

How do the KDIGO Clinical Practice Guidelines on the Care of Kidney Transplant Recipients apply to the UK?

Dr Richard Baker & Professor Alan Jardine, co-authors, forthcoming Renal Association module on management of the kidney transplant recipient

Dr Robert MacTier, Chairman, Renal Association Clinical Practice Guidelines Committee

Introduction

This report comments on the likely relevance and utility of the recently published global KDIGO Clinical Practice Guideline for the care of the kidney transplant recipient with respect to UK clinical practice ¹. The KDIGO report is a comprehensive and systematic review of the available evidence in all major areas of management of the renal transplant recipient. Guidance is provided in many aspects of the management of the renal transplant recipient and the guideline documents clearly where there is lack of robust evidence to inform these recommendations. For this reason many recommendations are either weak (GRADE 2) or not graded. There is very little in the guidelines about the mundane process of implementation. The KDIGO guideline is also available in a more concise form ².

Section 1: Immunosuppression

Chapters 1-3: Induction immunosuppressive therapy and initial and late maintenance immunosuppressive therapy

These guidelines are based on a large evidence base and reflect what would be considered standard current practice for immunosuppressive therapy in most UK renal units. IL-2 receptor antagonists are recommended universally in line with NICE guidance while more potent T-cell depleting agents are reserved for high immunological risk patients. Maintenance immunosuppression is recommended with a CNI (preferably tacrolimus) and a mycophenolic acid derivative and has been heavily influenced by the SYMPHONY study ^{3, 4}. The guidelines remain fairly uncommitted about steroid withdrawal but do suggest that such a strategy should be completed early on (i.e within the first month). After three months it is recommended that CNI doses are minimised (i.e Tacrolimus < 8ng/ml)

Chapter 4: Strategies to reduce drug costs

This chapter mainly concerns improving access to renal transplantation worldwide by offering guidance on how immunosuppressive drug costs may be reduced safely. Switching to lower cost generic drugs has raised concerns in the renal transplant community in the UK. Transplant surgeons and physicians in the UK have held meetings to provide guidance to ensure that all immunosuppressive drugs used in the UK meet regulatory standards and that adequate safeguards are followed after switching to generic immunosuppressants, such as close clinical monitoring of drug levels after switching between different drug formulations.

Chapter 5: Monitoring immunosuppressive medications

The recommendations to monitor all immunosuppressive drugs except prednisolone are routine practice in the UK apart from the weak recommendation (GRADE 2D) to monitor mycophenolate mofetil AUC which is infrequently performed in UK transplant centres.

Chapters 6 and 7: Treatment of acute rejection and chronic allograft injury

The recommendations for the management of suspected acute rejection and chronic allograft injury reflect routine practice in the UK whilst it is acknowledged that the evidence base for these recommendations is weak or very weak. Pulsed steroids are preferred for the initial treatment of acute cellular rejection with T-cell depleting agents reserved for recurrent and non-responsive episodes. It is recognised that there is no definitive treatment for antibody-mediated rejection and that steroids, plasma exchange, Ivlg, anti-CD20 monoclonal antibodies and T-cell depleting agents have all been used with some success. It is recommended to treat borderline rejection.

Chronic allograft injury is the preferred term for graft damage manifested by interstitial fibrosis and tubular atrophy. The need to identify a specific cause for this histological lesion is emphasised⁵. It is recommended to reduce or withdraw CNIs when there is evidence of toxicity. Curiously there is a recommendation to use Sirolimus as an alternative to CNIs if the GFR is estimated to be greater than 40 and the 24 hour protein excretion is less than 0.5g equivalent based on the CONVERT study although the evidence base for this is weak⁶.

Section II: Graft monitoring and infections

Chapters 8 and 9: Monitoring kidney allograft function and kidney allograft biopsy

All of the recommendations (8.1-8.4 and 9.1-9.5) are regarded as good clinical practice in the UK. Specifically it is recommended to quantify protein excretion in the first three months and then to monitor it every three months for the first year⁷. It is acknowledged that there is a lack of supportive evidence from for these recommendations from clinical trials. Protocol biopsies are discussed and it is acknowledged that their utility is related to the underlying subclinical rejection rate. Where this approaches 10% then there is no evidence that they are clinically useful⁸.

Chapter 10: Recurrent kidney disease

The weak recommendations (10.1-10.5) on screening, investigation and treatment of recurrence of the primary renal disease are regarded as good clinical practice in the UK.

Chapter 11: Preventing, detecting and treating nonadherence

The importance of these two (not graded) recommendations is recognised in the UK as is the lack of evidence of effective preventive strategies for non adherence. The importance of patient education is recognised and paediatric to adult transition is highlighted as a high risk period.

Chapter 12: Vaccination

The recommendations for vaccination in kidney transplant recipients are routine clinical practice in the UK apart from the recommendation for annual monitoring of anti-hepatitis B titres and revaccination when indicated (Titre < 10 miU/ml). The emphasis in the UK Renal Association 2009 guideline on Blood Borne Virus in the renal unit (www.renal.org/pages/pages/guidelines/current.php) was placed on hepatitis B vaccination and monitoring the antibody titres before starting renal replacement therapy and after starting dialysis if this could not be performed previously e.g. late referrals.

Chapters 13 and 14: Viral and other infections

The screening, preventive and treatment strategies recommended for viral infections, urinary tract infection, pneumocystis jirovecii pneumonia, tuberculosis and candida infections are broadly similar to good clinical practice in the UK. It is recommended that all patients are screened for BK virus by nucleic acid testing (i.e. PCR) monthly for three months and then every three months for the first year. Blood testing is recommended with advice to reduce immunosuppression if there is evidence of persistent viraemia⁹. There is no specific recommendation for treatment of BK nephropathy other than to reduce the total level of immunosuppression. The guidelines express a preference for chemoprophylaxis over pre-emptive therapy to manage CMV infection in part because it is far easier to organise logistically. In contrast to some UK units they recommend routine three month prophylaxis for not only high risk (D⁺,R⁻) recipients but also intermediate risk (D⁺,R⁺ and D⁻,R⁺) with valganciclovir. Prophylaxis is also recommended for six weeks after administration of T-cell depleting agents. Treatment of mild disease by oral valganciclovir is recommended with intravenous ganciclovir reserved for serious infections. Treatment should be continued until CMV is absent from the blood. Recommendations are made to check EBV serology and monitor EBV viral load in the blood in EBV -ve recipients since viraemia usually precedes PTLD by 4 to 16 weeks. There are also recommendations for treatment of HSV, VZV and hepatitis viruses which are broadly in line with UK practice. Patients with HCV and HBV should have annual liver ultrasounds and determination of alpha-fetoprotein to screen for the development of hepatocellular carcinoma. Daily cotrimoxazole for six months is recommended to avoid UTIs and also pneumocystis jirovecii pneumonia. Antifungal prophylaxis is recommended for the first three months since disseminated candidiasis usually stems from oral colonisation.

Section III: Cardiovascular disease

Chapters 15-17: Diabetes mellitus, hypertension, dyslipidaemia, tobacco use, obesity and cardiovascular disease management

The recommendations on screening for new onset diabetes after transplantation (NODAT) and treatment of NODAT and diabetes mellitus are established as good clinical practice in the UK. The target recommended for control of blood pressure (< 130/80) is based on data from high risk patient subgroups in the general population and the KDIGO guideline rationale accepts that it is unclear in kidney transplant recipients if the benefits of achieving the target BP < 130/80 outweigh the risks and it is unlikely that an adequately powered clinical trial will be performed to evaluate this in renal transplant patients. No particular antihypertensive agent is favoured unless protein excretion exceeds 1g/24hours equivalent when it is recommended to use

drugs that block the renin angiotensin system. The dyslipidaemia recommendations are very detailed, and are based on the KDOQI dyslipidaemia guidelines¹⁰ which have not been followed assiduously in the UK. Aspirin is only recommended for secondary prevention of cardiovascular disease. The recommendations on stopping smoking, and the prevention and treatment of obesity and cardiovascular disease should be routine clinical practice worldwide.

Section IV: Malignancy

Chapters 18-20

The recommendations on the prevention and surveillance of skin, oral and other malignancies and the reduction of immunosuppressive therapy in patients diagnosed with malignancy are established as good clinical practice in the UK. Annual inspection of the skin by a healthcare professional is recommended. Acitretin is recommended for those with previous non-melanoma skin cancer if it is not contraindicated¹¹. Sirolimus is also discussed but there is as yet limited evidence that it can prevent tumour recurrence. Screening is also discussed in the context of cervix, breast, prostate and colon cancers and it is recommended to follow local guidelines for the general population. It is acknowledged that renal cancer is far more common but there is no evidence for widespread screening. It is recommended to reduce overall immunosuppression levels with neoplasia and that this is likely to be more effective clinically in tumours with higher relative risk ratios in transplant populations i.e. likely to be valuable in PTLD but less so in lung cancer.

Chapters 21-27

The recommendations on transplant bone disease are derived from the KDIGO guideline on the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) upon which the Renal Association has already provided a commentary (www.renal.org/pages/pages/guidelines/other.php). The widespread use of DEXA scanning is not recommended since it predicts neither the occurrence of fractures nor the type of bone disease. The recommendations on the detection and treatment of anaemia, polycythaemia, gout, impaired growth in childhood, sexual dysfunction and fertility, lifestyle and mental health are all examples of good clinical practice applied to renal transplant recipients.

Summary

Almost all of the recommendations in the KDIGO guideline on the management of the renal transplant recipient are already followed in the UK with a few notable exceptions such as routinely performing drug monitoring of mycophenolate concentrations, annual post-transplant screening for hepatitis B antibody and post-operative screening for BKV. The greater problem for UK renal units is to ensure the widespread implementation of the guidelines. Managing simple risk factors in large populations has been a recurrent problem for all renal units as documented in the Renal Registry. The challenge is to organise the logistics of widespread and complete implementation. Computer based decision analysis and nurse-led annual review clinics are among the solutions being used in some units to overcome this difficulty.

Acknowledgement

This report on the utility and predicted implementation of the KDIGO Care of Kidney Transplant Recipients guideline within the UK has been reported to KDIGO and the authors of the KDIGO guideline. KDIGO has requested that this feedback is made available on the Renal Association's website.

Reference

1. Special Issue: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *American Journal of Transplantation* 2009;9:S1-S155.
2. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int* 2009.
3. Ekberg H, Bernasconi C, Tedesco-Silva H, et al. Calcineurin inhibitor minimization in the Symphony study: observational results 3 years after transplantation. *Am J Transplant* 2009;9:1876-85.
4. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007;357:2562-75.
5. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. *Am J Transplant* 2009;9:527-35.
6. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation* 2009;87:233-42.
7. Amer H, Cosio FG. Significance and management of proteinuria in kidney transplant recipients. *J Am Soc Nephrol* 2009;20:2490-2.
8. Rush D, Arlen D, Boucher A, et al. Lack of benefit of early protocol biopsies in renal transplant patients receiving TAC and MMF: a randomized study. *Am J Transplant* 2007;7:2538-45.
9. Hardinger KL, Koch MJ, Bohl DJ, Storch GA, Brennan DC. BK-Virus and the Impact of Pre-Emptive Immunosuppression Reduction: 5-Year Results. *Am J Transplant*.
10. Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant* 2004;4 Suppl 7:13-53.
11. Chen K, Craig JC, Shumack S. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005;152:518-23.