Maintenance therapy with triple versus double immunosuppressive regimen in renal transplantation: a meta-analysis
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Authors' objectives
To compare the effect of triple immunosuppressive maintenance therapy (cyclosporin, azathioprine, and prednisolone) with that of double-therapy (cyclosporin and prednisolone) in renal transplant patients.

Searching
MEDLINE was searched from 1984 to present using the keywords 'kidney transplantation', 'graft survival or graft rejection', 'prednisolone/prednisone/methylprednisolone', 'cyclosporine/cyclosporins', 'Azathioprine', 'restricted to human' and 'comparative study'. The authors also searched SciSearch from 1987 to 1995, using all the randomised controlled trials identified through MEDLINE to locate additional studies. The reference lists of all the primary studies, review articles, and major nephrology textbooks were examined for relevant studies. Experts were also contacted for other published and unpublished reports that might have been missed in the search strategy.

Study selection
Study designs of evaluations included in the review
The included studies had random allocation to treatment with either triple therapy or double therapy. The included studies had a follow-up ranging from 18 months to 6 years, with 3 of the studies reporting a follow-up of 95% or more.

Specific interventions included in the review
Triple-drug therapy (cyclosporin, azathioprine, and prednisolone) versus double-drug therapy (cyclosporin and prednisolone).

Participants included in the review
Renal transplant patients with a first or second cadaveric or live-donated kidney transplant, who received double- or triple-combination drug therapy. The mean age of the participants ranged from 34 to 50 years in the triple-drug group, and from 38 to 51 years in the double-drug group.

Outcomes assessed in the review
Graft failure, mortality, acute rejection episodes, and adverse effects were reported.

How were decisions on the relevance of primary studies made?
All titles and abstracts were assessed by two independent investigators. Inter-observer agreement was calculated using the K-statistic.

Assessment of study quality
The studies were evaluated for their mode of randomisation, blinding, and completeness of follow-up. The authors also distinguished between peer-reviewed publications and conference reports. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
Data on the outcome variables were sent to the first author for confirmation and clarifications of ambiguous data. Additional information was sought from the authors of the primary studies.

Methods of synthesis
How were the studies combined?
The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel fixed-effect model.

How were differences between studies investigated?
Homogeneity was assessed visually and on the basis of the chi-squared test of Breslow and Day (see Other Publications of Related Interest), with a significance level of p equal to 0.1. Subgroup analyses were planned to explore the following: treatment effect for diabetes versus no diabetes; live versus cadaveric kidney donors; and first versus second or more transplants. The parameters for assessing heterogeneity between the studies were methodological criteria, prognostic factors, and drug dosage.

Results of the review
Five studies (454 participants in the treatment group and 453 in the control group) met all of the inclusion and quality criteria. One of the studies was not blinded, while four did not state their method of blinding. Two of the studies did not state their method for randomisation.

The K-statistic for inter-observer agreement was 0.70.

The pooled analysis did not show a statistically-significant difference between triple-drug therapy and double-drug therapy for any of the reported outcome measures: graft failure (OR 0.82, 95% CI: 0.61, 1.16), survival (OR 0.83, 95% CI: 0.57, 1.21), or the occurrence of acute graft rejection (OR 1.02, 95% CI: 0.76, 1.36). The sensitivity analysis for graft failure and mortality confirmed the stability of the estimates. No heterogeneity was measured in the acute rejection outcomes.

There was a non significant trend for better graft survival under triple-drug therapy.

The adverse effects reported were hypertension (more frequent in the triple-drug therapy), rates of infection, and carcinomas.

Authors' conclusions
There was no statistically-significant difference between the two treatment regimens in the long-term management of renal transplant recipients.

CRD commentary
The authors conducted a very good search of the literature and presented their data in several detailed tables. The authors searched several databases and the reference lists of articles and textbooks for additional studies, and included unpublished data, abstracts and expert consultation. However, relevant studies could have been missed since language restrictions were not discussed.

The inclusion criteria and quality criteria were stated. The authors made a quality review of the included studies but did not score the studies. There was no discussion of how judgements were made about the validity of the included studies, or of how the data were extracted.

The studies were combined using an appropriate statistical model, and ORs and CIs were reported. No heterogeneity was found in either the chi-squared or sensitivity analyses. Although the sample size was larger through pooling the studies, there were insufficient participants to ensure adequate power to conclude statistically-significant results.

The authors' conclusions follow from their results. However, the results were affected by the small sample sizes in the studies and ambiguities in the reported data, which could be remedied with a larger, more clearly defined study.

Implications of the review for practice and research
Practice: The authors state that given the small non significant beneficial trend of triple-drug therapy, other factors,
such as the occurrence and severity of side-effects, should be taken into account when deciding whether to start patients on triple-drug or double-drug therapy.

Research: The authors state that further research is needed with longer follow-up and/or larger sample sizes to confirm or dismiss the reported trends. Future studies should also be more clear and unambiguous in reporting the side-effects and complications of immuno-suppressant therapy.

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**Other publications of related interest**

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