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Pediatric priority in kidney allocation: challenging its acceptability

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Summary

Any organ which is allocated to one individual represents a missed opportunity for someone else. Given the important repercussions which organ allocation policies inevitably have for certain people, any prioritization policy should rest on a solid argumentative basis. In this study, we analyze the widespread practice of prioritizing pediatric patients in the allocation of kidneys. While official policy documents offer no arguments in support of pediatric priority, such arguments can be found in the academic literature on pediatric renal transplantation. Our study is the first to bring together and critically analyze these. We identify five commonly cited arguments and show that none of these succeeds in justifying pediatric priority policies. We argue that the legitimacy of such policies may be further undermined by their potential adverse effects on both adults and children.

Introduction

Various organ-sharing organizations have kidney allocation policies in place which accord pediatric patients some priority. Within Eurotransplant, pediatric patients' points for HLA-antigen mismatches are doubled relative to adults. Children also receive bonus points for waiting time [1]. Scandiatransplant prioritizes pediatric recipients when a suitable HLA-matched kidney is available from a donor less than 40 years old [2]. Other European organ-sharing organizations, which accord priority to children, include the Agence de la Biomédecine and the NHSBT [3,4].

Within the United States, the pediatric priority policy has changed several times throughout the years. Initially, extra points were awarded to pediatric transplant candidates in an effort to minimize waiting time. Nevertheless, pediatric transplant rates remained unacceptably low. Therefore, in 1998, the OPTN/UNOS Pediatric Committee instituted a policy that allowed a child to rise to the top of the allocation sequence whenever he/she had not undergone transplantation within a predefined time frame. The threshold was 6 months for 0- to 5-year-olds, 12 months for 6- to 10-year-olds, and 18 months for 11- to 17-year-olds. Although pediatric candidates frequently received offers under this new policy, these were often declined (especially in the case of older donors) due to concerns about the longevity of the kidney. In order to address this issue, it was decided, in 2005, to accord pediatric patients high priority for kidney offers from donors aged <35 years [5]. This policy, known as 'Share 35', has proven highly successful in attaining the goal of reduced pediatric waiting times [6].[1]

[1]Share 35 will soon undergo a change. Rather than receiving priority for kidneys from donors aged <35 years, children will be prioritized for kidneys from donors with a kidney donor profile index (KDPI) score <35%. This change was recommended by the OPTN Pediatric Committee after simulation modeling forecasted that it would not alter the level of access of pediatric candidates. It is estimated that the new pediatric kidney allocation policy will be implemented by the end of 2014 (personal communication with Gena Boyle, liaison to the Kidney Transplantation Committee at UNOS).

Our study brings together and critically analyzes the arguments put forward in support of pediatric priority. We make a distinction between utility- and equity-based arguments. We show that neither type of argument succeeds in justifying pediatric prioritization. In addition, we point to some potential adverse effects of this practice on both children and adults. We argue that these effects may further undermine the legitimacy of pediatric priority policies.

Equity-based arguments

The justice-over-a-lifetime argument/fair innings argument

A renowned proponent of this argument is Robert Veatch. He states that the younger one is, the fewer opportunities for medical well-being one has enjoyed [7]. A concern for equalizing such opportunities, he argues, calls for prioritizing children over adults. Whereas Veatch refers to this view as the justice-over-a-lifetime perspective, others label it 'the fair innings argument' [8]. This argument uses age as a *proxy* for opportunities for medical well-being. However, as we argue below, this is unwarranted.

Age is not the only determinant of opportunities for medical well-being. More specifically, the critical role of social determinants of health, such as working conditions, income, and education level, is well documented. A recent report from the WHO indicates that such factors are responsible for a major part of health inequities within and between countries [9]. A child, therefore, need not necessarily have had fewer opportunities for medical well-being than an adult. For example, a 10 year old growing up in a rich, well-educated family may well have had more of such opportunities, relative to a 25 year old deprived of these privileges. In invoking this example, we are not claiming that kidney allocation ought to take into account the candidate recipient's social class, working conditions, education, etc. In any case, an allocation system based on such social characteristics would violate the final rule as well as Eurotransplant's regulatory framework, both of which impose the use of objective and measurable medical allocation criteria [10,11]. With our example, we merely intend to demonstrate that mistaken judgments concerning a patient's opportunities for medical well-being cannot be ruled out when using age as a proxy for such opportunities. Admittedly, this need not necessarily imply that the use of age as a proxy for opportunities for medical well-being is unwarranted. After all, any allocation criterion is likely to be subject to a certain degree of error. What matters is whether age is a *sufficiently* reliable predictor of opportunities for medical well-being. However, it is, at present, unclear how much of the variance in opportunities for medical well-being is accounted for by the factor 'age'. Given the high stakes involved in kidney allocation, it seems unwarranted to employ a factor the predictive strength of which is unknown. In short, neither a person's age nor his/her social characteristics should be relied upon in an effort to determine the number of opportunities for medical well-being.

The minority argument

Another equity-based argument is grounded in the observation that children represent a numerical minority (1–4%) on the kidney transplant waiting list. According to proponents of this argument, this implies that children statistically stand less chance of receiving a kidney, relative to adults [12,13]. The pediatric priority rule, it is argued, serves to rectify children's disadvantaged position.

The view that children are disadvantaged in the competition for an organ results from a focus on children as a group, rather than on the individual members of this group. As a group, children indeed stand a much smaller chance of receiving a kidney (i.e., a 1–4% chance). However, this focus on group-level chances is misguided because children have an interest in acquiring an organ as individuals rather than as a group. Consequently, it makes much more sense to concentrate on an individual child's chances for an organ. How does an individual child fare, relative to an adult, in this respect? Absent a pediatric priority rule, and all other things being equal, an individual child and adult have an equal chance of obtaining a kidney. Admittedly, all other things are not equal. The kidney donor pool to which pediatric kidney transplant candidates have access is smaller than that available to adults. Due to higher rates of graft thrombosis and technical failures, kidneys from pediatric deceased donors younger than 5 years are rarely, if ever, allocated to pediatric recipients [14]. The majority of such kidneys is transplanted into adult recipients, either as single or en bloc grafts. However, the disadvantage experienced as a result of this restriction in the donor pool is minimal, given that only 4% of all donors originate from donors under 5 years of age [15]. More importantly, this setback is more than made up for *in practice*. After all, both in Europe and the United States, pediatric candidates have *always* had *significantly* shorter waiting times compared with adults [16–18]. In short, despite being a numerical minority on the waiting list, children are not disadvantaged in the competition for a kidney.

Utility-based arguments

The growth and development argument

The most common utility-based argument in support of pediatric priority points to various complications of end-stage renal disease (ESRD) that are unique to the pediatric population. To begin with, the demands of ongoing treatment, combined with fatigue and unexpected medical

problems (e.g., infection), severely limit children's school attendance [19]. In addition, children with ESRD have great difficulty attaining normal adult height. According to an analysis of the North American Pediatric Renal Transplant Cooperative Studies, 47% of children on dialysis exhibit severe short stature [20]. Finally, children with ESRD are also at risk of neurodevelopmental delays and deficits. Compared with the general population, children with ESRD have lower IQ levels and academic achievement. Furthermore, they score lower on tests assessing functioning in specific cognitive domains such as language, visuospatial perception, attention, memory, and executive function [21].

Growth failure and neurodevelopmental delay are aggravated by increased duration of renal insufficiency [3]. Moreover, while both types of deficits may somewhat improve following renal transplantation, the latter does not appear to normalize statural growth and developmental status [21,22].[2] It is argued that expedited transplantation, in preventing the aforementioned complications from taking on a full-blown form, minimizes their adverse impact on quality of life (QoL). Children are also expected to derive additional QoL benefits from early transplantation through the restored ability for regular school attendance [12]. In short, this argument supports prioritization of pediatric patients on the basis that they stand to gain considerable QoL from timely transplantation [12,24].

The above-mentioned argument, which we shall label the 'growth and development argument', presupposes that the deficits in growth and development take on a substantial magnitude in the absence of expedited transplantation. There is relatively strong evidence in support of major disruptions in growth after long-term dialysis [25]. However, in the case of neurodevelopmental problems, the quality of the evidence is low to moderate. For example, across the various studies pointing toward significant developmental deficits in the absence of pediatric prioritization, there is no uniform assessment of neurocognitive functioning. Cross-study comparison is further hampered by the fact that, in the majority of studies, the samples are mixed age, mixed gender, and mixed severity of kidney failure [26]. In addition, most of the studies are cross-sectional and use only a small sample size. However, in pediatric research, it is difficult to overcome such problems.[3] Despite the limitations of the evidence, *the large number* of studies pointing toward important developmental deficits in the presence of long-term dialysis suggests that it is reasonable to assume that delayed transplantation significantly affects (neuro)cognitive development.

Another presupposition of the growth and development argument is that the various deficits encountered by children on dialysis significantly affect *QoL*. However, contrary to widespread belief, severe short stature does not impair QoL [see, e.g., 27,28]. The same applies to deficits in (neuro)cognitive development. The reasoning underlying the presumed link between the latter type of deficit and impaired QoL is that (neuro)cognitive delays lead to a lower education level, thereby thwarting job opportunities. The high level of unemployment, in turn, is said to adversely affect QoL [29]. However, follow-up studies of children transplanted prior to the introduction of a (full-blown) pediatric priority point toward an employment level similar to that of the general population, despite a lower education level [see, e.g., 30,31]. One might argue that a lower education level adversely affects QoL via a route other than that of (un)employment. However, the available studies suggest that there is no correlation between education level and QoL [see, e.g., 32].

Contrary to growth/developmental deficits, the limitations imposed by ESRD on everyday school life significantly affect children's QoL. When confronted with their lack of freedom to engage in school activities, pediatric patients receiving in-center hemodialysis reported an array of negative feelings. The latter ranged from a sense of failure to meet expectations to a feeling of being 'trapped' and 'stuck'. Anger and frustration were the most commonly described experiences [19].

Besides the mere constraints it imposes on full-time education, dialysis exerts yet another negative effect on children's school experiences. A recurrent theme in interviews with ESRD children is the inability to focus on homework in the over-busy hospital environment [19]. Strongly related to this is the commonly cited struggle to perform well academically. These difficulties elicit feelings of inferiority, incompetence, depression, and school phobia.

The inability to engage in certain extracurricular activities, such as contact sports and swimming, further

[2]Although transplantation, *in itself*, does not usually result in normal adult height, the latter can sometimes be achieved through additional measures. For example, steroid withdrawal has been associated with attainment of adult height within the normal range (see, e.g., [23]). Nevertheless, it remains important to prevent growth retardation in the pretransplant period. After all, a lower degree of stunting at the time of kidney transplantation increases the chance of attaining normal adult height under steroid avoidance protocols.

[3]There are several reasons why these limitations are difficult to overcome in pediatric research. First, various diseases, including ESRD, affect only a small number of children. Second, investigators are often reluctant to enroll children in randomized clinical trials. Third, in the absence of such reluctance, investigators face the challenging task of obtaining agreement for enrollment from both the child and the guardian. Finally, study instruments, including those to measure cognition, must be tailored to specific pediatric age-groups. We would like to thank an anonymous reviewer for drawing our attention to these limitations of pediatric research.

compounds children's negative school experience. Generally, children cite a sense of abnormality and a failure to fit in as a result of these social restrictions [33].

As deficits in growth and development do not impact upon QoL, proponents of the growth and development argument overestimate the impact of delayed transplantation on children. Nevertheless, pediatric patients still stand to gain considerable QoL benefits from expedited transplantation, as illustrated by their adverse experience of school and extracurricular activities. However, the growth and development argument seems to ignore that the adult population also faces unique complications which are reversed or significantly improved following transplantation [34–37]. For example, adults with ESRD experience sexual dysfunctions [38], infertility [39], and high levels of unemployment [40]. Below, we show that each of these problems is both highly prevalent and substantially damaging to QoL.

Erectile dysfunction affects approximately 82% of patients on hemodialysis [34]. Over 50% of women on chronic dialysis report decreased libido and reduced ability to reach orgasm [41]. Unsurprisingly, these sexual dysfunctions result in a marked decrease in the frequency of intercourse. In 33% of patients on hemodialysis, there is no sexual activity at all [42]. Sexual dysfunction elicits anxiety, psychological depression, marital problems, and loss of self-esteem, all of which severely impair QoL [43].

The unemployment rate among long-term dialysis patients varies from 70% to 90% [44]. The regained ability for (full-time) employment post-transplantation is a clinically relevant index of improved QoL [45]. Depression, which affects over 60% of adult hemodialysis patients, is strongly correlated with unemployment [46].

Both men and women with end-stage renal disease suffer from impaired reproductive function [47]. Over 50% of men on hemodialysis encounter impotence, due to spermatogenic abnormalities and impaired testosterone production [48]. Women exhibit disturbances in menstruation and fertility, generally resulting in amenorrhea and anovulation [49]. Early menopause has also been reported. Moreover, pregnancy is contraindicated for the very few fertile women on dialysis, given the risks involved for both mother and child [50]. Infertility is associated with grief and depression, a sense of worthlessness, inadequacy, isolation, and feelings of anger and resentment [51].

Evidently, prioritization of one group over another, on the basis of QoL considerations, is only warranted if transplantation provides the former with a *greater gain* in QoL. Can we conclude that children stand to gain more QoL from transplantation than adults (or *vice versa*)? The above discussion suggests that, in terms of QoL, both children and adults stand to gain substantially from transplantation. Of course, from this, it does not necessarily follow that children and adults stand to gain equally. However, whereas one group *may* stand to gain (significantly) more QoL, the current evidence does not allow one to determine whether this is, *in fact*, the case. In the absence of evidence pointing either way, it seems unjustifiable to side with either children or adults. Thus, in choosing the side of pediatric patients, proponents of the growth and development argument shoulder themselves with the burden of proof. In other words, they will have to gather evidence substantiating the claim that children stand to gain more QoL, relative to adults. This may prove to be a challenging task. Although further confirmation is required, preliminary studies suggest that younger onset of ESRD is associated with better coping mechanisms [19].

The life expectancy argument

Another utility-based argument in support of pediatric priority is that children, given their longer life expectancy, stand to benefit more from transplantation than adults [7,52]. This argument, however, is problematic in that it relies on an incongruous use of the term 'medical benefit'.

When assessing medical benefit, we generally focus on the benefit of a *single* intervention. For certain treatments, the medical benefit is that of restoring the patient's life expectancy to the average for his/her age. Examples include a mastectomy and the closure of an atrial septal defect. Such treatments may confer lifelong relief from the underlying condition.

In the case of an organ transplant, the medical benefit does not amount to life expectancy being restored to normal. A graft does not last a lifetime. For example, deceased donor kidney transplants have a half-life of 8.8 years [53]. A child will, therefore, often need several retransplants to come close to normalizing his/her life expectancy. Thus, in equating the benefit children derive from kidney transplantation with restoration of life expectancy, proponents of the life expectancy argument take into account the gain associated with *several* retransplants, rather than a *single* transplant. As such, the argument is at odds with the customary understanding of 'medical benefit'. Factors such as organ scarcity imply that there is no guarantee that a child will receive the number of retransplants needed to approximate normal life expectancy. In the absence of such a guarantee, why equate medical benefit with the gains incurred by several transplants, that is, with normalization of life expectancy? In other words, it seems advisable to abandon life expectancy as a criterion of medical benefit in the context of organ transplantation. The medical benefit incurred by receiving a transplant at a certain age is more accurately represented by the graft survival rates for that specific age-group.

When switching to the criterion of graft survival rates, the pediatric priority rule comes under fire. Of all age-groups, those between 0 and 11 years of age have the best 10-year graft survival rate for deceased donor kidney transplants. In contrast, adolescents (12–17 years of age), who represent the largest group of kidney transplant recipients in the group of children, have the poorest allograft outcome of all age-groups except for recipients aged 65 and older [54]. This is largely explained by widespread noncompliance with the immunosuppressive regimen among adolescents [55].[4] Given that there is a subgroup of adults with better outcomes than a subgroup of children, the prioritization of *all* pediatric age-groups seems untenable.

One might object that, despite the criterion of life expectancy relying on an incongruous use of 'medical benefit', it nevertheless represents a preferable alternative to the use of the graft survival rates criterion. Ladin and Hanto [8], for example, argue that in disadvantaging adolescents in kidney allocation, as the reliance on the criterion of graft survival rates seemingly compels us to do, we are punishing them for their tendency to noncompliance. This, they claim, is problematic as it goes against current practice which, at most, penalizes *actual* noncompliance, not a mere tendency to noncompliance. However, an allocation based on graft survival rates is indifferent toward the underlying cause of allograft outcomes. Thus, what the criterion of graft survival penalizes are adolescents' bad outcomes, not their tendency to noncompliance. Moreover, even if the latter is being penalized, the objection remains problematic. There might be compelling reasons for starting to penalize certain tendencies toward noncompliance. For example, we may thereby prevent an inefficient usage of organs. One might still object that this scheme is unfair for those adolescents who, when given an organ, would be compliant. However, this is a problem faced by any policy of prioritization. For instance, a policy emphasizing the criterion of life expectancy implies that, even though some adults may turn out to outlive children, they are nevertheless penalized.

The cost argument

The final utility-based argument defends pediatric prioritization as enabling financial savings. Proponents of this argument foresee a reduction in social welfare costs. The expected savings are premised on the same assumption as the growth and development argument – pediatric prioritization enables a better psychosocial rehabilitation which, in turn, enhances employment prospects [12]. As noted earlier, however, adults transplanted in childhood prior to the introduction of a (full-blown) pediatric priority rule have employment levels close to that of the general population. Pediatric prioritization therefore offers only little room for improvement. Admittedly, any cost reduction, regardless of its magnitude, might be worth pursuing. Nevertheless, the cost argument ignores the strain which the adult ESRD population puts on the social welfare system. Adults are likely to represent a much greater burden than the pediatric population, for two reasons. First, unemployment rates in dialysis patients with adult-onset ESRD are substantially higher than in those with childhood-onset ESRD [57]. Second, whereas adults already strain the social welfare system, children will do so only in the future. This difference in timing is relevant in terms of 'discounting', an economic concept which states that a cost represents a greater financial burden when incurred now than when incurred in the future. Thus, even if unemployment for childhood-onset ESRD was as high as that for adulthood-onset ESRD, the latter would still put more strain on the social welfare system. Taking this into account and given that a significant proportion of the adult ESRD population resumes work after transplantation [45], expedited transplantation for adults is likely to achieve greater financial savings than pediatric prioritization.[5]

The unexpected effect of pediatric priority policies

We have examined the arguments put forward in support of pediatric priority policies. However, the acceptability of such policies does not merely hinge on the strength of these arguments. We must also take into account that pediatric priority rules have had an unexpected consequence. Since the introduction of Share 35, the number of living donor (LD) kidney transplants for pediatric recipients has significantly declined [58]. A similar trend has emerged in Europe [59]. Below, we examine two considerations which arise in the context of this observed reduction in living donation.

A first consideration pertains to a condition to which many pediatric priority policies were subjected. During discussions leading up to their introduction, it was widely agreed upon that such policies would only be acceptable if they did not heavily penalize adult patients [5,60]. This condition was deemed to be clearly met, given that pediatric patients represented only a very small proportion of all wait-

[4]Noncompliance in adolescents is, among others, related to the cosmetic side effects of corticosteroids, such as acne, a swollen face, and increased BMI. Therefore, it has been hypothesized that steroid withdrawal protocols can be relied upon as a means of decreasing the risk of noncompliance. There exists preliminary evidence in support of this assumption (see, e.g., [56]). If steroid withdrawal protocols increase the adherence to the immunosuppressive regimen, they offer the prospect of improved graft survival rates in adolescents.

[5]Note that we are not hereby claiming that adults should be prioritized on the basis of these cost reduction considerations. We merely intend to show that such considerations fail to support pediatric prioritization.

listed candidates. In view of the limited information available at that time, this was a reasonable assessment. However, in light of our current knowledge, it is less clear whether this condition is still met. The decreased number of children receiving a living donor kidney implies that the overall deceased donor pool is increasingly being tapped for a waitlisted child [61]. Thus, the availability of deceased donor (DD) kidneys for adult patients may be being compromised to a greater extent than initially expected. It will be important to monitor the effect on adult transplant candidates in the long term. In the meantime, however, we should ask ourselves how much of an adverse effect on adults we are willing to accept in turn for reduced pediatric waiting times.

A second consideration is that Share 35 may, through both its impact on living donation and other effects, adversely affect children in the long run. Recent data show that children receiving a kidney from a LD have a superior 7-year graft survival rate than recipients of a DD kidney (80.5% vs. 67.9%, respectively) [62]. Thus, despite increasing the number of pediatric renal transplants with high-quality DD kidneys and reducing pediatric waiting times [6], Share 35 may, in increasing pediatric recipients' reliance on DD kidneys, adversely affect long-term pediatric graft survival rates. This policy may further impact upon the latter in that its implementation has been accompanied by a reduction in the degree of HLA matching between pediatric recipients and their allografts [63]. Although some maintain that the impact of HLA matching on graft survival has diminished in recent years, others argue that it remains highly significant [64]. While long-term follow-up is needed to fully address the aforementioned concerns, experience with 2-year graft survival rates in certain centers already suggests an adverse impact of Share 35 [61]. Besides potentially reducing pediatric graft survival, Share 35 may adversely affect children in yet another sense. A decreased degree of HLA matching in primary pediatric transplants may contribute to greater sensitization [63]. Consequently, pediatric patients may encounter more difficulty finding a compatible kidney for retransplantation.

Conclusion

Any organ which is allocated to one individual represents a missed opportunity for someone else. Given the important repercussions which organ allocation policies inevitably have for certain people, any prioritization policy should be solidly rooted. In our view, none of the arguments put forward in support of pediatric prioritization succeed. However, even if a compelling argument exists, questions may still arise concerning the future sustainability of pediatric priority policies. Specifically, one would need to determine whether pediatric prioritization is still reconcilable with minimal harm to adults. In addition, research is needed to establish whether the decline in adult-to-child living donation adversely affects pediatric graft survival rates in the long run. In the event of an adverse effect, the latter must be balanced against the positive outcomes of pediatric prioritization. If we are unwilling to accept shorter graft survival rates in return for reduced waiting times, the question arises whether it is feasible to increase living donation rates while maintaining pediatric prioritization policies.

Authorship

LC: researched the material and devised the argumentation. KVA, GP and SS: provided valuable input and rewrote certain sections of LC's original draft(s).

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