and Preservation of Kidney Function in Patients with Lupus Nephritis. *Kidney Int*. 2022 Feb;101(2):403–413.
79. Anders HJ, Furie R, Malvar A, Zhao MH, Hiromura K, Weinmann-Menke J, et al. Rovin BH. Effect of Belimumab on Kidney-Related Outcomes in Patients with Lupus Nephritis: Post Hoc Subgroup Analyses of the Phase 3 Bliss-Ln Trial. *Nephrol Dial Transplant*. 2023 Nov 30;38(12):2733–2742.
80. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Appel G. Efficacy and Safety of Rituximab in Patients with Active Proliferative Lupus Nephritis: The Lupus Nephritis Assessment with Rituximab Study. *Arthritis Rheum*. 2012 Apr;64(4):1215–26.
81. Atisha-Fregoso Y, Malkiel S, Harris KM, Byron M, Ding L, Kanaparthi S, et al. Dall'Era M. Phase Ii Randomized Trial of Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis. *Arthritis Rheumatol*. 2021 Jan;73(1):121–131.
82. Rovin BH, Furie RA, Ross Terres JA, Giang S, Schindler T, Turchetta A, et al. Malvar A. Kidney Outcomes and Preservation of Kidney Function with Obinutuzumab in Patients with Lupus Nephritis: A Post Hoc Analysis of the Nobility Trial. *Arthritis Rheumatol*. 2024 Feb;76(2):247–254.
83. Qayyum S, Shahid K. Comparative Safety and Efficacy of Immunosuppressive Regimens Post-Kidney Transplant: A Systematic Review. Cureus. 2023Aug;15(8): e43903.
84. Araya AA, Tasnif Y. Tacrolimus. [Updated 2023 May 29]. In: StatPearls. Treasure Island: StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544318/.
85. González CC, López-Jiménez V, Vázquez-Sánchez T, Vázquez-Sánchez E, Cabello M, Hernández-Marrero D. Efficacy and Safety of Eculizumab in Kidney Transplant Patients with Primary Atypical Hemolytic-Uremic Syndrome. Transplant Proc. 2022;54(1):25–26.
86. Woodle ES, Kaufman DB, Shields AR, Leone J, Matas A, Wiseman A, et al. Alloway RR. Belatacept-Based Immunosuppression with Simultaneous Calcineurin Inhibitor Avoidance and Early Corticosteroid Withdrawal: A Prospective, Randomized Multicenter Trial. Am J Transplant. 2020;20(4):1039–1055.
87. Grinyó JM, Del Carmen Rial M, Alberu J, Steinberg SM, Manfro RC, Nainan G, et al. Kamar N. Safety and Efficacy Outcomes 3 Years after Switching to Belatacept from a Calcineurin Inhibitor in Kidney Transplant Recipients: Results from a Phase 2 Randomized Trial. Am J Kidney Dis. 2017;69(5):587–594.
88. Budde K, Prashar R, Haller H, Rial MC, Kamar N, Agarwal A, et al. Vincenti F. Conversion from Calcineurin Inhibitor- to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients: A Randomized Phase 3b Trial. J Am Soc Nephrol. 2021;32(12):3252–3264.
89. Kitchens WH, Larsen CP, Badell IR. Costimulatory Blockade and Solid Organ Transplantation: The Past, Present, and Future. Kidney Int Rep. 2023;8(12):2529–45.
90. Budde K, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Pietruck F. Everolimus-Based, Calcineurin-Inhibitor-Free Regimen in Recipients of De-Novo Kidney Transplants: An Open-Label, Randomised, Controlled Trial. Lancet. 2011;377(9768):837–47.
91. Walsh C, Barkun J, Tchervenkov J, Deschenes M, Ghali P, Wong P, et al. Cantarovich M. Anti-Cd25 Monoclonal Antibody Replacement Therapy for Chronic Kidney Disease in Liver Transplant Recipients. Transplantation. 2013;95(3):495–500.
92. Kokosi M, Lams B, Agarwal S. Systemic Lupus Erythematosus and Antiphospholipid Antibody Syndrome. Clin Chest Med. 2019;40(3):519–29.
93. Kotzen ES, Roy S, Jain K. Antiphospholipid Syndrome Nephropathy and Other Thrombotic Microangiopathies among Patients with Systemic Lupus Erythematosus. Adv Chronic Kidney Dis. 2019;26(5):376–86.
94. Morales JM, Martinez-Flores JA, Serrano M, Castro MJ, Alfaro FJ, García F, et al. Serrano A. Association of Early Kidney Allograft Failure with Preformed Iga Antibodies to **B**2-Glycoprotein I. J Am Soc Nephrol. 2015;26(3):735–45.
95. Morales JM, Serrano M, Martinez-Flores JA, Perez D, Serrano A. Antiphospholipid Syndrome and Renal Allograft Thrombosis. Transplantation. 2019;103(3):481–6.
96. Furmańczyk-Zawiska A, Bułło-Piontecka B, Komorniczak M, Dębska-Ślizień A, Augustyniak-Bartosik H, Durlik M. Antiphospholipid Syndrome in Renal Allograft Recipients-a Long-Term Multicenter Analysis. J Clin Med. 2023;12(2).
97. Suenaga A, Sawa N, Miki K, Yokoyama T, Ishii Y, Mizuno H, et al. Ubara Y. Antiphospholipid Syndrome Nephropathy with Acute Thrombotic Microangiopathy after Renal Transplantation. Intern Med. 2023;62(18):2707–2713.
98. Albuquerque BC, Salles VB, Tajra RDP, Rodrigues CEM. Outcome and Prognosis of Patients with Lupus Nephritis Submitted to Renal Transplantation. Sci Rep. 2019;9(1):11611.
99. Agrawal A, Ison MG, Danziger-Isakov L. Long-Term Infectious Complications of Kidney Transplantation. Clin J Am Soc Nephrol. 2022;17(2):286–95.
100. Ness D, Olsburgh J. Uti in Kidney Transplant. World J Urol. 2020;38(1):81–8.
101. Tsai WT, Chang HC, Wang CT, Chiang BL, Lin YT. Long-Term Outcomes in Lupus Patients Receiving Different Renal Replacement Therapy. J Microbiol Immunol Infect. 2019;52(4):648–53.
102. Brennan DC. Introduction: Kidney Transplantation and Viral Infection. Semin Nephrol. 2016;36(5):343.
103. Kant S, Dasgupta A, Bagnasco S, Brennan DC. Bk Virus Nephropathy in Kidney Transplantation: A State-of-the-Art Review. Viruses. 2022;14(8).
104. Večerić-Haler Ž, Bizjak B, Romozi K, Arnol M. Expanded Valganciclovir Prophylaxis in Kidney Transplant Recipients Is Associated with Lower Incidence of Cytomegalovirus Infection. Clin Nephrol. 2017 Supplement 1;88(13):126–130.
105. Reischig T, Vlas T, Kacer M, Pivovarcikova K, Lysak D, Nemcova J, et al. Kormunda S. A Randomized Trial of Valganciclovir Prophylaxis Versus

Preemptive Therapy in Kidney Transplant Recipients. J Am Soc Nephrol. 2023;34(5):920–934.
106. Nolte Fong JV, Moore LW. Nutrition Trends in Kidney Transplant Recipients: The Importance of Dietary Monitoring and Need for Evidence-Based Recommendations. Front Med (Lausanne). 2018;5:302.
107. Liu Y, Tan RS, Zhou DY, Xiao X, Ran JM, Qin DP, et al. Zheng YY. The Effects of Protein Intake on Albuminuria in Different Estimated Glomerular Filtration Rate: A Population-Based Study. Eur J Intern Med. 2018;48:80–88.
108. Jhee JH, Kee YK, Park S, Kim H, Park JT, Han SH, et al. Yoo TH. High-Protein Diet with Renal Hyperfiltration Is Associated with Rapid Decline Rate of Renal Function: A Community-Based Prospective Cohort Study. Nephrol Dial Transplant. 2020;35(1):98–106.
109. Narasaki Y, Okuda Y, Moore LW, You AS, Tantisattamo E, Inrig JK, et al. Rhee CM. Dietary Protein Intake, Kidney Function, and Survival in a Nationally Representative Cohort. Am J Clin Nutr. 2021;114(1):303–313.
110. Lim MA, Bloom RD. How to Maximize Graft Survival. Curr Opin Organ Transplant. 2023;28(1):55–63.
111. Loutradis C, Sarafidis P, Marinaki S, Berry M, Borrows R, Sharif A, Ferro CJ. Role of Hypertension in Kidney Transplant Recipients. J Hum Hypertens. 2021;35(11):958–69.
112. Di Cocco P, Okoye O, Almario J, Benedetti E, Tzvetanov IG, Spaggiari M. Obesity in Kidney Transplantation. Transpl Int. 2020;33(6):581–9.
113. Quero M, Montero N, Rama I, Codina S, Couceiro C, Cruzado JM. Obesity in Renal Transplantation. Nephron. 2021;145(6):614–23.
114. Wissing KM, Pipeleers L. Obesity, Metabolic Syndrome and Diabetes Mellitus after Renal Transplantation: Prevention and Treatment. Transplant Rev (Orlando). 2014;28(2):37–46.
115. Stone JH, McDowell PJ, Jayne DRW, Merkel PA, Robson J, Patel NJ, et al. Heaney LG. The Glucocorticoid Toxicity Index: Measuring Change in Glucocorticoid Toxicity over Time. Semin Arthritis Rheum. 2022;55:152010.
116. Contreras G, Mattiazzi A, Guerra G, Ortega LM, Tozman EC, Li H, et al. Roth D. Recurrence of Lupus Nephritis after Kidney Transplantation. J Am Soc Nephrol. 2010;21(7):1200–7.
117. Horta-Baas G, Camargo-Coronel A, Miranda-Hernández DG, Gónzalez-Parra LG, Romero-Figueroa MDS, Pérez-Cristóbal M. Renal Transplantation in Systemic Lupus Erythematosus: Comparison of Graft Survival with Other Causes of End-Stage Renal Disease. Reumatol Clin (Engl Ed). 2019;15(3):140–145. Trasplante renal en lupus eritematoso sistémico: comparación de la supervivencia del injerto con otras causas de enfermedad renal terminal.
118. Norby GE, Strøm EH, Midtvedt K, Hartmann A, Gilboe IM, Leivestad T, et al. Holdaas H. Recurrent Lupus Nephritis after Kidney Transplantation: A Surveillance Biopsy Study. Ann Rheum Dis. 2010;69(8):1484–7.
119. Vale P, Quinino R, Costa K, Júnior T, Araújo S, Fechine L, Cunha R. Post-Transplant Lupus Nephritis Recurrence: A Case Report and Review of the Literature. Transplant Proc. 2019;51(5):1614–7.
120. Lightstone L, Hladunewich MA. Lupus Nephritis and Pregnancy: Concerns and Management. Semin Nephrol. 2017;37(4):347–53.
121. Campise M, Giglio E, Trespidi L, Messa P, Moroni G. Pregnancies in Women Receiving Renal Transplant for Lupus Nephritis: Description of Nine Pregnancies and Review of the Literature. Lupus. 2015;24(11):1210–3.
122. Shinzato T, Shimizu T, Iwami D, Fukushima N, Tabata K. Recurrent Lupus Nephritis in Renal Allograft Triggered by Pregnancy. CEN Case Rep. 2022;11(2):237–41.
123. Jiang Y, Tao M, Chen J, Luo L, You Q, Wu H, Zhang N. Calcineurin Inhibitors in the Treatment of Systemic Lupus Erythematosus During Pregnancy: A Narrative Review with Emphasis on Efficacy and Safety. Eur J Obstet Gynecol Reprod Biol. 2024;294:148–55.
124. Silver R, Craigo S, Porter F, Osmundson SS, Kuller JA, Norton ME. Society for Maternal-Fetal Medicine Consult Series #64: Systemic Lupus Erythematosus in Pregnancy. Am J Obstet Gynecol. 2023;228(3):B41-b60.
125. Merlob P, Stahl B, Klinger G. Tetrada of the Possible Mycophenolate Mofetil Embryopathy: A Review. Reprod Toxicol. 2009;28(1):105–8.
126. Fischer-Betz R, Specker C, Brinks R, Aringer M, Schneider M. Low Risk of Renal Flares and Negative Outcomes in Women with Lupus Nephritis Conceiving after Switching from Mycophenolate Mofetil to Azathioprine. Rheumatology (Oxford). 2013;52(6):1070–6.
127. de Azevedo FVA, Maia DG, de Carvalho JF, Rodrigues CEM. Renal Involvement in Antiphospholipid Syndrome. Rheumatol Int. 2018;38(10):1777–89.
128. Sciascia S, Cuadrado MJ, Khamashta M, Roccatello D. Renal Involvement in Antiphospholipid Syndrome. Nat Rev Nephrol. 2014;10(5):279–89.
129. Irish GL, Jesudason S. Case Study of Tacrolimus as an Effective Treatment for Idiopathic Membranous Glomerulonephritis in Pregnancy. Obstet Med. 2020;13(3):148–50.
130. Pastore DEA, Costa ML, Surita FG. Systemic Lupus Erythematosus and Pregnancy: The Challenge of Improving Antenatal Care and Outcomes. Lupus. 2019;28(12):1417–26.

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