Recurrence of glomerulonephritis (GN) and newly occurring GN (de novo GN) in the transplanted kidney are a frequent cause of allograft loss at 10 years [1] (Table 1). For example, studies in large US databases found a recurrence of the underlying disease in 3–8% of the patients [2, 3]. However, these retrospective analyses are biased by many confounding factors, such as the enormous disparity in the number of diseases, the different periods of transplant, the different treatments, the different policy for biopsy etc.

New immunosuppressive drugs have improved the short- and long-term graft survival and offered better control of acute and chronic rejection. However, they have not appreciably changed the occurrence and outcome of recurrent and de novo GN after renal transplantation. Indeed, it is estimated that up to 50% of patients developing recurrence or de novo GN lose their graft on long-term follow-up [4]. More than 75% of recurrent diseases in renal allografts are recurrent GN, and we will therefore focus on these disease entities. Given the increase in overall allograft survival rates, it is predictable that the relevance of recurrent GN will increase in the future. Indeed, even in diseases where recurrence was initially considered to be relatively benign, such as IgA-nephropathy [5], more recent data [6] with a much longer follow-up indicate a high frequency of clinically relevant disease including recurrence-related graft loss.

In addition, recent insights into the pathogenesis of several glomerulopathies are not only likely to help in assessing the risk of recurrence but might also provide a clue for prevention or targeted treatment of these entities. This seems particularly promising in diseases with detectable pathogenic factors like anti-PLA2R antibodies in membranous GN, dysregulation of the complement system in C3-related GN, circulating urokinase receptor (suPAR) in focal segmental glomerulosclerosis (FSGS) and aberrantly glycosylated IgA in IgA nephropathy. The pathogenic role of these factors in recurrent diseases has been postulated but still awaits confirmation in proper studies on sufficiently sized patient cohorts. Investigating the role of these ‘soluble factors’ in transplant recipients might not only be diagnostically or clinically beneficial but could also be essential for confirming and/or refining the underlying concepts.

However, recurrent GN is also challenging for several reasons: (a) native kidney disease is often misdiagnosed or mislabelled, (b) biomarkers for the diagnosis of recurrent GN are lacking, (c) recurrent GN is difficult to differentiate from drug toxicity and alloantigen-dependent chronic immunologic damage, (d) a better characterization of recurrent GN may improve our knowledge of glomerular diseases and (e) due to the development of new therapeutic approaches [3, 7, 8].

In caring for transplant patients with an underlying GN, we previously recommended the following [9]:

(i) Try to obtain a precise diagnosis of the primary disease wherever possible;
(ii) Consider a renal biopsy prior to kidney donation in living-related donors in potential familial disease (e.g. IgA nephropathy); according to our policy, we accept living-related donors for recipients with membranous GN, membranoproliferative GN type I IgA nephropathy and anti-GBM nephritis. Living donors should be accepted in a highly restrictive fashion and only after intensive discussion in patients with dense-deposit disease or children with FSGS and a high chance of recurrence. The latter includes patients with mesangiproliferative changes upon renal biopsy, who are younger than 15 years of age and/or with a less than 3-year duration between diagnosis and renal failure. However, even if this high-risk constellation is present, the risk of recurrence needs to be balanced with the risks of continued dialysis, in particular if children are involved.

(iii) Try to identify causes of prior graft losses as thoroughly as possible;

(iv) If recurrent GN did lead to graft loss in the past, we caution against living donation, as there is an inappropriately high risk for another recurrence and graft loss [10];

(v) Modify, when possible, immunosuppression according to underlying disease (controversial);

(vi) After renal transplantation, pathological laboratory findings should be clarified aggressively including graft biopsy, evaluated ideally by a combination of light microscopy, immunohistology and electron microscopy to distinguish recurrent GN from other pathological entities observed in chronic allograft nephropathy.

However, even when all these recommendations are followed, the real dilemma starts with therapy.

In large databases, there is little evidence that the choice of immunosuppression after transplantation affects recurrence rates [3]. However, rapid steroid discontinuation after transplantation has been proposed as a factor contributing to early GN recurrence but not graft loss [11, 12]; these data need to be confirmed in larger studies. Finally, bilateral nephrectomy prior to transplantation does not prevent recurrence [13].

We are currently left with a scenario where in most instances recommendations are based on individual cases or small case series and we are not aware of a single randomized controlled trial addressing this important issue. In addition, there is concern that publication bias may lead to the wrong impression that some treatments are effective when in fact many non-successful attempts may not have been published.

With respect to particular disease entities, case reports or small case series have reported some benefit from the following:

(i) Focal segmental glomerulosclerosis (FSGS): increased immunosuppression and/or plasma exchange or immunoabsorption [14], rituximab [15–17], oral galactose therapy [18] or anti-TNF alpha therapy [19].

(ii) Membranous GN: rituximab [20].

(iii) Membranoproliferative (mesangiocapillary) GN (MPGN) type I: long-term cyclophosphamide [21] or plasmapheresis [22].

(iv) Dense-deposit disease and other C3 glomerulopathies: eculizumab or therapy targeted against autoantibodies that activate the complement cascade [23, 24].

(v) IgA-nephropathy: ACE inhibitors [25], high-dose corticosteroid bolus therapy for recurrent crescentic IgAN [26].

(vi) ANCA-associated vasculitis: cyclophosphamide-based regimens as used for renal vasculitis in native kidneys [27].

(vii) Lupus nephritis: corticosteroids, cyclophosphamide and plasma exchange, all with variable results [28]. Anticoagulation should be considered for those with a history of thrombosis or lupus anticoagulant positivity.

Table 1. Overview of recurrence and recurrence-related graft loss as reported in the literature (modified from Floege [9])

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical recurrence rate [% of transplanted patients]</th>
<th>Graft loss after 5–10 years [% of transplanted patients]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>10–25% (&gt;50% histologically)</td>
<td>2–16%</td>
</tr>
<tr>
<td>FSGS</td>
<td>20–40%</td>
<td>10–20%</td>
</tr>
<tr>
<td>MPGN Type I</td>
<td>20–50%</td>
<td>10–30%</td>
</tr>
<tr>
<td>Dense-deposit disease</td>
<td>&gt;80% (histologically)</td>
<td>10–25%</td>
</tr>
<tr>
<td>Membranous GN</td>
<td>5–30%</td>
<td>5–20%</td>
</tr>
<tr>
<td>Anti-GBM nephritis</td>
<td>Exceptional</td>
<td>Exceptional</td>
</tr>
<tr>
<td>ANCA vasculitis</td>
<td>20%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>5–30%</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

aThe most important differential diagnosis is transplant glomerulopathy.

bNote 3-fold higher rate of de novo membranous GN.

J. Floege et al.
In summary, while some disease-specific approaches are emerging, good supportive care, similar to that used in the primary diseases, is all we can currently offer to the majority of patients with recurrent GN. Given the relative infrequency of recurrent GN even in the more common GN types, it is clear that multi-centre studies on how to treat recurrent GN will be difficult to achieve, even if recurrent GN offers the unique opportunity of not only early but also preventive therapy. It is against this background that the Immunonephrology Working Group of the European Renal Association has initiated a database on recurrent GN.

The ERA-EDTA Database on Recurrent Glomerulonephritis (RGNdatabase: www.recurrentgn.net; Figure 1) will serve to collect and define cases of recurrent or de novo GN but will particularly focus on therapeutic interventions to provide more than just anecdotal information on the therapy of recurrent disease. We hope that the RGN database can thereby generate better information on the treatment of recurrent GN, reduce publication bias in which only positive experiences are published and, ideally, can even lay the basis for randomized trials.

The RGN database will be established to address questions on recurrent GN affecting the kidney only (such as IgA nephropathy, membranous GN etc.) or systemic diseases (such as lupus nephritis, thrombotic microangiopathy and ANCA-associated vasculitis) or de novo GN after transplantation. The true rate of recurrent GN in Europe is not clear due to the lack of studies. To this purpose, at least 40 renal transplant centres will be recruited throughout Europe. To subscribe, the user should fill in all the mandatory fields of the registration form available on the website (www.recurrentgn.net). After registration, the user will receive the credentials (user name and password) to access the database (Figure 2). Starting 1 January

FIGURE 1: Recurrent GN website.

FIGURE 2: Registration form.
**Figure 3**: Recurrent GN dataset (baseline).
FIGURE 4: Recurrent GN dataset (follow-up).
2013, all renal allograft recipients with recurrent primary or secondary glomerulonephritides should be registered in the Web-based dataset by each centre (Figure 3). All transplant recipients will be informed that selective clinical data will be collected and submitted to the database. Each patient will sign an informed consent. To maintain anonymity, patient data will be coded during compilation, and for data analysis, only anonymous data will be released by the database. Baseline clinical information and follow-up will be collected annually regarding outcomes and therapeutic interventions. Every event occurring during the year (recurrent GN identified by transplant biopsy, acute and chronic rejection, ESKD, therapy changes, death etc.) will also be recorded (Figure 4). An alert system will control, during the submission process, the quality of the data inserted highlighting the missing and incorrect data.

News items, appearing on the homepage of the website, will provide information about the activities (meetings, courses, articles published etc.).

Biopsy-documented recurrent or de novo GN reported by the single centre will be confirmed by an independent nephropathology group. Diagnosis of recurrent GN can be challenging. The pattern of glomerular lesions may be complex due to an overlap of chronic transplant glomerulopathy with the injury of native kidney glomerular disease. The exact diagnosis therefore frequently requires extended immunohistology and electron microscopy.

A central review by a panel of experienced pathologists will ensure uniform terminology in disease classification and might also provide technical help in difficult cases. The central review will be based on digital pathology with whole slide scans. The plan is to collect original histology slides centrally for an initial reading by an expert renal pathologist. Slides will then be scanned and stored in a digital slide database. This strategy ensures a short handling time of original slides that can be sent back to the contributing centre within a few days, providing an opportunity for the slides to be read by a panel of remote expert pathologists as well. Telepathology ensures panel reading without the need for regular consensus meetings that might be difficult to organize. If the contributing centre has a slide-scanning facility, the digital slides can also be submitted electronically. Centrally stored digital slides will be available for all participants and enable reassessment of cases for specific features that might not have been scored originally, at any time. Furthermore, this provides a unique source of high-quality images for publications or advanced analysis methods like morphometry and automated cell counting.

The first step in a central review process will be a consensus confirmation of the original diagnosis by a panel of
three expert nephropathologists. If a consensus cannot be achieved, the panel might ask the contributing centre for additional material like tissue blocks for further immunohistochemical staining and/or material for EM studies. Only cases with a definite consensus diagnosis will be entered into the database.

The RGN database will also be accessible on smartphone or tablet to provide a mobility-related feature to the platform (Figure 5).

REFERENCES