

## Donor-specific transfusions

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### GUIDELINES

- a. The best designed randomised controlled trial demonstrates no advantage of donor-specific transfusions (DSTs) in graft survival at 2 years or in the incidence of acute rejection. (Level II evidence)
- b. There is randomised controlled trial evidence (in a small trial) for a beneficial effect of DSTs in cyclosporine-treated recipients of one haplotype mismatch living related donations in terms of less acute rejection and lower serum creatinine in the short term. (Level II evidence)

### SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- The high risk of sensitisation does not justify the routine use of DSTs (Level III evidence)
- A single pre-transplant DST is as effective as multiple DSTs. (Level III evidence)
- The potential benefit of DST needs to be weighed against the risk of sensitisation (approximately 30%) and infection.
- There is insufficient evidence on the use of DSTs to assist deletion of donor-specific antibodies pre-transplant to support their use.

### IMPLEMENTATION AND AUDIT

No recommendation.

### BACKGROUND

Maximising graft survival from living donors is a major goal in transplantation given the mismatch between the number of available donors and the ever-increasing number of recipients. Blood transfusion from living donors to the recipient prior to kidney transplantation was introduced several decades ago with the aim of improving graft outcome. However, with reduced acute rejection rates associated with newer immunosuppressive agents and recombinant erythropoietin use, DST is rarely practised. Nevertheless, modulating the immune response to the donor and inducing 'pseudo-tolerance' without having to rely heavily on immunosuppression continues to be a goal of transplantation medicine.

When reviewing the evidence, it needs to be recognized that there may be fundamental differences between early reports of DST use and the DST of today; red blood cells are now washed and are essentially free of white blood cells –

which may have been an important mediator of the observed effects. Furthermore, more recent literature suggests that the beneficial effect of tolerance develops only if the blood donor and recipient have one HLA haplotype or at least one HLA-B and one HLA-DR antigen in common.<sup>1</sup> Many of the studies reviewed below do not specify these details.

The purpose of these guidelines is to review the evidence on DST in living kidney donation (LKD) and to provide recommendations on when and whether its use is warranted.

### SEARCH STRATEGY

**Databases searched:** MeSH terms and text words for kidney transplantation and living donor were combined with MeSH terms and text words for blood transfusion. The search was carried out in Medline (1966 – September Week 2, 2006). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of search:** 26 September 2006.

**Update search:**

**Databases searched:** MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor and combined with MeSH terms and text words for open and laparoscopic nephrectomy. The search was carried out in Medline (1966 – March Week 1, 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** 9 March 2009.

### WHAT IS THE EVIDENCE?

#### Level II evidence

The beneficial effect of DST in one haplotype mismatch living related donors was first suggested by Salvatierra *et al.*<sup>2</sup> Since then, two prospective randomized trials have been reported.<sup>3,4</sup>

Alexander *et al.*<sup>3</sup> compared patients given DST 24 hours prior to transplant and 7–10 days post-transplant (n = 115) with patients who did not receive DST (n = 97). The immunosuppression regimen was routine triple immunosuppression commenced post-transplant. All patients were -HLA non-identical (>50% had more than two Class I mismatches and more than one Class II mismatch). There was a similar distribution of HLA mismatch between the two groups. Biopsy-proven rejection episodes were seen more frequently in the DST group (81 vs 54 in non-DST) but this difference was not statistically significant. A significantly higher creatinine level was seen in the DST group at 7 and 14 days but this did not translate into a difference in 1- or 2-year graft survival. One of the primary outcomes of the study was the ability to withdraw steroid treatment; no significant difference was seen between the two groups for this outcome. There was no difference in adverse events between the two groups. Limitations of this study include the inclusion of a diverse degree of HLA matches and too small a sample size to adequately study the effect of DST for the different HLA matches.

In a smaller prospective trial, Sharma *et al.*<sup>4</sup> randomized living related recipients (n = 15) to receive DST (one transfusion 24 hours prior to transplant) or no DST (n = 15). All patients received cyclosporine 3 days prior to transplant and continued routine triple therapy post-transplant. In addition, all patients received third-party transfusions 2–3 weeks prior to transplantation to correct anaemia. Sharma *et al.* found a significantly greater incidence of acute rejection in the non-DST group (1.1 vs 0.26 per patient,  $P < 0.01$ ). A significantly lower creatinine level was also seen in the DST group from 3 months to 12 months post-transplant (at 12 months, 1.12 vs 2.02 mg/dL,  $P < 0.05$ ). However, there was no difference in graft survival in the short term (1 year). It is difficult to extrapolate results from this study to current practice because the degree of HLA match was not specified and patients in both groups received third-party transfusions to correct anaemia (prior to standard erythropoietin usage).

Bordes-Aznar *et al.*<sup>5</sup> reported a small randomized trial comparing the outcome of DST to cyclosporine and prednisone followed by azathioprine in living related recipients who were haploidentical but who had highly reactive mixed lymphocyte cultures (MLC). This group traditionally has a lower graft survival and is considered high risk. There was no difference in patient or graft survival at 1 year between the two groups (70% graft survival in both). In the DST group, 30% of potential donors were not able to be used because of sensitisation. Immunosuppression was not given during the transfusion periods. Bordes-Aznar *et al.* did not clearly state sample size or immunosuppression regimen, and the randomization method was not explained.

### Level III evidence

In 2006, Marti *et al.*<sup>6</sup> reported a prospective study of 61 potential allograft recipients (adults >16 years), both living related and unrelated, who received DSTs and compared them to carefully selected matched controls from the

Collaborative Transplant Study Group (CTS). The controls were matched for age, sex, related vs unrelated, original disease, cold ischemia time, number of transplants, year of transplant, time on dialysis and HLA match. All patients were on cyclosporin and prednisone with 31/55 also receiving either azathioprine or mycophenolate. There was no significant difference in induction therapy between the DST and matched control group. Although there was a trend to better allograft survival in the DST group (98% vs. 82%) this failed to reach statistical significance and when examined on an intention-to-treat basis, the 6-year graft survival of the DST group was 88.5%. There were no statistically significant differences in 1-year serum creatinine or treated acute rejection rate between the two groups. Of concern was the fact that 10% of patients (n = 6) in the DST group developed positive T cell crossmatches following the transfusions and living donation did not proceed. This study was underpowered to look at graft survival differences and historical controls were used. There were more pre-emptive transplants in the DST group (although time on dialysis was similar).

Sonoda and Ishibashi<sup>7</sup> retrospectively analyzed patients in the Japanese transplant registry. One HLA haplotype mismatch living related donor (LRD) patients (n = 1292) were analyzed in subgroups according to immunosuppression (cyclosporin n = 315; no cyclosporine n = 977) and DST transfusion (97/315 cyclosporin; 298/977 without cyclosporin). In the cyclosporin groups, the graft survival rate at 4 years for those with DST was 93.5%, compared with 76.2% for those with third-party transfusion (not DST) and 62.7% for those without transfusion. This improvement in graft survival was not seen in the non-cyclosporin group, where the 4-year graft survival for DST was 73.3%, 73.2% for third-party transfusion and 69.0% for those with no transfusion.

Davies *et al.*<sup>8</sup> prospectively (not randomized) compared three different protocols for DST:

1. multiple pre-transplant DST with azathioprine during the period and oral cyclosporin post-transplant (n = 34),
  2. multiple pre-transplant DST with azathioprine during this period and oral cyclosporin 1 day pre-transplant (n = 31), and
  3. single pre-transplant DST 24–48 hours prior to transplant with pre-transplant intravenous cyclosporin (n = 21).
- All patients were LRD recipients with a 1 haplotype mismatch. There were no significant differences in recipient age, panel reactive antibodies (PRA) or the number of third-party transfusions between the three groups. Davies *et al.* found no significant differences in the acute rejection rate or in the 1-year patient or graft survival between the three groups. There was, however, a significantly greater incidence of CMV infection in Group 2 compared with the other groups (16% for Group 2 vs 0% for Groups 1 and 3).

Satoh *et al.*<sup>9</sup> retrospectively examined long term (3–13 years) graft survival in 52 one-haploidentical living related first renal transplants conducted between 1983 and 1996. Twelve patients received prednisone, azathioprine and cyclosporin plus DST and 38 received prednisone,

azathioprine and cyclosporine alone. Recipients received 3 DSTs without immunosuppression. Historical controls were not extensively matched as in the study by Marti *et al.*<sup>6</sup> and the DST group had significantly lower donor age. There was no significant difference in acute rejection or long-term graft survival rates between the two groups. Two patients (16.7%) in the DST group developed donor specific antibodies which were subsequently removed by plasmapheresis and T and B cell crossmatches became negative. This study was important in demonstrating that longer term graft survival was not improved by DST, as one of the hypotheses regarding use of DSTs was that it may reduce chronic rejection and therefore alter long-term outcome.

Otsuka *et al.*<sup>10</sup> retrospectively analyzed 40 potential recipients of DST and cyclosporine, comparing them to a historical control who received a one haplotype matched living related kidney but no DST during the same period (n = 13). All patients received a calcineurin inhibitor. Cyclosporin was administered at the time of DST. There was no significant difference in graft survival rate at 5 and 10 years between the two groups, and no difference in acute rejection rates within 3 months after transplant. The sensitization rate was 7.5%, and one of the three patients who developed positive crossmatches could not proceed with living donation. One patient developed CMV infection as a consequence of the DST.

Lezaic *et al.*<sup>11</sup> retrospectively compared living related transplant recipients who had received DST with azathioprine cover (n = 19) to untransfused patients (n = 15) and 25 random polyinfused patients. Post-transplant immunosuppression consisted of azathioprine, cyclosporine and prednisone. Serum creatinine was significantly higher at 1 and 3 years in the non-transfused group compared with the DST and the randomly transfused group, despite the fact that there were no differences in the incidence of acute rejection or early graft function. There was also no difference in HLA mismatch, MLC reactivity and panel reactivity. This report provides little detail on the patients included or how the groups were selected and the numbers included are small. Three patients (15.7%) developed cross-reactivity with their donors in the DST group.

Flye *et al.*<sup>12</sup> examined the effect of three 200 mL aliquots of DSTs given biweekly with azathioprine cover in 163 one- or two haplotype-mismatch living related or living unrelated potential renal transplant recipients. Following transplantation, only prednisone and azathioprine were given. Their outcome was compared with a group of HLA-identical living recipients (n = 53) and a group of one- or two haplotype-mismatched living donor recipients (n = 54) treated with triple immunosuppression and induction therapy. Permanent T cell crossmatch sensitization occurred in 11 of the 163 patients (7%). Actual one- and five-year graft survivals were 94%, 100%, 100% and 72%, 85% and 71% for DST-treated groups with one HLA haplotype mismatched donors (n = 121), two HLA haplotype mismatched related donors (n = 14) and two haplotype-mismatched unrelated donors, respectively. This was comparable to the HLA identical group. No lymphoproliferative or CMV disease was seen in the DST group.

In a retrospective paediatric study (Leone *et al.*<sup>13</sup>), the results of DST plus post-transplant immunosuppression with prednisone and azathioprine were compared with a routine triple immunosuppression group. All received haploidentical grafts. Three of 24 patients treated with DST had circulating cytotoxic antibodies to the donor. There was no difference in graft or patient survival at 1 year or in mean rejection episodes. However, there was less hospitalization and less severe rejection during the first 3 months in the cyclosporine (non-DST) group. Given the equivalent graft survival and the risk of recipient sensitization, the authors concluded that routine triple immunosuppression is preferable.

Anderson *et al.*<sup>14</sup> administered donor-specific whole blood or buffy coat in conjunction with azathioprine immunosuppression in 163 patients. Transient sensitization occurred in 2% and permanent sensitization in 7%. Over the 10 year duration, DST + azathioprine graft survival was similar to the HLA-identical sibling transplantation. The CMV sepsis rate was 2% and there was no occurrence of lymphoproliferative neoplasms.

## SUMMARY OF THE EVIDENCE

Please refer to the enclosed evidence tables.

## WHAT DO THE OTHER GUIDELINES SAY?

**Kidney Disease Outcomes Quality Initiative:** There is some evidence that donor-specific transfusion with living donor transplantation improves survival, but the decision to perform donor-specific transfusion must still be made on a case-by-case basis. Blood transfusions can induce antibodies to histocompatibility leukocyte antigens that can reduce the success of kidney transplantation; thus, transfusions generally should be avoided in patients awaiting a renal transplant.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**International Guidelines:** No recommendation.

## SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

## CONFLICT OF INTEREST

Fiona Mackie has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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## APPENDICES

**Table 1** Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Main conclusions
Alexander <i>et al.</i> 1999 <sup>3</sup>	212	Randomised controlled clinical trial	8 centres, US	Non-HLA identical living kidney transplant recipients	Donor-specific transfusion	No intervention	21 months	DST had no practical effect on patient or graft survival for up to 2 yrs, donor-specific responsiveness was more frequent in transfused patients
Sharma <i>et al.</i> 1997 <sup>4</sup>	30	Randomised controlled clinical trial	India	Haplotype-matched living related renal transplant recipients	Donor-specific transfusion	No intervention	13 to 18 months	DST and cyclosporine administered 24 h before Tx is effective in improving graft function and reducing acute rejection

**Table 2** Quality of randomised trials

Study ID (author, year)	Method of allocation concealment*	Blinding			Intention-to-treat analysis†	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Alexander <i>et al.</i> 1999 <sup>3</sup>	Central	No	No	No	No	5.8%
Sharma <i>et al.</i> 1997 <sup>4</sup>	Computer generated	No	No	No	Not stated	0.0%

\*Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

†Choose between: yes; no; unclear.

**Table 3** Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
	Mortality at 2 yrs	4/115	2/97	13.69 (95%CI: 0.32, 9.01)	0.01 (95%CI: -0.03, 0.06)
	At least one rejection	60/115	44/97	1.15 (95%CI: 0.87, 1.52)	0.07 (95%CI: -0.07, 0.20)
Sharma <i>et al.</i> 1997 <sup>4</sup>	Severe steroid-resistant rejections	2/15	3/15	0.67 (95%CI: 0.13, 3.44)	-0.07 (95%CI: -0.33, 0.20)
	Mortality	1/15	2/15	0.50 (95%CI: 0.05, 4.94)	-0.07 (95%CI: -0.28, 0.15)
	Graft loss	2/15	3/15	0.67 (95%CI: 0.13, 3.44)	-0.07 (95%CI: -0.33, 0.20)