Rationing Lung Transplants

TO THE EDITOR: In their Perspective article, Ladin and Hanto (Aug. 15 issue)[1] misrepresent the lung-allocation policy of the Organ Procurement and Transplantation Network (OPTN) by stating that candidates younger than 12 years of age are restricted to receiving lungs from donors younger than 12 years of age. In fact, within each organ procurement organization (OPO), lungs from donors younger than 18 years of age must be made available to all pediatric patients before being made available to adults. Children younger than 12 years of age may receive lungs from adult donors if the lungs are declined by adolescents and adults.[2]

Ladin and Hanto ignore critical references. The decision to exclude children younger than 12 years of age from receiving allocation scores was based on careful data review[3]; it did not result from insufficient data. Cystic fibrosis is indeed "the most common diagnosis among pediatric candidates" — but not among children younger than 12 years of age. This is another reason why calculating an allocation score was difficult. Waiting time was retained as a criterion in this age group because of the diversity of diagnoses and limited information about the risk of death among these patients and the effect of these diagnoses on survival after transplantation.

The authors propagate the misperception that there are too few pediatric donors of lung transplants for children. Each year, less than 10% of organ donors younger than 11 years of age provide lungs, as compared with more than 35% of adolescent organ donors (Table 1). Nearly 30% of lungs from donors younger than 12 years of age are transplanted into adults (unpublished data from the OPTN). Thus, the reduced likelihood of transplantation in children 6 to 11 years of age cannot be ascribed solely to donor availability.[4] We believe it results from a combination of geography and conservative pediatric transplantation programs.

Finally, most children younger than 12 years of age are too small to receive lobar lung transplants from adult donors. In contrast to lobar liver transplants, lungs must fit into the thorax.

Table 1. Pediatric Lung Donors, Patients on Waiting Lists, and Transplant Recipients in the United States, 2003–2012.*

Variable	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Organ donors, 0–10 yr of age										
All donors (no.)	364	433	388	446	433	447	480	411	453	460
Lung donors (%)	10	7	7	8	5	6	6	9	5	4
Organ donors, 11–17 yr of age										
All donors (no.)	523	542	511	523	495	432	433	436	429	395
Lung donors (%)	27	31	34	33	37	34	41	40	37	36
Patients, 0–10 yr of age										
Patients added to lung-transplant waiting list (no.)	31	47	36	27	44	30	36	36	39	24
Patients who underwent lung transplantation (no.)	15	14	18	20	15	9	14	24	17	10
Patients, 11–17 yr of age										
Patients added to lung-transplant waiting list (no.)	62	74	61	60	47	50	72	45	39	38
Patients who underwent lung transplantation (no.)	32	40	36	35	37	36	47	31	26	22

* There are enough pediatric donors in each age category to meet the demand; the inadequate number of transplantations performed is not due to too few donors, but rather to the method of allocation. Data are from the Organ Procurement and Transplantation Network (http://optn.transplant.hrsa.gov/latestData/rptData.asp), which reported the age cohorts shown in the table.

Indeed, in the study by Marasco et al. cited by the authors, only 2 of the 23 recipients of lobar lung transplants were younger than 12 years of age. Thus, there is insufficient evidence to support changing allocation policy to encourage the increased use of lobar lung transplants from deceased donors in children.

Instead of lobar transplantation, children younger than 12 years of age would be best served by broader geographic sharing of lungs through elimination of local OPO priority. This change would increase the likelihood that pediatric organs would be available to and transplanted into children. It would ensure that lungs are available to all candidates — pediatric and adult — and that they are best matched for size, urgency, and benefit, in contrast to the existing system in which local priority often prevents donor lungs in one place from being transplanted into a patient who has a higher allocation score and who lives in a nearby state.

Thomas M. Egan, M.D.

University of North Carolina at Chapel Hill
Chapel Hill, NC
ltxtme@med.unc.edu

Stuart C. Sweet, M.D., Ph.D.

Washington University
St. Louis, MO

Drs. Egan and Sweet report serving as chairs of the lung-allocation subcommittee of the United Network for Organ Sharing Thoracic Organ Committee, which designed and oversees U.S. lung-allocation policy (Dr. Egan was chair from 2000 to 2005, and Dr. Sweet was chair from 2010 to 2012). No other potential conflict of interest relevant to this letter was reported.

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2. Organ Procurement and Transplantation Network. Policy OPTN. 3.7: allocation of thoracic organs. Washington, DC: Department of Health and Human Services (http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_9.pdf).
3. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. Am J Transplant 2006;6:1212-27.
4. Lung allocation policy review from the Executive Committee of the Organ Procurement and Transplantation Network and United Network for Organ Sharing. June 10, 2013 (http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Exec_Comm_mtng_materials_06-10-13.pdf).

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THE AUTHORS REPLY: The revised allocation policy has resulted in an uneven distribution of benefits and burdens. Pediatric candidates have a higher risk of dying while they are on the waiting list, and those 6 to 11 years of age have lower transplantation rates.

Our Perspective article accurately reflects the lung-allocation policy.[1] Although transplantation of adult lungs into pediatric candidates is possible, it is rarely performed. Adults and adolescents are prioritized for those transplants. Adolescent lungs must be declined for adolescent candidates before they are made available to pediatric candidates. The small numbers of pediatric candidates and donors exacerbate the struggle to match need with availability. Furthermore, some pediatric candidates who are close to 12 years of age may be able to receive a small adult lung. At a minimum, these patients should be afforded this opportunity. We also suggest that the United Network for Organ Sharing (UNOS) review the rates at which organs are declined in children.

Egan and Sweet cite their own article, which contradicts their statement that sufficient data exist to exclude pediatric candidates from the use of the lung-allocation score (LAS). In that article, they state that "because of the small number of potential recipients younger than 12 years, risk factors for death cannot be reliably calculated with the available data." This conclusion provides support for our article and the decision by UNOS to collect more data about the LAS in younger populations.

Egan and Sweet misconstrue our argument about lobar lung transplants. We do not advocate these as a general policy, but we support their use in certain circumstances, given evidence of good outcomes achieved by some programs. The patient described in our article, Sarah Murnaghan, is recovering at home because of such a transplant.

Broader geographic sharing of lungs may increase the availability of pediatric lungs and should be examined, though potential gains should be weighed against the costs of longer ischemic time.

The authors conflate potential and available organs. We support efforts to increase pediatric lung donation. However, UNOS policy must fairly allocate actual, not potential, organs.

Fairness for pediatric candidates requires equal access to treatment. The exception afforded to Sarah Murnaghan should be extended to all children.

Keren Ladin, Ph.D.
Tufts University
Medford, MA

Douglas W. Hanto, M.D., Ph.D.
Washington University School of Medicine
St. Louis, MO

Since publication of their article, the authors report no further potential conflict of interest.

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Valganciclovir in Patients with Glioblastoma

TO THE EDITOR: Söderberg-Nauclér et al. (Sept. 5 issue)[1] report that cytomegalovirus (CMV) antigens are detected in more than 99% of human glioblastomas. In their trial, in which the benefit of valganciclovir was evaluated in patients with glioblastoma,[2] 29% of the 42 participating patients were seronegative for CMV IgG, a result similar to that obtained in larger studies.[3] A large proportion of the patients with intratumoral expression of CMV antigens are therefore unlikely to have had CMV infection.

In a recent large-scale analysis of transcriptome-sequencing data of viral nucleic acids,[4] significant levels of CMV RNA were not detected in human gliomas (glioblastoma multiforme). Out of 22.8 billion sequencing reads from 167 tumors, only 1 sequence corresponded with CMV RNA. These results imply that CMV does not replicate in gliomas and thus that treatment with virus-replication inhibitors, such as valganciclovir, may be futile. Questions regarding the intratumoral expression of CMV antigens in seronegative patients and the apparent lack of intratumoral replication of CMV should be resolved before larger trials of valganciclovir in glioma are initiated.

Kristoffer Hellstrand, M.D., Ph.D.
Anna Martner, Ph.D.
Tomas Bergström, M.D., Ph.D.

University of Gothenburg
Gothenburg, Sweden
kristoffer.hellstrand@gu.se

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS AND A COLLEAGUE REPLY: Current evidence suggests that CMV does not replicate in glioblastoma. CMV is found in 90 to 100% of glioblastomas with the use of polymerase-chain-reaction assays, immunohistochemical analysis, Western blot analysis, and CMV deep-genome sequencing,[1-4] although large-scale DNA and RNA transcript sequencing have failed to detect CMV nucleic acids. Even though few tumor cells are positive for CMV DNA, many cells in glioblastomas are positive for CMV proteins. Thus, the biology of CMV in glioblastoma is not fully understood and is more complex than currently appreciated.

Clearly, many patients with glioblastoma have CMV infection without levels of IgG or IgM antibodies that can be detected by means of conventional enzyme-linked immunosorbent assays. Clinical virologists are therefore encouraged to improve the clinical diagnostics for CMV in patients with glioblastoma.

Valganciclovir inhibits tumor growth in vitro and in animal xenograft studies of tumors that are CMV-positive, but not in tumors that are CMV-negative,[5] and it has greatly improved survival rates among patients with glioblastoma, possibly by inhibiting the late expression of CMV proteins and CMV-induced regulatory mechanisms. Further prospective, randomized clinical trials are needed to determine whether valganciclovir truly extends survival in patients with glioblastoma by as much as four times that in patients not receiving valganciclovir, and these trials should be conducted concomitantly with studies intended