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Increased transplant opportunity following improved definition of patient sensitisation

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Abstract

Purpose – The paper is targeted to health service management teams as an aid to understanding the relationship between investment in process redesign in a clinical laboratory environment and improved quality of service/increased clinical activity.

Design/methodology/approach – An audit of the unit's serum screening capability was performed against the standards of the current UK allocation scheme for cadaveric kidneys. Based on findings of this audit the laboratory's serum screening protocol was redesigned involving development of a new testing strategy and introduction of novel methods. A concurrent review of the effects of this initiative in terms of cadaveric kidney offers received/transplant numbers was undertaken and a cost-benefit analysis made.

Findings – An improved eligibility of the patient cohort for cadaveric kidney offers was obtained together with a reduced unexpected positive crossmatch rate. These factors have together contributed to an increase in transplant numbers at the centre. Significant cost benefits have been achieved

Research limitations/implications – The relevance of the findings relating to patient eligibility for available cadaveric grafts is limited to organ-sharing schemes in which recipient sensitisation is considered as part of the allocation process.

Originality/value – The experience reported demonstrates the necessity of assessing the clinical impact of changes in practice when judgements are being made regarding the costs of laboratory services. In this respect the paper is the first from within this discipline to make this association.

Keywords Transplant surgery, Patients, Body systems and organs, Mass screening, Clinical audit

Paper type Research paper

Introduction

From both an economic and clinical viewpoint, renal transplantation represents the treatment of choice for the patient in end-stage renal failure. Cadaveric kidneys for transplantation are a limited resource, making their best use imperative. An indication that best use has been obtained can be gained through comparison of the number of years a transplant recipient remains dialysis-free with expected transplant half-life, which is the time by which 50 per cent of transplanted kidneys are expected to have failed. For the UK, half-life for transplanted kidneys is between ten and 12 years. Loss of function under this time represents sub-optimal usage of donor organs. From a purely financial perspective a functioning renal transplant becomes cost-neutral within

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one year and each additional year the recipient remains off dialysis generates a cost saving of £23,500 for the NHS (National Health Service, 2003). A number of factors have been shown to influence graft survival and these have been integrated into the rule sets for organ distribution operated by most donor sharing networks.

Under the current UK strategy for the allocation of cadaveric kidneys (National Health Service, 1999), consideration is primarily given to the degree of human leucocyte antigen (HLA) match between donor and recipient, reflecting the beneficial influence of HLA matching reported in the literature (Opelz *et al.*, 1999). The donor is processed through a hierarchy of priority levels involving increasing levels of HLA mismatch until an offer is made. Thereafter a series of criteria linked to a points system are applied to permit unprejudiced allocation in situations where recipients with equal degrees of HLA mismatch are identified. Amongst the criteria considered at this juncture is the HLA sensitisation of the recipient and the extent to which this has been defined. In this context, "sensitisation" refers to the previous exposure of the patient to HLA mismatches (usually as a result of pregnancy, blood transfusion or previous transplant), manifest through the development of an immune response with production of antibodies against HLA. In order to establish their sensitisation status, patients awaiting transplantation are longitudinally monitored for development of HLA antibodies ("serum screening").

A patient's level of sensitisation can be described in percentage terms based on the extent of reactivity demonstrated in the screening test. This measure is termed the percentage antibody reactivity. More usefully, the specificities of the antibodies contributing to this value can be deduced by consideration of the patterns of reactivity demonstrated. Subtraction of reactivity attributed to individual HLA antibodies from the percentage antibody reactivity produces a second measure termed the residual percentage antibody reactivity, which represents the undefined component of serum reactivity. Definition of an antibody specificity against a particular HLA type precludes that type from consideration in a potential donor owing to the associated risk of rejection. In view of this risk, laboratories supporting a renal transplant programme will also perform a "crossmatch" test between recipient and potential donor immediately prior to transplant in direct evaluation of the presence of any donor relevant HLA antibodies present in the patient. A positive crossmatch test is a contraindication to transplantation and will usually result in the kidney being reallocated via the national organ-sharing network. From the foregoing, it will be understood that the results of serum screening should serve to predict crossmatch outcome, and that positive crossmatches reflect inferior serum screening. In recognition of this relationship, the UK allocation strategy restricts the access of sensitised patients to available organs in accord with the extent to which their HLA sensitisation has been defined. The rationale for this is the avoidance of "unexpectedly positive" crossmatch results and the resultant prolongation of organ ischaemia time consequent upon transport of kidneys between recipient centres. A benefit to the patient also results through avoidance of the disappointment of being called to the unit only to be told sometime later that the donor kidney was incompatible. Conversely the patient is placed at a relative disadvantage if serum profiles of HLA specificity are over-reported and imprecise since individuals of the corresponding HLA types are made unavailable as donors. It follows that the level to and confidence with which a laboratory is able to provide definition of serum specificity impacts directly upon the

opportunity for patient call-up and the attendant chance of transplantation. Variation between laboratories in terms of this capability therefore raises important issues of equality of access to treatment and represents a clinical governance concern for poorly performing laboratories.

This publication details work performed by the Leeds laboratory in establishing a high-confidence serum screening strategy towards ensuring maximum eligibility of sensitised patients for available cadaveric organs.

Audit and implementation

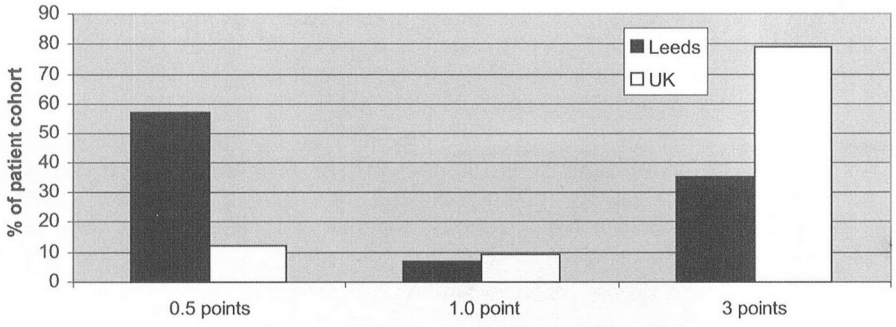
Following publication of the UK kidney allocation scheme in 1998 an audit of the Leeds laboratory's serum screening capability was performed which concluded that the laboratory lacked the ability to match the standards required to ensure maximum eligibility of patients for available cadaveric kidneys under the new scheme. Key features of this data are presented in Figure 1[1].

Of particular concern was the number of patients who were classified as "highly sensitised" (HSP, percentage antibody reactivity > 85 per cent) who constituted 18 per cent of our patient group compared with the UK average of 10 per cent.

Following presentation of audit findings to service users, the laboratory was given the remit to review serum screening methods and protocols in use and to reconfigure these as necessary to deliver the fullest possible characterisation of serum reactivity. Joint funding for a scoping study focused on the highly sensitised patient cohort was agreed between the Department of Renal Medicine and the Directorate of Pathology and a project group was established. A timescale of six to eight months was agreed for project completion.

The initial work of the project group sought to establish why the existing serum-screening programme was failing to match the required standard of performance. Conclusions drawn were that:

- the method in use was an in-house cell-killing assay that had become unsustainable owing to the difficulty of obtaining the cells upon which the method was based;
- configuration of the in-use method did not permit discrimination of reactivity due to HLA antibodies from that due to non-HLA antibodies, creating the prospect of "false positive" results[2];



Note: Mean sensitisation score in Leeds was 1.18, compared with the national average of 2.51

Figure 1. Comparison of sensitisation score profiles (Year 1 scheme) for Leeds patients on the September 2000 UKT list versus data for the rest of the UK

- there was no systematic, robust and easily understood method of data interpretation for derivation of HLA antibody specificity from results of screening tests;
- there was a lack of reliable patient clinical information available to the laboratory concerning potential sensitising events; and
- there was no rationalised schedule of sample collection/testing.

These findings were reported to laboratory and clinical colleagues together with proposed actions for their resolution:

- replacement of existing in-house methodologies with sustainable alternatives capable of providing high-confidence serum screening;
- development of a standardised approach to serum specificity analysis affording objective interpretation of data;
- education of service users regarding the importance of supplying good clinical event information to the laboratory; and
- establishment of a schedule for sample collection based on the British Transplantation Society best practice guidelines (British Transplantation Society, 1998).

While some initial resistance to the proposals was encountered within the laboratory this was rapidly overcome using the evidence provided by the service audit together with the findings of follow-up investigations. At this stage it was important to maintain staff confidence in the project through strong leadership. The project plan was constantly reinforced through regular laboratory meetings and seminars. By taking an inclusive approach to the restructuring of the serum-screening programme all staff had the opportunity to become engaged in and take ownership of certain aspects of the project.

Following review of the published literature (Shroyer *et al.*, 1985; Martin and Taylor, 1999; Rebibou *et al.*, 2000), preliminary trials of available methods and discussion with colleagues in other centres, a tiered approach to testing utilising both tests which were new to the laboratory and others that, at the time, were novel within the UK was devised and applied to the HSP cohort. The combination of tests in each tier sought to provide answers to the following questions:

- *Tier 1* – Does the sample contain non-HLA antibodies that may confound the interpretation of screening and crossmatch tests for HLA antibody? For this purpose use was made of a non-HLA expressing cell line in a flow-cytometric assay configured to detect IgG and IgM antibody.
- *Tier 2* – Does the sample contain HLA antibody? If so, at what level (percentage antibody reactivity) and against which type of HLA? Two flow cytometry based methods were employed for this, a commercially available, bead-based assay system, FlowPRA Screen (One Lambda) together with an in-house flow-cell method.
- *Tier 3* – Can the profile of HLA antibody specificities contributing to the percentage antibody reactivity be comprehensively defined? Antibody specificities were determined using the FlowPRA Specific (One Lambda) method. A computer algorithm for data analysis was developed in-house.

In taking such an approach it was anticipated that the majority of samples would be reported as negative in tiers 1 and 2, so that the main focus of work effort concerning the definition of serum specificities would be limited to fewer samples in tier 3.

Raw data from tests to establish serum profiles of HLA antibody specificity ("inclusions") were subjected to statistical interrogation using software developed in-house. Decisions relating to identification of a particular specificity as an inclusion were based on three standard measures (Brown and Navarrete, 2000):

(1) inclusion value;

(2) strength index; and

(3) $p < 0.05$.

Through application of the testing strategy and method of data analysis described it was possible to redefine the HSP cohort as comprising three groups:

(1) a group for which no evidence of the presence of HLA antibody was obtained;

(2) a group with HLA antibody but having percentage antibody reactivity values below the threshold for classification as HSP; and

(3) a smaller group with HLA antibody and having percentage antibody reactivity values consistent with their classification as HSP.

Patients in the first group had been inappropriately classified as HSP owing to the failure of the original method to discriminate reactivity due to HLA antibody from that due to non-HLA antibody.

A more comprehensive definition of serum antibody inclusions was achieved for patients in the second and third groups than had previously been attained. Consistent with these improvements, patient sensitisation points scores following the work were increased (Figure 2), increasing patient opportunity for transplant.

These findings were reported back to clinical colleagues in a series of meetings and communicated to the wider transplant community at the British Transplantation Society (BTS) meeting in 2002.

Following completion of the HSP scoping study, a business case was developed for implementation of a routine serum screening strategy based around the methods employed. Based on British Transplantation Society recommended screening intervals

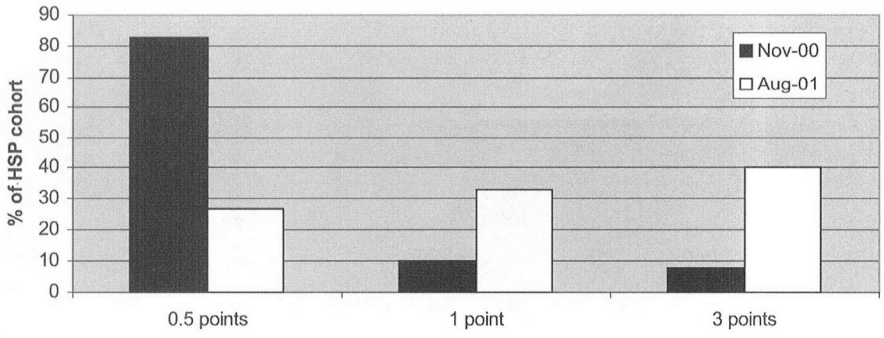


Figure 2.
Comparison of sensitisation points profile (Year 1 scheme) for Leeds "highly sensitised" patients prior to and following introduction of revised serum-screening protocol

of every three months (British Transplantation Society, 1998) recurring costs of the strategy were calculated as £161,782.00 per annum. When set against existing funding, the additional budgetary implication of the strategy was £78,214.00. On a cost per patient basis this equated to £561.70. To put these figures in context, in order for the scheme to be cost effective it needed to increase the number of offers received by four *per annum* or decrease the unexpected positive crossmatch rate by the same number. Providing these additional four transplants functioned for more than a year, the additional cost of funding the programme would be balanced by the cost saving on dialysis.

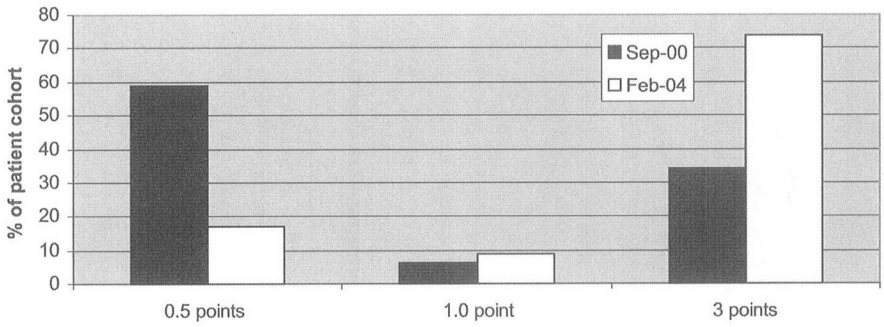
Concurrent audit of the revised serum-screening programme has demonstrated that the benefits obtained for the HSP cohort in the scoping study have been achieved for the wider group of patients (Figure 3). In consequence, the unexpected positive crossmatch rate at the centre has been considerably reduced, with no such result having been obtained in the centre for more than six months (Figure 4).

Importantly, the number of sensitised patients receiving a kidney in the period since implementation of the revised serum screening strategy has remained proportionate to their numbers on the local list of patients awaiting transplantation. Hence the decrease in the "unexpected positive" crossmatch rate is not attributable to a lower "risk" for this result type owing to a reduced representation of sensitised patients amongst those receiving "offers".

Over the three-year period since implementation of the revised strategy the number of transplants performed at the centre has increased by more than 36 per cent ($n = 38$). While the contribution of other initiatives to this growth must also be acknowledged, the revised serum screening programme and resultant decrease in the unexpected positive crossmatch rate has undoubtedly been influential as indicated by the ratio of transplants performed to offers accepted (Table I). These additional transplants represent a potential saving of £893,000 *per annum* until failure.

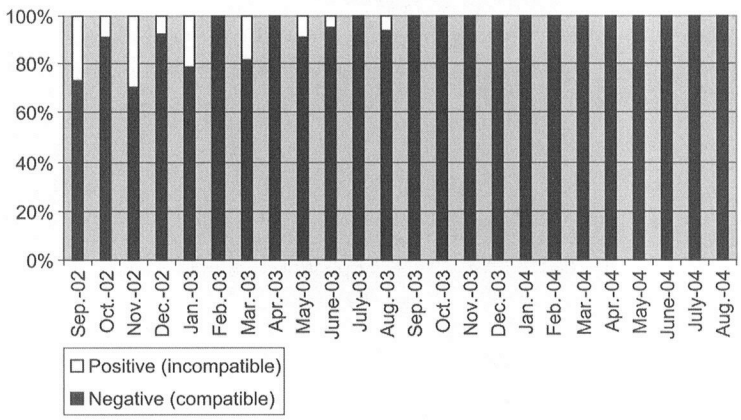
Discussion

This experience serves to emphasise the importance of adequate assessment of sensitisation in potential transplant recipients. Eligibility for transplantation under current UK allocation rules and lower risk for positive crossmatch result are both



Note: Mean sensitisation score on the September 2000 list was 1.18 compared with 2.4 on the February 2004 list

Figure 3.
Comparison of sensitisation score profiles (Year 1 scheme) for Leeds patients on the September 2000 UKT list versus data for patients on the February 2004 list



Note: The declining rate of "unexpected positive" (incompatible) results reflects the improvements in the quality of serum screening over this period. The "unexpected positive" crossmatch rate for the centre over the twelve month period March 2003-February 2004 is 3.4 per cent. A 24 per cent rate had been recorded prior to introduction of the revised serum screening programme

Figure 4.
Percentage breakdown of crossmatch tests by interpretation, September 2002-February 2004

Year	Ratio of transplants to offers accepted
1998	0.7:1
1999	0.8:1
2000	0.8:1
2001	0.8:1
2002	0.9:1
2003	0.9:1
2004 (to date)	1:1

Note: The increment from 2001 follows the reduction in unexpected positive crossmatch rates linked to improved serum screening

Table I.
Ratio of transplants performed to offers received, 1998-2004

shown to be directly linked with quality of serum screening. From a purely financial perspective it is demonstrated that development of "high-confidence" serum screening strategies produces a cost benefit for the NHS if an integrated view of laboratory and medical services is taken.

Increasing the transplant supply as planned by UKT is expected to change the number and proportion of patients with a transplant by 2010 (Department of Health, 2001). To take fullest advantage of this increased availability, transplant units will need to ensure that their sensitised patients have been investigated to the standard required to ensure maximum eligibility for available organs under the current allocation rules.

Directors of renal units should review UKT sensitisation points profiles of listed patients and unexpected positive crossmatch rates with laboratory colleagues at

regular intervals. However, it is cautioned that these measures of performance should not be viewed in isolation. Most importantly, it should be ensured that representation of sensitised patients amongst those transplanted remains proportionate to numbers awaiting transplantation.

Notes

1. At scheme inception sensitised patients were awarded sensitisation points dependent on their percentage antibody reactivity (or residual percentage antibody activity) in accord with the following scheme: ≥ 20 per cent: 0.5 points; ≥ 10 per cent but < 20 per cent: 1 point; < 10 per cent: 3 points. In the UKT kidney allocation scheme, a higher sensitisation points score equates with increased eligibility for available cadaveric organs.
2. While non-HLA antibodies have no influence on transplant outcome, their unrecognised presence in a patient may result both in misclassification of the patient as sensitised and confound the interpretation of the crossmatch test leading to inappropriate denial of a transplant opportunity.

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