# Nephrotoxicity and calcineurin inhibitors

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### GUIDELINES

**No recommendations possible based on Level I or II evidence**

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## SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)
• **There is currently insufficient evidence to favour one calcineurin inhibitor (CNI) over another purely on the basis of nephrotoxicity. (Level II evidence)**

## BACKGROUND

The CNI (cyclosporin and tacrolimus) are now the mainstay of current immunosuppressive protocols for renal transplantation.[1] Both cyclosporin and tacrolimus cause nephrotoxicity which is indistinguishable on renal allograft biopsy. The nephrotoxicity of CNI can be divided into acute and chronic neprotoxicity. Acute calcineurin nephrotoxicity is related to haemodynamic changes on the afferent arteriole, which are dose-dependent and reversible. The cardinal features of chronic CNI nephrotoxicity are focal or striped tubulointerstitial fibrosis, hyaline arteriolopathy and focal collapsing glomerulosclerosis. The contribution of CNI therapy to the development of chronic allograft nephropathy is one of the factors that has prompted studies on the withdrawal of these agents after renal transplantation or alternatively, the development of new immunosuppressive protocols/agents that allow the avoidance of CNI therapy. The gold standard for diagnosis of CNI nephrotoxicity remains renal allograft biopsy. One study, addressing the pathological effects of CNI withdrawal on renal architecture documented a reduction in chronic interstitial tubular lesions in 12 month protocol biopsies following withdrawal of CNI and continuation of sirolimus at 3 months.[3]

The objective of this guideline is to compare biopsy-proven nephrotoxicity of both currently available CNI (tacrolimus and cyclosporin). There have been no well-controlled studies examining calcineurin nephrotoxicity and its management in kidney transplant recipients.

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## SEARCH STRATEGY

**Databases searched:** Medline (1966 to October Week 3, 2004). MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for CNI. The results were then combined with the Cochrane search strategy for randomized controlled trials (RCT). An additional search combining MeSH terms and text words for CNI with MeSH terms and search headings for haemolytic-uremic syndrome was also conducted to provide a more comprehensive list of titles. The Cochrane Renal Group Specialized Register of RCT was also searched for relevant trials not indexed in Medline.
**Date of searches:** 27 October 2004; 29 September 2006.

## WHAT IS THE EVIDENCE?

Level I evidence: There are no systematic reviews comparing nephrotoxicity of relevant RCT.

Level II evidence: Two-year protocol biopsies performed in the US FK506 study were reviewed by one pathologist blinded to the randomization. Biopsies from tacrolimus-treated patients were indistinguishable from cyclosporin-treated patients and chronic allograft nephropathy prevalence was similar between the two groups.[4] Although this study is incomplete in that it represents 41% of the patients active in the study, it remains a large series (144 biopsies).

In an RCT comparing CNI-free regimens with CNI-based regimens for de novo kidney transplants, graft histology at 2 years was significantly improved in the CNI avoidance arm of the study.[5]

Level III evidence: Studies by Nankivell *et al.* have shown that 100% of kidney-pancreas transplant recipients treated with cyclosporin will develop biopsy-proven nephrotoxicity after 10 years of treatment.[6,7]

Level IV evidence: A large US registry study compared the outcome of paired kidneys from single donors in whom one kidney received tacrolimus and the other cyclosporin. Graft survival between the two groups was equivalent at 5 years, although allograft biopsy for nephrotoxicity was not performed.[8]

## SUMMARY OF THE EVIDENCE

Based on Level II evidence, there is comparable prevalence of biopsy-proven nephrotoxicity in both cyclosporin- and tacrolimus-treated patients.

## WHAT DO THE OTHER GUIDELINES SAY?

**Kidney Disease Outcomes Quality Initiative:** No recommendation.
**UK Renal Association:** No recommendation.
**Canadian Society of Nephrology:** No recommendation.
**European Best Practice Guidelines:** No recommendation.
**International Guidelines:** No recommendation.

## IMPLEMENTATION AND AUDIT

No specific recommendations.

## SUGGESTIONS FOR FUTURE RESEARCH

**1** The optimal time for CNI withdrawal could be determined.
**2** The role for renal allograft biopsy in predicting optimal time for CNI withdrawal could be determined.
**3** A comparison of renal allograft biopsies and clinical outcome could be performed (long-term outcome graft failure versus development of chronic allograft nephropathy).
**4** Allograft biopsy comparisons of low-dose CNI-treated patients to determine the prevalence of histopathological lesions in stable patients treated with low-dose CNI could be performed.
**5** The long-term outcome of CNI withdrawal on allograft structure has not been studied in detail. Longitudinal studies

using allograft biopsies should allow this question to be answered.

## CONFLICT OF INTEREST

Toby Coates has a Level II b conflict of interest according to the conflict of interest statement set down by CARI.

## REFERENCES

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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) |
|---|---|---|---|---|---|---|---|
| Gonwa *et al.*, 2002[2] | 246 | Randomized controlled clinical trial | 17 centres in the USA and Europe | 246 first cadaveric renal allograft recipients | Full-dose cyclosporin and fixed-dose sirolimus | Reduced-dose cyclosporin and concentration controlled sirolimus | 12 |
| Solez *et al.*, 1998[4] | 144 | Randomized controlled clinical trial | 19 centres in the USA | 144 patients enrolled in the US FK506 kidney transplant study, recipients of cadaveric kidney transplant | Tacrolimus | Cyclosporin | 24 |

OUT OF DATE

**Table 2**  Quality of randomized trials

| Study ID (author, year) | Method of allocation concealment | Blinding | | | Intention-to-treat analysis | Loss to follow up (%) |
|---|---|---|---|---|---|---|
| | | Participants | Investigators | Outcome assessors | | |
| Gonwa et al., 2002[2] | Not specified | No | No | No | Yes | 0.0 |
| Solez et al., 1998[4] | Not specified | No | No | Yes | Yes | 0.0 |

**Table 3**  Results for continuous outcomes

| Study ID (author, year) | Outcomes | Intervention group (mean (SD)) | Control group (mean (SD)) | Difference in means (95% CI) |
|---|---|---|---|---|
| Gonwa et al., 2002[2] | Mean serum creatinine | 1.99 (1.48) | 1.64 (1.20) | 0.35 (−0.03, 0.73) |
| | Total cholesterol | 238.6 (71.90) | 260.0 (61.00) | −21.40 (−42.77, −0.03) |

CI, confidence interval; SD, standard deviation.

**Table 4**  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 (95% CI) | Risk difference (95% CI) |
|---|---|---|---|---|---|
| Gonwa et al., 2002[2] | Patient survival | 94/97 | 96/100 | 1.01 (0.96, 1.06) | 0.01 (−0.04, 0.06) |
| | Graft survival | 90/97 | 95/100 | 0.98 (0.91, 1.05) | −0.02 (−0.09, 0.04) |
| | Acute rejection | 1/97 | 1/100 | 1.03 (0.07, 16.25) | 0.00 (−0.03, 0.03) |
| Solez et al., 1998[4] | Acute rejection | 7/79 | 6/65 | 0.96 (0.34, 2.72) | 0.00 (−0.10, 0.09) |
| | Chronic allograft nephropathy | 49/79 | 47/65 | 0.86 (0.68, 1.08) | −0.10 (−0.26, 0.05) |

CI, confidence interval.