Antiviral therapy for neonatal herpes simplex virus: a cost-effectiveness 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 subject of this study was antiviral therapy for neonatal herpes simplex virus. The two types of antiviral therapy considered were vidarabine and acyclovir as opposed to no drug treatment.

Type of intervention
Treatment.

Economic study type
This was primarily a cost-effectiveness analysis although a cost-utility approach was used in the sensitivity analysis.

Study population
Little information was given in this paper about the study population except that they were neonates and had virological confirmation of the disease regardless of severity. Several references were cited for further information on the original studies on which this paper was based.

Setting
The effectiveness study was based in community care and hospital settings. The economic study was conducted at the University of Alabama, Birmingham, USA.

Dates to which data relate
Effectiveness data related to trial data collected in four trials with the following dates: 1974-1979; 1979-1983; 1984-1989; and 1989-1997. Information from these trials was compared with a historical database of non-treated neonates for which other references were given. Resource use data derived from data collected between 1974 and 1989. 1995 US dollar prices were used.

Source of effectiveness data
The evidence on treatment outcomes was based on a series of previously conducted trials (NIAID CASG trials), the results of which were reported to be already pooled in another study, supplemented by information from other sources. The source of evidence relating to the comparator (i.e. no treatment) was a historical database.

Link between effectiveness and cost data
The costing appears to have been undertaken on a separate sample of patients from that used in the effectiveness studies and it is not clear whether it was undertaken retrospectively or prospectively.

Modelling
Decision tree analysis was used to consider the outcome effects of treatment and no treatment on the three main forms
of neonatal herpes simplex virus, listed in increasing order of severity: SEM (skin, ear and mouth), CNS (central nervous system) and DIS (disseminated multiorgan)

Outcomes assessed in the review
Although the authors used data from different sources, there was no specific review of the literature. In terms of outcomes the authors considered lives saved, including those of future generations, and disease occurrence as the main measures of effectiveness.

Study designs and other criteria for inclusion in the review
Data from the NSAID CASG therapeutic trial series were included in the analysis of effectiveness of treatment; these studies were a mixture of placebo-controlled trials, dose-comparison studies and controlled trials. For information concerning the distribution of outcomes in neonates treated and not treated with antiviral therapy, a further source was used, the nature of which is not clear but a reference was provided. Data on the comparator group were obtained from a historical database.

Sources searched to identify primary studies
There does not appear to have been a search of sources.

Criteria used to ensure the validity of primary studies
It does not seem that criteria were used to ensure the validity of the studies included.

Methods used to judge relevance and validity, and for extracting data
There was no systematic review of the literature.

Number of primary studies included
Data on outcomes for patients receiving treatment was reported to have been obtained from four NIAID CASG studies involving a total of 323 patients. The source of data on outcomes for those not receiving treatment was obtained from a historical database of 235 untreated neonates. A further source was given for data on the distribution of outcomes in neonates treated and not treated with antiviral therapy, for which no details are given.

Methods of combining primary studies
It was stated that outcome data from the NIAID CASG were previously pooled and another paper was referenced for this.

Investigation of differences between primary studies
An analysis of differences in the results of primary studies was not carried out, despite the fact that the authors stated that differences in drug toxicity were found.

Results of the review
The authors presented data on the progression of the herpes simplex virus infection in untreated neonates and the distribution of outcomes in neonates treated and not treated, although with regards to the latter, not all the patients in the four NIAID CASG trials seem to have been included. The authors found that a larger percentage of treated infants were considered to have normal outcomes than untreated neonates (56% versus 25%) and a smaller percentage of treated neonates died compared to those not treated (17% versus 47%). These values were not tested for statistical significance. The relative proportions of those with mild, moderate or severe outcomes did not differ greatly. Survival data were not presented separately from the model and are therefore summarised in the measure of benefits below.
Measure of benefits used in the economic analysis
In the base-line analysis, life years gained were the main outcome measure, although quality-adjusted lives (QALYs) saved were imputed in the sensitivity analysis. QALYs were calculated using the EuroQol scale which ranks death at 0 and normal life at 1. The clinical team rated patients according to the following dimensions: mobility, self-care, usual activity, pain and anxiety using a scale of 1 (normal) to 3 (very dysfunctional).

Direct costs
Direct medical costs were evaluated by comparing the data from the historical database with data on 93 patients treated with antiviral drugs at a US hospital (University of Alabama, Birmingham) between 1974 and 1989. Costs were based on 74% of the daily hospital charges for a stay in a semi-private room and the paediatric intensive care unit (PICU) (since the authors stated that many payers were able to negotiate discounts) and an estimate of the expenses for a 10 day drug regimen of acyclovir with associated use of intravenous fluids and pumps. Data were presented on days of use of hospital ward and PICU by neonates treated and not treated. It was assumed in the cost analysis that survivors with a severe outcome do not live beyond 19 years of age. The base case analysis also included the costs of institutional care for those with severe outcomes (based on a survey of 22 families with a child under treatment at the University of Alabama at Birmingham) and the costs of special education for those with moderate outcomes (another paper was referenced as the source of this data). The analysis did not consider the costs for the patient beyond 20 years of age as the authors stated that most patients with severe outcomes will not live beyond this age and that after this age it is difficult to apportion the costs of health care purely to HSV sequelae. All costs were converted to 1995 dollars and discounted by 3%.

Statistical analysis of costs
No statistical analysis was performed on costs.

Indirect Costs
Indirect costs were not included in the analysis in this paper, although the authors stated that they examined this issue and did not find it to be at odds with the base case analysis presented here (no reference was provided).

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were performed on discount rates (at 5% and 10%) and the cost of drug treatment (increased and decreased by a factor of two). To examine alternative measures of life, a sensitivity analysis was performed using quality-adjusted life years saved (as described above).

Estimated benefits used in the economic analysis
In the base case analysis, marginal lives saved were calculated. In terms of the societal perspective (which includes lives saved in future generations discounted at 3%), treatment for neonates with SEM saved 0.8 lives per case, treatment for neonates with CNS saved 0.7 lives per case and treatment for neonates with DIS saved 0.4 lives per case. When the impact on future generations was excluded, 0.4 lives per case were saved in the SEM and the CNS groups whilst 0.2 lives per case were saved in the DIS group. In the sensitivity analysis, quality adjusted life years (QALYs) were used as an outcome measure. The authors applied the EuroQol scale to derive QALY values of 1.0, 0.82, 0.52, 0.16 and 0 for normal, mild, moderate, severe and dead outcomes respectively. It was reported that without treatment an average of 28 lives were saved per SEM case whereas with treatment 58 QALYs were saved so that the marginal gain from treatment was 30 QALYs per case treated. Turning to the case of CNS, without treatment 16 QALYs were saved and with treatment 33 (a gain of 17 QALYs) were saved. Lastly, without treatment for DIS, 9 QALYs were gained and with treatment, 20 QALYs (for a gain of 11 QALYs) were gained.
Cost results
When all costs were included (i.e. medical, special education and institutional care) for a duration of 20 years, the cost per patient with SEM treated with antiviral therapy was reported to be $19,873 and without treatment, $98,474. For neonates with CNS, the cost of treatment was $172,808 per patient whilst no treatment cost $120,859. Finally, for neonates with DIS, the cost of treatment was $86,714 per patient whilst the cost of no treatment was $69,054. When only direct medical costs were included and the costs of future care and education ignored, drug treatment for neonates with SEM cost $13,638 and without treatment, $35,870. For CNS patients, the cost of drug treatment was $50,858 whilst no treatment cost $42,717. And for patients with DIS, drug treatment cost $32,107 per patient whilst no treatment cost $32,736.

Synthesis of costs and benefits
When the societal perspective was considered (all special education and institutional costs plus the benefits to future generations of survivors in this generation), the authors found that when neonatal herpes simplex virus appears in the SEM form, treatment with antiviral drugs is a dominant strategy, i.e. lives were saved at reduced cost. Considering the CNS form, the additional cost per additional life saved was $75,125 whilst for the case of DIS, the additional cost per additional life saved was $46,619. When the narrower health care perspective was considered and the future generations ignored, antiviral therapy for neonatal HSV in the SEM form was again found to be a dominant strategy. For the CNS case, the additional cost per additional life saved was $19,975, whilst giving antiviral therapy to neonates with HSV with a DIS presentation was also found to be a dominant strategy. The costs and benefits in terms of the stream of future lives were all discounted at 3%. The sensitivity analysis on the discount rates did not change the nature of the findings and the authors stated that only small changes in the results were found to occur when the cost of drug treatment was varied (no details given).

Authors' conclusions
The authors concluded that antiviral therapy can save lives and reduced costs when the disease was discovered in the SEM form. When the disease had progressed to the CNS and DIS forms saving lives was associated with increased costs, although treatment was more cost-effective when considered from only a health service perspective. The prospect of home administration of antiviral therapy has the potential to make antiviral therapy a dominant form for all presentations of neonatal HSV.

CRD COMMENTARY - Selection of comparators
The comparator in this case was standard treatment which did not include drug therapy. It would have been helpful to know how widespread the use of drug therapy really is and whether the option of not giving drug therapy actually exists.

Validity of estimate of measure of benefit
The estimate of the benefit from antiviral therapy was derived from several studies which did not form part of an overall review of literature so results may be biased. Results from these trials were stated to have been pooled elsewhere and no summary statistics of this pooling were provided here. In addition a historical database was used to derive information on patients not treated which may again contain biases. In addition data does not seem to have been presented on all cases treated (table 2 shows the outcome of 235 patients treated rather than the 323 referred to in the earlier section on data sources). Utility data were derived from the clinical team which may not be representative.

Validity of estimate of costs
This paper considered the costs of institutional care and special education which is very commendable. The cost data presented would have been rather more transparent if it had been broken down into these elements and it is not clear how the summary measures of costs in tables 5 and 6 were calculated.

Other issues
The authors did mention that the clinical trials reported statistical a difference between the two types of treatment for neonatal HSV in terms of drug-toxicity which however did not form part of the authors’ model. Cost data may not be generalisable to other settings.

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