Coming back to dialysis after kidney transplant failure

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Preliminary considerations

Advances in immunosuppressive therapy in recent decades have led to excellent renal transplant survival rates at 1 year, but the advantages are lower in the long term. As reported by Meier-Kriesche et al. [1], the actual kidney allograft half-life showed only a marginal improvement over the past decade. Recent data from the United States Renal Data System (USRDS) report an almost invariable 4% annual rate of graft failure among renal transplant recipients [2]. Given the continuing expansion of the transplanted patient pool, this figure translates into a progressive increase in the number of transplanted patients re-entering a dialysis programme [3].

Outcome of patients starting dialysis after graft failure

Since the first reports, the mortality rate in patients starting dialysis after graft loss has been reported as variable, though higher than that observed in patients with a functioning graft and basically similar to that observed in patients on dialysis treatment [4–9] (Table 1).

However, the assessment of mortality rate in the cohort of patients starting dialysis after graft failure has methodological limitations. First, transplanted patients arriving at the time of graft failure represent a selected cohort, since the most compromised transplanted patients often die with a functioning graft. Furthermore, it is not easy to establish which is the most appropriate cohort to be compared with patients starting dialysis after graft failure as far as morbidity and mortality are concerned. In fact, when the surviving transplanted patients are taken as the comparison cohort, the expected result is to overestimate the risk of mortality in patients starting dialysis after graft failure, as the different degree of renal function may represent per se a mortality risk factor. On the other hand, when compared with patients on dialysis treatment, the mortality risk of patients with graft failure might be underestimated, since the global dialysis population includes patients who were not waiting-listed for transplantation due to higher co-morbidities.

Two recent studies better addressed the problem of mortality rate after graft loss. Gill and co-workers [10] studied death rates between 1995 and 2003 during the continuum of the waiting list, during transplantation and after graft failure in patients who had begun dialysis treatment and were subsequently admitted to the transplant waiting list. When the three periods were compared, the lowest death rate was found in the transplant period and the highest in the period following allograft failure. The highest mortality rate was found during the periods of transition from waiting list to transplant (8.2/100 patient-years) and during the re-initiation of dialysis after transplant failure (17.9/100 patient-years). The second study from Rao and co-workers [11] analysed data from the Scientific Registry of Transplant Recipients (no. 174 436). The authors compared the risk of death in patients waiting-listed between 1995 and 2004, between those who thereafter experienced allograft failure after receiving a kidney transplant and patients entering the waiting list during the same period who did not receive a transplant. Overall mortality risk was ~80% greater in patients who experienced a graft loss than in patients remaining on the waiting list. The mortality risk was particularly elevated during the first 3 months after graft failure, but remained significantly higher even after 5 or more years. However, it is worth stressing that also the results of this study are hampered by a potential selection bias and most importantly, information on comorbidities is missing.

Cardiovascular disease and infection are the main causes for the increased mortality rate in patients starting dialysis after losing their allograft [7]. It has also been underlined that non-immunological conditions represent the main mortality risk factors in this cohort of patients [12]. In particular, in addition to more advanced age and female gender, also diabetes, peripheral vascular disease, congestive heart failure and low albumin levels were all found to be significantly associated with an increased risk of death. An additional...
and often underestimated causal factor for increased death in these patients might be the presence of anaemia. It has been underlined that patients who return to dialysis with failed transplants are at a higher risk of anaemia than other patients who start dialysis [13]. The pattern of this anaemia is characterized by higher ratios of epoetin-to-haemoglobin, suggesting a relative epoetin resistance status [14].

Furthermore, Ansell and co-workers [13], reporting data from the UK renal registry, underlined that transplant patients with chronic kidney disease (CKD) at stage 5 are usually poorly treated as far as comorbidities are concerned and this may greatly affect their clinical outcome.

Special topics

When to start dialysis treatment?

There is no clear indication about the optimal timing for starting dialysis after graft failure, so we can only rely on the indications available for the general population of patients with CKDs, based on clinical symptoms and biochemical changes. However, if we take as good the recently revised K/DOQI recommendations for the initiation of the first dialysis treatment, a calculated glomerular filtration rate (GFR) <15 ml/min should prompt clinicians to start dialysis treatment in a patient with a failing graft [15].

In fact, many reports on patients with renal allograft failure tell us that dialysis is often started at GFR levels far below the optimal suggested threshold [16–18]. These studies suggested that the delay in starting dialysis after graft loss might negatively impact on morbidity and mortality. The delay in starting dialysis might be due, at least in part, to the difficulty in assessing the renal function in transplanted patients. In fact, serum creatinine levels consistently underestimate the true GFR reduction, due to the frequently reduced muscle mass in transplanted patients. Furthermore, it is worth underlining that in these patients, none of the equations utilized for calculating GFR in the general CKD population reaches the level of accuracy required by the K/DOQI standards [19]. However, in addition to the above-mentioned objective difficulties, the reluctance of both patient and doctor to accept the irreversible failure of the graft may also play a role in delaying dialysis initiation. Furthermore, it is also common experience that the tolerance to uraemic symptoms differs greatly from one patient to another.

In summary, even if there are some arguments suggesting that starting dialysis earlier than usually done might have some benefits on morbidity and mortality, it is as yet not possible to give any definitive recommendation on the level of GFR at which a patient should be submitted to dialysis after graft failure.

What type of dialysis?

Whether peritoneal dialysis (PD) or haemodialysis (HD) is the preferred modality when starting dialysis treatment after graft failure is far from being clarified. Only scanty, retrospective studies have addressed this topic. Sasal et al. [17] found that mortality was higher in 42 patients starting PD after graft failure than in 43 randomly selected PD patients who had never had a transplant. At variance with this, other studies [20–22] did not find any significant difference in survival among patients who started PD after graft loss and never-transplanted patients who started renal replacement therapy with PD. Nor was any significant difference in patient survival reported by other groups that compared PD or HD as dialysis treatment after graft failure [20,23].

It is worth stressing that all these studies are retrospective, and suffer from biases (selection bias, survival bias) and lack of much critical information (e.g. maintenance of immunosuppressive therapy). On the basis of the available data, it is not possible either to draw firm conclusions or to offer recommendations on whether PD or HD are preferable for starting dialysis in patients with a failed allograft. However, in our opinion, both PD and HD can be considered valid treatment options.

How to handle immunosuppressive therapy?

There are pros and cons in maintaining immunosuppression (IS) after graft failure. In favour of the maintenance of IS therapy, we should consider that a complete IS withdrawal may induce acute rejection even in a failing kidney allograft. An acute rejection, in the absence of any form of IS, might result in a spontaneous rupture of the graft, complicated by a life-threatening haemorrhage, which would require an urgent life-saving graft removal. Another potential advantage of maintaining IS is the preservation of, at least in part, a residual renal function. Finally, in our personal experience, the complete withdrawal of steroids is often followed by the appearance of general symptoms such as fever, arthralgia, hypotension, asthaenia that enhance the subtle symptomatology of an underlying rejection. On the other hand, it is well known that maintaining IS in patients on dialysis may be associated with unacceptably high rates of infections, worsening of cardiovascular risk factors, increased risk of malignancies and a negative impact on bone metabolism.

### Table 1. Variable mortality rates, reported by different authors, of patients starting dialysis after graft failure (GF) compared with patients on dialysis (HD) or with a functioning renal transplant (RTx)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort (no. of patients)</th>
<th>Comparison</th>
<th>Results</th>
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<tbody>
<tr>
<td>[4]</td>
<td>Monocentric (63)</td>
<td>GF versus HD</td>
<td>No significant difference in mortality rate</td>
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<tr>
<td>[5]</td>
<td>Monocentric (83)</td>
<td>GF versus HD</td>
<td>No significant difference in mortality rate</td>
</tr>
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<td>[6,7]</td>
<td>USRDS (15 528)</td>
<td>GF versus RTx</td>
<td>Increased mortality in GF</td>
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<tr>
<td>[8]</td>
<td>CORR (4753)</td>
<td>GF versus RTx</td>
<td>Increased mortality in GF</td>
</tr>
<tr>
<td>[9]</td>
<td>CORR (25 632)</td>
<td>GF versus HD and RTx</td>
<td>Increased mortality versus RTx; no significant difference versus HD</td>
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was performed as an urgent clinical necessity. Furthermore, the interventions of the published studies have been performed on small cohorts of patients and that the greater part of the interventions described in Table 2.

| 1. Immediate withdrawal of anti-proliferative drugs (AZA, MPA/MMF, SRL) |
| 2. Tapering and withdrawal of CNI over a brief period (1–3 weeks) if the graft failure followed a chronic and slow progression |
| 3. Tapering and withdrawal of CNI over a longer period (4–8 weeks) if the graft failure followed more acute immunologic events |
| 4. Slow tapering of steroids with possible withdrawal (in a few months) |
| 5. Maintain the same dose of steroids taken when dialysis is initiated for 1 month |
| 6. Then halfsteroid dose every month until complete withdrawal. |
| 7. In the case of disturbing symptoms requiring relatively high doses of steroids, a graft nephrectomy should be considered |
| 8. Check for symptoms (fever, pain, graft swelling) |
| 9. Check for signs (CRP, WBC; graft tomography) |

There are few papers addressing this critical issue. Gregoor et al. [24] evaluated the morbidity and mortality in 177 patients who received 197 kidney transplants and who thereafter experienced a failure of their graft. In the follow-up of these patients, the authors considered separately the period with and the period without IS and compared the occurrence of major events between these two periods. They found a significantly increased morbidity and mortality rate during the period on IS. However, it is important to underline that this study has some biases. First, the reason for discontinuing or maintaining IS was based on clinical criteria which might indirectly suggest that the more clinically stable the patients were the higher was the probability of IS withdrawal. Furthermore, it is highly likely that the period on IS therapy was the early phase after graft failure, a period that is burdened with the highest morbidity and mortality rate [11,12].

Our clinical policy for tapering IS therapy after return to dialysis is shown in Table 2. The main rationale for withholding antiproliferative drugs first is based on the consideration that the use of these drugs is well known to induce an increased bacterial infection rate and higher bone marrow suppression. Since patients who return to dialysis after graft failure are mainly burdened by high infection rates and erythropoietin-resistant anaemia, it is our opinion that antiproliferative drugs should be the first drugs to be discontinued when irreversible graft failure is established.

How to handle the failed kidney?

Another issue in patients with graft failure is whether and when the graft should be removed after its failure. Again there are both pros and cons regarding this topic. The possibility of preserving a residual renal function is a noteworthy point in favour of maintaining the kidney allograft, even after its failure. In addition, many transplant nephrologists and surgeons stress the risk of graft nephrectomy. Mortality associated with graft nephrectomy ranges from 0 to 39% (reviewed in [25]). However, it is worth stressing that most of the published studies have been performed on small cohorts of patients and that the greater part of the interventions was performed as an urgent clinical necessity. Furthermore, the mortality of patients starting dialysis after graft failure from April 1995 to December 2003 were collected. In 6213 patients, graft nephrectomy was performed, almost invariably during the first year after starting dialysis. Nephrectomy was twice as common in patients who had a renal transplant functioning for <1 year than in patients with a longer transplant survival. Nephrectomized patients were also more likely to be females, Afro-Americans, non-diabetic, not suffering from heart failure, cardiac ischaemic disease, peripheral vascular disease and cerebrovascular accident, and had higher PRA levels. The authors also found that the risk of death in nephrectomized versus non-nephrectomized patients was completely different depending on whether graft survival was lower or greater than 1 year. In the former group, mortality risk was higher in nephrectomized than in non-nephrectomized patients (RR of death 1.13), while in the latter group, nephrectomized patients had a consistent survival advantage (RR of death 0.89). However, the results of these studies are flawed by some limitations: (i) the clinical indication to nephrectomy was not specified, (ii) the concomitant immunosuppressive therapy was not reported and (iii) the cohort of studied patients was only a part of the patients starting dialysis after graft failure.

Another issue raised against graft nephrectomy has been the observation that graft removal may be followed by Ayus and Achinger [25] in their editorial underline that the highest mortality was reported in the historical series, while in the more recent studies the mortality rate is near zero.

On the other hand, the maintenance of the graft requires us to continue IS, with its possible negative impacts as discussed above. Furthermore, a failed graft represents per se a chronic inflammatory stimulus that might negatively affect the nutritional status and further increase the already high cardiovascular risk in these patients. Last but not least, maintenance of the graft after its failure requires continuous monitoring in order to promptly diagnose an acute rejection episode that might rapidly evolve towards daunting complications such as graft rupture.

Even if it is still unclear how to handle the failed graft, a paper from Lopez-Gomez et al. [26] gives some support to the notion that maintaining the graft after its failure can be dangerous. These authors followed up 43 patients who started dialysis after graft failure. Twenty-nine of these patients were submitted to an early graft nephrectomy due to general and/or local symptoms (group A), while the remaining 14 asymptomatic patients maintained their graft (group B). At the start of these observations, the 29 group A patients had consistently more evident signs of inflammation and malnutrition (high CRP, resistance to erythropoietin, low albumin levels) than the group B patients. However, 6 months after nephrectomy for group A and the start of dialysis for group B, the situation had completely reversed with a near complete normalization of inflammation and nutrition parameters in group A, while group B patients, though initially asymptomatic, had decisively altered inflammatory and nutrition indices. The authors concluded that maintaining a failed graft represents a chronic inflammatory state, independently of the presence or absence of any overt symptom.

A more recent paper [27] dealt with the present topic, using the USRDS registry. Data from 19 107 patients who started dialysis after graft failure from April 1995 to December 2003 were collected. In 6213 patients, graft nephrectomy was performed, almost invariably during the first year after starting dialysis. Nephrectomy was twice as common in patients who had a renal transplant functioning for <1 year than in patients with a longer transplant survival. Nephrectomized patients were also more likely to be females, Afro-Americans, non-diabetic, not suffering from heart failure, cardiac ischaemic disease, peripheral vascular disease and cerebrovascular accident, and had higher PRA levels. The authors also found that the risk of death in nephrectomized versus non-nephrectomized patients was completely different depending on whether graft survival was lower or greater than 1 year. In the former group, mortality risk was higher in nephrectomized than in non-nephrectomized patients (RR of death 1.13), while in the latter group, nephrectomized patients had a consistent survival advantage (RR of death 0.89). However, the results of these studies are flawed by some limitations: (i) the clinical indication to nephrectomy was not specified, (ii) the concomitant immunosuppressive therapy was not reported and (iii) the cohort of studied patients was only a part of the patients starting dialysis after graft failure.
Table 3. Indications to transplant nephrectomy after graft failure

<table>
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<tr>
<th>Indications</th>
<th>Description</th>
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<tr>
<td>1. Forced nephrectomy</td>
<td>Peri-transplant graft failure (primary non-function, technical failure, acute vascular events, hyper-acute rejection, etc.)</td>
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<tr>
<td>2. Strongly indicated nephrectomy</td>
<td>HCV+ patients where interferon therapy has been planned after return to dialysis and before a re-transplantation (risk of acute rejection episode in the failed graft)</td>
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<tr>
<td>3. Relatively indicated nephrectomy</td>
<td>Symptoms and signs of acute rejection and/or severe inflammation</td>
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<tr>
<td>4. Elective nephrectomy (need for trials)</td>
<td>No major symptoms</td>
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a rise in anti-HLA antibodies and this might negatively impact on subsequent transplantations [28]. However, subsequent studies in part challenged this belief, demonstrating in both animal models and observations in humans that the observed increase of anti-HLA antibody titres does not negatively impact on the subsequent transplant outcome [29].

From these data, we cannot draw any definitive conclusions about whether to maintain or remove the graft after its failure, because there are also manifold clinical aspects that can interfere in the decision of performing or not performing graft nephrectomy.

Table 3 summarizes the indications of if and when to perform a failed graft nephrectomy in different clinical situations.

Re-transplantation

One of the main problems for the patient whose graft has failed is the acceptance of this unfortunate event, burdened with the often compromised health conditions and the unclear view of his/her future. The return to haemodialysis, particularly when it follows a short duration of graft function, has been demonstrated to lead to deep depression [30]. This condition is often undervalued by nephrologists, and the opportunity for psychiatric help is seldom offered to these patients.

However, in most cases, planning a new transplant can mitigate this negative feeling.

It is well recognized that the higher the number of re-transplants, the lower the expectation of graft survival [31]. However, no difference in patient survival has been reported when comparing the first with further transplantations [31] and, most importantly, also for patients submitted to a re-transplantation, there is a clear survival benefit when compared with patients remaining on dialysis treatment [32]. Unfortunately, data from USRSD [1] tell us that only 15–20% of patients who return to dialysis after graft failure are re-transplanted. How much this unsatisfactory figure reflects the real health conditions of the patients or is dependent on some pre-conceptual opinion of medical staff is not clear.

A question strictly related to the re-transplantation problem is whether a pre-emptive re-transplantation gives the same advantage for graft and patient survival as the first transplant [33]. At variance with the first transplant, Goldfarb-Rumyantzev et al. [31] reported a worse patient and graft survival in pre-emptive re-transplanted patients when compared with re-transplanted patients after the beginning of dialysis. However, it is worth commenting that many factors might contribute to this negative result, among which is an underdiagnosed uraemic state in patients with a failing graft, with a consequent delay in planning the pre-emptive transplant.

In summary, there is evidence that re-transplantation gives survival benefit when compared with maintaining patients on dialysis treatment, so every effort is needed to include in the transplant waiting list all possible recipients of a further transplant. However, one should also be aware that a meticulous work-up is required in these patients for a precise definition of their clinical risk. On the present data, pre-emptive transplantation does not appear to give the same advantage as in the first transplant. We suggest that patients who received an aggressive IS and those who were loaded by important side effects of IS may benefit from a waiting time on dialysis (1 year or so depending on the clinical conditions) to wash out the morbidity acquired with the previous transplant. Instead, patients developing a relentless progression of graft failure and who are receiving an already reduced IS regimen might benefit from a pre-emptive re-transplantation.

Conclusions

Patients with a failing graft represent a challenging clinical problem for the nephrology community. A great number of uncertainties are still present, including the handling of these patients. This is mainly due to the fact that during the transition from transplant to dialysis, the patient with a failed graft enters a no-man’s land, where all and none of the physicians involved (transplant nephrologists, transplant surgeons, dialysis nephrologists) feel to have the primary clinical charge of the patient. For this reason, very scattered data and no trials at all have been produced on the topics we have dealt with in the previous paragraphs. There are several reasons to explain our dubiousness in this field. First of all there is not always an agreement between the transplant team and the dialysis team (usually working in a different hospital) about the time for restarting dialysis or re-transplanting in a patient with a failing allograft. Second, there are huge differences (clinical conditions, age, gender, ethnicity, type and intensity of IS, etc.) between one patient and another. This makes it difficult to find precise parameters to establish when a subject should start a renal replacement treatment. Furthermore, strictly linked to the above point, are the topics related to anaemia and metabolic and bone disease treatment in these patients that are far from having been defined. Third, we are lacking good prospective (ideally randomized) studies indicating which of the different types of renal replacement therapy is best; however, it is not expected that such trials could be easily carried out. Fourth, there are no data on what to take with the IS therapy and it is to be hoped that some multicentre trial might address this topic. Fifth, the indications for graft nephrectomy should be better established.

In summary, there is a lot of room for increasing awareness of these problems and improving clinical handling of this critical condition. Whilst waiting for further contributions in this critical area, the physician, directly or indirectly
involved in renal transplantation still has to face and solve the everyday problems of transplant recipients, based on his/her clinical expertise and level-headedness.

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