Glomerulonephritis Recurrence in the Renal Graft

STEVEN JAMES CHADBAN
Department of Nephrology, Monash Medical Centre, Clayton, Australia.

Renal transplantation is a treatment, not a cure. Although transplantation may return renal function to the recipient, it does not necessarily remove the cause of the recipient’s original renal disease. Glomerulonephritis is the cause of renal failure for 20 to 40% of those who receive a transplant; for these recipients, the threat of recurrent disease is real. The transplant setting of immunsuppression, different antigenic characteristics of the graft versus the native kidney, and different chronology may attenuate or prevent recurrence of some forms of glomerulonephritis. Others will, despite these barriers, recur and may result in allograft failure.

Allograft survival rates have steadily improved over the past 20 yr, largely as a result of our increasing ability to prevent and treat rejection (1). Recurrent glomerulonephritis is at present a minor contributor to allograft failure, responsible for 3% of all grafts lost in Australia and New Zealand from 1979 to 1998 (E. Briganti and S. Chadban, unpublished data) and a similar number in the United Kingdom (2). However, the propensity for glomerulonephritis to recur seems to be time dependent (3). Thus, as graft survival increases, so, too, does the likelihood of disease recurrence. As the average cadaveric graft is now projected to function for more than 13 yr and the average live-donor graft for more than 21 yr (1), we can expect to see an increased incidence of recurrent glomerulonephritis and a greater number of grafts failing as a result of recurrence.

By implication, the diagnosis of recurrent glomerulonephritis requires an accurate diagnosis of both the primary renal disease and subsequent disease in the transplant kidney. In most cases, these criteria will be fulfilled only by obtaining renal biopsy material from both organs for diagnostic assessment, which may need to include electron microscopy and immunohistology (4,5). Although biopsy of native and transplant kidneys is simple, safe, and widely practiced, it is not performed in all cases of suspected glomerulonephritis in native or transplanted kidneys (6). Electron microscopy and immunohistology also are not routinely performed on transplant biopsies. Thus, the true incidence and impact of recurrent glomerulonephritis is not accurately known and is probably underestimated.

This article discusses recurrent glomerulonephritis in the current era. The strength and quality of data reported in the literature are variable; where evidence is cited, its strength is considered. The epidemiology of recurrence is reviewed in a general sense, and recurrence of specific forms of glomerulonephritis is addressed individually. The incidence of recurrence and recurrence leading to graft failure is examined, and risk factors for disease recurrence are assessed. Where available, data on the pathogenesis and management of recurrent glomerulonephritis also is presented. Controversies in the area are discussed, including the diagnosis of recurrent glomerulonephritis and the implications of recurrence for retransplantation. The issues of de novo glomerulonephritis posttransplantation and recurrent metabolic diseases have been reviewed elsewhere (6–8) and are not directly addressed here.

Epidemiology of Recurrent Glomerulonephritis

Diagnosis and Definitions

By implication, the diagnosis of recurrent glomerulonephritis requires an accurate identification and characterization of glomerulonephritis in the native kidney and subsequent identification of the same disease affecting the transplant kidney. These criteria mandate a renal biopsy of both native and transplant kidneys. Such criteria are not fulfilled in many cases of recurrent glomerulonephritis cited in the literature (6). Patients who are presumed to have glomerulonephritis (no biopsy) as the primary cause of renal failure and who go on to develop biopsy-proven glomerulonephritis after transplantation are frequently labeled as having recurrent glomerulonephritis (9). Such patients may have either recurrent or de novo glomerulonephritis (7,8). Given this difficulty, many studies group de novo glomerulonephritis with recurrent glomerulonephritis. Conversely, underdiagnosis of recurrent glomerulonephritis is also likely to be a major flaw in the literature, as many patients with the clinical features of deteriorating renal function and proteinuria posttransplantation are misclassified as having “chronic rejection” and are not biopsied or assessed adequately (see the section Clinical Features and Differential Diagnosis of Recurrent Glomerulonephritis). Thus, the true incidence and impact of recurrent glomerulonephritis are not accurately known and are probably underestimated in the published literature (6).

Reports on recurrent glomerulonephritis vary in terms of diagnostic criteria and definition. Recurrent glomerulonephritis is categorized in the present article in three ways:

1. Recurrent glomerulonephritis—confirmed (biopsy proven) or presumed (clinical criteria alone)
2. Recurrent glomerulonephritis causing graft loss—clinical and biopsy features demonstrating recurrence as the sole or
dominant pathology resulting in loss of graft function that requires renal replacement therapy or causes death as a result of uremia.

3. **Recurrent glomerulonephritis contributing to graft loss**—
recurrent glomerulonephritis as one of two or more pathologies, such as chronic rejection or chronic cyclosporin nephrotoxicity, identified as contributing to graft failure that requires renal replacement therapy or causes death as a result of uremia.

**Frequency and Significance of Recurrence**

Virtually all recognized forms of glomerulonephritis may recur posttransplantation. Published data suggest that recurrent glomerulonephritis occurs in 6 to 19.4% of all renal transplant recipients, largely dependent on the time of assessment after transplantation (2,3,10,11), and causes the loss of 1.1 to 4.4% of all renal allografts (2,3,9,11). The rate of recurrence and recurrence causing graft loss is obviously higher in patients with end-stage renal failure as a result of glomerulonephritis but varies enormously depending on the type of glomerulonephritis. For example, lupus nephritis recurs in fewer than 10% of cases and graft losses are uncommon, whereas recurrence is almost universal in cases of type II mesangiocapillary glomerulonephritis and graft losses are frequent. Although the impact of recurrent glomerulonephritis on graft survival depends on the type of glomerulonephritis, at a population level, the presence of recurrent glomerulonephritis clearly incurs an increased risk of graft failure (12). Data from the Renal Allograft Disease Registry in the United States demonstrate the negative impact of disease recurrence on graft survival, documenting a relative risk of 1.9 (95% confidence interval [CI], 1.57 to 2.40) for graft loss at 5 yr as compared with those without recurrence (12).

Factors in addition to the underlying type of glomerulonephritis may influence the risk of recurrence. Time of follow-up clearly is important and may be related to the duration of exposure of the graft to the nephritogenic factors that are responsible for causing glomerulonephritis (3). In general, grafts that are lost early as a result of rejection are exposed relatively briefly and rarely develop recurrence. In contrast, grafts that survive long term are exposed to nephritogenic factors for longer and are more likely to develop recurrent glomerulonephritis. This concept is borne out by registry data from the United States and ANZDATA. Renal Allograft Disease Registry data show that the incidence of recurrent disease (glomerulonephritis and metabolic diseases) increases with duration of follow-up, from 2.8% at 2 yr to 9.8% at 5 yr and 18.5% at 8 yr of follow-up (12). As the overall duration of graft survival has improved (1), largely because of a decline in graft loss caused by rejection, the incidence of graft loss caused by recurrent disease paradoxically has increased. In Australia, from the period 1979 to 1988 to the period 1989 to 1998, the incidence of all-cause graft loss fell by 45.5 per 1000 transplants (95% CI, 40.9 to 50.2), largely because of a fall in the incidence of graft loss caused by acute rejection, which fell by 28.5 per 1000 transplants. In contrast, the incidence of recurrent disease rose by 1.3 per 1000 (95% CI, 0.6 to 2.1; Figure 1; E. Briganti and S. Chadban, unpublished data). Consistent with these observations, the recipients of human leukocyte antigen (HLA)-identical transplants rarely experience rejec-

![Figure 1. Incidence of graft loss: Australia 1979 to 1998, all causes versus recurrent disease. The incidence of graft loss has fallen progressively over the past 20 yr, largely as a result of reductions in loss from acute and chronic rejection. In contrast, graft loss caused by recurrent disease has increased over the same period (P < 0.05), particularly in the 14- to 55-yr recipient age group (E. Briganti and S. Chadban, unpublished data).](image-url)
tion, they enjoy prolonged graft survival, but they have a high rate of recurrent glomerulonephritis (13). In one report, recurrent glomerulonephritis was present in 36 to 42% of those biopsied and resulted in 24% of graft losses, thereby being the second most frequent cause of graft loss after death in this group (13).

Other groups of recipients may experience higher rates of recurrent glomerulonephritis. Higher rates of recurrence have been reported in pediatric transplant recipients, in whom recurrent glomerulonephritis has been the cause of 6% of first allograft losses and 12% of subsequent graft losses (14). Patients who experience first allograft loss from recurrent glomerulonephritis are also at higher risk of recurrence in a subsequent graft, documented at up to 48% (9).

Several measures aimed at reducing the risk of recurrence have been reported. Bilateral native kidney nephrectomy, as a means of eliminating antigenic stimulation, has been examined in a large, single-center, retrospective study (10). Of 361 patients with end-stage renal failure caused by glomerulonephritis, 61 received bilateral native nephrectomy pretransplantation (nonrandomized). After 10 yr of follow-up, a higher rate of recurrence was recorded in nephrectomized patients (42% versus 19.4% for non-nephrectomized patients), demonstrating a clear lack of benefit. Other strategies have included induction of disease remission before transplantation, prolonged time on dialysis pretransplantation, avoidance of living related donation, and variations in posttransplantation maintenance immunosuppression. These issues are discussed within specific disease categories (see below).

Thus, recurrent glomerulonephritis seems to be a significant problem. It is important, however, to view these general data with several reservations:

1. Many of the reported data include patients with de novo glomerulonephritis and recurrent metabolic diseases pooled into a single group labeled recurrent disease (12). Where possible in this article, these conditions are separated from recurrent glomerulonephritis.
2. Most data are retrospective and are therefore subject to limitations of documentation, recall, variations in local practice, and changes in practice over time.
3. Many data, particularly reports on specific disease entities and their treatment, have been obtained from single-center studies that generally include relatively small patient numbers. Patient demographics and the clinical approach may differ from the global transplantation population.
4. The broadest data have been collected by registries: UNOS (United Network for Organ Sharing), Renal Allograft Disease Registry (USA), ANZDATA (Australia and New Zealand), ERA-EDTA, Eurotransplant, and the UK Transplant Support Service Authority (Europe). Registries capture data on large numbers of patients; however, unit participation rates, quantity and type of data collected, accuracy, uniformity and consistency of reporting by units, and the reliability of data entry vary among the registries, which may introduce bias to the data. For example, recurrent glomerulonephritis was reported to cause graft loss in 3% of first transplants reported to the ERA-EDTA registry (9). However, because of the variability across Europe in the use of renal biopsy to diagnose glomerulonephritis, 54% of patients included were diagnosed as having native kidney glomerulonephritis without biopsy confirmation. Thus, it is not possible to distinguish recurrent from de novo disease in these registry data.

Despite these reservations, the pattern and significance of recurrent glomerulonephritis are becoming clearer over time. The remainder of this article discusses current understanding, prevention, and management of recurrent glomerulonephritis. Data specific to individual types of glomerulonephritis are summarized in Table 1 and are discussed in the text.

Clinical Features and Differential Diagnosis of Recurrent Glomerulonephritis

The typical features of recurrent glomerulonephritis are those of nephritis involving the native kidney, including proteinuria, hematuria, and deterioration in renal function. Renal function may be normal or impaired at the time of recurrence, and the rate of progression is extremely variable. Most important, recurrent glomerulonephritis may be one of several concurrent conditions that affect an allograft, with chronic allograft nephropathy or calcineurin-inhibitor toxicity commonly coexisting with glomerulonephritis. The presence of some forms of recurrent glomerulonephritis may actually predispose the graft to rejection, e.g., focal and segmental glomerulosclerosis (FSGS), and vice versa (15).

For most types of recurrent glomerulonephritis, clinical features of the recurrence are similar to those of the primary disease. Extrarenal features of the primary condition may recur with recurrence in the transplant, such as thrombocytopenia and hemolysis in hemolytic uremic syndrome (HUS) and extrarenal vasculitis in recurrent Wegener’s granulomatosis. Serology may be helpful in some cases, such as in anti–glomerular basement membrane (GBM) detection in Goodpasture disease, but may be variable in others, such as in recurrent lupus nephritis. Knowledge of hepatitis B or C antigenemia is important when considering recurrent membranous or mesangioproliferative glomerulonephritis.

Renal biopsy is essential. When the diagnosis of recurrence is suspected, full evaluation of the biopsy specimen by light microscopy, immunohistology, and electron microscopy is desirable and in many cases essential (4,5). Light microscopy and immunohistology are necessary to differentiate recurrent from de novo glomerulonephritis, rejection, and calcineurin-inhibitor toxicity. The presence of tubulitis plus or minus vascular/glomerular changes should suggest acute rejection (16). Chronic rejection may produce chronic interstitial inflammation and glomerular changes, including cellular proliferation and basement membrane reduplication, which may be difficult to differentiate from mesangiocapillary glomerulonephritis (MCGN) by light microscopy (4,16). The use of immunohistology (content of deposits) and electron microscopy (location and structure of basement membrane and deposits) may clarify
the diagnosis (4,5). The major differential diagnoses of recurrent glomerulonephritis are outlined in Table 1.

**IgA Nephropathy and Henoch Schonlein Purpura**

IgA nephropathy (IgAN) and Henoch Schonlein purpura (HSP) may reflect the same disease process, with HSP representing the more severe and less common end of the spectrum. Numerically, both have been thought of as uncommon causes of graft failure—HSP because of its rarity and IgAN because of its “benign” nature despite a high rate of recurrence. However, recent data suggest that we should expect to encounter an increasing burden of disease from recurrent IgAN as its not-so-benign nature becomes more evident with longer follow-up (17–21).

IgAN is the most common form of glomerulonephritis that leads to end-stage renal failure, and patients who have this condition frequently receive transplants. Histologic recurrence is seen beyond 3 mo posttransplantation (17). Most series have reported a histologic recurrence rate of 26 to 46% (18–21); however, the only study in which all patients were biopsied found recurrence in 58% (17).

The clinical expression of disease is variable and time-dependent. Reports on short-term graft survival in patients with IgAN have suggested an excellent graft survival rate for those who experience recurrence (9,22). The long-term consequences seem not so benign, as reported in five recent, substantial, retrospective, single-center reports of the clinical recurrence rate of IgAN and its impact on graft outcomes (17–21). Mean follow-up in all series was approximately 5 yr, with renal biopsies performed as clinically indicated for investigation of graft dysfunction, hematuria, or proteinuria. Recurrence was detected in 26 to 46% of cases, resulting in or contributing to significant graft dysfunction or loss in 22 to 26% of cases. Graft loss during the first 3 yr posttransplantation was uncommon; however, functional impairment and eventual graft losses increased in number with longer follow-up, with recurrence assuming progressively greater importance as a cause of graft failure over time. In one series with an average follow-up of 61 mo, the mean time to clinical recurrence was 31 mo and to graft failure was 63 mo (21); it is clear that with long-term follow-up, additional late recurrences may be expected and the mean time to events will increase.

Recurrence is difficult to predict. Patient characteristics—pretransplantation course (23), IgA structure (24), and angiotensin-converting enzyme (ACE) genotype (18)—have been found to have no predictive value. Immunosuppression posttransplantation (cyclosporin or not) and posttransplantation course have no impact (17,18,23). Timing of biopsy is critical; later biopsies are more likely to reveal IgA deposits (17).

Living related donor transplantation has been associated with an increased risk of recurrence and graft loss in some series (21,23) but not in others (20). The increase in risk is the reduction in graft survival seems to be small, however, and does not justify the avoidance of living related donor transplantation in patients with IgAN.

Recurrence of HSP is less well characterized. A report describing two pooled series of patients from Belgium and Japan found recurrence in 35% and graft loss in 11% at 5 yr of

### Table 1. Differential diagnosis of recurrent glomerulonephritis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency and Timing Posttransplantation</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent glomerulonephritis</td>
<td>Common; variable timing—days to months</td>
<td>Hematuria, proteinuria, renal impairment</td>
</tr>
<tr>
<td>De novo glomerulonephritis</td>
<td>Uncommon; variable timing but typically late than recurrent glomerulonephritis</td>
<td>Hematuria, proteinuria, renal impairment</td>
</tr>
<tr>
<td>Graft pyelonephritis</td>
<td>Common; may occur early or late</td>
<td>Fever, renal impairment, pyuria</td>
</tr>
<tr>
<td>Calcium toxicity</td>
<td>Very common; acute or chronic</td>
<td>Renal impairment, oliguria, hypertension</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>Common; early</td>
<td>Renal impairment, hypertension, renal mass</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>Uncommon; rare; early or late</td>
<td>Renal tumor/PTLD</td>
</tr>
</tbody>
</table>

PTLD, posttransplantation lymphoproliferative disorder; HUS, hemolytic uremic syndrome; EBV, Epstein-Barr virus.
follow-up (25). Small numbers precluded statistical analysis; however, a tendency toward higher risk of recurrence in patients with a shorter initial disease course (renal failure within 3 yr of diagnosis) was noted. Delaying transplantation until 1 yr after the disappearance of purpura was not believed to prevent relapse (25). Thus, the pattern of recurrence seems to be similar to that of IgAN.

Treatment of recurrent IgAN and HSP has not been systematically evaluated. The use of nonspecific measures to prolong renal survival, such as tight BP control, ACE inhibition, and avoidance of nephrotoxins, is reasonable.

**Antineutrophil Cytoplasmic Antibody-Associated Vasculitis—Wegener’s Granulomatosis, Microscopic Polyangiitis, and Idiopathic Necrotizing Crescentic Glomerulonephritis**

A comprehensive, pooled analysis of all reported series of recurrent antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has largely clarified the behavior of the following group of disorders after transplantation (26): ANCA-associated vasculitis—Wegener’s granulomatosis (WG), microscopic polyangiitis (MP), and idiopathic necrotizing crescentic glomerulonephritis (CGN). Nine reported series and the author’s own series from Europe and the United States were included in the final analysis, covering a total of 127 patients. Single-case reports were excluded from the analysis to avoid positive reporting bias; however, as all series analyzed were retrospective, the risk of underdetection of recurrence was present.

Overall, recurrence was detected in 17% of cases after 4 to 89 mo of follow-up (26). Renal (60%) and extrarenal (50%) manifestations were detected, with graft losses reported in a minority of these. Relapse was reported at all stages of follow-up, with an average time to relapse of 31 mo but both early and late relapses reported (26). Clinical parameters were not useful in predicting patients who were likely to experience a relapse posttransplantation. Pretransplantation disease course, duration of dialysis, ANCA titers at time of transplantation and during follow-up, cANCA or pANCA specificity, disease subtype (WG, MP, or CGN), and type of transplant (live or cadaveric donor) had no discernible impact on recurrence rate (26).

The prevention and management of relapse have not been prospectively examined. In most reports, patients did not receive a transplant until in clinical remission (as distinct from being serologically ANCA negative), and thus the requirement of achieving clinical remission before transplantation has not been addressed. Although the addition of cyclosporin to azathioprine and steroid-based immunosuppression was not found to influence the rate of relapse (26), the use of cyclophosphamide-based prophylactic regimens from the time of transplantation has not been studied. In reported literature, patients with renal relapses were most commonly managed with cyclophosphamide-based immunosuppression, and this was successful in inducing a remission in 11 of 16 (69%) cases (26).

The prognosis of patients who receive transplants with ANCA-associated vasculitis seems to be at least as good as that of the general ANCA-associated vasculitis population (27,28). The relapse rate is approximately half in the transplant population as compared with the general ANCA-associated vasculitis population, possibly because of the degree and duration of immunosuppression given after transplantation (26). Potential disparities between the two populations must be noted in making this comparison, such as the prognostic impact of renal failure (transplant population), the prevalence of comorbidities (which may exclude patients from transplantation), and age (typically younger in the transplant group). Patient and graft survival posttransplantation seem to be equivalent in the ANCA-associated vasculitis group, as compared with the general transplant population (26).

Despite the potential for relapse and the lack of characteristics that predict this risk, transplantation seems to be an advisable mode of therapy for patients with renal failure caused by ANCA-associated vasculitis. The potential for relapse at any stage should be recognized and should prompt frequent review for clinical evidence of relapse, such as hematuria, renal impairment, and symptoms and signs of extrarenal vasculitis. Serologic monitoring is of little value in predicting or detecting relapse. In the absence of prospective, controlled data, cyclophosphamide-based therapy seems to be effective in the treatment of relapse.

**Anti-GBM Disease**

Histologic recurrence is seen in 50% of patients who receive transplants while circulating anti-GBM antibodies persist (29) but in only 5 to 15% of patients who receive transplants 6 mo or more after the disappearance of anti-GBM antibodies (7). With delayed transplantation, the rate of clinical recurrence is low, although late recurrences have been described (30). Recurrent anti-GBM disease should be treated with steroids, cyclophosphamide, and aggressive plasma exchange.

Recurrent anti-GBM disease is distinct from de novo anti-GBM disease seen in some patients with Alport’s syndrome, who develop anti-GBM antibodies in response to neoantigen exposure (α-chain of type IV collagen) via the transplant (31).

**Hemolytic Uremic Syndrome**

Recurrence of HUS posttransplantation has been the subject of a recent meta-analysis that examined 10 reports covering 159 grafts in 127 patients (32). Recurrence occurred in 28% of cases and was strongly associated with a poor outcome—1-yr graft survival was 33% for those with recurrence versus 77% in those free of recurrence ($P < 0.001$) (32). Recurrence was associated with an older age of onset, rapid progression of the original disease, earlier transplantation, living-related transplantation, and the use of calcineurin inhibitors (32). Miller et al. (33) also documented a low rate of recurrence in those with diarrhea-associated “classical” HUS as compared with a high rate in those with other forms, including familial HUS. Recurrence should be distinguished from de novo HUS when possible, which may be related to cyclosporin, tacrolimus, OKT-3, or vascular rejection. Recurrence is generally within the first 6 mo posttransplantation; however, late recurrences have been reported (32). The clinical presentation may be gradual or abrupt, with thrombocytopenia, hemolysis, and progressive renal dysfunction.
Although de novo disease may respond to withdrawal of the inciting agent, management of recurrent disease is unproved. A trial of plasma exchange and withdrawal of any potentially contributory medication, e.g., cyclosporin, is a reasonable approach. In cases of life-threatening thrombocytopenia or hemolysis, hematologic stability may be restored by transplant nephrectomy. The prognosis of recurrent disease is poor. More than 50% of grafts are lost within the first year, and graft survival beyond 5 yr is uncommon (32,33).

**Focal and Segmental Glomerulosclerosis**

Much has been written about the recurrence of FSGS post-transplantation, because of the frequency of FSGS as a cause of end-stage renal failure and its widely recognized tendency to recur early and dramatically after transplantation. As opposed to most forms of glomerulonephritis, significant insights into the pathogenesis of recurrence of FSGS have been made and logical and moderately effective therapies have resulted.

Patients with renal failure cause by FSGS incur a risk of recurrence of 20 to 30% for first transplants (34–36). Recurrence typically is early, occurring at a mean time of 14 d posttransplantation in children (35), and is commonly manifest by heavy proteinuria, hypertension, and graft dysfunction. Patients with recurrent disease are more susceptible to acute rejection and acute renal failure (15), as well as graft loss, which occurs in 40 to 50% of cases (36). The rate of recurrence is more than 75% in subsequent grafts when the first graft was lost through recurrence but is less when the first graft was lost through other causes (37).

Patients who are at highest risk of recurrence are those with an aggressive initial course (renal failure within 3 yr of onset), age less than 15 yr, mesangial proliferation on biopsy, or recurrence in a previous transplant (34,35). Early reports focused on an apparent increase in recurrence after living related donation; however, subsequent reports have highlighted the safety of this approach (38,39). Cyclosporin seems to confer no benefit over azathioprine and steroids in terms of prevention.

Recurrence FSGS seems to be mediated by a circulating 50-kD plasma protein, which is bound to Ig (40,41). This factor can be removed by plasma exchange or immunoabsorption against either a protein A or an anti-Ig column and can induce proteinuria when applied to rat glomeruli (40,41). Precise identification of the protein is awaited. Attempts to use the presence of the “permeability factor” as a guide to the risk of recurrence have shown some promise (42) but have not yet produced a clinically useful test (43). Removal of the permeability factor does seem to be the mechanism responsible for the success of plasma exchange in the therapy of recurrent FSGS (40–42). Although not assessed by a randomized, controlled, prospective trial, several series have reported the success of plasma exchange (or immunoabsorption) in inducing remission in the majority of patients treated within 2 wk of relapse (40,42,44). Relapse after cessation of plasma exchange has been encountered but may be prevented or reversed by either chronic plasma exchange (44) or concurrent treatment with cyclophosphamide (42). Case reports have described treatment of relapse with cyclophosphamide alone, increased dose of cyclosporin, nonsteroidal anti-inflammatory drugs, and ACE inhibitors; however, these treatments should be considered as secondary to therapy with plasma exchange, plus or minus adjunctive cyclophosphamide.

Recurrent FSGS is a feared complication but should not preclude transplantation in this group of patients. Live-donor transplantation probably should be reserved for those without features that suggest a high risk of recurrence or be performed in high-risk cases only after in-depth discussion of the risks involved with all participants. Monitoring for the development of proteinuria should be intensive for the first months after transplantation in all cases, and recurrence should be treated early with plasma exchange and cyclophosphamide.

**Membranous Glomerulonephritis**

Data on recurrent membranous glomerulonephritis (MN) is clouded by two key issues—the paucity of reports involving significant numbers of patients and the frequency of de novo MN posttransplantation. De novo MN has been reported to occur in 2 to 9% of transplant recipients (45) and tends to present more insidiously and later than recurrent MN (mean time to onset, 22 versus 10 mo) (45).

The largest series (pooled from centers in Belgium and France) reported a recurrence rate of 29% in 30 patients at 3 yr posttransplantation (46) and graft survival of 38% at 5 yr and 52% at 10 yr of follow-up. This recurrence rate is higher than earlier estimates (6) but consistent with another recent study from Spain (47). This series looked for factors to predict the risk of recurrence but was unable to link pretransplantation disease course, duration of dialysis before transplantation, HLA genotype, graft source, or use of cyclosporin to recurrence risk (46).

Management of recurrent MN is based on anecdotal reports and extrapolation of data on the management of native kidney MN. Spontaneous remissions, responses, and failures with immunosuppressive treatment all have been reported (47). As a note of caution against excessive use of immunosuppressants, three lymphomas occurred during follow-up of 19 patients with recurrent MN, possibly related to treatment of the primary lesion (48). Live-donor transplantation seems to be warranted for first grafts but probably should be avoided for second grafts if graft loss was the result of recurrence, because the risk of recurrence in subsequent grafts is probably high.

**Mesangiocapillary Glomerulonephritis**

Given the histologic similarities between chronic allograft nephropathy/chronic rejection and MCGN, comprehensive assessment of transplant biopsies as well as accurate diagnosis of the native kidney disease is crucial in distinguishing MCGN from the far more common entity of chronic rejection. MCGN is suggested by the presence of crescents on light microscopy, stronger staining for C3, and weaker staining for IgM on immunohistology and by the presence of dense subendothelial deposits on electron microscopy (4,5). This distinction is important to consider in reviewing the literature on recurrent MCGN (potential for overdiagnosis of MCGN) and in considering the implications for individual patients (higher risk of...
recurrence and graft loss in subsequent grafts after graft loss caused by recurrent MCGN).

**MCGN Type I**

MCGN type I seems to be mediated by glomerular deposition of immune complexes, triggered by exposure to endogenous, e.g., native DNA in systemic lupus erythematosus, or exogenous, e.g., hepatitis B or C, antigens. As the antigens are not removed by transplantation, recurrence of disease is predictable and is seen in 20 to 33% of graft recipients (7,49). Graft loss has been reported in up to 40% of those with recurrence, and the risk of recurrence in subsequent grafts approaches 80% (49). Patients who receive HLA-identical grafts seem to be at particular risk of recurrence (49). No form of treatment is proved, and the underlying cause of recurrent MCGN type I should be considered in each case. Recurrences related to persistent hepatitis B antigenemia may warrant a trial of lamivudine, although strong data are lacking. Liver transplantation has been reported with short-term success (50). Other forms of MCGN type I have been treated with immunosuppression (51) and plasma exchange (52) with success in single cases.

**MCGN Type II (Dense Deposit Disease)**

MCGN type II has been found to recur in 50 to 100% of grafts (2,6,7,53). The clinical presentation typically shows hematuria and proteinuria during the first year after transplantation, with slowly declining renal function thereafter. Graft losses have been reported in 10 to 25% of recurrent cases, with male gender, crescents on biopsy, and heavy proteinuria indicating a higher risk of graft loss (2,6,53). No effective therapy is known. Plasma exchange and immunosuppression have been described in case reports (2).

**MPGN Type III**

One case of MCGN type III recurrence 13 mo posttransplantation has been reported, culminating in graft loss after 7 yr (54).

**Lupus Nephritis**

The reported recurrence rate of lupus nephritis (LN) has varied from <1 to 8% (2,55). Recurrence has been reported early (days) and late (years) after transplantation, with a mean time to recurrence of 3.1 yr in the largest series reported (55). Duration of dialysis before transplantation and serologic activity have not been found to predict recurrence (56). Similarly, antinuclear antibody titer and complement level have been found to be unreliable markers of disease recurrence posttransplantation (56). The clinical and histologic pattern of recurrence is variable; mesangial proliferative (class II), focal and diffuse proliferative (classes III and IV), and membranous (class V) subtypes all have been reported (56).

In contrast to earlier reports, recent pooled data suggest that overall graft and patient survival may be worse in the lupus population, despite the younger age of lupus patients (56). Recurrent LN may result in graft loss, and graft loss may also occur as a result of thrombosis in association with the presence of a lupus anticoagulant (56). Of nine reported series comparing transplant outcomes in lupus and non-lupus recipients, three studies reported equivalent outcomes but six studies reported worse outcomes for those with lupus. Graft survival seems to be better after live-donor transplantation than cadaveric-donor transplantation (56).

Management of recurrent LN has not been formally studied; however, the use of steroids, cyclophosphamide, and plasma exchange all have been reported, with variable results (57). We induced a partial remission in one patient by changing from azathioprine to mycophenolate, together with prednisolone and tacrolimus maintenance immunosuppression (unpublished data). Anticoagulation during the perioperative and early posttransplantation phases should be considered for patients with LN and a history of thrombosis or lupus anticoagulant positivity. Retransplantations have been performed after graft loss caused by disease recurrence; however, the small number of cases reported does not allow conclusions to be drawn on the success of retransplantation (55).

Recurrent lupus does occur more frequently than was initially appreciated, and graft outcomes in LN seem to be slightly worse than for the general transplant population. However, the majority of patients who receive transplants for LN can expect a low probability of recurrence (<90%) and a reduction in general activity of their lupus; for these reasons, transplantation remains a good therapeutic option.

**Systemic Sclerosis/Scleroderma**

A large retrospective analysis of patients reported to the UNOS registry after receiving a kidney transplant for scleroderma has been performed (58). Eighty-six patients reported between 1987 and 1997 were analyzed. Graft survival was 62% at 1 yr and 47% at 5 yr posttransplantation, and 24% of patients died during the 10-yr observation period (58). The recurrence rate could not be determined accurately; however, recurrence was responsible for graft loss in 21% of cases in which the cause was identified, which is consistent with a previously reported recurrence rate of 20% (2). Risk factors for recurrence were not identified, and cyclosporin use did not seem to affect the recurrence rate (58). The effect of transplantation on the nonrenal manifestations of scleroderma has not been well documented.

The management of recurrent scleroderma is undefined. The use of ACE inhibitors posttransplantation to treat hypertension in this group of patients seems reasonable. Overall, the posttransplantation course of scleroderma seems to be similar to that of lupus (58), and renal transplantation seems to be a reasonable procedure for those with end-stage renal failure.

**Fibrillary Glomerulonephritis and Immunotactoid Glomerulonephritis**

Although only a small number of transplant recipients have been reported to have fibrillary glomerulonephritis and immunotactoid glomerulonephritis, the recurrence rate of this disease seems to be more than 50% (59). Documentation of recurrence, as with the primary diagnosis, requires electron microscopy (4,5,59). The authors of the largest series reported a slower rate of decline in renal function in three patients with
recurrent disease, as compared with those with native kidney involvement. They concluded that transplantation is an attractive option in patients with end-stage renal disease caused by fibrillary glomerulonephritis or immunotactoid glomerulonephritis (59). As a note of caution, one case of early recurrence that led to graft failure has been reported (60).

Conclusions

Strong data have emerged on patterns of recurrence, risk factors for recurrence, and the implications for patient and graft outcomes after recurrence of the most common glomerulopathies. Such data allow us to make rational decisions about transplantation—who should receive a transplant, when, how many times, and from what donor source. These data allow us to provide patients and their families with adequate information to enable them to make decisions and to provide informed consent to transplantation.

In contrast, data currently available on recurrence patterns of the less common nephropathies sadly are inadequate and our practice is therefore guided by small series, case reports, and local experience. It is hoped that this deficit will be addressed in the near future through the use of powerful databases and registries, some of which are prospectively collecting data on specific disorders.

Prospective studies of treatment of recurrent glomerulonephritis are lacking. As grafts last longer and recurrent glomerulonephritis becomes a more significant entity, affecting greater numbers of patients, the opportunity to study management prospectively will arise. This likely will require a cooperative, multicenter approach and clearly is the way forward.

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