Anaemia in Renal Transplant Patients: Report of the European survey

R. Trevitt, L. Bennett on behalf of the EDTNA/ERCA Anaemia and Transplant Interest Groups 2007.

Keywords: anaemia, prevalence, renal transplantation

Abstract
In order to assess the frequency of post-transplantation anemia and the working guidelines for its diagnosis and treatment, a questionnaire was sent to 123 transplantation centers in 13 European countries, including Israel. Results from the 39 centers (32%) that responded indicate wide variation with 16% of recipients anaemic (range 2-60%). Working protocols varied with respect to the laboratory tests upon which anemia was diagnosed, who monitored and/or treated anemia, Hb threshold for treatment, and treatment. Treatment of anaemia in this population is inconsistent with some centres showing ineffective use of erythropoietin.
It is suggested that standard guidelines for the monitoring and treatment of anemia following kidney transplantation be developed and agreed upon.

Introduction

A functioning renal transplant can be expected to improve quality of life and patient survival (1,2). However, among the issues affecting recipients, Post Transplant Anaemia (PTA) can be a real problem and has previously been found to occur commonly in both Europe and the USA (3,4).
Anaemia causes significant symptoms, causing the same problems as anaemia in chronic kidney disease: it contributes to cardiovascular morbidity and mortality and may reduce renal function. The reasons for PTA are multi-factorial, but the functions of the transplanted kidney are not usually completely restored in the patient, and this is the case for erythropoietin synthesis (5,6)
The Transplant European Survey on Anaemia Management (3) included 72 centres and 4263 pts. Anaemia was defined as 13g/dL or less in men and 12g/dL or less in women. Severe anaemia was defined as Hb $\leq$ 11g/dL in men or $\leq$ 10g/dL in women. This is the largest European study of PTA and found that 38.6 % of patients were anaemic with 8.5% of renal transplant recipients severely anaemic.
Yorgin et al. (4) in the United States carried out a longitudinal study over 5 years and found a rate of 30% anaemia (<13g/dL males; <12g/dL females) with renal function being the greatest risk factor. Previous studies have found PTA to be associated with immunosuppression (7).
A prospective study, after controlling for several variables, found that patients with PTA had a 1.69 times higher risk of death within four years, and a 2.46 times higher risk of returning to dialysis during the same period than patients with higher Hb levels (8).
The aim of this study was to look at any inter and intra-country differences in PTA by use of a survey.

Method

A questionnaire was developed to map the extent of anaemia, as reported by nurses in transplant centres across Europe, and to examine how anaemia was identified and managed. These were sent by post to the head nurse of each transplant centre in 13 countries with an addressed envelope for return. No reminder was sent. The countries were selected on the basis of understanding English or the research group having access to translation.
We used the existing guidelines to define anaemia as being serum Hb<11 g/L, which is the threshold that is suggested to trigger treatment with erythropoiesis stimulating agents (ESAs) in patients with CKD, including kidney-transplanted patients, by the NKF-K/DOQI guidelines (9) and the European Best Practice guidelines (10). The questionnaire did not distinguish between erythropoietin and other erythropoiesis stimulating agents. The results are presented using simple descriptive statistics.

Results

A total of 39 out of 123 (32%) centres responded to the questionnaire, with Germany providing the most respondents at 10 (26%) centres (Table 1). The response rate was lower then might be expected from some countries. For consistency across countries and centres the addressee of the questionnaire was the Head Nurse, rather than a specific person or role, as it was not possible to obtain such detailed information for all countries. In the UK particularly this would have had an adverse effect on response as most centres have a specific anaemia nurse. Another reason for the low response could be that some nurses may not have access to data on numbers of patients anaemic or on erythropoietin use and so did not return the form. This has resulted in non-response bias in the results, thereby reducing their generalisability.

	No. centres	responses	%of total
Germany	41	10	26
Austria	6	3	8
Belgium	7	2	5
Holland	9	0	0
Luxembourg	1	1	3
UK	28	3	8
Eire	1	0	0
Sweden	4	0	0
Spain	40	6	15
Slovenia	1	1	3
Israel	4	4	10
Hungary	4	1	3
Bosnia/Herzegovina	2	2	5
Serbia	1	1	3
Croatia	1	1	3
Greece	4	4	10

Table 1: number of centers responding by country

Of the 39 centres, 33 (85%) reported that transplants were carried out at their centre and the median number of transplant patients followed up per centre was 340, with a range of 35 patients at a centre in Bosnia-Herzegovina to over 2000 patients at a centre in Spain. In centres for which a figure was given for number of transplant patients using erythropoietin, the mean percentage of patients using Erythropoietin was 20%. This ranged from 2% to 71%, with both centres located in Spain (Table 2), a huge intra-country variation in transplant recipients using erythropoietin. Despite the low response rate from Spain (6/40 centres) the difference between the two extremes is large.

Transplant Carried Out	Yes	33 (85%)
	No	1 (3%)
	No Answer	5 (13%)
Number of Transplant Patients FollowedUp	Number of centres responding	38
	Mean (SD)	512 (512)
	Median	340
	Range	35->2000
% Transplant Patients Using Epo	Number of centres responding	28
	Mean (SD)	20 (16)
	Median	14
	Range	2-71

Table 2: transplant activity

In nearly all centres (37 centres, 95%) a doctor was responsible for monitoring blood counts, while a transplant nurse was also responsible for this in 11 centres (28%) and a nephrology nurse in 3 (8%). Furthermore, in 12 centres (31%) a specific, identified person monitors anaemia, which was nearly always a doctor.
The mean percentage of patients per centre with haemoglobin <11 g/dL was 16% (median 15%), though this varied substantially, from 2% at two centres in Spain to 60% at a centre in Israel. The largest response rate was from Germany which had an intra-country variation of 5-35%.
After haemoglobin, ferritin was the most commonly used parameter in evaluating anaemia (33 centres, 85%). Table 3 gives a breakdown of the parameters used .One centre did not use haemoglobin but did use red cell indices.

Parameter	n (%)
Hb	38 (97%)
Ferritin	33 (85%)
Transferrin	25 (64%)
PTH	25 (64%)
Folate	24 (62%)
Reticulocytes	22 (56%)
Vitamin B12	22 (56%)
Red Cell Indices	18 (46%)
% Hypochromic Red Cells	14 (36%)

Table 3: parameters used to evaluate anaemia

The median haemoglobin threshold for starting treatment with Erythropoietin was 10.5 g/dL. Indeed, a haemoglobin threshold in the range 10-11 g/dL was most common (23 centres, 79%) of centres which specified a threshold, although this ranged from as little as 8 g/dL at a centre in Germany to 12 g/dL at a centre in Austria (Table 4). There is a range of 8-12.0g/dL (mean 10.4, median 10.5) and there is variation within countries. In Germany, which provided the most responses from a single country, the range was 8-10.5g/dL. In 79% of centres the Hb threshold was reported to be 11-12 g/dL.

Hb (g/dl)	
No threshold given	10
8.0	1 (3%)
9.0	2 (7%)
10.0	9 (31%)
10.5	7 (24%)
11.0	7 (24%)
11.5	2 (7%)
12.0	1 (3%)
Mean (SD)	10.4 (0.8)
Median	10.5
Range	8.0-12.0

Table 4: Hb threshold to start erythropoietin

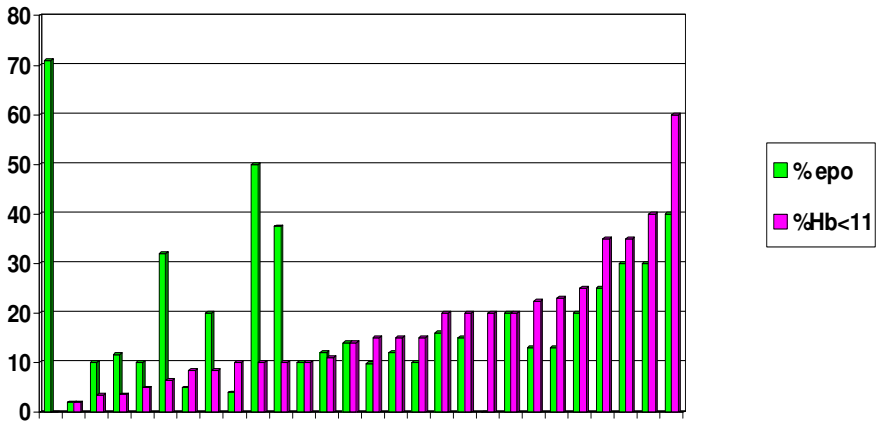

Fig. 1: % anaemic patients and % patients using erythropoietin by centre

Figure 1 shows the % anaemic patients by centre. There was no correlation between centre size and PTA (r=0.0418). The range of PTA is wide at 2-60%. It might be expected that the more patients on erythropoietin in a centre, the less anaemia would be found. Some centres with low levels of PTA are using less erythropoietin than centres with high levels. Some centres have both high levels of anaemia and high levels of erythropoietin use. We found low correlation between threshold for erythropoietin treatment and % patients using it (r=0.396) and almost no correlation with %anaemic patients (r=0.012). Other factors must be involved, including the sub-optimal use of erythropoietin. The TRESAM (3) study found that only 18% of patients with severe anaemia were treated with erythropoietin.

Parameter	n(%)
Use of Epo	29 (74%)
IV Iron Administration	27 (69%)
Immunosuppression Review	25 (64%)
Modification of Other Drugs	21 (54%)
Blood Transfusion	13 (33%)
Folate	1 (3%)
Would Find Algorithm Useful	30 (88%)

Table 5: use of protocols for the management of anaemia

Table 5 shows that most centres had at least one protocol for the management of anaemia. Most commonly, this was an Erythropoietin protocol (29 centres, 74%), though an IV iron administration protocol (27 centres, 69%) and immunosuppression review (25 centres, 64%) were also very common. Furthermore, 30 centres (88%) out of 34 which answered the question said that they would find it useful to have a comprehensive algorithm for the management of anaemia in transplant patients

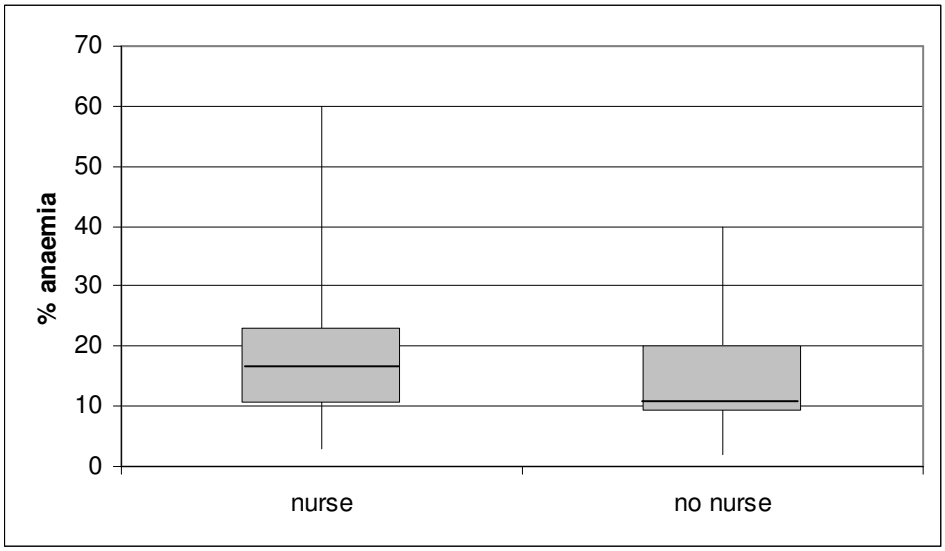

Fig.2: %anaemic patients in centers with or without a nurse monitoring Hb

One of the questions asked was about whether a nurse was responsible for monitoring Hb. In figure 2 it can be seen that no significant difference was found between % anaemic transplant patients in centers where a nurse was responsible compared to centers without a nurse, in fact there was slightly more anaemia in centers with nurse responsibility for Hb monitoring. Of those reporting nurse involvement in monitoring, only half used an algorithm for anaemia with no difference in anemia between the two groups. It is not possible to explain this without detailed information from participating centers; however it could be that giving nurses responsibility for monitoring PTA is initiated by recognizing that there is a problem in a particular centre and therefore PTA starts from a worse position than other centers.

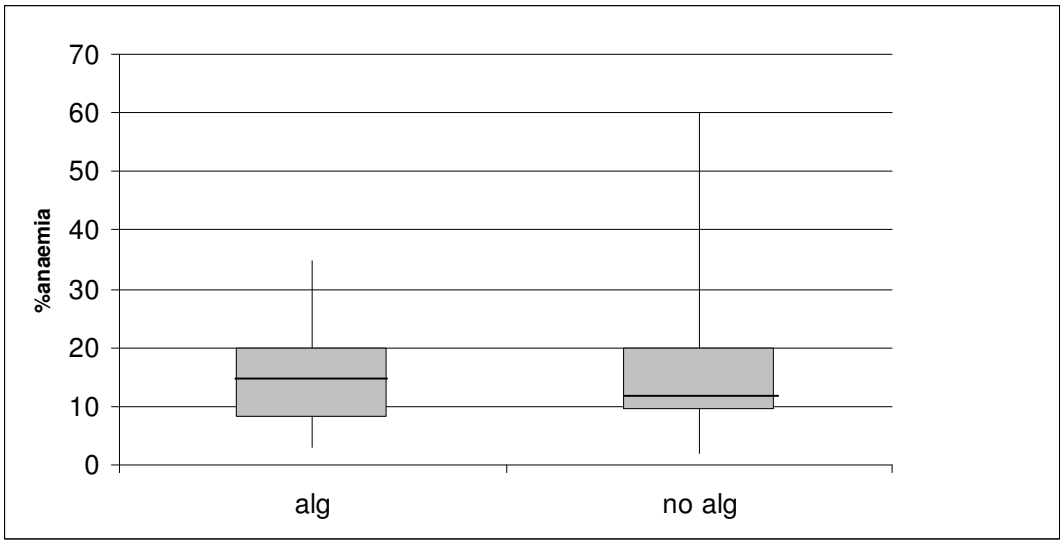

Fig.3: %anaemia vs. use of an anaemia algorithm

The survey also asked about use of an algorithm for anaemia in transplanted patients. Fig.3 shows no significant difference between the two groups: mean 15.8%, median PTA with and mean 17.2%, median without use of an algorithm.

Median needed

Discussion

The response rate of 32% introduces bias to the results. The response rate from larger countries was poor, with Germany providing the best response at 10/42 centres. Some smaller countries provided up to a 100% response rate but from a small number of centres. This increases the risk that the responses may not be representative, and also that the non-responders, if they belong to a different group than the responders, are ignored. However, there is no defined acceptable response rate (11) to a postal survey. The results do display a wide variation in the proportion of anaemic transplant patients, even within single countries, and also a variation in management. The survey response rate from the UK was poor but data from the UK Renal Registry (12) shows that in the UK, 51.5% of transplant patients at Chronic Kidney Disease Stage 5T (GFR<15ml/min) have Hb<11g/dL compared to 30% in dialysis patients. Transplant patients at Stage 4T (GFR 15-29ml/min) had 34% and at Stage 3T (GFR30-59ml/min) 13% Hb<11g/dL, indicating inadequate management of PTA in the UK. Interestingly, this study also reported increasing ferritin levels as transplant function deteriorated, suggesting that there may be decreased ferritin utilisation as erythropoietin levels fall, inflammatory factors causing a rise in ferritin, increased use of iron supplementation and a lack of erythropoietin provision.

PTA is multifactorial and involves the interaction of a number of factors: renal function, and drug therapy, viral illnesses, immunosuppressive protocol, ACE inhibitors and angiotensin-II receptor blockers and in view of the prevalence of PTA we must also add local policy or strategy to deal with anaemia.

Yorgin et al (13) found PTA in 63% patients switching from azathiaprine to mycophenolate mofetil. PTA was also found to increase with each new era of immunosuppression in a single centre retrospective study of paediatric patients; 7.8% pre- and 29% post calcineurin inhibitors, and 32% after mycophenolate mofetil was introduced (14). The use of Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB) has also been associated with PTA (5, 15). Some researchers (16,17) however found no association of PTA with immunosuppression, ACEI or ARB use, only with renal function, and serum erythropoietin levels (independent of the level of renal function) were negatively predictive of anaemia, implying that other non-renal factors were involved.

Our survey found that working protocols varied with respect to the laboratory tests upon which anaemia was evaluated, who monitored and/or treated anaemia, Hb threshold for treatment, and treatment itself. The inter- and intra-country variation in PTA and erythropoietin use indicate that not only does anaemia management need to be improved but that erythropoietin is being used sub-optimally in many centers. Specific date on iron levels and use of supplementary iron was not collected. Only 1 centre reported not monitoring ferritin, transferrin or hypochromic red cells.

The studies quoted by Yorgin et al (4) found 30% PTA (<13male, <12g/dL female), TRESAM (3) 8.5% severe PTA (≤11 male, ≤10g/dL female). Our study found 16% (<11g/dL) which is consistent with their findings.

In addition to funding or protocol issues, it can be speculated that another reason why anaemic transplant patients are not given erythropoietin is cultural. Perhaps an attitude change is required to admit to an inadequate or failing graft; it may be difficult for some clinicians to increase the number of transplant patients placed in the category of poorly functioning graft. Similarly it may be hard for the patient to embrace erythropoietin as it is associated with approaching renal failure and dialysis.
Nurses can and should make an important contribution to the management of PTA in their own centers by the use of audit together with published evidence to highlight the local situation and implications for patients, thus promoting better care. Once the problem is recognized and acknowledged the solution can be promoted.

Conclusion

Anemia is relatively common in recipients following kidney transplantation with an overall range of 2-60% (mean 16%) reported. There are wide differences even within the same country.
Working protocols varied with respect to the laboratory tests upon which anemia was diagnosed, who monitored and/or treated anemia, Hb threshold for treatment, and treatment. Treatment of anaemia in this population is inconsistent with some centers showing ineffective use of erythropoietin.
This treatable complication is significantly and independently associated with mortality and graft failure in kidney-transplanted patients (8,18). This is particularly important if, as Meier-Kriesche et al (19) found in North America, that projected graft survival rates are greatly over-estimated. They suggested that the focus needs to shifts towards maintaining long-term graft function, rather than short term success rates. Ansell et al's (12) data from the UK Renal Registry show that many aspects of long-term transplant management could be improved for CKD Stage 4T and 5T transplant patients, including anaemia, compared to dialysis patients, and that patients were at increased risk of graft loss because of this.
The benefits of renal transplantation cannot be fully realized while patients still have treatable anaemia.
More prospective studies are needed on PTA, in particular the role of different immunosuppressive regimes and the use of ACE inhibitors and angiotensin-II receptor blockers in relation to renal function, iron status and endogenous and exogenous erythropoietin.
Regular screening for anemia and careful evaluation of the multiple factors that may contribute to it are recommended following transplantation. PTA, as in the CKD population, needs to be managed. Until specific PTA target Hb guidelines at local, national or international level are developed this group should be treated in the same way.

This project was supported by an unrestricted educational grant from Amgen

References

1. Parsons DS, Harris DCH. A review of quality of life in chronic renal failure. Pharmacoeconomics 1997 Aug; 12 (2 pt 1): 140-60
2. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. Kidney Int. 2000; 57(1):307-313.
3. Vanrenterghem Y, Ponticelli C, Morales JM et al. Prevalence and management of anaemia in renal transplant recipients – a European survey (TRESAM). Am J Transplant 2003; 3: 835-45
4. Yorgin PD, Scandling JD, Belson A, Sanchez J, Alexander SR, Andreoni KA. Late post-transplant anemia in adult renal transplant recipients. An under-recognized problem? Am J Transplant 2002; 2:429–435
5. Winkelmayer WC, Kewalramani R, Rutstein M, Gabardi S, Vonvisger T, Chandraker A. Pharmacoepidemiology of anemia in kidney transplant recipients. J Am Soc Nephrol 2004; 15: 1347–1352.
6. Nampoory MR, Johny KV, al-Hilali N, Seshadri MS, Kanagasabhapathy AS. Erythropoietin deficiency and relative resistance cause anaemia in post-renal transplant recipients with normal renal function. Nephrol Dial Transplant 1996; 11:177–181.
7. Besouw NM, van der Mast BJ, Smak Gregoor PJH, Cees J. Hesse CJ, IJzermans JNM, van Gelder T, Weimar W. Effect of mycophenolate mofetil on erythropoiesis in stable renal transplant patients is correlated with mycophenolic acid trough levels. Nephrol Dial Transplant 1999; 14: 2710-2713
8. Molnar, M. Z.; Czira, M.; Ambrus, C.; Szeifert, L.; Szentkiralyi, A.; Beko, G.; Rosivall, L.; Remport, A.; Novak, M.; Mucsi, I. Anemia Is Associated with Mortality in Kidney-Transplanted Patients–A Prospective Cohort Study
Am J Transplant 2007; 7(4) 818-824
9. National Kidney Foundation - KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006; 47(Suppl. 3): S110-S116
10. European best practice guidelines for renal transplantation Section IV: Long-term management of the transplant recipient. IV.9.1. Haematological complications. Anaemia. Nephrol Dial Transplant 2002; 17(Suppl 4): 48-49
11. Charlton R. Research: is an 'ideal' questionnaire possible? Int J Clin Pract 2000; **54:** 356–359
12. Ansell D, Udayari U, Steenkamp R et al. Chronic Renal Failure in Kidney Transplant Recipients: Do They Receive Optimum Care? Am J Transplant 2007;7:1167-1176
13. Yorgin PD, Scandling JD, Belson A, Sanchez J, Alexander SR, Andreoni KA. Late post-transplant anemia in adult renal transplant recipients. An under-recognized problem? Am J Transplant 2002; 2: 429-435
14. Mitsnefesa MM, Subat-Dezulovicc M, Khouryb PR, Goebela J Strifea CF. Increasing Incidence of Post-Kidney Transplant Anemia in Children. Am J Transplant 2005; 5: 1713–1718
15. Vanrenterghem Y. Anaemia after renal transplantation. Nephrol Dial Transplant 2004; 19 (suppl 5) v54-8

16. Sinnamon KY, Courtney AE, Maxwell AP. McNamee PT, Savage G, Fogarty DG. Level of Renal Function and Serum Erythropoietin Levels Independently Predict Anaemia Post-renal Transplantation. Nephrol Dial Transplant. 2007; 22(7):1969-1973
17. Kim T. Sinnamon; Aisling E. Courtney; A. Peter Maxwell; Peter T. McNamee; Geraldine Savage; Damian G. Fogarty Level of Renal Function and Serum Erythropoietin Levels Independently Predict Anaemia Post-renal Transplantation. Neph Dial Transpl 2007; 22(7)
18. Weir, M. R. Is Anemia a Predictor for Mortality and Loss of Graft Function in Kidney Transplant Recipients? American Journal of Transplantation, Volume 7, Number 4, April 2007 , 731-732
19. Meier-Kriesche H, Schold JD, Kaplan B. Long-Term Renal Allograft Survival: Have we Made Significant Progress or is it Time to Rethink our Analytic and Therapeutic Strategies? Am J Transplant 2004; 4(8):1289-1295.