Treatment of polyomavirus infection in kidney transplant recipients: a systematic review

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CRD summary
This review concluded that cidofovir or leflunomide addition to immunosuppression reduction therapy for polyomavirus-associated nephropathy management in kidney transplant recipients may not decrease graft failure rate; however, the evidence base was poor and more research is needed. Given this poor evidence base and the risk of bias in the review, the reliability of the authors' cautious conclusions is unclear.

Authors' objectives
To determine the most effective therapy for treatment of polyoma virus (BK) infection (viruria, viraemia or polyomavirus-associated nephropathy) in recipients of kidney transplants.

Searching
The reviewers searched MEDLINE and EMBASE (both from inception), and the Cochrane Central Register of Clinical Trials for relevant studies published until October 2008. The search was not restricted to English. Search terms were reported. Bibliographies of previous reviews, eligible trials, and published abstracts from relevant annual meetings (American Transplant Congress meetings, 2005-2008) were scanned for further relevant studies.

Study selection
Eligible studies were of adults (over 18 years) who developed BK viruria, BK viraemia, or biopsy-proven polyomavirus-associated nephropathy after receiving primary or repeat kidney transplantation. Eligible specified interventions to treat the polyomavirus complications were immunosuppression reduction alone or immunosuppression reduction plus cidofovir, leflunomide, quinolone antibiotic, interferon, or intravenous immunoglobulin. Eligible patients may have received kidney transplantation from a deceased or living donor. No exclusion criteria were reported.

In included studies, methods of screening for BK virus varied substantially and were often not reported. Included studies were conducted in the USA, Europe, Canada, Australia, Korea and Kuwait.

Two reviewers independently screened articles for inclusion. Disagreements were resolved by consensus or arbitration with two other reviewers.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale (blinding, randomisation, withdrawals and dropouts; score between zero and five) for randomised controlled trials (RCTs), or the Newcastle-Ottawa Quality Assessment scale (study group selection, group comparability, ascertainment of exposure/outcome of interest; score between zero and nine) for cohort studies.

Data extraction
Two reviewers independently extracted data required to calculate the primary outcome, graft failure rate, with 95% confidence intervals (CIs); and rates with 95% CIs for a range of secondary outcomes including acute rejection, patient survival and adverse events.

Methods of synthesis
Event rates (numbers of graft losses per person-year), with 95% CIs, were pooled using random-effects models, using an exact Poisson method to calculate confidence limits for each study.

Results of the review
Overall, 40 studies (total sample size unclear; range 2 to 200) were included in the review. These included three randomised controlled trials, two prospective cohort studies, six retrospective cohort studies and 29 case series. The mean Jadad score for the randomised trials was 2.3 out of 5; the mean Newcastle Ottawa quality score for cohort
studies was 6.9 out of 9. Mean follow-up duration ranged from eight to 43 months.

The rates of graft failure following immunosuppression reduction alone were estimated to be 0.08 (95% CI 0.04 to 0.12; based on 15 observational studies) or a graft loss rate of 8/100 patient years of follow-up.

Following immunosuppression reduction plus cidofovir, the graft failure rates were 0.08 (95% CI 0.03 to 0.13; based on nine observational studies).

Following immunosuppression reduction plus leflunomide, the graft failure rates were 0.13 (95% CI 0.02 to 0.23; based on four observational studies).

A range of secondary outcomes were also reported.

**Authors' conclusions**
The addition of cidofovir or leflunomide to immunosuppression reduction therapy for the management of polyomavirus-associated nephropathy in kidney transplant recipients may not decrease graft failure rate, but the evidence base was poor and more research is needed.

**CRD commentary**
The review question was clear, with appropriate inclusion criteria for participants, interventions and outcomes. The search included relevant sources, with no language restrictions (which reduced the risk of language bias). It was unclear whether attempts were made to identify unpublished studies, although the authors did scan the published abstracts from the American Transplant Congress annual meetings. Study selection, data extraction and quality assessment were conducted in duplicate to reduce the risk of reviewer error and bias.

The method of quality assessment appeared appropriate; most of the included studies were observational, with a comparatively high risk of bias. Sufficient primary study details were reported. The method of synthesis seemed appropriate. The authors acknowledged that their findings were based on poor quality data mostly from uncontrolled case series; their recommendation for further research appeared appropriate.

Given the poor evidence base and the risk bias in the review, the reliability of the authors' cautious conclusions is unclear.

**Implications of the review for practice and research**
**Research:** The authors stated there is an urgent need for adequately powered randomised trials to define the optimal treatment plan for kidney transplant patients with polyomavirus-associated nephropathy.

**Practice:** The authors did not state any implications for practice.

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