Screening to prevent polyoma virus nephropathy: a medical decision analysis

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The present study compared two strategies related to polyoma virus nephropathy (PVN). Specifically, a strategy of screening with pre-emptive immunosuppression reduction was compared with no screening for PVN (the default or “do nothing” strategy). The adjunctive therapy was mycophenolate mofetil since this is the most commonly used drug with calcineurin inhibitors and often the first to be reduced.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The hypothetical population comprised adult kidney transplant recipients.

Setting
The setting was tertiary care. The economic study was carried out in Canada.

Dates to which data relate
The epidemiological, effectiveness and utility data were taken from several trials and studies published between 1971 and 2005. The cost and resource use data were taken from several sources dating from 2001 to 2004. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from published studies, with some estimates based on author’s assumptions.

Modelling
A decision analysis model was developed to simulate the screening strategy for PVN with pre-emptive immunosuppression reduction and the no screening strategy. Health states in the model included death, dialysis and functioning transplant. The baseline case was projected over a 25-year follow-up period.

Biopsies were not performed to confirm parenchymal infection since the purpose of screening was to prevent clinical disease. Successive reductions in immunosuppression were not modelled if viral titres did not fall, since these data were not known and could be captured with variations in the rate of progression to PVN.

Outcomes assessed in the review
The outcomes considered in the study were:

PVN cumulative incidence,

the acute and chronic graft loss rates,

the risk for acute rejection with or after the diagnosis of PVN,

the mortality rates with a functioning transplant and graft function,

mortality for patients on dialysis,

the false-positive rates, and

the rates of chronic allograft nephropathy.

Study designs and other criteria for inclusion in the review
The author reported that a proper systematic review was difficult because most of the reports were small case series with repeated publications. There were no randomised controlled trials comparing screening with pre-emptive immunosuppression reduction to no screening.

Sources searched to identify primary studies
Clinical data were collected by searching MEDLINE in November 2004, using "polyomavirus" and "kidney transplantation" as keywords. The author also reviewed abstracts from the American Society of Transplantation and American Society of Nephrology from 2000.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The author reported that 38 primary studies were included in the review for different purposes.

Methods of combining primary studies
A narrative method was used to combine the studies.

Investigation of differences between primary studies
Not reported.

Results of the review
For the baseline case, the annual mortality rate was 0.029 for a functioning transplant and 0.13 for dialysis.

The annual graft loss rate was 0.034 for baseline, 3.0 for post acute rejection, 4.0 for PNV and 1.4 for the lower immunosuppression.

The PVN incidence was 0.04.
The risk of acute rejection in false positives with treatment reduction was 10%.

Patients developing acute rejection were modelled to have chronic graft loss rates 3 times higher than baseline.

In the patients destined to have PVN (baseline cumulative PVN incidence), immunosuppression reduction reduced the rate of progression to overt PVN by 80%.

**Methods used to derive estimates of effectiveness**
This analysis was based on published data and author's assumptions.

**Estimates of effectiveness and key assumptions**
All patients in the screen arm underwent polyomavirus screening. It was assumed that screening would detect all patients at risk, but some screens would be false positive. These correspond to patients with positive blood viral titres that never develop clinical nephropathy. It was assumed that the adjunctive therapy was mycophenolate mofetil since this was the most commonly used drug with calcineurin inhibitors and often the first to be reduced. Patients developing overt PVN despite screening and therapy reduction were modelled to have outcomes similar to patients in the "no-screen" arm. The patients not developing PVN because of early screening and therapy reduction were modelled to have outcomes similar to the false-positive patients who were at higher risk of both acute and chronic graft loss.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the quality-adjusted life-years (QALYs). The health states were death, dialysis and functioning transplant. PVN patients were not included as a separate health state. The estimation of utility weights was taken from the literature, and no further detail was provided.

**Direct costs**
The direct costs to the health service were included. These were appropriately discounted at a rate of 5% per year. The direct costs included annual costs for functioning transplant, reduced therapy, first year dialysis and subsequent dialysis, and event costs for screening, rejection and evaluation of PVN. Annual transplant, acute rejection and dialysis costs were taken from the United States Renal Data System database and published literature. Other costs were estimates taken from the author's setting. The quantities and the costs were analysed separately. The estimation of resource use was derived using modelling. The price year was 2000.

**Statistical analysis of costs**
The costs were treated deterministically and no statistical tests were carried out.

**Indirect Costs**
The indirect costs were not reported.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-, two- and three-way sensitivity analyses were performed. These looked at the key cost-drivers and key variable estimates, such as reduction in progression to PVN with screening, impact of acute rejection with therapy reduction, and impact of increased chronic allograft nephropathy with therapy reduction. A Monte Carlo simulation was also performed, incorporating uncertainty in the variables using a combination of sampling distributions of the variables and trial simulations. The types of distribution used were not reported.
Estimated benefits used in the economic analysis
Over a 25-year follow-up screening would save 0.020 QALYs.

The cumulative discounted QALYs were 7.468 in the "no-screen" arm and 7.488 in the "screen" arm.

The QALYs were discounted at a rate of 5% per year.

Cost results
Over a 25-year follow-up screening would save $1,912. The cumulative discounted costs were $213,079 in the "no-screen" arm and $211,167 in the "screen" arm.

Synthesis of costs and benefits
For the baseline case, screening was dominant since it saved money and increased QALYs. Most of the savings in this baseline case were accrued from false-positive and true-positive viraemic patients who had their therapy reduced.

The incremental cost-effectiveness ratios from a Monte Carlo simulation were presented graphically. About 60% of the simulations fell below the $100,000/QALY line, an implicit threshold value used by the author. Complete elimination of mycophenolate mofetil would further increase savings in the screen arm and would increase the numbers of simulations that were cost-effective. These data were not shown.

Authors' conclusions
This study examining the impact of polyoma virus nephropathy (PVN) on kidney transplant outcomes has shown that, under many of the assumptions, screening might not only improve outcomes but might also save money. However, under some circumstances, screening could not only be costly but could result in greater harm. Screening is clearly not harmful if the incidence rate is above 2.1%.

CRD COMMENTARY - Selection of comparators
The comparator "non screening" was a natural choice for the study. Only one screening strategy was considered. You should judge whether these strategies are relevant in your own setting, or whether other comparators from other tests and treatments may also be relevant.

Validity of estimate of measure of effectiveness
The author performed a review of the literature; it was well reported. No randomised controlled trials were found. The author appears to have used the data from the available studies selectively. The estimates were investigated in a sensitivity analysis.

Validity of estimate of measure of benefit
The author used QALYs as a measure of benefits. The health outcomes valued with utility weights were reported. The source of the utility weights was reported, but no details of the methods used. The estimation of benefits was modelled through a decision analysis model.

Validity of estimate of costs
The author reported that the costs were estimated from a health service perspective (Medicare), acknowledging that rejection and screening costs from this perspective were not available. The costs and the quantities were reported separately, which means that it should be possible to rework the analysis for other settings. Sensitivity analyses of the costs were conducted to assess the robustness of the estimates used. Discounting was appropriately carried out since the time horizon of the model was 25 years. The price year was reported, which will aid any future reflation exercises.
Other issues
The author compared the findings with those from other studies and found them generally to be concordant. The author addressed the issue of generalisability of the results to other settings by considering that centres with modest or high PVN rates could benefit from screening. The author's conclusions reflected the scope of the analysis but, because different age groups for effectiveness estimates were selected, the population targeted was not clear.

The author acknowledged some limitations of the study, such as the large variations in costs and difficulty in predicting long-term outcomes. Also, the possible change in natural history of PVN as clinicians have greater index of suspicion will diminish the relative benefits of screening. A further limitation was the potential role of leflunomide, which was not included in the analysis. Converting to sirolimus and prednisone (calcineurin withdrawal) may also improve outcomes. However, sirolimus is expensive and there are the risks of rejection with changes in therapy. These options have not been systematically explored in clinical practice over the long term as part of a screening strategy for polyomavirus control. Also, it should be noted that the cut-off choice of $100,000/QALY was arbitrary given the high uncertainty in the model. The probability of cost-effectiveness would have been roughly the same regardless of the cut-off.

Implications of the study
Centres using low-risk protocols that are certain PVN is uncommon should not be under pressure to screen. However, centres with modest or high rates (>3%) could benefit. Under these circumstances, active research and properly designed trials will be critical. The decision on which of a number of possible strategies (reduce immunosuppression or substitute) should be tried in patients that have significant viraemia also needs consideration.

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