

Can Parents Refuse a Potentially Lifesaving Transplant for Severe Combined Immunodeficiency?

Andrew S. Nickels, MD,^a G. Douglas Myers, MD,^b Liza-Marie Johnson, MD, MPH, MSB,^c Avni Joshi, MD,^d Richard R. Sharp, PhD,^e John D. Lantos, MD^b

If untreated, most children with severe combined immunodeficiency disorder (SCID) will die of complications of infection within the first 2 years of life. Early hematopoietic stem cell transplant (HSCT) is the current standard of care for this disease. Although potentially lifesaving, prognosis of HSCT in SCID is variable depending on a number of host and donor factors. Of the survivors, many develop secondary problems such as chronic graft-versus-host disease or even second malignancies. Posttransplant care is complex and requires great effort from parents to adhere to difficult treatment regimens. In this article, we address the difficult ethical question of what to do if parents choose not to have their child with SCID undergo HSCT but prefer palliative care.

One of the most heart-wrenching cases of the past half-century was the famous case of David Vetter, the Boy in the Bubble.¹ Vetter had severe combined immunodeficiency disorder (SCID). At the time, there was no curative treatment. He had to live his life in hermitic isolation to avoid a life-threatening infection. Today, SCID can be detected prenatally and treated successfully, in many cases, with hematopoietic stem cell transplantation (HCST).² However, HCST is a risky treatment. Not everyone survives. It is also a burdensome treatment with both short-term and long-term morbidity. So what should doctors do if parents of a child with SCID refuse HCST and instead prefer to take their infant home to die? We present such a case and the responses of experts in immunodeficiency, transplant care, and ethics. Andrew Nickels is an immunologist and faculty member at Vanderbilt University's Center for Biomedical Ethics and Society, Avni Joshi is the lead clinical immunologist

at The Mayo Clinic, Liza-Marie Johnson is a hospitalist and chair of the hospital ethics committee at St. Jude Children's Research Hospital, G. Douglas Myers is a pediatric oncologist and chair of the hospital ethics committee at Children's Mercy Hospital, and Richard R. Sharp directs the Biomedical Ethics Program at The Mayo Clinic.

THE CASE

A 3-month-old boy presented to the emergency department with respiratory distress after 3 days of increased work of breathing, difficulty breastfeeding, and poor sleep quality. The parents report 6 weeks of coughing fits. Birth history was unremarkable. In the emergency department, the infant was noted to be in moderate respiratory distress, hypoxic, and have a fine maculopapular rash on his torso. Weight was less than the second percentile. Intubation was performed due to hypoxic respiratory failure, and chest radiograph confirmed right upper

abstract

^aDivision of Allergy, Pulmonary, Critical Care, Department of Pediatrics, Department of Medicine, Center for Biomedical Ethics and Society, Vanderbilt University, Nashville, Tennessee; ^bDepartment of Pediatrics, Children's Mercy Hospital, University of Missouri, Kansas City, Missouri; ^cDepartment of Hospital Medicine, St. Jude Children's Research Hospital, Memphis, Tennessee; and ^dDivision of Pediatric Allergy/Immunology, Department of Pediatric and Adolescent Medicine, and ^eBiomedical Ethics Research Program, Mayo Clinic, Rochester, Minnesota

Drs Nickels, Myers, Johnson, Joshi, Sharp and Lantos contributed to the design of this article and the drafting and review of the manuscript, and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-0892

Accepted for publication Mar 23, 2016

Address correspondence to Andrew S. Nickels, MD, Center for Biomedical Ethics and Society, Vanderbilt University, 2525 West End Ave, Suite 400 Nashville, TN 37203. E-mail: anickels@alumni.nd.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Nickels AS, Myers GD, Johnson L, et al. Can Parents Refuse a Potentially Lifesaving Transplant for Severe Combined Immunodeficiency?. *Pediatrics*. 2016;138(1):e20160892

and middle lobe pneumonia. Failure to improve on standard antibiotic regimen led to a bronchoscopy that revealed a diagnosis of *Pneumocystis jiroveci* pneumonia.

Further evaluation revealed that the infant had SCID. Genetic testing confirmed homozygous mutation in the *RAG1* gene. Newborn screening for SCID was not performed.

The patient's pneumonia was treated with antibiotics. Doctors recommended HSCT as definitive treatment of his immunodeficiency. They explained that without a transplant, the child would likely die within a year. The child had no siblings, and the parents were an incomplete HLA match, so an unrelated matched donor was proposed. Given the age of the infant, current infectious status, and lack of related donor, the prognosis for this patient was estimated between 60% to 80% 5-year survival.

After a full discussion of the child's condition, the parents expressed their preference not to move forward with a stem cell transplant. They felt the financial and medical burdens of treatment outweighed the chances of success. Instead, they preferred to take the child home and focus on comfort care in anticipation of death. The treating physicians were uncomfortable with this decision and called for an ethics consult, asking whether they should seek protective custody to proceed with the transplant.

Liza-Marie Johnson MD, MPH, MSB, Comments

Most children with untreated severe combined immunodeficiency SCID will die of complications of infection within the first 2 years of life. Early HSCT is the definitive treatment of SCID and the current standard of care for this disease. In this case, in which the parents are declining transplant, the decision to respect parental autonomy will almost certainly result in this child's death. The question at

hand is whether the benefits of HSCT are sufficient to justify a decision to seek a protective custody order to override the parents' decision should their refusal persist.

The medical team and parents have reached different conclusions. My first step as an ethics consultant would be to talk with the family to learn more about how they reached their decision. Presumably the parents believe they are making the best decision for their child and family. I need to know how they got there.

The medical features of this case are complex. The prognosis for this infant, estimated between 60% to 80% 5-year overall survival, falls into an ethically challenging gray area due to the degree of prognostic uncertainty. If prognosis was the single variable, survival, and was known to be >80%, most physicians would challenge a parental refusal. With an 80% likelihood of survival, we have a fiduciary responsibility to act on behalf of the child's best interests by seeking a court order. Precedent for state intervention is well established by case law in many states if the benefits of intervention are clear and unambiguous. Conversely, if the prognosis was poor (<50% survival), then parental refusal to proceed with HSCT would probably be less distressing to the clinical team. In that situation, a court would be unlikely to override parental authority.

However, survival is not the only variable. Survivors of the transplant can have long-term morbidities. Allogeneic HSCT requires months and often years of an intensive series of interventions and supportive therapies. After HSCT, proper adherence to immunosuppressant medications, anti-infective prophylaxis, and lifestyle choices minimizing infection risks are essential while the recipient remains immunocompromised. Chronic GVHD can occur years after allogeneic

transplant, can significantly affect quality of life, and may result in secondary mortality. The presence of these long-term morbidities makes HSCT different from time-limited medical interventions, such as a blood transfusion or an operation.

Because this case involves an infant fully dependent on adult caregivers, his posttransplant environment and long-term interests, including medical and psychosocial needs, requires consideration of the parental willingness to commit to this investment, especially if they did not want the transplant and it was forced on them.

Given these complexities, the perspective of the parents becomes crucial. I would want to understand the psychosocial concerns of the family. In my experience with parental refusal consults, there are often undisclosed salient details that have shaped the decision-making process. These important details are either unknown or have not been directly addressed. For example, sometimes families are concerned about financial burdens. When the financial fears of these families are adequately addressed, they are nearly always willing to proceed with the intervention once this barrier is removed. Without knowing specific details about the reasons for their refusal, it is difficult to recommend that the HSCT team seek a protective order at this time.

I would ask the HSCT team if the infant was an optimal transplant candidate, that is, one with an 80% chance of survival. If so, and the refusal persisted, I would recommend that the case be reported to child protection agencies and that a judge decide whether to order the transplant or to permit parental refusal. The need for transplant is urgent, but not emergent, allowing time for further exploration of parental concerns before referral. An immediate protective custody order may alienate the parents at a time

TABLE 1 Conditions for Justified State Interference With Parental Decision-making

1	By refusing to consent, are the parents placing their child at significant risk of serious harm?
2	Is the harm imminent, requiring immediate action to prevent it?
3	Is the intervention that has been refused necessary to prevent the serious harm?
4	Is the intervention that has been refused of proven efficacy and therefore likely to prevent the harm?
5	Does the intervention that has been refused by the parents not also place the child at significant risk of serious harm, and do its projected benefits outweigh its projected burdens significantly more favorably than the option the parents have chosen?
6	Would any other option prevent serious harm to the child in a way that is less intrusive to parental autonomy and more acceptable to the parents?
7	Can the state intervention be generalized to all other similar situations?
8	Would most parents agree that the state intervention was reasonable?

Adapted from Diekema.³

when enhanced communication and partnering with the family is key.

In either case, I would recommend expert consultation from our palliative care team whose proficiency in communication and complex medical decision-making may help address parental hesitations around HSCT and support the parents no matter which treatment choice is ultimately made. They could help posttransplant or could help them anticipate how death from complications of untreated SCID might be experienced. Their expertise would provide the bridge to continued involvement with the institution whether the infant eventually receives HSCT or palliative care.

Andrew S. Nickels, MD, Avni Joshi, MD, and Richard R. Sharp, PhD, Comments

When parental decisions place a child at a significant level of harm, we are left questioning if the limits of parental decision making authority have been reached. The ethics consultant has 2 roles: (1) explore the reasons why the parents are making this decision and (2) make a recommendation about whether it is appropriate and necessary to report the case to child protection authorities.

The reasons for the parents' resistance and their goals should be explored. During the conversation, the ethics consultant must ensure

the parents have an adequate understanding of the disease, its prognosis, and the details of the proposed course of treatment. In this case, the parents express a desire to take their child home and focus on providing the child a "good death": one that upholds the patient's dignity, focuses on alleviation of suffering, and allows family to fully surround and support their child. Proceeding with a bone marrow transplant opens the door to a life focused on cure, potentially at the cost of quality of life. The parents may be intolerant of the possibility of their child being exposed to potential adverse events like graft failure, graft-versus-host disease, secondary infections, recurrent hospitalizations, trips to the ICU, and multiple invasive and painful procedures, for example. All of these concerns open the up possibility of what could be described as a "bad death."

The reasons listed here may not be sufficiently compelling to permit refusal of potentially curative treatment, but it is essential that the ethics consult team helps bring the parents' values and reasons to the surface. By better understanding of the parents' motives, the clinical team will be able to respond to them and, perhaps, find common ground on which to move forward.

Ultimately, we must ask whether it is ethically permissible to allow this particular child to pass away from SCID without an attempt at standard

of care treatment. In the United States, if the answer is no, then the case can be taken to a judge, who may order that the state take protective custody to consent to the HSCT. When parental decision-making is called into question, the "harm principle" is often used as a rubric to determine if state intervention is justified.³ Table 1 outlines the conditions necessary to justify state interference with parental decision making.

This disease clearly satisfies the first 3 criteria outlined. However, because SCID is a rare disease and the outcomes data are based mainly on retrospective analyses, it is less clear whether this case satisfies the later of the proposed criteria. Retrospective data suggest that in optimal conditions, chances of 5-year survival after a bone marrow transplant can be as high as 90%.⁴ This case presents less-than-optimal conditions (serious infection before transplant and lack of a matched sibling donor), and 5-year survival after transplant may be as low as 50%. In this case, the treating physicians' estimates of the chances of survival are between these 2 prognostic extremes.

If, after discussion with the parents, they continue to refuse, and if the clinical team feels strongly that transplant is the best choice for the child, then we would recommend a report to child protection. The clinical team should not face the burden alone of wondering whether their action (or lack of action) is morally acceptable. In cases when providers feel parental or patient decisions are morally problematic, the ethics consult service can and should provide an outlet to alleviate this clinical anxiety. By assisting the clinical team to broach this concern, efforts can be made to preserve their trusting relationship with the family. The ethics committee should take responsibility for the recommendation for judicial involvement.

The act of petitioning for state intervention does not automatically mean that the state will intervene to override the parents' decision.⁵ If the state does decide to intervene, the clinical team will likely have a difficult challenge ahead, particularly in regaining the parents' trust. Because SCID is a rare disease and prognosticating can be difficult, this case may not meet the high bar set for state intervention. Even if the state does not rule to intervene, the efforts to appeal to a higher authority may help the clinicians be more comfortable aligning their efforts with the parents' stated goals.

This child faces a devastating, rare, but potentially curable disease. Every effort should be made to find common ground with his parents. It is possible that, after discussion with the family and the team, they will agree that palliative measures are the best choice. That decision would be acceptable as well. When significant uncertainty is present, as in this case, clinical humility and honesty about the uncertainty may dictate that clinicians defer to parents.

G. Douglas Myers, MD, Comments

Here we find a child caught in the tension of a disagreement over which course of action would serve his best interest. Providers propose a curative therapy, but one that is, itself, potentially life threatening. Parents propose therapy focused on comfort care measures only, expecting death in a relatively short period of time. It is appropriate to engage the ethics committee to assist in assessing the rationale for HSCT refusal and move forward from there with open and honest communication in an effort to gently relieve this tension. Third-party assistance is necessary because the child is caught in the conflict between 2 equally well-intentioned entities with diametrically opposed ideas on how to serve that child's best interests.

The medical providers believe HSCT to be in the child's best interest, presumably because survival rates are better with such therapy than without it. They are considering overriding parental authority to initiate this plan. However, survival data do not tell the whole story when it comes to treatments such as HSCT. HSCT comes with serious risks that take the form of long, difficult hospital stays, major financial burdens, toxic chemotherapy, potentially life-threatening infections, early life-threatening or life-limiting autoimmune disorders, and a "shadow" of sorts that can hang over a child for the rest of his or her life in the form of late organ toxicity, autoimmune disorders, and potential higher risks of cancer related to the therapy. In fact, immune dysfunction in SCID patients later in life after HSCT may require a second HSCT or cell infusion with all the accompanying risks.

So how should the benefits of HSCT be weighed against the burdens and both the short-term and long-term risks? The precedent for seeking court-ordered treatment comes from other situations in which survival is high with treatment and low without it, such as chemotherapy for diagnoses of leukemia or lymphoma that carry survival rates similar to that quoted here. I do not think that these analogies are apt. HSCT involves toxicities similar to chemotherapy, but also something very different. With chemotherapy, a patient can start, decide that the toxicities are too high, and stop treatment. That is not the case with HSCT. Once a transplant is done, there is no going back. The transplanted hematopoietic stem cells (and the immune system) are permanently engrafted. This can create myriad other problems as delineated here.

Although most doctors recommend an HSCT for SCID, not all doctors would feel comfortable overriding

parental refusal. This professional disagreement suggests that the question of whether such transplants are unambiguously in the child's best interest is unresolved.

We have no reason to believe that these parents do not want what is best for their child. However, their analysis of the risk/benefit ratio and potential harm of the therapy lead them to desire a focus on comfort care. We do not have information about this family's "calculation" of the risk/benefit ratio. We do not know their experience with the medical field, with HSCT, their value system, or their sources of information regarding HSCT for SCID. Clarification of some points here might lead to a change in position within the parents or providers.

So should medical providers seek protective custody to proceed with the transplant? My own experience, as an oncologist and transplant physician, is that HSCT for SCID, in the absence of serious comorbid factors such as concomitant infections or organ dysfunction, usually leads to survival with minimal short- and long-term significant toxicities or late effects. Children often tolerate chemotherapy well and have lower rates of serious graft-versus-host disease and major infections than older transplant patients. I also have seen fatal outcomes and serious, life-limiting complications of HSCT in patients for whom statistics suggested they would likely do well.

Ethics consultation is essential. Consultation with the hospital legal counsel and administration would likely be prudent as well. Practically speaking, providers may fear immediate or future litigation without documentation of exhaustive education and consideration of consequences of either coerced HSCT or acquiescence to parental demands.

Court involvement may simply be undertaken to cover for litigation

risks and may be sought even when providers do not want to override parental authority. If it was foreseeable that long-term care would be overly burdensome to the family for reasons beyond their control and that the only way to care for the child after transplantation would be by placing the child in medical foster care, legally coerced HSCT would not, in my opinion, be in the child's best interest. Considering the potential for lifelong complications, treatment, and thus separation from his parents, I do not anticipate medical foster care services to be adequate in the case of HSCT.

If a judge deemed the family's choice for palliative care to be legally acceptable, providers should respect that decision and continue to provide compassionate palliative care. If a judge imposed HSCT, I would only comply if the parents agreed to abide by the order. I do not think that medical foster parents could care for an infant after an HSCT. Without committed parents, the risks and burdens of HSCT override the potential benefits.

One hopes for the best long-term outcome for this family, but it is hard to know exactly how to get there. If the parents take their child home to die, one cannot presume to know whether they would come to regret the decision. This would clearly be a scenario for physicians and/or the ethics consultant to discuss with the parents and likely contribute to the recommendation of the ethics consultation. It is possible that the family will be left with lifelong psychological peace because they were able to comfort their child in his last moments, avoid trauma of HSCT, and enjoy the brief time that they had with him.

Legally coerced HSCT carries potentially serious emotional and

psychological risks for the patient and family. If the child undergoes a legally coerced transplant, and the child survives, one would hope that the family would be grateful, but there is no guarantee. Although the providers might see a cure as an unambiguously positive outcome, families must live with the memories of the ways in which their decisions were judged, by both themselves and others, as good or bad. It is conceivable that, even with a good outcome, the trauma induced by overriding parental authority, a sense of guilt from having ever suggested not proceeding, or myriad other potential traumas placed on or self-induced by the family could lead to lasting psychological trauma.

If the outcome after a coerced HSCT is not good, the potential psychological sequelae are even more distressing to contemplate.

John D. Lantos, MD, Comments

In some cases, it becomes clear that there is no clear right answer. This is such a case. All the choices are bad, all the options are legal, somebody must make a decision that will have irreversible consequences for a child and a family, and nobody seems certain about which choice is ethically best. Each of the respondents beautifully articulates the reasons for the uncertainty. We hate to let an infant die when there is a potentially curative treatment available. We hate to override the reasonable choices of loving parents. We worry because there is no guarantee of the good outcome for which all would hope. The worst-case scenario, a forced transplant that leads to horrific posttransplant complications, weighs heavily on everyone's mind.

In my opinion, the best approach in such a case would be to seek judicial review. However, I would hope that such review could occur in a

nonadversarial way. A judge, whose commitment is to justice and who has no preexisting loyalties to any party in the debate, might be in the best position to weigh the competing arguments on both sides. A judge could offer all sides a chance to have their voices heard. Judicial review would acknowledge that the issues in this case, although deeply personal, also have societal implications.

Most cases can be resolved without judicial intervention. This is not one of them.

ABBREVIATIONS

HSCT: hematopoietic stem cell transplant
SCID: severe combined immunodeficiency

REFERENCES

1. Haberman C. The boy in the bubble moved a world he couldn't touch. *New York Times*. Dec 6, 2015. Available at: www.nytimes.com/2015/12/07/us/the-boy-in-the-bubble-moved-a-world-he-couldnt-touch.html?_r=0. Accessed March 15, 2016
2. Booth C, Silva J, Veys P. Stem cell transplantation for the treatment of immunodeficiency in children: current status and hopes for the future. *Expert Rev Clin Immunol*. 2016;4:1–11
3. Diekema DS. Parental refusals of medical treatment: the harm principle as threshold for state intervention. *Theor Med Bioeth*. 2004;25(4):243–264
4. Pai SY, Cowan MJ. Stem cell transplantation for primary immunodeficiency diseases: the North American experience. *Curr Opin Allergy Clin Immunol*. 2014;14(6):521–526
5. Hord JD, Rehman W, Hannon P, Anderson-Shaw L, Schmidt ML. Do parents have the right to refuse standard treatment for their child with favorable-prognosis cancer? Ethical and legal concerns. *J Clin Oncol*. 2006;24(34):5454–5456

Can Parents Refuse a Potentially Lifesaving Transplant for Severe Combined Immunodeficiency?

Andrew S. Nickels, G. Douglas Myers, Liza-Marie Johnson, Avni Joshi, Richard R. Sharp and John D. Lantos

Pediatrics 2016;138;

DOI: 10.1542/peds.2016-0892 originally published online June 15, 2016;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/138/1/e20160892>

References

This article cites 4 articles, 1 of which you can access for free at:
<http://pediatrics.aappublications.org/content/138/1/e20160892#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Ethics/Bioethics
http://www.aappublications.org/cgi/collection/ethics:bioethics_sub
Allergy/Immunology
http://www.aappublications.org/cgi/collection/allergy:immunology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Can Parents Refuse a Potentially Lifesaving Transplant for Severe Combined Immunodeficiency?

Andrew S. Nickels, G. Douglas Myers, Liza-Marie Johnson, Avni Joshi, Richard R. Sharp and John D. Lantos

Pediatrics 2016;138;

DOI: 10.1542/peds.2016-0892 originally published online June 15, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/138/1/e20160892>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

