Comments for Consideration on the Question Regarding
The Impact of Pre-Transplant Red Blood Cell Transfusions in Renal Allograft Rejection

The American Society of Transplantation
The American Society of Transplant Surgeons

The American Society of Transplantation (AST) and the American Society of Transplant Surgeons (ASTS) appreciate the opportunity to comment on the use of pre-transplant red blood cell transfusion on renal allograft outcomes. The AST is the largest organization of transplant professionals, representing over 3200, physicians, surgeons, scientists, histocompatibility technologists, and transplant coordinators who are actively involved in the care of transplant patients, research, education and the development of clinical practice guidelines. The ASTS is the oldest transplant society serving over 1750 surgeons, physicians, scientists, pharmacists, coordinators, and advanced transplant providers. ASTS is committed to fostering the practice and science of transplantation and guiding those who make policy decisions by advocating for comprehensive and innovative solutions to the needs of our members and their patients. As such, the AST and ASTS are uniquely positioned to comment on and present relevant data as it pertains to the potential implications of administration of blood transfusions pre-transplant for access to transplant for patients with CKD, and the impact on outcomes post-transplantation.

In the document put forward for public comment entitled "**The Impact of Pre-Transplant Red Blood Cell Transfusions in Renal Allograft Rejection**" it was concluded that "number of transfusions/transfused units versus no transfusion, or a smaller number of, transfusions/transfused units either resulted in either beneficial or small/null effects on rejection, graft survival, or patient survival. So the literature, weak as it is, supports a neutral to positive effect resulting from transfusion and does not support a detrimental effect resulting from transfusion of a larger number of transfusions". We believe this statement to be inaccurate, and the data presented in the document to be limited in scope and applicability based on the following points:

- The data are predominantly drawn from publications in the 1980's, many of which specifically examined the use of Donor Specific Transfusions (DST) prior to transplantation and their impact on graft survival. The conclusion does not take into consideration the effect of DST on access to transplantation and the development of positive cross matches preventing transplantation in up to 50% of cases. Indeed this is briefly mentioned in the document itself: "It should be noted that in some studies, patients who were candidates for transplantation were ultimately not offered the transplant due to high PRA levels. Some other studies did not disclose the number of patients who were ultimately not transplanted due to a high PRA as they focused on the population undergoing transplant."
- The extrapolation of DST in the immediate pre-transplant period to the general use of transfusion for chronic treatment of anemia pre-transplant is not based on scientific evidence and is unwarranted. The premise of the benefit of DST is that the transfusion of blood from the potential specific kidney donor results in the direct exposure to donor

antigens prior to transplantation resulting in modulation of the immune responses toward those antigens. As noted above, in a significant percentage of cases, this resulted in the development of anti-donor antibodies thereby precluding transplantation from that donor, rather than facilitating graft acceptance. Accordingly, DST is significantly different to transfusion from multiple random donors which likewise exposes the potential recipient to multiple HLA antigens, increasing the risk of sensitization and thereby decreasing the potential candidate donor pool for a prospective recipient [1, 2].

- The data used refer to Panel Reactive Antibodies, a measure of general reactivity toward the potential donor pool. This measure is used in the allocation of organs and does not indicate reactivity to the recipient's specific donor. Current methodology is based on the identification of Donor Specific Antibodies (DSA), a better predictor for an adverse impact on graft survival through the development acute or chronic antibody mediated rejection [3-5].

In short, the review and conclusions are largely irrelevant to current practices and do not take into account current technology and immunosuppression. The difficulty with generating any broad conclusion based on the data presented is further emphasized by the following statement in the document itself: "Given the problems with internal validity with these individual studies and the heterogeneity contained within the studies, we only have a low or insufficient strength of evidence for any of these findings". The strength of evidence presented for all articles referred to was ranked as low to insufficient data.

We would strongly urge that more recent data, which provide stronger evidence for the deleterious effects of sensitization and transfusion on transplant outcomes, and access to transplantation, be considered. A recent study examining the effect of DST and random pre-transplant blood transfusion (rPTF) on sensitization found that 25% of potential recipients did not receive a transplant following DST due to the development of DSA. Of those that received a rPTF, 27% developed anti-HLA antibodies and these were donor specific in 20.3% of cases. Synder et al presented data at the National meeting of the American Society of Nephrology in 2010 based on findings from the USRDS 2010 report. This data showed that patients with PRAs greater that 80% at the time of listing had a higher three year cumulative incidence of transfusion prelisting compared to those with PRAs less than 19% while patients with PRAs of 20 to 79% were intermediate. Patients that had a transfusion prior to listing had an increased adjusted hazard ratio of 4.04 risk of death on the transplant waiting list compared to those who had not received a transfusion, and a 28% reduction in the likelihood of transplantation. Fifty percent of waitlisted patients with a PRA of >80% die on the waiting list. Patients with a PRA >80% comprise 30% of the current renal transplant waiting list. The adjusted hazard ratio for death with a functioning graft was 1.41 for those with a PRA of 80%, compared to 1.21 for 20-79%, and 1.08 for 1-19%, with 0% as reference. The effect of transfusion is greatest for African Americans and women, with both groups being more likely to become sensitized [6]. This further disenfranchises two groups that already have decreased access to transplantation due to immunological and social factors. Kakaiya et al examine the prevalence of anti-HLA antibodies in blood donors that had had previous transfusions themselves using current methodologies [7]. They found that overall there was an increase in anti-HLA antibodies, and this was particularly so for parous females that received a transfusion compared to those that had not (OR 1.39). Similarly, Eikmans et al found that 35%

of parous females that received a single transfusion developed sensitization. These are just a few of the more recent publications linking transfusion and sensitization [8].

There is limited evidence that treatment of post-transplant anemia is beneficial to anemic kidney transplant recipients since large randomized studies have not been performed in this population. The TREAT study examining ESAs versus placebo in diabetic patients with CKD demonstrated that 24.5% of patients in the placebo control arm required transfusion [9]. The impact on sensitization was not measured in this study but studies referred to above and others would suggest that this population would have a significant risk of developing anti-HLA antibodies. This is also inferred from data from the USRDS 2010 report which shows that the rate of pretransplant transfusion has decreased from 49% to 15% from 1991 to 2008, reflecting the increased use of ESAs in ESRD patients. At the same time the percentage of patients with 0% PRA on the waiting list has increased from 20% to over 40%. Vella et al showed that the number of transfusions in waitlisted patients decreased by 34% in the period before and after the introduction of ESAs [10]. Parallel with this the number of patients sensitized as a result of transfusion decreased from 63% to 28%, and this was associated with a significant reduction in the mean time to transplantation.

The origin of anemia after transplantation is multifactorial. In the absence of ESA's renal transplant recipients would almost universally have anemia due to ESRD at the time of transplant. While recovery of erythropoesis occurs following transplant this is not immediate and fails to occur in up to 30% of patients. In the perioperative period anemia is worsened by the intraoperative loss of blood, the presence of delayed graft function, the initiation of immunosuppression (sirolimus and mycophenolate mofetil) and other medications, including ACEI. Perioperative anemia is recognized to contribute to perioperative complications [11]. In a study by Djamali et al, they found that in a population of patients on ESAs at the time of transplant, with hematocrits (Hct) ranging from 17% to 40% on post-op day 1, the average drop in Hct was 5.9±5.6% [12], Patients that had a Hct of less than 30%, representing 60% of the study population, had 17% incidence of acute cardiovascular events, significantly greater than those with a Hct > 30%. Increasing Hct was associated with a significant risk reduction for CV events. Death due to an acute CV event is the greatest cause of death with a functioning graft in the months post-transplant.

One must also consider that from the practical perspective, reliance on blood transfusions for treatment of anemia prior to transplant would require referral to a hospital and potentially an admission, since most free standing dialysis units do not have the capabilities to transfuse patients in the unit. This has implications for cost and must be considered in the financial analysis overall.

In conclusion, we strongly disagree with the statement that "number of transfusions/transfused units versus no transfusion, or a smaller number of, transfusions/transfused units resulted in either beneficial or small/null effects on rejection, graft survival, or patient survival". The rationale leading to this conclusion is severely flawed for the following reasons: (1) the age and the weak scientific strength of the data considered; (2) failure to take into consideration newer data and techniques; and (3) failure to consider the overall impact of pre-transplant transfusion on access to transplantation. Use of these

data in any decision-making process regarding the use of ESAs relative to transplantation would be misguided and has the potential to significantly impact our patients' ability to get transplanted and their outcomes following transplantation. We strongly urge that appropriate randomized control trials of the treatment of anemia in the transplant population be conducted, and that the results from these studies form the basis for any future decision-making regarding appropriate therapy in our patients. The AST and the ASTS stand ready to provide any needed assistance as this important issue is considered.

References

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