Management recommendations for kidney transplantation in patients with plasma cell dyscrasia

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Patients with plasma cell dyscrasia, including multiple myeloma, AL amyloidosis, and monoclonal gammopathy of renal significance, face a high burden of end-stage kidney disease, which limits survival and quality of life. Although kidney transplant offers potential benefits, it remains underused because of the high risk of recurrence and historically poor outcomes. A multidisciplinary panel of transplant nephrologists, hematologists/oncologists, and pathologists convened to evaluate contemporary evidence and evolving strategies in kidney transplant for plasma cell dyscrasias and end-stage kidney disease. Advances in plasma cell dyscrasia therapies are improving survival and expanding kidney transplant eligibility. However, key challenges remain, including optimizing hematologic response pre–kidney transplant and managing immunosuppression to mitigate recurrence and avoid infection complications. Ongoing research and multidisciplinary collaboration are essential to refine transplant selection, integrate biomarkers for risk stratification, and develop tailored post–kidney transplant surveillance. These efforts may increase access to kidney transplant and improve outcomes for patients with plasma cell dyscrasia and end-stage kidney disease.

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Kidney disease is common in patients with plasma cell dyscrasia (PCD), such as multiple myeloma (MM), AL amyloidosis, and monoclonal gammopathy of renal significance, many of whom progress to end-stage kidney disease (ESKD). Historically, patients with PCD have been excluded from kidney transplant candidacy because of concerns about limited life expectancy and the risk of disease recurrence and progression (Figure 1). Recent therapeutic advances in PCD have remarkably improved hematologic responses, resulting in unprecedented overall survival. These improvements have shifted the risk-benefit ratio for kidney transplant in patients with PCD and ESKD.

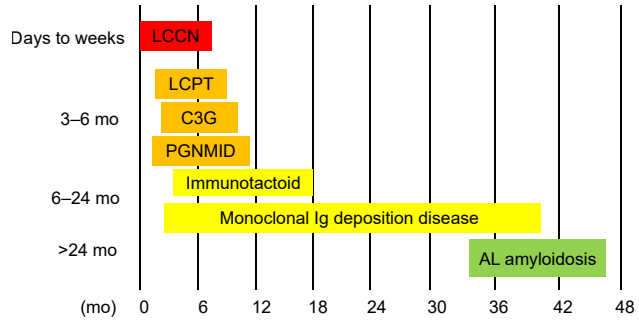


Figure 1 | Timing of recurrence of various plasma cell dyscrasias in kidney transplant allograft. C3G, C3 glomerulopathy; LCCN, light chain cast nephropathy; LCPT, light chain proximal tubulopathy; mo, month; PGNMID, proliferative glomerulitis with Ig deposit.

A multidisciplinary panel of experts, including transplant nephrologists, hematologists, renal pathologists, and infectious disease specialists, discussed the feasibility and challenges of kidney transplantation for patients with PCD over the course of a year. Meetings included the International Kidney and Monoclonal Gammopathy Research Group meeting in May 2024, the Inaugural Symposium on Kidney Transplantation in Plasma Cell Disorders meeting in September 2024, and regular meetings of the Kidney and Pancreas Community of Practice Transplant Onconephrology workgroup of American Society of Transplantation. In this meeting report, we summarize our recommendations regarding the management of PCD before and after kidney transplant based on the available literature and expert opinion.

Multiple myeloma

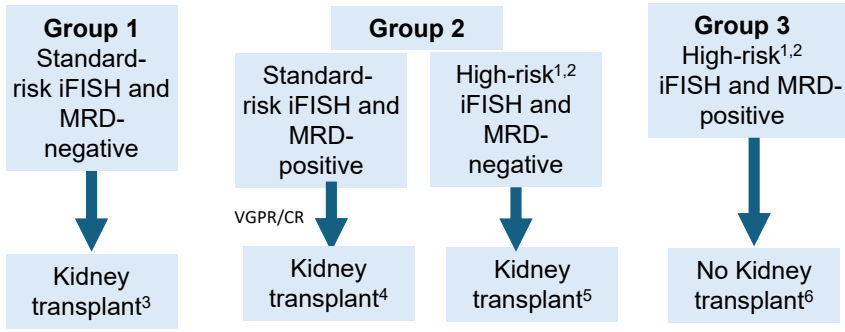
A 64-year-old man was diagnosed with IgG kappa MM. At his initial presentation, serum creatinine was 4.8 mg/dl, with 6 g of Bence-Jones protein on a 24-hour urine assessment, and he required hemodialysis for light chain cast nephropathy. Bone marrow biopsy showed 30% kappa-restricted plasma cells with no high-risk cytogenetics. After plasma cell–targeted therapies, he achieved a very good partial response (VGPR) but remained dialysis dependent. What assessment should be done to evaluate his kidney transplant candidacy?

Early experiences in the 1980s and 1990s in kidney transplant recipients with MM were poor, partly because of low disease response rates. The past decade has seen a remarkable improvement in treatment options and disease response, requiring a reevaluation of kidney transplantat as an option in patients with MM and advanced chronic kidney disease (eGFR <20 ml/min per 1.73 m^2). Autologous stem cell transplantation (ASCT) after quadruplet induction regimens has significantly improved clinical outcomes.[1–4] Modern therapy results in high rates of complete response (CR), extending progression-free survival to >6 years.[5] Kidney involvement occurs in 50% of patients with MM, and ESKD in this population is associated with worse survival compared with non-ESKD, suggesting that ESKD could be a life-limiting complication rather than MM itself.[5] Recent data indicate improved kidney transplant outcomes in selected patients with MM. Analysis of United Network for Organ Sharing data from 2006–2018 suggests a recurrence risk of MM of up to 30% post–kidney transplant but the allograft survival rate was 60% at 5 years post-transplant.[6] With improved overall and disease outcomes, selected patients with MM may undergo successful kidney transplant, with caution warranted because of an increased risk of infection.[7]

Pretransplant evaluation for patients with MM. Although patients with MM and ESKD have suboptimal outcomes on dialysis, available data guide critical decisions regarding pretransplant evaluation, focusing on disease characteristics[8] (Figure 2), in addition to center-based selection criteria based on frailty and comorbidities. Special attention should be paid to the risk of infection and performance status in this population.[9]

MM risk assessment for pre–kidney transplant evaluation. MM risk assessment is essential in determining kidney transplant candidacy. The major disease-related factors that determine prognosis in MM include the presence of (i) high-risk cytogenetic abnormalities, (ii) extramedullary disease, and (iii) the depth and duration of disease response after therapy. Unlike solid cancers, where a defined cancer-free waiting time before active listing is recommended, MM relapse is inevitable during follow-up. The goal of kidney transplant for patients with MM is to achieve the longest relapse-free and dialysis-free survival.

In 2024, a refined definition of high-risk disease was adopted by the International Myeloma Working Group[5,10] (Figure 2). High-risk cytogenetics and extramedullary disease are associated with a higher risk of relapse and a poor prognosis[11] and thus are considered high risk for kidney transplantation (Figure 2). Standard-risk patients who achieve a VGPR or CR after therapy are considered to have acceptable disease control and may proceed to kidney transplant without delay, irrespective of whether clonal disease control was achieved with quadruplet therapy or ASCT. However, high-risk patients benefit from more stringent and durable disease control before considering kidney transplant. More specifically, achieving undetectable minimal residual disease at a level of 1 tumor plasma cell in 100,000 (10^{-5}) or 1 million (10^{-6}) is reassuring, as it is associated with significantly longer progression-free and overall survival,[12] whether in the first-line setting or at relapse, especially if sustained for at least 6 months.[13,14] In high-risk patients, ASCT is associated with the highest likelihood of achieving deep remission.[15] However, ASCT is not a prerequisite for kidney transplantation, and it is reasonable to collect and cryopreserve stem cells for future use in patients who have an unfavorable risk-benefit ratio with high-dose therapy. With or without ASCT, a sustained response for at least 6 months should be documented before proceeding to kidney transplantation in the subset of patients who are at increased risk of relapse.



1. High-risk category is defined as 1 of the following: Having high-risk cytogenetics (below), high β_2-microglobulin (>5.5 mg/dl) with a normal creatinine (<1.2 mg/dl), extramedullary disease, or plasma cells clones in circulation at diagnosis.
2. High-risk cytogenetics (iFISH or NGS): Deletion (del) (17p) in >20% CD38+ plasma cells and/or TP53 mutation, monoallelic del (1p32), along with +1q, or biallelic del (1p32). One of the translocations: t(4;14), t(14;16), or t(14;20), which must co-occur with +1q or del(1p32).
3. In standard-risk, MRD-negative (10e-5 or 10e-6, depending on availability) MM patient, kidney transplant can be considered within 6 mo of achieving a hematologic response.*
4. In standard-risk, MRD-positive MM patient, kidney transplant can be considered 12 mo after achieving a VGPR/CR, but consider continuing/maintenance therapy.*
5. In high-risk, MRD-negative MM patient, kidney transplant can be considered 12–24 mo of achieving a hematologic response, but recommend continuing/maintenance therapy.*
6. High-risk patients who remain MRD-positive are not considered optimal kidney transplant candidates but could be considered in selected circumstances

*Contingent on overall transplant candidacy and availability of a living donor.

Figure 2 | Decision tree for patients with multiple myeloma (MM) and end-stage kidney disease based on risk category and response to therapy. CR, complete response; iFISH, interphase fluorescence *in situ* hybridization; MRD, minimal residual disease; NGS, next generation sequence; VGPR, very good partial response.

With treatment for MM rapidly evolving, patients who require multiple lines of therapy before achieving a VGPR or CR may cautiously proceed with kidney transplant but may require maintenance therapy. In the first-line or relapsed setting, it is also crucial to discuss available salvage therapy options in case of myeloma relapse post–kidney transplant.

Proposed management of MM peri– and post–kidney transplant. Pre–kidney transplant management of MM requires coordinated care by hematology/oncology and kidney transplant teams (Table 1). Based on the critical nature of timing, transplant from a living donor is optimal. Having a planned surgery allows plasma cell–directed therapies to be held in advance of the procedure to reduce the risk of complications. Kidney transplant from a deceased donor is more complex to manage but is feasible if patients are expected to receive an offer within 1–2 years while in remission during yearly evaluations.[8] To avoid complications (e.g., cytopenia, infection, and thrombosis), immunomodulatory drugs (IMiDs) should be held for 4 weeks and proteasome inhibitors and daratumumab should be held for 2 weeks before living donor kidney transplant. Maintenance therapy for MM can be restarted after kidney transplant, as clinically indicated. However, clinicians should be aware of the risk of acute rejection and thrombosis due to IMiDs.[16,17] Whether rejection results from a specific effect of IMiDs[18] or from reduction of immunosuppression is undetermined, but especially for patients without living donors, IMiD maintenance[19–21] should be carefully considered. For patients on IMiD maintenance, enhanced thromboprophylaxis post-transplant with aspirin should be considered (Table 1). Disease monitoring should be continued post–kidney transplant, including serum free light chain (sFLC) measurement and serum protein electrophoresis/immunofixation (SPEP/IFX) monitoring every 3 months. Kidney biopsy would be considered when clinically indicated, usually for worsening urine protein-creatinine ratio and decrease in estimated glomerular filtration rate (eGFR).

Immunosuppression regimens for induction and maintenance require special consideration. The choice of induction immunosuppression can follow the center's standard

Table 1 | Proposed management of MM peri–kidney transplant

Pre–kidney transplant requirement
1. Confirm candidacy on the basis of selection criteria (Figure 2).
2. Avoid positive crossmatch and ABO-incompatible transplant, if possible.
3. LDKTx: BM assessment within 3 mo and sFLC within 4 wk of transplant.
4. DDKTx: BM assessment within 6 mo and sFLC within 3 mo of transplant.
5. Hematologic assessment (sFLC and SPEP/IFX) every 3 mo while on the waiting list.
6. Hold IMiD 4 wk and PIs/Dara 2 wk before transplantation, if possible.
Post–kidney transplant management
1. Induction therapy as per transplant center.
2. Consider thromboprophylaxis (e.g., starting aspirin as early as postoperative day 2) for patients on IMiD receiving a deceased kidney transplant.
3. Maintenance immunosuppression as per transplant center.
4. Maintenance therapy for MM: Initiate maintenance as indicated, typically 2–3 wk after kidney transplant.
5. MM surveillance with SPEP and sFLC: Every 3 mo.
6. Protocol allograft biopsy not required but could be considered.
7. Recurrence or relapse of MM: Salvage therapy by the hematology team.
8. Consider reducing the antimetabolite dose by 50% at the time of introduction of MM maintenance therapy and in case of cytopenia.

BM, bone marrow; Dara, daratumumab; DDKTx, deceased donor kidney transplant; IFX, immunofixation; IMiD, immunomodulatory drug; LDKTx, living donor kidney transplant; MM, multiple myeloma; PI, proteasome inhibitor; sFLC, serum free light chain; SPEP, serum protein electrophoresis.

practice, but maintenance antimetabolite agents (e.g., mycophenolate) could be reduced by 50% in cases of cytopenia. Plasma cell–directed therapies, ASCT, chimeric antigen receptor T (CAR-T) cells, and bispecific T-cell engagers (BiTEs) before kidney transplantation increase the risks of infectious complications and secondary myeloid and non-myeloid neoplasms.[22] More data are needed to make recommendations regarding reduction of immunosuppression post–kidney transplant, infection prophylaxis, and cancer surveillance in patients exposed to these therapies.

AL amyloidosis

A 56-year-old woman was diagnosed with AL lambda amyloidosis. At her initial presentation, serum creatinine was 2.5 mg/dl with proteinuria of 8 g/24 h. She had no cardiac involvement. She began bortezomib-based therapy and was being considered for high-dose melphalan and ASCT in the future. What depth of hematologic response is necessary, and is it required to wait before being considered for kidney transplant after completion of first-line therapy?

Historically, kidney transplant for patients with AL amyloidosis was limited by high rates of infection, recurrence, and early deaths.[23] However, outcomes for AL amyloidosis have improved with novel therapies, especially with the approval of daratumumab-based induction therapy.[24]

Pretransplant evaluation for patients with AL amyloidosis. Growing data suggest slow recurrence and reasonable kidney allograft and patient survival for patients with AL amyloidosis. Four large single-center studies from Mayo Clinic,[25] Boston University Amyloidosis Center,[26] Memorial Sloan Kettering,[27] and the UK National Amyloidosis Centre[28] combined account for 176 patients (Table 2). Cardiac involvement, ASCT, and living donor kidney transplant rates vary among these studies, but overall post-transplant outcomes are encouraging. Median overall survival ranged from 7.9 to 13.1 years. One-, 3-, and 5-year survival ranged from 93% to 96%, from 84% to 91%, and from 66% to 87%, respectively. One- and 5-year death-adjusted renal allograft survival ranged from 94% to 98% and from 81% to 96%, respectively. Acute rejection was reported between 0% and 23% in 2 studies. Recurrence was reported in 14%–29% of patients at a median time of 3.7–10.1 years. This is longer compared to other types of monoclonal Ig–related kidney lesions (Figure 1). Graft loss due to recurrence of AL amyloidosis was low. Analysis of all 4 studies found that achievement of a hematologic VGPR or better was associated with improved overall and allograft survival as well as a decreased risk of recurrence. Although time to recurrence was longer in patients with a CR, no significant difference in overall or allograft survival was identified compared with those with a VGPR. Aside from a VGPR or better hematologic response, 1 study found that interventricular septal thickness >12 mm on echocardiography was associated with poorer survival.[28] ASCT was not associated with better outcomes when adjusted for a hematologic response. Because of the slow time to recurrence, 1 study found that outcomes of treatment-naive patients were similar to those who were treated before

Table 2| Summary of key cohort studies of AL amyloidosis and kidney transplantation

Studies	Study years	Cardiac involvement, %	HSCT, %	Living donor tx, %	mOS, yr	Allograft survival, yr	Recurrence, %, estimated time, yr	Prognosis factors
Mayo Clinic ($N = 60$)	1997–2018	47	60	80	10.3	NR	22, 10.2	CR/VGPR: longer mOS
BU Amyloidosis Center ($N = 49$)	1987–2017	33	80	65	10.5	8.3	29, 3.7	CR/VGPR: longer mOS and lower recurrence
Memorial Sloan Kettering ($N = 16$)	1999–2018	25	100	87	13.1	11.3	25, ND	ND
UK National Amyloidosis Centre ($N = 51$)	1989–2018	22	24	41	7.9	NR	14, 4.5	CR: improved mOS, IVSd >12 mm: worse mOS and higher recurrence
IKMG multicenter study ($N = 237$)	1987–2020	41	62	54	8.6	7.8	29, 6.6	CR/VGPR: longer mOS, lower recurrence, and longer allograft survival

BU, Boston University; CR, complete response; HSCT, hematopoietic stem cell transplant; IKMG, International Kidney and Monoclonal Gammopathy Research Group; IVSd, interventricular septal diameter; mOS, median overall survival; ND, not described; NR, not reached; tx, transplant; VGPR, very good partial response.

kidney transplant as long as they achieved a VGPR or better after the kidney transplant.[25] In a larger multinational study of 237 patients,[29] the results were very similar, with a median overall survival after kidney transplant of 8.6 years and allograft survival of 7.8 years, respectively (Table 2). A study using the Organ Procurement and Transplantation Network (OPTN) found improved patient and allograft survival in kidney recipients with amyloidosis over the period of 2002–2021, acknowledging that OPTN data do not distinguish AL from AA amyloidosis.[30] The study also showed that patient survival did not significantly differ between recipients with amyloidosis and those with diabetes, consistent with previous studies.[6,31] Nonetheless, allograft survival and 12-month eGFR post-transplant were lower in recipients with amyloidosis than in those with other causes of ESKD.

Overall, patients with AL amyloidosis with adequate cardiac function should proceed with kidney transplant when a hematologic VGPR or better is achieved. However, hemodynamic risks such as autonomic involvement, profound hypotension, and gastrointestinal bleeding due to AL amyloidosis should be carefully evaluated. There is no need to postpone kidney transplant once an optimal hematologic response is achieved because the risk of hematologic progression is low in patients with AL amyloidosis.[24]

Proposed management of AL amyloidosis peri– and post–kidney transplant. Maintenance therapies for AL amyloidosis could be continued until 2–4 weeks before a living donor kidney transplant and held in the peritransplant period to avoid cytopenia. A pre–kidney transplant regimen without an IMiD is ideal to mitigate the risk of perioperative thrombosis and acute rejection. There are no data to suggest an optimal induction or maintenance immunosuppression regimen, but clinicians can consider reducing antimetabolites to avoid overimmunosuppression. sFLC, SPEP/IFX, and urinary protein-to-creatinine ratio should be assessed every 3 months post-transplant to monitor recurrence of AL amyloidosis.

Treatment of recurrence relies on bortezomib-based regimens, whose tolerance is acceptable. Repeat ASCT has also been successful.[26] Other options such as daratumumab, venetoclax, and T cell–redirecting therapies could also be considered. Achievement of a deep hematologic response is common, which may explain the low rates of allograft loss due to recurrence. Longer-term data are required to assess the impact of daratumumab, other novel therapies, and maintenance strategies after kidney transplantation.

Monoclonal gammopathy of renal significance: focus on proliferative glomerulonephritis with monoclonal Ig deposits and monoclonal Ig–associated C3 glomerulopathy

A 46-year-old man was diagnosed with proliferative glomerulonephritis with monoclonal Ig deposits (PGNMIDs) (IgG3 kappa deposition on kidney biopsy). At his initial presentation, serum creatinine was 1.8 mg/dl with proteinuria of 2.4 g/g creatinine. No clone was detected by SPEP/IFX, sFLC, or bone marrow analysis. He underwent 6 cycles of cyclophosphamide, bortezomib, and dexamethasone treatment but progressed to ESKD requiring hemodialysis. How should he be evaluated for kidney transplant?

Monoclonal gammopathy of renal significance represents a group of disorders caused by monoclonal Ig deposition produced by plasma cell or B-cell clones, without meeting diagnostic criteria for MM or lymphoproliferative disorders.[32]

Pretransplant evaluation for patients with PGNMID and monoclonal Ig–associated C3 glomerulopathy. Unlike other monoclonal Ig–related kidney lesions, in PGNMID, only 30%−35% of patients have detectable plasma cell or B-cell clones in the bone marrow, paraprotein identified by sFLC or SPEP/IFX, or evidence of extramedullary disease on positron emission tomography.[32] In the absence of biochemical or other biomarkers, noninvasive assessment of treatment response is challenging. After kidney transplant, recurrence occurs frequently (80%−85%) and rapidly (3–6 months post-transplant) (Figure 1).[32–35] In those with measurable disease, disease control is essential before proceeding to kidney transplant. Although only limited data exist on the duration and depth of response before kidney transplant, experts recommend clone-directed therapies for B cells and/or plasma cells,[36] with the use of cyclophosphamide, bortezomib, and dexamethasone or daratumumab-based combinations in patients with plasma cell clones to achieve a VGPR or better before transplant.[37] Similarly, patients with monoclonal Ig–associated C3 glomerulopathy should undergo clone-directed therapy before kidney transplant. As it is challenging to assess disease response in patients without detectable culprit clones, some experts suggest treating empirically with a set regimen (e.g., 6 cycles) of plasma cell– or B cell–targeted therapy before kidney transplant, combined with early post-transplant protocol biopsy, as discussed below (Figure 3).

Proposed management of PGNMID and monoclonal Ig–associated C3 glomerulopathy post–kidney transplant. Because of the high recurrence rate, patient engagement and monitoring for post-transplant recurrence are crucial. In a series of 26 cases, Said *et al.* reported poor allograft survival after recurrence of PGNMID in the allograft but recurrence was likely detected late in this study, which relied on clinically indicated kidney biopsy.[35] Buxeda *et al.* suggested protocol biopsies for the early diagnosis of recurrent PGNMID to facilitate empirical therapy.[38] Their cohort of 20 kidney transplant recipients with PGNMID (2003–2016), most without a detectable clone, underwent protocol biopsies at 4, 12, 24, 60, and 120 months post-transplant. Treatment was initiated if there was clinical or histopathologic evidence of recurrence. Initially, cyclophosphamide was used, but more recently, recurrence was treated with rituximab (2 doses of 1000 mg at a 2-week interval). Using this approach, the rate of death-censored allograft survival was 87% at 5 years, despite histologic recurrence observed in 18 patients (90%), occurring at a median of 7 months (interquartile range: 1–65 months) after transplantation. There were 5 graft failures, but

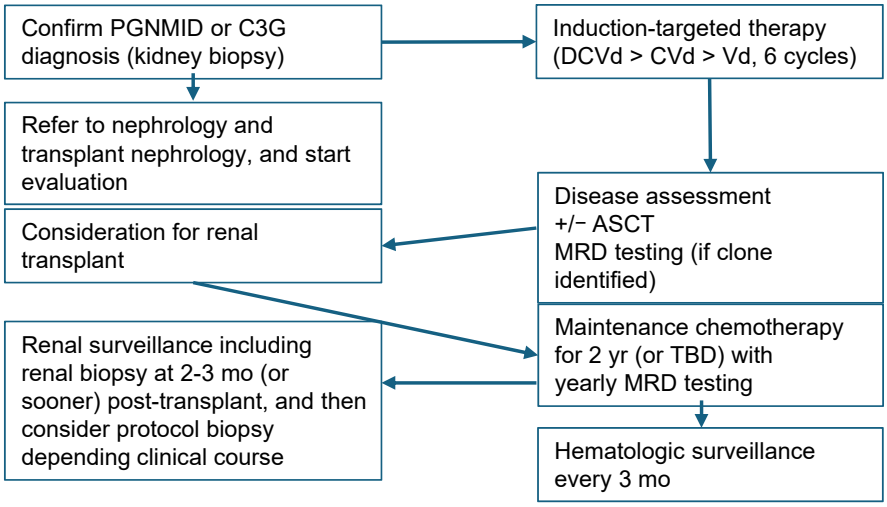


Figure 3 | Algorithm for proliferative glomerulitis with Ig deposits (PGNMIDs) and monoclonal gammopathy–associated C3 glomerulopathy (C3G). ASCT, autologous stem cell transplant; CVd, cyclophosphamide, bortezomib, and dexamethasone; DCVd, daratumumab, cyclophosphamide, bortezomib, and dexamethasone; MRD, minimal residual disease; TBD, to be determined; Vd, bortezomib and dexamethasone.

recurrent PGNMID was responsible in only 3 patients (15%). Many recurrences were diagnosed by protocol biopsies, and most patients had preserved allograft function (eGFR: >30 ml/min per 1.73 m^2) and only low-grade proteinuria (<500 mg/24 h). Allograft loss occurred in 1 untreated patient. In 9 patients treated with rituximab, there was an initial improvement in eGFR and reduction of proteinuria, despite therapy being delayed 5–49 months after the initial diagnosis in 5 patients. Preemptive therapy did not prevent recurrences (3 of 4 patients), although the authors suggested that the post-transplant course was less aggressive in these patients. Daratumumab has also been studied in PGNMID,[37] and similarly to the approach in the ANDROMEDA trial for AL amyloidosis,[24] maintenance daratumumab may be considered to prevent relapses.

Overall, kidney transplant can be considered in patients with PGNMID with careful strategies to monitor and treat post-transplant recurrence, incorporating protocol allograft biopsies (Figure 3). Given the lack of hematologic markers to follow in those without detectable clones, the evaluation of pre- and post-transplant treatment of PGNMID relies on kidney-related markers (eGFR and proteinuria).

Monoclonal Ig–associated C3 glomerulopathy derives from abnormal activation of the complement alternative pathway through antibody activity of monoclonal Ig toward complement regulatory proteins (such as factor H) or other unknown mechanisms.[39] Most patients have an underlying plasma cell clone and detectable serum monoclonal gammopathy. Deep hematologic responses have been shown to predict favorable long-term outcomes[40] and should be achieved before considering kidney transplant in this population. There are little data regarding the results of kidney transplant. The post-transplant recurrence rate appears to be high (55%–86%), occurring within a few weeks to months, and often resulting in allograft loss. In incidental cases, allograft function was maintained after hematologic treatment that resulted in a CR. Still, the outcome is dismal in patients with early recurrence. Protocol biopsies should be considered to detect early recurrence, as early as 3 months, with possible serial protocol kidney biopsies, in addition to routine monitoring of proteinuria, allograft function, and hematologic parameters to initiate appropriate therapy in a timely manner.

For peritransplant management, there are no data on optimal induction or maintenance therapies in patients with PGNMID and monoclonal Ig–associated C3 glomerulopathy but the same precautions should be considered as in other monoclonal Ig–related disorders.

Precursor conditions (monoclonal gammopathy of undermined significance and smoldering multiple myeloma)

A 62-year-old man with ESKD due to presumed hypertension had been on hemodialysis for the past 5 years. The patient had no suitable living kidney donor. During kidney transplant evaluation, he was found to have a serum monoclonal M protein (IgG kappa: 0.5 g/dl; sFLC ratio: 2.4). In addition to the usual evaluation process, what additional workup does he need to be eligible for kidney transplant?

MGUS and SMM are 2 precursor conditions, defined by the presence of an M protein in the serum for MGUS, and in the case of SMM, the same finding with >10% bone marrow plasma cells, but without clinical evidence of end-organ damage[41] (Table 3).

MGUS and SMM carry different risks of disease progression to plasma cell or lymphoid disorders. MGUS progresses to these malignant conditions ~1% annually,[42] with the caveat that data are lacking for kidney transplant recipients who are on long-term immunosuppression. The main risk factors for progression include IgA or IgM (vs.

Table 3 | Diagnosis criteria and risk stratification of MGUS, SMM, and MM

Variables	MGUS			SMM			MM
Serum monoclonal protein	<3 g/dl			>3 g/dl			Any
BMPC, %	<10			10–60			>10
End-organ damage[a]	Absent			Absent			Present
Risk of progression[33–36]	Non-IgM MGUS with risk factors			20–2–20 risk stratification[b]			
	M protein >1.5 g/dl, abnormal FLC ratio			Low risk	Intermediate risk	High risk	NA
	0	1	2	0	1	≥2	
	7% in 20 yr	20% in 20 yr	30% in 20 yr	6% in 2 yr	18% in 2 yr	44% in 2 yr	NA

BMPC, bone marrow plasma cell; FLC, free light chain; MGUS, monoclonal gammopathy with undetermined significance; MM, multiple myeloma; NA, not applicable; sFLC, serum free light chain; SMM, smoldering multiple myeloma.
[a]CRAB criteria: calcium elevation (>11 mg/dl), renal dysfunction (serum creatinine >2 mg/dl or creatinine clearance <40 ml/min), anemia (hemoglobin <10 g/dl, or a >2 g/dl decrease from baseline), bone disease (≥1 osteolytic lesion detected on skeletal radiography, whole-body low-dose computed tomography, or positron emission tomography–computed tomography), or other clinical manifestation.
[b]20–2–20 criteria: BMPC >20%, M protein >2 g/dl, sFLC ratio >20, or high-risk cytogenetics.

IgG) type, an M protein concentration of >1.5 g/dl, and an abnormal sFLC ratio.[43,44] Twenty years after the diagnosis of MGUS, the risk of progression to MM in IgM MGUS is 55%, 41%, and 19% with 2, 1, and 0 other risk factors, respectively. In non-IgM MGUS, the risk of progression is 30%, 20%, and 7%, respectively.

In SMM, the risk of progression is higher, averaging 10% per year for the first 5 years, 3% per year for the next 5 years, and then decreasing to 1%–2% per year afterward.[45] Recently, the International Myeloma Working Group and Mayo Clinic developed the 20–2–20 risk model, which stratifies SMM into 3 groups—low, intermediate, and high risk—on the basis of bone marrow plasma cells, M protein concentration, sFLC ratio, and high-risk cytogenetics (Table 3).[46,47] Within a 2-year follow-up period, the low-, intermediate-, and high-risk groups progress to MM in 6%, 18%, and 44%, respectively.

Pretransplant evaluation for patients with MGUS and SMM. MGUS is present in 3.2% of people 50 years and older and 5.3% of people 70 years and older.[48] The prevalence of MGUS in patients with ESKD varies among studies between 0.5% and 2.6%.[49–53] Although not widely adopted, 1 study suggests MGUS screening in all patients older than 50 years undergoing evaluation for kidney transplantation.[9] The role of urine protein electrophoresis assessment is limited for patients with ESKD and negligible renal residual function. In addition, interpretation of the sFLC assay may be difficult, as low eGFR alters the sFLC concentration and kappa/lambda ratio.[54] Recent data from the Iceland Screens, Treats, and Prevents Multiple Myeloma (iStopMM) study on the reference range for sFLC and light chain (LC)–MGUS can help guide interpretations of sFLC levels in patients with chronic kidney disease (CKD). Kidney transplant candidates with modestly elevated sFLC ratios but no M spike or evidence of end-organ damage do not necessarily require bone marrow biopsy.

Patients with a monoclonal gammopathy require a thorough hematologic evaluation before transplant to rule out a more active plasma cell or lymphoproliferative disorder. Kidney biopsy should be considered on the basis of risks and yield to ensure no evidence of monoclonal protein–associated kidney disease, which would merit clone-directed therapy before kidney transplant (see Monoclonal Gammopathy of Renal Significance section). However, biopsy risks should be carefully evaluated for patients with ESKD. Once the diagnosis of MGUS or SMM is confirmed, it should not preclude the patient from receiving a transplant, but the risk of progression should be discussed with candidates along with the need for regular post-transplant monitoring of a monoclonal gammopathy. Although patients with MGUS and low- to intermediate-risk SMM do not require treatment, those with high-risk SMM could be considered for pretransplant plasma cell–targeted therapy with lenalidomide or daratumumab while data are lacking for patients with advanced CKD or ESKD[55] (Figure 4).

Post-transplant management of MGUS and SMM. Currently, there are limited data on the optimal induction and maintenance immunosuppression regimen in kidney transplant candidates with a history of MGUS. However, multiple studies have shown that the intensity of immunosuppression is associated with a higher risk of developing MGUS after transplant.[56–58] Historically, the use of OKT3 was associated with a higher risk of MGUS development.[57] Although long-term studies are limited, there is no evidence that patients on immunosuppression for kidney transplant are more likely to progress from MGUS to MM.[51] Conversely, primary cytomegalovirus infection, BK virus, and Epstein-Barr virus latency seem more frequent in patients with MGUS.[52,56,59] Although MGUS can be transient after kidney transplant, it can rarely progress to clinically significant diseases such as SMM, MM, post-transplant lymphoproliferative disorder, or light chain deposit disease.[51,52] For patients with pre- or post-transplant MGUS, no treatment is recommended but patients should be followed as per International Myeloma Working Group recommendations (Table 4). Although multiple trials are underway to evaluate the utility of routine treatment of SMM,[55,60] none specifically evaluate treatment after a kidney transplant and standardized risk stratification models (including genetic data) are needed to predict the risk of progression to MM post–kidney transplant.

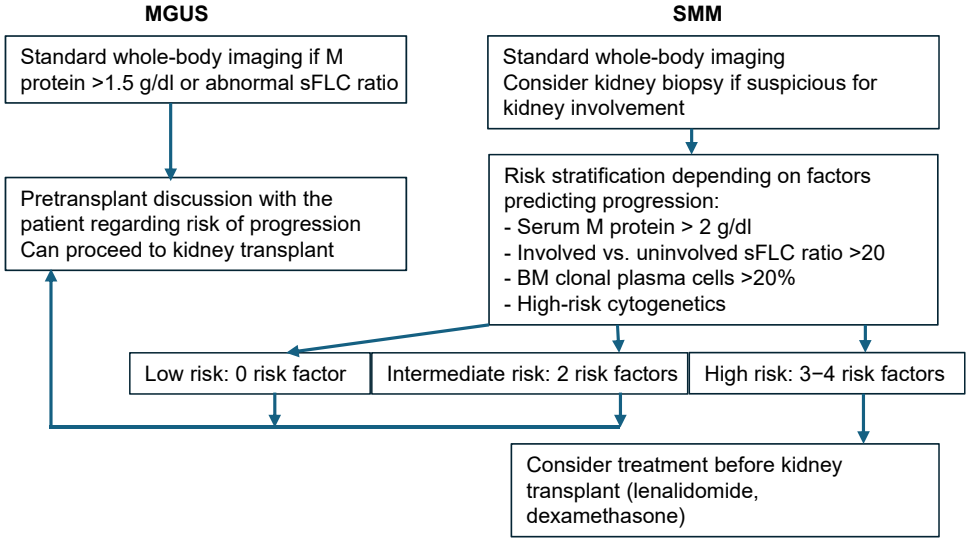


Figure 4 | Algorithm for monoclonal gammopathy precursor conditions. BM, bone marrow; MGUS, monoclonal gammopathy with undetermined significance; sFLC, serum free light chain; SMM, smoldering multiple myeloma.

Infectious risk

Infection is the leading cause of death in patients with PCD because of immunodeficiency caused by the disease and therapy.[61] Limited data suggest that the infection risk in kidney transplant recipients with PCD is likely higher than in nontransplant patients with PCD because of the use of maintenance immunosuppression.[39] Kidney transplant candidates with PCD should receive vaccinations according to their center's standard practice (Table 5). Patients who have received or will receive proteosome inhibitors, anti-CD38 antibodies, BiTEs, or ASCT require herpes zoster prophylaxis (i.e., acyclovir). *Pneumocystis jirovecii* pneumonia prophylaxis is recommended for patients receiving high doses of dexamethasone or BiTEs and for those recovering from ASCT or CAR-T cell therapy. i.v. Ig replacement may be considered in patients with hypogammaglobulinemia and those with a history of BiTE therapy. Other preventive strategies, such as monitoring for viral infections, have unclear benefits and represent another key knowledge gap.

Novel therapies and future directions

A 62-year-old man with standard-risk IgG lambda light chain MM and ESKD, who received ASCT and multiple lines of therapy (cyclophosphamide, bortezomib, and dexamethasone, or daratumumab), underwent anti–B cell maturation antigen (BCMA) CAR-T cell therapy 12 months ago. He has no evidence of disease, with normal SPEP/IFX and sFLC. What implication does a history of CAR-T cell therapy have on kidney transplant candidacy?

New therapies for MM are rapidly being developed. CAR-T cells are engineered T cells that target specific antigens expressed on myeloma cells. Two anti-BCMA CAR-T cells have been approved by the US Food and Drug Administration for relapsed/refractory MM: ciltacaptagene autoleucel and idecabtagene vicleucel.[62–64] The overall response rate of CAR-T cell therapy is remarkable (71%–98%),[65,66] and these CAR-T cell products are now being used in earlier lines of therapy.[67,68] CAR-T cell therapy has unique toxicities—cytokine release syndrome, immune effector cell–associated neurotoxicity syndrome, cytopenias, and infections—that require specific mitigation strategies.[69]

BiTE antibodies are a new therapeutic option for MM. BiTEs simultaneously bind to a target molecule on plasma cells (e.g., BCMA and G protein-coupled receptor class C group 5 member D [GPRC5D]) along with one on T cells (CD3) to enhance T-cell activation. Anti-CD3/anti-BCMA (teclistamab) and anti-CD3/anti-GPRC5D (talquetamab) BiTEs are US Food and Drug Administration approved for the treatment of refractory or relapsed MM.[70–72] Adverse events from BiTEs include cytokine release syndrome, cytopenias, and infections occurring throughout the treatment course.[4] Acute kidney injury has also been reported in 13%–29% of patients receiving BiTE therapies.[73]

Ongoing clinical trials include novel treatment targets, dual CAR-T cell therapies, BiTEs, and combination

Table 4 | Monitoring a kidney transplant recipient with smoldering multiple myeloma

Tests and frequency for monitoring
CBC, renal panel, SPEP, sFLC, and IFE at baseline and every 3–6 mo. UPCR/UACR or UPEP every 3–6 mo. If either is positive, obtain 24-h protein and perform urine protein electrophoresis
Vitamin B_{12}, folate, iron studies, and TSH if the Hgb level drops
Standard whole-body imaging every 6–12 mo if M spike or sFLC is increasing
BM biopsy and FISH when suspecting disease progression

BM, bone marrow; CBC, complete blood count; FISH, fluorescence *in situ* hybridization; Hgb, hemoglobin; IFE, immunofixation electrophoresis; sFLC, serum free light chain; SPEP, serum protein electrophoresis; TSH, thyroid-stimulating hormone; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio; UPEP, urine protein electrophoresis.

Table 5 | Infection prevention and monitoring for kidney transplant patients with PCD

Infection prevention strategies	Recommendations
Vaccination	Center's standard guidance
Prophylaxis	Acyclovir (or alternative) for herpes simplex virus and varicella zoster virus for regimens including monoclonal antibodies (e.g., daratumumab), PIs (e.g., bortezomib), and bispecific antibodies (e.g., teclistamab) for the duration of targeted therapy and for 12 mo after HCT or CAR T cell therapy[a]
	TMP-SMX (or alternative) for an increased risk of *Pneumocystis jirovecii* pneumonia in regimens including high-dose corticosteroids and bispecific antibodies for the duration of treatment and for 6 mo after HCT and CAR T cell therapy
	Consider levofloxacin (or alternative) for patients with prolonged neutropenia
	Consider thrush prophylaxis with fluconazole (or alternative) for patients receiving prolonged high-dose glucocorticoid therapy
	Consider fungal prophylaxis with fluconazole (or alternative) for treatment with bispecific antibodies or CAR-T cell therapy in patients with prior fungal infections, neutropenia, or concomitant high-dose corticosteroid regimens
Monitoring	Monitor for hypogammaglobulinemia and consider i.v. or s.c. Ig for levels <400 mg/dl in patients with serious or recurrent infections
	Monitor regularly for CMV, EBV, and BKV if screened positive in patients with PCD, especially those undergoing bispecific or CAR-T cell therapy

BKV, BK virus; CAR, chimeric antigen receptor; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCT, hematopoietic cell transplantation; PCD, plasma cell dyscrasia; PI, proteasome inhibitor; TMP-SMX, trimethoprim/sulfamethoxazole.
[a]Longest duration of either kidney transplant indication or hematologic treatment.

treatments. Although patients with CKD are often excluded from clinical trials, there is growing experience with BiTEs in patients with CKD and those on hemodialysis, indicating that these therapies can also be safely used in patients with CKD.[74]

For kidney transplant candidacy evaluation, it is crucial to discuss the risk and therapeutic options for progressive or recurrent PCD before and after kidney transplant with a multidisciplinary team involving the patient, hematologists, and transplant clinicians. Patients receiving CAR-T cell therapy after progression on multiple lines of therapy may have limited therapeutic options after relapse post–kidney transplant. The use of CAR-T cell therapy as an earlier line of therapy may not have the same implications. How lymphodepleting induction for kidney transplant and post-transplant maintenance immunosuppression affect the persistence of CAR-T cells and the durability of hematologic response is unclear. Likewise, whether pre- or post-transplant CAR-T cell therapy affects the risk of rejection is unknown. Some laboratory data suggest that the persistence of BCMA CAR-T cells lasts 4–6 weeks, and 6 months after achieving hematologic response, it may not be affected by lymphodepleting therapies; however, more data are needed.

Treating patients with relapsed MM post–kidney transplant needs special consideration for both efficacy and infection risks. Concurrent immunosuppression may theoretically blunt the efficacy of CAR-T cell therapy (especially within 4–6 weeks of CAR-T cell infusion) and BiTEs. Infection prophylaxis and treatment in kidney transplant recipients receiving BiTEs likely need to be intensified because of deeper immunosuppression.

Areas for future research

We identified several unanswered clinical questions through expert meetings. First, whom to screen for PCD as part of pretransplant evaluation remains unclear and more data are required to refine strategies. SPEP/IFX and sFLC testing in all transplant candidates may detect undiagnosed PCD pre-transplant, potentially avoiding post-transplant recurrence. Yet, sFLC interpretation is challenging in patients with advanced CKD or ESKD and the yield of pursuing additional evaluation in patients with abnormal sFLC ratios is likely low. Additionally, the incidence of MGUS is high in the general population, especially in older adults. Some guidance on which patients with MGUS require bone marrow testing exists from the iStopMM study.

Second, which patients merit a kidney biopsy is unknown. Only a fraction of kidney transplant candidates undergo kidney biopsy at the time of transplant evaluation. Not pursuing kidney biopsy may lead to missed diagnosis of PCD-associated kidney disease. At the same time, kidney biopsy in patients with ESKD may be unsafe because of bleeding risk or uninformative because of extensive fibrosis. Moreover, additional testing may lead to unnecessary delays in transplant waitlisting or other unintended consequences. Thus, the benefit of kidney biopsy should be carefully balanced considering risks and diagnostic probability.

Lastly, post-transplant infectious prophylaxis in patients with PCD is a critical issue without clear answers. Infections are a leading cause of death in both patients with MM and kidney transplant recipients, independently. Whether and how we should modify the prophylaxis of viral, bacterial, and fungal infections for kidney transplant recipients with a history of PCD remains unsolved.

Conclusions

Therapeutic options for patients with PCD are rapidly evolving, and patient outcomes are markedly improving, warranting consideration of kidney transplant for many of these patients. These expert opinions are based on the best available data to date, and we acknowledge that guidance will require continued updates. To transition these opinion-based recommendations to data-driven guidelines, ongoing data collection, research, and collaboration are needed. Informed discussions with patients about the latest treatments and the

timing of PCD management before and after kidney transplant will enable optimal patient outcomes, including appropriate opportunities for transplant. As multidisciplinary teams work to learn, apply, and share the latest knowledge, more patients will experience improved survival and quality of life before and after transplant.

DISCLOSURE

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