No Progress in ABO Titer Measurement: Time to Aim for a Reference?

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No Progress in ABO Titer Measurement: Time to Aim for a Reference?

Transplantation across antibody barriers has become routine in many centers, with increasingly improved short- to medium-term results. This has coincided with significant technical developments in testing for HLA-specific antibodies; extensive guidelines have been published on how to detect and characterize these antibodies and use this information clinically (1, 2). In contrast, there has been little corresponding development in ABO antibody testing.

ABO-incompatible (ABOi) live donor or kidney pairs are assessed according to risk based on antibody level, and high-risk patients (depending on local policy) are placed in paired exchange programs. However, group O recipients have a lower chance of matching in the current paired exchange program in the United Kingdom.

The testing of ABO-specific antibody is not standardized between transplant centers. Currently, all centers use hemagglutination (HA) methods developed for pretransfusion compatibility testing. There is consensus in published data demonstrating significant variation in titers with different HA techniques between transplant centers (3). The UK National External Quality Assessment Scheme is currently conducting pilot studies across all centers performing ABO HA titration.

HA assays determine an activity-specific (i.e., agglutination) rather than quantifying specific immunoglobulin and, in principle, may not be appropriate in the transplant setting where donor-specific antibody quantification is needed. Initial data associate ABO-specific IgG levels with poorer outcomes, but the different roles of isotypes and IgG subclasses have not been well described (4). Flow cytometric techniques are beginning to address these questions (5, 6). Synthetic antigen-binding assays have the potential to provide a more detailed analysis of ABO antibodies but have yet to demonstrate sufficient specificity (7). There is no gold standard test; however, an HA reference technique and a standard reagent to compare each assay against are under development to improve reproducibility and precision between centers.

The implications for not having a standardized assay include poor allograft outcome, listing for paired exchange programs unnecessarily, and excessive desensitization. The UK registry 3-year ABOI kidney allograft survival is lower than ABO-compatible (88% vs. 94%) and lower than internationally published single-center experience (88% vs. 92.9%) (8). Using non-standardized testing causes considerable variability in the ABO titer targets used for clinical decision making and may play a role in poorer allograft outcomes. The growth in the number of ABOI transplant centers in

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the United Kingdom, basing their practice on protocols at other centers, but with variation in local technique may find different ABO titer results. Whereas a standard protocol for ABO titration is desired, there is no evidence yet to demonstrate the effect of titer variation on clinical outcomes. In a three-center study, a standard method was compared to local results; however, no clinical outcomes were correlated with differences in titer values (9).

We performed a survey of 14 UK centers undertaking ABOi transplantation (n=359 transplants). The median IgG HA titers that clinicians would accept patients onto the ABOi program for treatment was 512 (range, 128–4096). The median target for acceptable titer on the day of transplantation was 8 (range, 2–16). These centers had up to a five-dilution titer difference from National External Quality Assessment Scheme data comparing in-house techniques in the respective laboratories; reduced to 1 dilution using a reference technique (see Fig. 1). Variation in local in-house titer results did not correspond to acceptable titers onto ABOi programs.

Adoption of a reference technique should give equivalent access to transplantation regardless of geographical area if a live donor pair are ABO-incompatible and not restricted by potentially locally high titers, and conversely, locally low titers might explain higher allograft loss.

Our data demonstrate that there is a wide range in the titers that each center accepts, and discrepancy between local centers will reduce the opportunity for recipients to be entered into an ABOi kidney transplant program. Whereas centers using local titer results are confident in their results, implementation of a reference technique across laboratories would allow comparison of titers between transplant centers and at least facilitate discussions to be had with patients regarding risk and referral to other center that might accept higher titers. It will enable better evidence-based techniques for minimizing risk in ABOi transplantation to be developed in multicity centers. We suggest that, to provide equality of access and timely transplantation across the United Kingdom, and equally worldwide, a reference technique and antibody standard should be implemented. However, to distinguish between the higher-titer patients who experience early antibody-mediated rejection and those who have good allograft outcomes, a quantitative assay may be required as one aspect of improved clinical care.

Andrew Bentall1
Fiona Regan2
Jenny White3
Clare Milkins3
Megan Rowley4
David Briggs1

1 University Hospitals Birmingham
Birmingham, UK
2 NHS Blood and Transplant, UK
3 National External Quality Assessment Scheme
Watford, UK

On behalf of National External of Quality Assessment Scheme ABO titration group

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Address correspondence to: Andrew Bentall Renal, MBChB, Institute of Birmingham Queen Elizabeth Hospital Birmingham Birmingham, B15 2WB United Kingdom
E-mail: andrew.bentall@uhb.nhs.uk
A.B. participated in research design, writing of the article, performance of the research, and data analysis. F.R., M.R., and S.B. participated in writing of the article. J.W. and C.M. participated in the performance of the research and data analysis. D.B. participated in research design and writing of the article.

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New Findings in Anatomy of Blood Supply to Rat Femur Isolated Vascularized Bone Marrow Transplantation Model

Vascularized bone marrow transplantation (VBMT) was first described in 1985 by Black (1). It is a possible method of introducing donor-specific tolerance in allotransplantation, especially vascularized composite tissue allotransplantations. Suzuki then performed rat femur allotransplantation as an isolated vascularized bone marrow transplantation.

**FIGURE 1.** A, blood supply of the rat femur, superior view of the graft. B, blood supply of the rat femur, inferior view of the graft. MCFA, medial circumflex femoral artery; LCFA, lateral circumflex femoral artery; NA, nutrient artery; PA-SCIA, periosteal artery from superficial circumflex iliac artery; PA-HGA, periosteal artery from highest genicular artery; HGA, highest genicular artery; MGA, middle genicular artery; LSGA, lateral superior genicular artery. C, differences in blood supply between the side with ligation of the nutrient artery (NA; left) and the contralateral side (right) in the same rat, after contrast agent perfusion. D, micro-CT scanning of the same femurs in C. E, first kind of NA that arises from superficial circumflex iliac artery. F, second type of NA that arises from lateral circumflex femur artery.