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Prioritization for Kidney Transplantation due to Medical Urgency

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Policies guiding the allocation of deceased donor kidneys for transplantation were developed in the context of available alternative therapy for end-stage renal disease (ESRD), namely dialysis. For decades, there was no evidence demonstrating a clear survival benefit between dialysis or kidney transplantation. Rather the major benefits of transplantation were improved quality of life, avoidance of dialysis-related complications, and cost-effectiveness. Priority allocation of kidneys based on medical urgency has historically been limited to those patients developing severe uremic complications despite optimal dialysis or where dialysis could no longer be reliably performed. The following clinical situations are the most common indications for prioritization based on medical urgency.

1. Uremic cardiomyopathy

Uremic patients have a high prevalence of cardiovascular diseases, including ischemic heart disease, congestive heart failure, and sudden death (1). Even mild abnormalities in renal function present additional risk such that ischemic heart disease and congestive heart failure are each present in up to 50% of patients initiating dialysis (2). The major cardiac indication for prioritization is progressive uremic cardiomyopathy. This is based on the observation that progression of symptoms of congestive heart failure despite dialysis support is associated with a significantly increased risk of death (3,4,5); 83% of patients died after 3 years of follow-up in one large study (6). Identified risk factors for myocardial dysfunction include older age, presence of ischemic heart disease, anemia, and hypertension (reviewed in 7,8). Left ventricular hypertrophy (LVH), commonly present upon initiation of dialysis, is also a significant risk factor (9). Although difficult to quantitate in cohort studies, chronic volume overload adversely affects cardiac function and is a risk factor that may be particularly amenable to intervention with dialysis (reviewed in 10).

Due to the high prevalence of cardiomyopathy, echocardiography is recommended upon initiation of dialysis once the dry weight has been achieved (usually within 1-3 months of dialysis start) and should be repeated every 3 years thereafter (11). Progression in echocardiographic abnormalities or the development of symptoms of congestive heart failure may warrant additional investigations and referral to a cardiologist. Dysfunction due to cardiac ischemic or infarction should be excluded. High-output cardiac failure due to a large arteriovenous fistula for hemodialysis access or chronic anemia must also be considered in the differential diagnosis. Review of the dialysis prescription, with particular emphasis on interdialytic weight gain, dialysis frequency, and ultrafiltration is also recommended. Conversion to daily and longer duration dialysis (e.g. nocturnal hemodialysis) may be beneficial compared to standard intermittent hemodialysis (12). In a series of 6 patients, conversion to nocturnal hemodialysis yielded an improvement in LV ejection fraction from 28% to 41%. The investigators in this study noted improvements in blood pressure control despite the less use of anti-hypertensive medications however they were unable to demonstrate improved extracellular volume status by bioelectrical impedance measurements. Unfortunately most other recommendations for the management of heart failure (e.g. inhibitors of the renin-angiotensin system, β-blockers, digoxin etc) in the general population have not been adequately studied in dialysis-dependent patients and may not necessarily be safe or effective.

Despite aggressive intervention with optimized dialysis, use of appropriate medical management for congestive heart failure and control of anemia and blood pressure, a small proportion of dialysis-dependent patients may experience worsening of myocardial dysfunction even in the absence of ischemic heart disease. It has been suggested that uremic toxins may exert direct effects of myocardial function (13). In these patients, prioritization for earlier kidney transplantation may be warranted.

Kidney transplantation is associated with reduced cardiovascular mortality when compared to wait-listed patients receiving dialysis (14). Unfortunately many patients with significant systolic dysfunction are not referred for or undergo kidney transplantation because of the perceived increased risk for poor outcomes (reviewed in 15). However, kidney transplantation may result in improved survival in these patients (16). Regression of LVH is frequently seen following transplantation, in part due to improved blood pressure control. Decrease in left ventricular dilatation and systolic dysfunction are well described (16,17,18,19). In one recent study of more than 100 dialysis patients with decreased left ventricular ejection fraction (≤40 percent) and heart failure prior to kidney transplantation, the mean LV ejection fraction increased from 32% pre-transplant to 52% at one year post-transplantation; 70% of patients achieved an LV ejection fraction of ≥ 50% after transplant. Importantly there were no perioperative deaths. In another long-term cohort study of 102 patients who received a successful renal transplant, the 12% with systolic dysfunction prior to transplantation experienced normalization of fractional shortening; the 41% with LVH saw improvements in left ventricular mass index; and the 32% with left ventricular dilatation experienced improvement in LV volume from 116 ± 3.1 to 89 ± 21ml/m^2 (17). It is unclear in these studies if improvement results from elimination of the uremic milieu, improvements in blood pressure control, or other unrecognized factors. Nonetheless it has been the anecdotal experience of almost every renal transplant program, that the occasional patient with sufficiently severe uremic cardiomyopathy to be considered for cardiac transplantation, undergoes dramatic improvement in cardiac function with successful kidney transplantation alone.

Prioritization for kidney transplantation for uremic cardiomyopathy may be considered in the event that other risk factors have been evaluated and addressed, and the dialysis prescription has been optimized (including a trial of more frequent, longer-duration dialysis) without improvements. The great majority of patients will respond to these strategies and do not require priority allocation of a kidney transplant. Of note it is critical that valvular heart disease and ischemic cardiomyopathy be excluded; severe LV dysfunction in these settings is unlikely to improve with transplantation. Such patients may warrant consideration of combined heart-kidney transplantation.

2. Peripheral neuropathy

Peripheral and autonomic neuropathy associated with uremia was not fully appreciated until the advent of dialysis as patients with renal failure did not survive sufficiently long to develop clinically significant peripheral neuropathy. There is evidence to suggest that the frequency of this complication has fallen over recent years, particularly in non-diabetic patients. This has been attributed to earlier initiation of and improvements in dialysis.

Uremic polyneuropathy typically does not appear until the GFR ≤ 10 ml/min/1.73m^2. It is characterized by distal and symmetric involvement affecting both sensory and motor components, with lower limbs affected more seriously than upper limbs (reviewed in 20,21). Characteristic features include restless legs syndrome (6-62% of patients), parasthesia and burning pain (10%), or stocking-glove loss of sensation. Sensory symptoms typically precede motor symptoms. Postural hypotension, blunted heart rate responses, and impaired sweating may signal autonomic involvement. Damage arises from both demyelination and axonal degeneration, and can not be distinguished from other causes of peripheral neuropathy such as diabetes, amyloidosis, or multiple myeloma; diseases themselves associated with renal failure.

The development of peripheral neuropathy is an indication to initiate renal replacement therapy (22,23). It is assumed that these therapies remove poorly described uremic toxins that induce neuronal injury through unknown mechanisms. With renal replacement therapy, axonal regeneration is slow (about 1 mm/day). Thus recovery of nerve function may take months or years and may be incomplete even after several years of dialysis. Motor involvement tends to respond less well. Rarely, patients undergoing apparently adequate dialysis may develop rapidly progressive symptoms simulating Guillaine-Barré syndrome or chronic inflammatory demyelinating polyneuropathy (24). This syndrome is usually seen with inadequate dialysis; its appearance should prompt a review of the dialysis prescription. Patients on dialysis should be routinely prescribed multivitamins to avoid peripheral neuropathy secondary to a deficiency water-soluble thiamine. Evidence suggests that no one modality of dialysis is superior, but improvements in neuropathy may be seen with increasing dialysis intensity and frequency (25,26,27,28). The impact of renal transplantation is more consistent than that of dialysis. Improvement is often biphasic, with rapid initial improvement followed by continued gradual improvement through the first post-transplant year (29). Recovery may be incomplete in the most severely affected individuals. In contrast restless legs syndrome usually resolves within days or weeks of transplantation.

The superior response of peripheral neuropathy to successful renal transplantation is the predominant reason to recommend urgent renal transplantation when symptoms progress despite frequent and aggressive dialysis, vitamin supplementation, and therapy to address other potential causes. The appearance of motor involvement may be a particularly strong indication for early transplantation.

3. Inability to maintain adequate vascular access

Successful hemodialysis requires the availability of consistently functioning access to the central blood volume, preferably with an arteriovenous fistula or graft. Tunneled central venous catheters are usually considered adequate, although they are prone to infection and clotting. Inability to maintain vascular access, due to either stenosis/thrombosis of appropriate veins in the upper and lower extremities or repeated catheter-associated complications, may indicate priority for renal transplantation. Most require that the hemodialysis-dependent patient also fail a trial of peritoneal dialysis or have an absolute contraindication to peritoneal dialysis to be considered for priority allocation.

Survey of international practice regarding allocation for medical priority

France:
"Super-urgent" patients as defined by a national group of experts have priority at a national level (as do the highly sensitized with ≤ 1 ABDR mismatch, and fully HLA-matched unsensitized patients). Further details as to eligibility for "super-urgent" status were not available.

Eurotransplant:
Patients are considered medically urgent when they meet one of the following criteria:

- imminent lack of access for either hemodialysis or peritoneal dialysis
- severe uremic polyneuropathy
- inability to cope with dialysis with a high risk for suicide
- severe bladder problems (hematuria, cystitis etc) due to kidney graft failure after simultaneous kidney-pancreas transplantation, provided that the pancreas graft is bladder-drained and functioning adequately

A transplant centre must communicate the reasons for request for medically urgent designation in writing to Eurotransplant. The Eurotransplant medical staff reviews the request. In questionable cases, the case is reviewed by two members of Eurotransplant Kidney Allocation System (ETKAS) drawn from outside the country of the requesting centre. In the event of a tie, a third ETKAS member will determine if the request is approved or denied. Although local centres can not input the medical urgency status in the ETKAS database, they are able to downgrade the patient to a less urgent status should the patient's condition change. Patients listed as medically urgent receive a bonus of 500 points but do not get any additional points based on sensitization. For comparison purposes, the number of points assigned to a zero HLA- mismatched donor-recipient pair is 400 points with fewer points assigned for each level of mismatching (i.e. 200 points for 3 HLA mismatches); for pediatric recipients (<16 years old), the HLA mismatched points are doubled and patients are given a bonus of 33 to 100 points depending upon age; and 33 points are assigned per year of dialysis in most region.

During ETKAS allocation of kidneys from deceased donors < 65 years, priority is given to sensitized (historical or current PRA ≥ 85%) patients based on acceptable mismatches, followed by zero HLA-mismatched recipients. Medically urgent patients "compete" for the remaining kidneys based on point score. The relatively high number of points awarded for medically urgent listing would favour allocation to these patients after reasonably well-matched pediatric recipients.

Scandiatransplant:
Not stated in allocation policy.

UK Transplant (excludes Ireland):
The points scoring system guiding kidney allocation does not include national points for medical urgency. From review of their allocation algorithm, it appears that medically urgent patients would be allocated kidneys retained for local use (i.e. kidneys where there is no zero-mismatched adult recipient nationally or locally, or no favorably matched pediatric recipient

nationally or locally). How local allocation proceeds to include such prioritized patients is unclear.

Australia and New Zealand:
Not stated in allocation policy.

United States:
"No points are awarded to patients based upon medical urgency for regional or national allocation of kidneys. Locally, the physician has the authority to use medical judgment in assignment of medical urgency points if there is only one renal transplant centre [within the organ procurement organization]. When there is more than one local renal transplant center, a cooperative medical decision is required prior to assignment of medical urgency points".

It is not clear from annual reports or published data, to what extent medical urgency plays a role in the allocation of deceased donor kidneys locally.

Survey of practice in Canada regarding allocation based on medical priority
See Table 1 for details by jurisdiction.

Data was collected from a review of provincial/regional allocation algorithms supplemented by a survey of centres within those regions (See Appendix 1 for details of the survey questions). Most but not all regions surveyed have the ability to list patients based on medical urgency. In all jurisdictions a consensus decision is reached by transplant programs and in a single centre (Hamilton), the consensus group includes the non-transplant nephrologists. Most centres do not have formal policies outlining a review process. However in Quebec, failure to accept the first kidney offered for a patient listed as a medical priority would result in delisting of that patient from this urgency category. In programs with the medically urgent category, such patients are allocated kidneys ahead of the usual dominant criteria of waiting time and HLA match (with some exceptions for zero-HLA matched recipients). In all programs, it was felt that kidney allocation on this basis occurred rarely over recent years, if at all.

Due to their careful development of guidelines around medically urgent patients, the policy in Hamilton (as described by Dr. Dianne Arlen, January 2006) may be instructive.

> "Patients qualify for this if they have a clear complication of dialysis that can only be solved by renal transplantation. This usually consists of a lack of dialysis access and uremic cardiomyopathy, although other complications of dialysis can be vetted but are almost universally denied by the transplant group as being medically urgent. The lack of dialysis access or cardiomyopathy is brought to the transplant group to review.
>
> In terms of lack of dialysis access, a transplant physician who has no involvement in the patient's assessment independently reviews the file. If the patient is on their last access (including a mandatory attempt at peritoneal dialysis unless clearly medically contraindicated), the case is brought before our entire nephrology group (including dialysis physicians) for approval since having a patient listed as medically urgent has an impact on other patients waiting. We are considering having our dialysis access

committee review this as well as we have some new local expertise capable of creating access where previously it was not thought possible.

For uremic cardiomyopathy, the patient must have had coronary angiography demonstrating no coronary artery disease as a contributing factor, and have had a trial of high intensity dialysis and still have a poor ejection fraction. This is reviewed by the transplant group, which also includes a cardiologist. If the patient is approved by the transplant group, it then goes to the whole nephrology group as per dialysis access problems.

If patients are turned down for medical urgency, they will be re-reviewed at the request of the referring nephrologist.

The decision of medical priority has not required repeated review as the patient usually gets transplanted fairly soon. Medical priority supersedes high PRA in allocation [of locally allocated kidneys]."

Conclusions

Medical urgency remains a priority category for the allocation of deceased donor kidneys in most jurisdictions around the world. In general it is reserved for those patients in whom the alternative renal replacement modality, namely dialysis, has failed to alleviate a uremia-related complication. The decision is usually reached by consensus and the small numbers of patients entered into this category are given high priority for transplantation. In most jurisdictions, medical urgency is not a criterion for mandatory organ sharing between organ procurement regions but rather is applied to locally allocated kidneys. Due to improvements in dialysis, the need for priority allocation in this category appears to be diminishing and currently it determines allocation in a very small number of cases (<5%).

It should be noted that these guidelines were developed in an era where there was lack of data demonstrating a clear survival benefit of kidney transplantation over dialysis. With recent evidence of improved survival of transplant recipients compared to wait-list patients (30), there may be a need to discuss the role of medical urgency in allocation. It could be argued that other patients are at high risk of death on the kidney wait-list; some of these may gain significant survival benefit with earlier transplantation. Medical urgency dominates allocation of life-saving organs such as livers or hearts in the belief that wait-list mortality is unacceptably high for those with the most severe stage of organ failure. Adoption of this strategy in kidney allocation would have very substantial consequences. It would clearly disadvantage those with the greatest life expectancy, namely the younger person without other comorbid conditions. In addition, it is likely that many patients with the greatest risk of death on the wait-list would also have the greatest risk of premature death post-transplant. The co-morbidities that limit long-term survival of ESRD patients are unlikely to be substantially ameliorated by a return of kidney function with successful transplantation. Thus extremely careful consideration of the impact of any changes arising from prioritization based on projected wait-list mortality or net survival benefit will be required to ensure that transparent equitable access to this scarce resource is not compromised but rather enhanced.

The special case of combined organ transplants

A full discussion of this topic is beyond the scope of this review but suffice to say that many transplant programs consider the need for a combined organ transplant an indication for priority kidney allocation. Allocation in the setting of simultaneous pancreas-kidney (SPK) transplantation is addressed by Dr. Bryce Kiberd in an associated article and will not be further discussed. In general kidneys are allocated to those awaiting combined organ transplants using an algorithm separate from that used for kidney alone transplants. In virtually all jurisdictions, deceased donor kidneys will follow the allocation of the extra-renal organ irrespective of the wait-time for kidney transplantation.

Transplantation of a heart, lung, liver, or small bowel is considered life-saving when optimized medical management fails. In contrast to the priorities of wait-time and HLA matching often used in kidney allocation, allocation of these life-saving organs emphasizes the medical urgency of transplantation. Those least likely to survive an extended waiting time are given priority for transplantation. Nowhere has this been more clearly defined than in liver allocation within the United States with the adoption of the MELD (Model for End-stage Liver Disease) score in 2002. This score, derived from information concerning kidney function (serum creatinine), bilirubin, and hepatic synthetic function (PT INR), has been shown to predict 3-month mortality more accurately than the Child-Pugh system (31,32) across a broad spectrum of chronic liver diseases. Patients with a high MELD score are prioritized for liver allocation as they are unlikely to survive an extended wait-time. An analysis of the survival benefit of liver transplantation (33) has demonstrated that patients with MELD scores of 18-20 have a 38% lower chance of dying with liver transplantation than remaining on the wait-list; those with the highest MELD scores (> 30) had a 93-96% lower risk of death with transplantation. In contrast those with lower MELD scores experienced a greater risk of death with transplantation than if they had remained on the wait-list; MELD scores of 12-14 were associated with a 2.35-fold greater risk of dying with liver transplantation. Implementation of MELD-based liver allocation in the United States has reduced wait-list mortality without significantly affecting one year post-transplant survival. This is despite an increased severity of illness at the time of transplantation (34). The impact of MELD-based allocation on long-term liver transplant survival is unknown.

When a uremic patient (pre-dialysis or dialysis-dependent) requires a life-saving organ transplant (liver, lung, or kidney), many programs allocate a deceased donor kidney to follow the other organ. Advocates of this practice point to the potential immunologic advantages (fewer donor HLA mismatches if both allografts are derived from a single organ donor) and non-immune benefits (avoiding the adverse impact of renal failure on outcomes of heart and liver and [presumably] lung transplants, the need for a single operation etc.) (35,36,37). Wait-times for these other organ transplants are generally shorter than those for kidney transplantation. Of patients added to the wait-list in 2003, 13.3%, 46.7%, and 64.8% of patients listed for first kidney, liver, or heart transplantation respectively were transplanted within one year of wait-listing in the United States (38). Thus with priority kidney allocation, the majority of candidates for combined organ transplants will receive their kidney transplant with shorter wait-times than those ESRD patients awaiting kidney transplantation alone. Opponents of priority kidney allocation to those requiring combined transplants argue that this practice is unjust as it violates the "first come, first serve" philosophy guiding much of kidney allocation. They also point to the increased early mortality of combination transplants

compared with kidney transplant alone in most series (37,39,40,41,42), arguing that a substantial increase in early patient mortality (and therefore renal allograft loss) may make allocation of a deceased donor kidney to high status patients requiring combined transplantation an unwise choice (36).

To date, the numbers of deceased donor kidney transplants allocated in this fashion have been small, with little impact on the wait-times for kidney transplant alone. However increasing numbers of combined liver-kidney and heart-kidney transplants are now being performed. In 2005, 318 liver-kidney transplants were performed in the United States, an almost 4-fold increase from the 82 performed in 1995 (www.optn.org). In one organ procurement region in the United States, combined liver-kidney transplants comprise 7.4% of all standard criteria deceased donor kidney transplants (43), significantly greater than the number of kidneys allocated as SPK transplants during the same time period. Not only will this significantly impact the wait-times for kidney transplant alone but good quality kidneys may be diverted preferentially to recipients of combined organ transplants, further disadvantaging the patient with ESRD. The inequities arising from priority allocation may be particularly apparent given recommendations that kidneys also be allocated to those individuals requiring liver transplants who have stage 4 chronic kidney disease (GFR <30 ml/min/1.73m^2) not yet requiring renal replacement therapy (35,36). In contrast, patients with stage 4 CKD are generally not eligible for kidney transplants alone.

There is a need for discussions regarding the optimal approach to patients requiring a life-saving organ transplant in the context of chronic kidney disease. This should include: optimal strategies to identify those who are unlikely to recover or maintain sufficient renal function to permit good early to intermediate outcomes without a kidney transplant; methods to protect residual renal function in those receiving life-saving organ transplants; optimal recipient selection and management to ensure reasonable early outcomes with combined organ transplants; evaluation of the relative merits of simultaneous versus sequential combined organ transplants; and exploration of combining a deceased donor organ with a living donor kidney transplant in a staged procedure. Until then, the decision to recommend combined organ transplantation and the mechanisms by which organs be allocated to such an individual will remain an area of controversy.

Region	Ability to list based on medical urgency	Priority in allocation scheme	Frequency of allocation based on medical urgency	Method of decision-making	Review process
British Columbia (BCTS)	Yes No formally defined criteria	Compete with those with PRA > 80% and children ≤ 18	Rare	Not stated	No formal process
Southern Alberta (ALTRA)	Yes No formally defined criteria	Priority is given to SPK, followed by recipient age < 18 and zero HLA-mismatches, then medically urgent.	Rare	Consensus after presentation to multidisciplinary transplant group	No formal process
Northern Alberta (NARP)	Yes Suggested criteria listed but are not limiting.	Allocated after zero HLA-matches. Compete equally with SPK, PRA > 75%, and recipient age < 17.	Rare, no cases in last 3 years.	Consensus after presentation to multidisciplinary transplant group	Reviewed every 6 months.
Saskatchewan	Unknown				
Manitoba	Yes No formally defined criteria	No set criteria for allocation. All relevant factors are considered, including PRA, pediatric recipients, degree of HLA match, and length of waiting time.	Rare. No cases in last few years.	Consensus after presentation to multidisciplinary transplant group	No formal process

Ontario	Yes. Some centres have specific criteria that include uremic polyneuropathy or cardiomyopathy or access failure.	Priority for locally-allocated kidneys only (i.e. no mandatory sharing for medically urgent patients). In all programs, medical urgency is the highest priority for kidney-alone allocation..	Rare in all centres. SMH reports <0.5% of time; at the time of survey had no patients in this category of 450 patients listed.	Consensus after presentation to multidisciplinary transplant group in most centres. Hamilton also reviews each request with the entire nephrology group.	No formal process
Quebec-Transplant	Yes	Highest priority in allocation. First kidney offered must be accepted by transplant program or the patient is delisted from the medically urgent priority.	< 5% of kidneys. 5-8 requests approved annually. Usually transplanted within 3 months.	Local program sends written request to Quebec-Transplant. Review by committee of 1 representative/ transplant centre. Majority rules.	No formal process
Atlantic Canada	No				

Table 1. Allocation based on medical priority in Canada

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Appendix A

Questions asked of Canadian transplant programs:

1. Does your program have a category of "medically urgent" in your allocation scheme?

2. If yes, what are the criteria used to enter this category?

3. If yes, how is the decision made regarding prioritization – by the patient's physician/surgeon or by a multidisciplinary team?

4. If yes, is their a mechanism for review? How often does this review occur?

5. If yes, where does this category fit in your allocation algorithm?

6. If yes, how often is this priority actually used in the allocation of deceased donor kidneys?

   Rarely (<5%) Occasionally (5-15%) Sometimes (15-25%)