Suitability for Kidney Transplantation in AL Amyloidosis: A Survey Study of Transplant and Amyloidosis Physicians

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Key Points
- Patient survival was viewed by amyloidosis and transplant program respondents as the most important determinant of transplant suitability.
- Amyloidosis program respondents were less concerned than transplant program respondents about extrarenal involvement.
- Overall, there was a lack of consensus across specialties about criteria for kidney transplantation for patients with amyloid light chain amyloidosis.

Abstract
Background Historically, kidney transplantation has been considered inappropriate for most patients with AL amyloidosis–associated kidney failure because of concerns about recurrent disease in the allograft and poor long-term survival. With improvements in rates and durability of hematologic responses and survival that have accompanied treatment advances, a greater proportion of patients with AL amyloidosis may be suitable for kidney transplantation. However, there are no widely accepted criteria for kidney transplant eligibility for this patient population.

Methods We administered surveys electronically to transplant nephrologists and amyloidosis experts at a geographically diverse set of academic medical centers in the United States. Questions were designed to elucidate views about suitability and timing of kidney transplantation for patients with AL amyloidosis–associated kidney failure.

Results The survey was completed by 20 (65%) of invited amyloidosis experts and 20 (29%) of invited transplant physicians. Respondents indicated that, for patients with AL amyloidosis, most transplant nephrologists have limited experience with both determining eligibility for and providing care after kidney transplantation. Most transplant nephrologists and amyloidosis experts viewed anticipated patient survival as the most important determinant of suitability for kidney transplantation. Compared with transplant program respondents, amyloidosis program respondents reported a higher degree of confidence in determining suitability for kidney transplantation, were comfortable proceeding with kidney transplantation earlier after patients attained a hematologic response, and were less concerned about extrarenal amyloid involvement as a barrier to kidney transplantation. In both groups, most respondents indicated that there is a lack of consensus between amyloidosis and kidney transplant physicians about criteria for determining suitability for kidney transplantation.

Conclusion Views about criteria for kidney transplantation for patients with AL amyloidosis–associated kidney failure differed between amyloidosis and transplant nephrology program respondents, with amyloidosis specialists generally favoring a less-restrictive approach to transplant eligibility. The findings suggest a need for consensus building across specialties.

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per million adults in the United States (2,3). AL amyloidosis results from the production of amyloidogenic immunoglobulin light chains by clonal plasma cells in the bone marrow that deposit as amyloid in the kidney, heart, liver, and/or autonomic nervous system (4). Progressive accumulation of this deposit as amyloid in the kidney, heart, liver, and/or autonomic nervous system (4). Progressive accumulation of that deposit as amyloid in the kidney, heart, liver, and/or autonomic nervous system (4). Progressive accumulation of that deposit as amyloid in the kidney, heart, liver, and/or autonomic nervous system (4). Progressive accumulation of that deposit as amyloid in the kidney, heart, liver, and/or autonomic nervous system (4). Progressive accumulation of that deposit as amyloid in the kidney, heart, liver, and/or autonomic nervous system (4).

Advances in treatments targeting plasma cells, such as high-dose melphalan with autologous stem cell transplantation, lenalidomide, bortezomib, and, more recently, daratumumab, have led to higher rates of hematologic responses, clinical responses, and survival (5–8). With improvements in the attainment and durability of hematologic responses, kidney transplantation may be considered as an alternative to dialysis for kidney replacement therapy among patients who develop AL amyloidosis-associated kidney failure. A recent retrospective analysis by a single center found that survival for patients with AL amyloidosis who underwent kidney transplantation was 12.4 years, compared with 24–39 months for those treated with dialysis, and that allograft survival was >5 years for 81% of the patients (9).

Currently, there are not established criteria for determining suitability for kidney transplantation for patients with AL amyloidosis-associated kidney failure. Because the disease is rare, many transplant programs have limited experience with pre- and post-kidney transplant care for patients with AL amyloidosis. Conversely, amyloidosis specialists have limited experience caring for patients with AL amyloidosis who have undergone kidney transplantation. As an early step toward a longer term goal of developing criteria for kidney transplantation in AL amyloidosis, we performed a survey study of both amyloidosis specialists and kidney transplant specialists to characterize approaches and considerations when determining kidney transplant suitability for this patient population.

Materials and Methods

We developed surveys consisting of 23 questions for transplant nephrologists and amyloidosis experts using the Qualtrics platform (see Supplemental Appendices 1 and 2 for surveys). Multiple-choice, Likert-scale, and ranking-style questions were used. Although most questions were common to both surveys, there were also specialty-specific questions. Before its distribution, each survey was reviewed by content experts who were not eligible for subsequent participation in the study.

Transplant nephrology programs were identified from the website of the US Scientific Registry of Transplant Recipients (10). Surveys were sent to the medical directors of kidney transplant programs that had annual kidney transplant volumes within the top 100 of the 256 programs. If the website did not designate a medical director, the survey was sent to a different transplant nephrologist from the program. Email addresses for the transplant medical director or a transplant nephrologist were obtained from the program’s website or the American Society of Nephrology membership directory. Invitations to participate were sent by electronic mail during the period from November 1, 2018 through March 1, 2019. A maximum of three contacts were made to each potential participant.

We identified 31 dedicated amyloidosis treatment programs in the United States and initially contacted one member from each program. We initially contacted hematologist-oncologists, and, if there was no response, we contacted a physician member from a different discipline. Email addresses were obtained from program websites. Invitations to participate were sent by electronic mail during the period from March 2, 2018 through April 3, 2019. A maximum of three contacts were made to each potential participant.

Recipients of the surveys were informed that participation was voluntary and that responses would not be identified by name or institution. The study was conducted in accordance with the Declaration of Helsinki and deemed exempt for review by the Institutional Review Board of the University of Pennsylvania (protocol number 828184), as authorized by title 45 of the Code of Federal Regulations, section 46.101, category 2.

Results

Characteristics of Survey Respondents and Programs

The amyloidosis program survey was sent to 31 physicians, each representing a single amyloidosis center. Completed surveys were received from 20 programs (65%). The transplantation program survey was sent to 70 physicians, each representing a single kidney transplantation center. Completed surveys were received from 20 programs (29%).

The characteristics of the survey respondents are shown in Table 1. For the amyloidosis programs, the respondents described themselves as hematologist-oncologists (90%) or hematologists (10%), and for the kidney transplant programs, all of the respondents were nephrologists. Program age ranged from <5 to >20 years for the amyloidosis programs and was ≥20 years for most of the transplant programs. For the transplant programs, 75% had four or more transplant nephrologists, 75% had four or more transplant surgeons, and the median annual number of kidney transplants performed per year was 234 (interquartile range, 164–271), which falls within the top 75th percentile for United States centers (10). All of the amyloidosis program respondents and most of the kidney transplant program respondents reported availability of autologous stem cell transplantation at their institutions. Among the kidney transplant program respondents, 55% reported having physicians at their institution with particular expertise in amyloidosis. A greater proportion of amyloidosis program respondents (85%) were comfortable or very comfortable answering the survey questions compared with kidney transplant program respondents (60%) (Supplemental Figure 1).

At the amyloidosis programs, the number of patients during the prior 3 years who received care after a kidney transplant ranged from zero to more than ten (Figure 1). Most of the kidney transplant program respondents reported that, during the prior 3 years, their program had performed kidney transplants for one to five patients with amyloidosis (Figure 1). For both the kidney transplant and amyloidosis programs, most respondents reported that their programs had evaluated one to ten patients with amyloidosis for kidney transplantation during the preceding 3 years (Supplemental Figure 2).
Perceptions about Assessing Suitability for Kidney Transplantation

There was general agreement between the amyloidosis and transplant program respondents that transplant nephrologists have limited experience with both evaluating suitability for kidney transplantation and providing post-transplant care for patients with AL amyloidosis (Figure 2). The level of confidence in assessing suitability for kidney transplantation was greater among the amyloidosis program respondents than among the transplant program respondents, with 80% of amyloidosis program respondents, compared with 45% of transplant program respondents (Supplemental Figure 3). Most amyloidosis and kidney transplant program respondents agreed or strongly agreed that there is greater uncertainty about the outcome of the kidney allografts for patients with AL amyloidosis than for most other kidney transplant recipients (Figure 2). Furthermore, both amyloid and kidney transplant program respondents expressed the view that there is not a strong consensus among kidney transplant physicians about which patients with AL amyloidosis are suitable for kidney transplantation (Figure 2).

Key Factors for Determining Suitability for Kidney Transplantation

Amyloidosis programs rated from most important to least important the following factors when considering suitability of patients with AL amyloidosis for kidney transplant: (1) anticipated patient survival, (2) potential for amyloid deposition in the allograft, (3) available therapeutic agents for treating AL amyloidosis after kidney transplantation, (4) anticipated allograft survival, and (5) effects of transplant immunosuppression on clonal plasma cells (Figure 3A). The rankings by the kidney transplant

### Table 1. Characteristics of programs for survey respondents

| Characteristics | Amyloidosis Programs | Kidney Transplant Programs |
|-----------------|----------------------|-----------------------------|
| **Type of center, n (%)** | | |
| Academic medical center | 19 (95) | 17 (85) |
| Community hospital, not affiliated with an academic medical center | 0 (0) | 2 (10) |
| Veterans Administration hospital | 1 (5) | 1 (5) |
| **Age of program, yr, n (%)** | | |
| <5 | 0 (0) | 0 (0) |
| 5–9 | 0 (0) | 0 (0) |
| 10–19 | 4 (20) | 4 (20) |
| >20 | 16 (80) | 16 (80) |
| **Number of affiliated amyloidosis physicians, n (%)** | | |
| <5 | 9 (45) | NA |
| 5–9 | 7 (35) | NA |
| 10–19 | 2 (10) | NA |
| >20 | 2 (10) | NA |
| **Number of affiliated transplant nephrologists, n (%)** | | |
| 1 | NA | 0 (0) |
| 2 | NA | 3 (15) |
| 3 | NA | 2 (10) |
| 4 | NA | 4 (20) |
| 5 | NA | 7 (35) |
| >5 | NA | 4 (20) |
| **Number of affiliated transplant surgeons, n (%)** | | |
| 1 | NA | 0 (0) |
| 2 | NA | 3 (15) |
| 3 | NA | 2 (10) |
| 4 | NA | 1 (5) |
| 5 | NA | 5 (25) |
| >5 | NA | 9 (45) |
| **Number of kidney transplants per year, median (IQR)** | | |
| Yes | 20 (100) | 17 (85) |
| No | 0 (0) | 3 (15) |
| **Autologous stem cell transplantation available, n (%)** | | |
| Yes | 0 (0) | NA |
| No | 20 (100) | NA |
| **Medical specialty for survey respondent, n (%)** | | |
| Amyloidosis program hematologist-oncologist or hematologist | 20 (100) | NA |
| Other amyloidosis program specialist | 0 (0) | NA |
| Transplant program nephrologist | NA | 20 (100) |
| Other transplant program specialist | NA | 0 (0) |

NA, not applicable; IQR, interquartile range.

*From the Scientific Registry of Transplant Recipients (https://www.srtr.org/transplant-centers/?organ=kidney).
programs were similar, except that allograft survival was ranked more highly by transplant program respondents than by amyloidosis program respondents (Figure 3B). Most amyloidosis program respondents (65%) and kidney transplant program respondents (75%) reported that the minimum expected life expectancy should be 5 years to

Figure 1. Experience during the prior 3 years with kidney transplantation in amyloid light chain amyloidosis. (A) Amyloidosis centers: number of patients with amyloidosis receiving care after kidney transplantation. (B) Transplant centers: number of amyloidosis patients receiving a kidney transplant.

Figure 2. Perspectives about kidney transplantation for amyloid light chain (AL) amyloidosis–associated kidney failure. Survey respondents indicated their level of agreement with the statements shown along the x axis.
Figure 3. Relative importance of factors for determining suitability for kidney transplantation. (A) Amyloidosis program respondents and (B) transplantation program respondents. Respondents ranked each factor using a scale of 1 to 5, with 1 indicating least important and 5 indicating most important. Each ranking could be applied to only one factor.
be suitable for kidney transplantation (Supplemental Figure 4). There was greater comfort proceeding with kidney transplantation as early as 6 months after autologous stem cell transplantation among amyloidosis program respondents (50%) than among transplant program respondents (15%), most of whom felt that kidney transplantation should not be performed until 1 year (40%) or 2 years (40%) after autologous stem cell transplantation (Figure 4). For both the amyloidosis and transplant programs, most respondents (75% and 60%, respectively), recommended not proceeding with kidney transplantation if the 6-month evaluation after autologous stem cell transplantation indicates a partial, rather than complete, hematologic response (Supplemental Figure 5).

The type of treatment approach used to achieve pre-kidney transplant complete hematologic response was important in determining kidney transplant suitability to some, but not all, of the survey respondents and, overall, was ranked as less important by the amyloidosis program than the transplant program respondents (Figure 5). Among those responding that treatment type was an important determinant of transplant suitability, both the amyloidosis program and transplant program respondents responded more favorably if the hematologic response had been achieved with a bortezomib-based treatment or with high-dose melphalan/stem cell transplantation than if the hematologic response had been achieved with a lenalidomide-based regimen (Figure 6).

For patients with a complete hematologic response, extrarenal involvement was a relevant determinant of suitability for kidney transplantation for both amyloidosis and kidney transplant program respondents. For patients with
a mild degree of amyloid liver disease, 68% of amyloidosis program respondents and 55% of kidney transplant program respondents found kidney transplantation to be acceptable (Figure 7A); however, with moderate liver involvement, kidney transplantation was considered appropriate by only 27% and 18% of amyloidosis program and kidney transplant program respondents, respectively. Only 5% of amyloidosis program respondents, compared with 27% of kidney transplant program respondents, felt that any evidence of liver involvement precluded kidney transplantation (Figure 7A). For cardiac involvement, approximately half of respondents in both groups were comfortable proceeding with kidney transplant if the involvement was mild, but few respondents in either group (5% for amyloidosis programs and 0% for transplant programs) were comfortable with kidney transplantation in the presence of severe involvement. For transplant program respondents, 38% felt that any degree of cardiac involvement, even subclinical disease, precluded kidney transplantation. In contrast, only 9% of amyloidosis program respondents indicated that any degree of cardiac involvement precluded kidney transplantation. (Figure 7B).

As shown in Figure 8, views about the use of anti–plasma cell therapy, if required, after kidney transplantation differed on the basis of the treatment regimen. For both amyloidosis and transplant program respondents, the greatest comfort was with bortezomib-based treatment and the lowest level of comfort was with lenalidomide-based treatment. For all of the treatment approaches, amyloidosis program respondents had a greater level of comfort than did transplant program respondents. Nearly all amyloidosis program respondents (90%) reported no concerns about bortezomib use after kidney transplantation. In contrast, kidney transplant program respondents were approximately equally divided between having no concerns (50%) and having some degree of concern (45%) about the use of bortezomib (Figure 8A). For treatment with high-dose melphalan with autologous stem cell transplantation, 35% of amyloidosis program respondents reported some degree of concern, compared with 50% of kidney transplant program respondents (Figure 8B). Among kidney transplant program respondents, 40% were sufficiently concerned about high-dose melphalan and autologous stem cell transplantation to indicate that they would avoid its use unless there were no other options for treatment, whereas none of the amyloidosis program respondents reported that level of concern (Figure 8B). For both the amyloidosis and kidney transplant program respondents, the greatest degree of concern was with the use of lenalidomide-based treatment; 20% and 15% of amyloidosis and transplant program respondents, respectively, reported that lenalidomide should not be used after kidney transplantation.
transplantation (Figure 8C). Among the kidney transplant program respondents, 25% indicated not knowing enough about lenalidomide to answer the question, compared with 5% of amyloidosis program respondents (Figure 8C).

Discussion

Our survey of amyloidosis and kidney transplantation programs suggests that, while there are some areas of general agreement, overall there is a lack consensus across these specialties about criteria for kidney transplantation for patients with AL amyloidosis. Both groups conveyed views that there is less certainty about outcomes after kidney transplantation for patients with AL amyloidosis than for those with other causes of kidney failure, and that there is not a high degree of agreement among kidney transplant physicians about appropriate criteria for kidney transplantation for this patient population. Both groups considered anticipated patient survival and potential deleterious effects of post-transplant immunosuppression as the most important and least important factors, respectively, for determining kidney transplant suitability. However, compared with transplant programs, amyloidosis programs reported a higher confidence level in determining suitability for transplant, preferred to proceed with kidney transplantation earlier for patients who were in complete hematologic remission, were less concerned about extrarenal amyloid involvement as a determinant of transplant...
suitability, and had less concern about use of autologous stem cell transplantation if anti-plasma cell therapy is needed after kidney transplantation.

There are several potential reasons for the differences in perspectives between the specialties. Transplant physicians may be more cautious about proceeding with kidney transplantation because of (1) limited experience with AL amyloidosis given the rare nature of the disease, (2) historically poor outcomes for this patient population before relatively recent advances in anti-plasma cell therapies, and (3) the importance of post-transplant patient and allograft outcomes for maintaining program certification by payers (11–13). Amyloidosis clinicians likely have a higher level of comfort monitoring for and managing hematologic relapses or extrarenal manifestations, and may be more aware than are transplant physicians, of the pace of development of new treatments for AL amyloidosis.

Most of the data on patient and allograft outcomes with kidney transplantation for patients with AL amyloidosis come from an era when the treatment of AL amyloidosis was much less effective than it is currently (14–19). More recent studies indicate that outcomes have improved. A United States registry-based, retrospective, propensity-matched analysis found no significant difference in risk of death or allograft loss when patients with amyloidosis received a kidney transplant compared with other high-risk subgroups, such as older individuals or those with diabetes-associated kidney failure (20). A single-center prospective study found that, among the selected group of patients who underwent kidney transplantation, median patient survival after transplantation was 10.5 years, and 1-, 3-, and 5-year graft survivals were 94%, 89%, and 81%, respectively (9). In that study, outcomes were better among patients who had a complete or very good partial

Figure 8. Degree of concern, if anti-plasma cell therapy is required after kidney transplantation. For a treatment regimen that includes (A) proteasome inhibitor, (B) high-dose melphalan with autologous stem cell transplantation, and (C) lenalidomide.
hematologic response before transplantation compared with those with either partial or no response, with median patient survivals of 11.7 and 7 years, respectively, and median allograft survivals of 10.4 and 5.5 years, respectively (9). A recent analysis that included patients receiving kidney transplants as far back as 1989 found that, for both patient and allograft survival, outcomes for patients with AL amyloidosis were similar to those with diabetic nephropathy (21). The findings of these analyses may not have been widely disseminated at the time our surveys were completed.

A recent consensus expert opinion report addressing organ transplantation in the setting of hematologic malignancies and melanoma includes a statement that kidney (or other single-organ) transplantation is possible in AL amyloidosis in selected circumstances; specifically, when there is a difference between the concentrations of involved and uninvolved serum free light chains of <4 mg/dl, single organ involvement, absence of symptomatic myeloma, and candidacy for autologous stem cell transplant after organ transplantation (22). The report does not address several of the issues included in our survey, such as timing of organ involvement, absence of symptomatic myeloma, and resultant improvements in patient survival, consideration for kidney transplantation among this patient population will likely increase. The findings from our survey should inform future efforts to generate consensus-based criteria for kidney transplantation in AL amyloidosis–associated kidney failure and suggest that there is a need for more interaction between amyloidosis and transplant specialists.

Disclosures
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Author Contributions
L.M. Dember provided supervision and was responsible for project administration; L.M. Dember and R. Lam wrote the original draft and were responsible for formal analysis, investigation, and methodology; L.M. Dember and M.A. Lim reviewed and edited the manuscript; R. Lam was responsible for data curation and visualization; and all authors conceptualized the study.

Supplemental Material
This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0004232021/-/DCSupplemental.

Supplemental Figure 1. Comfort with answering survey questions.

Supplemental Figure 2. Number of patients with amyloidosis evaluated for kidney transplantation during the past 3 years.

Supplemental Figure 3. Confidence in evaluating kidney transplantation suitability for patients with AL amyloidosis.

Supplemental Figure 4. Minimum expected life expectancy for kidney transplantation suitability.

Supplemental Figure 5. Earliest acceptable time for kidney transplantation if there is ongoing evidence of a partial hematologic response after autologous stem cell transplantation for AL amyloidosis.

Supplemental Appendix 1. Amyloidosis program survey.

Supplemental Appendix 2. Kidney transplant program survey.

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