And Justice for All
Consideration of ABO Compatibility in Allocation of Hearts for Infant Transplantation

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Pediatricians have long argued that children are not little adults, and it seems intuitive that clinical practices and regulations should follow appropriately from this paradigm. One can find no better evidence to support this contention than the report by Almond et al published in this issue of Circulation. ABO incompatibility has been considered a relative or, by United Network for Organ Sharing standards, an absolute contraindication to transplantation of hearts and, until recently and only under certain circumstances, kidneys. This practice is based on abundant evidence that ABO-incompatible cardiac and renal grafts in unmodified recipients are often rejected very quickly. Early rejection of ABO-incompatible transplants is thought to be caused by antibodies direct against A or B antigens expressed on graft endothelium. These antibodies can initiate a cascade of events culminating in widespread graft thrombosis. Thus, the clinical protocols that evolved and gained eventual widespread acceptance initially for successful kidney transplantation stipulated that donors must be ABO compatible with any proposed recipient. Over time, further evidence suggested that ABO-identical transplantation resulted in superior results compared with ABO-compatible transplantation, presumably because of antibodies to minor blood group antigens. In the United States, blood group O recipients were found to be significantly disadvantaged in terms of obtaining organs by the practice of allowing unrestricted allocation to ABO-compatible nonidentical recipients (such as a group O donor to a group A recipient). Thus, on the recommendation of the Thoracic Organ Transplantation Committee, United Network for Organ Sharing rules for allocation of donor hearts in the United States were changed in 1999 to mandate allocation preferentially to ABO-identical over ABO-compatible recipients, regardless of age. It is ironic that this broad application of a change in regulations prompted by the well-intentioned need to remove an allocation rule that disadvantaged one group of potential transplant recipients (blood group O adults) appears to have resulted needlessly in an important disadvantage for another group (infants).

The need for ABO compatibility in organ transplantation is due to the presumed universal presence of naturally occurring preformed antibodies. The premise that these antibodies are present in all patients needing transplants (except for individuals of the AB blood group, who lack anti-A and anti-B antibodies) was formulated at a time in the evolution of the field of organ transplantation when only adults were considered for transplants. Thus, the rule requiring ABO compatibility for safe transplantation evolved for a population of individuals that did not include infants. When human heart transplantation began in 1967, early clinical protocols were based on principles that had been learned from kidney transplantation, including the fundamental importance of ABO compatibility. The disastrous consequences that occurred with the occasional reported cases of accidental ABO-incompatible heart transplantation reinforced adherence to this requirement, particularly because graft loss in the setting of heart transplantation typically equates to patient loss, in contrast to kidney transplantation, when a patient can be returned to dialysis. However, it must be remembered that inadvertent ABO-incompatible heart transplantation will be catastrophic in adults for several reasons. Not only are there generally high levels of circulating isohemagglutinins, but additionally, without preoperative recognition of ABO incompatibility, the hazard will be further increased by administration of recipient-type blood products that contain additional antibodies to donor blood group antigens.

When developmental immunology pathways are considered, it is clear that clinical “rules” developed for organ transplantation in mature patients should not be applied arbitrarily to infants. There is abundant evidence that the immune status of young infants is unique. Infants lack immunologic memory but also manifest a number of well-described developmental immaturities. Failure to

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recognize this fact results in the loss of important opportunities for infants who need transplantation to survive.

Given the well-recognized high risk of death without a transplant for infants, as pointed out by Almond et al.\textsuperscript{1,9,10} the absence of the immune elements that necessitate ABO compatibility for transplantation in older patients offers a unique opportunity to infants to gain access to donor organs that otherwise would be unavailable to them. This was the compelling rationale that led us to develop a clinical protocol for intentional ABO-incompatible heart transplantation in infants.\textsuperscript{11} Since our first report of 10 patients in 2001,\textsuperscript{11} we estimate that more than 120 intentional ABO-incompatible infant heart transplants have been performed in 9 different countries using our original protocol. Several independent publications now confirm the consistency of clinical success of ABO-incompatible infant heart transplantation.\textsuperscript{12–15} In distinct contrast to the aggressive pretransplantation maneuvers required to achieve successful transplantation of ABO-incompatible kidney grafts in adult recipients, which typically include plasmapheresis and B-cell–directed agents, ABO-incompatible transplantation in infants is typically performed with minimal treatments beyond those used for ABO-compatible transplantation. If low levels of isohemagglutinins are present before transplantation, these are quickly and effectively removed during the transplant procedure by plasma exchange directly from the cardiopulmonary bypass circuit. No episodes of ABO-related hyperacute rejection have been reported. Moreover, there have not been any reported problems due to isohemagglutinins late after transplantation, because donor-directed antibody levels generally remain absent or clinically insignificant.\textsuperscript{16} Estimated actuarial patient survival has been identical to that observed in ABO-compatible infant heart transplants.\textsuperscript{17}

With regard to infant immune responses, in contrast to older individuals, no evidence has emerged to justify requiring ABO compatibility when transplantation occurs before the onset of endogenous isohemagglutinin production. Therefore, based on infant immune development and on the clinical success to date of intentional ABO-incompatible heart transplantation in this age group, a general approach has evolved in Canada and the United Kingdom that allows the listing of appropriate infant patients for heart transplantation from the first available donor of appropriate size, regardless of blood type. Because blood group O recipients are not disadvantaged when an “ABO-neutral” approach is taken, preferential allocation of donor organs to ABO-identical or -compatible recipients is not required, nor is it justified. In these countries, this strategy has resulted in an improvement in terms of achieving successful transplantation for infants, decreasing wait-list mortality, and reducing wastage of rare donor organs.\textsuperscript{11,13} The report by Almond et al,\textsuperscript{1} which used data from nearly 200 children wait-listed in the United States with a strategy that allowed acceptance of ABO-incompatible donors compared with a propensity-matched cohort listed for acceptance of ABO-compatible donors only, demonstrates a significant advantage for blood group O recipients in terms of more patients being transplanted and shorter waiting times to transplantation. Despite this advantage, the authors show that although it is becoming more common in US centers to list infants for consideration of ABO-incompatible transplantation, the strategy is still preferentially undertaken for younger and more critically ill patients than for all children of appropriate developmental age. Furthermore, the authors show that in the most recent 3 years, 13% to 18% of patients listed for possible ABO-incompatible donors were considered for this strategy not initially but only later in their course, presumably as their clinical condition deteriorated to a more urgent status. As proposed by the authors\textsuperscript{1} and in agreement with a similar recent study by Everitt et al,\textsuperscript{18} the full benefit of infant transplantation in the United States, unlike in other countries, cannot be achieved without alteration of listing and allocation practices, which should be based on appropriate consideration of the unique developmental status of children.

The numbers analyzed by the authors\textsuperscript{1} almost certainly underestimate the potential benefits that could be achieved by regarding ABO status as irrelevant for potential infant heart transplant patients. The presumed age of eligibility for ABO-incompatible transplantation was a conservative 6 months for this analysis. Because the pace of immune maturation differs from individual to individual, age is not an ideal measure of a patient’s suitability for ABO-incompatible transplantation. Rather, absent or low titers of agglutinating anti-A and anti-B antibodies generally indicate that a patient is an appropriate candidate. Although no absolute “upper” limit has yet been defined above which ABO-incompatible transplantation would be considered inadvisable, evidence is accumulating that even infants with detectable isohemagglutinins may still be considered “safe” candidates for ABO-incompatible transplantation, particularly since the alternative may be death without a transplant.\textsuperscript{13} This is reinforced by the increasing availability of effective tools such as plasmapheresis and immunoadsorption for antibody removal and rituximab and bortezomib for depletion of B cells and antibody-secreting plasma cells, should treatment for antibody-mediated rejection be required after transplantation.

With regard to outcomes from listing, the authors\textsuperscript{1} demonstrate a clear advantage when a listing strategy is used that includes ABO-incompatible donors in that significantly more blood group O recipients received transplants than with a listing strategy limited to ABO-compatible donors, and within a shorter time before clinical deterioration resulted in a less optimal clinical state. Although the net gain may appear to be only a small number of patients achieving transplantation, it should be remembered that infants represent a fragile group of patients who will perish without transplantation, yet they generally will have superior outcomes compared with patients undergoing heart transplantation at any later age if donor organs are obtained.\textsuperscript{19} With regard to outcomes from transplantation, ABO-incompatible heart transplantation has been shown to be at least “noninferior” to ABO-compatible infant transplantation.\textsuperscript{20} As numbers continue to increase, advantages of intentional ABO-incompatible transplantation over ABO-compatible transplantation may emerge. For example, we have demonstrated that most children develop donor-specific immune tolerance after ABO-incompatible heart transplantation in a unique form of specific B-cell elimination that appears to mirror animal models of neonatal tolerance.\textsuperscript{16} Similar to experimental tolerance models, donor-
specific B-cell tolerance in ABO-incompatible heart transplant recipients is likely related to the persistence of donor A/B antigens, which we showed were present in endomyocardial biopsy samples several years after transplantation. If elimination of the immune response to donor A/B antigens proves to be durable as the child matures, and if a second organ transplant is eventually required, an organ from another ABO-incompatible donor of the same blood type as the first ABO-incompatible donor theoretically could be transplanted safely later in life, whether this is a second heart or a different organ graft. Thus, for patients receiving ABO-incompatible grafts as infants, the advantage of an expanded potential donor pool would be retained later in life.

Another important potential advantage of ABO-incompatible transplantation may be diminished immune responses to other donor antigens, such as HLA. This may be manifest as protection from development of de novo HLA antibodies, as we recently demonstrated in a cohort of 122 pediatric heart transplant patients assessed at a median age of 3.5 years after transplantation. Compared with age-matched ABO-compatible transplant recipients, class II HLA antibodies were significantly diminished and donor-specific HLA antibodies were absent in all 28 ABO-incompatible recipients. Whether this will prove to be true in all ABO-incompatible recipients and whether it reflects a broader state of donor-specific tolerance to other donor antigens is currently under investigation.

In the field of organ transplantation, as in other areas of medicine, the presumption that individuals of all ages should be governed by identical considerations is both inappropriate and inadvisable. In order for the field of pediatric transplantation to advance to its full potential, regulations both for listing practices and for organ allocation need to be applied in a developmentally appropriate manner. Almond et al. propose that the current allocation algorithm of donor hearts is outdated. It seems clear that the current limitations were never appropriate for infants. The restriction of transplantation practices for children to regulations that were formulated for adult patients, under the guise of a “cautionary” approach to protect children, has solely on parameters devised for adult patients, under the current regulations both for children to regulations that were formulated never appropriate for infants. The restriction of transplantation practices for children to regulations that were formulated solely on parameters devised for adult patients, under the guise of a “cautionary” approach to protect children, has likely contributed to an unnecessary loss of life-saving opportunities for a vulnerable group of patients.

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