Cost-effectiveness analysis of herpes simplex virus testing and treatment strategies in febrile neonates
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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.

CRD summary
This study compared four diagnostic and therapeutic strategies for herpes simplex virus (HSV) infection in febrile neonates with or without cerebrospinal fluid (CSF) pleocytosis. The authors concluded that diagnostic testing with CSF HSV polymerase chain reaction combined with empirical treatment with acyclovir sodium was a cost-effective strategy for febrile neonates with CSF pleocytosis, but not for all febrile neonates. Despite some limitations to the quality of the clinical data, it is likely that the results reflected the available evidence.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
This study compared diagnostic and therapeutic procedures for herpes simplex virus (HSV) infection in neonates with either fever alone and no symptoms of HSV infection, or fever and cerebrospinal fluid (CSF) pleocytosis. The neonates were aged up to 28 days.

Interventions
Four strategies for testing and treatment were evaluated. Strategy one was HSV testing and empirical treatment whilst awaiting the test results. Strategy two was HSV testing and treatment if the HSV test was positive or symptoms and signs of HSV developed. Strategy three was empirical treatment alone without testing. Strategy four was no HSV testing or treatment unless signs and symptoms of HSV developed.

The treatment of HSV consisted of acyclovir sodium 60mg per kilogram per day intravenously for 21 days in neonates with disseminated or central nervous system disease, or for 14 days in neonates with skin, eye or mouth disease. The HSV test consisted of isolation by viral culture and detection of HSV DNA using polymerase chain reaction (PCR) on CSF alone or a comprehensive assessment using different tests.

Location/setting
USA/secondary care.

Methods
Analytical approach:
A decision tree was constructed to compare the cost-effectiveness of the four clinical strategies. They were compared for febrile infants both without and with CSF pleocytosis. The results were also presented for two alternative tests within each strategy; comprehensive HSV testing, and CSF HSV PCR testing. The time horizon was not explicitly stated. However, a 20-year care-giving period was mentioned. The authors stated that the perspective was that of society.

Effectiveness data:
The effectiveness data were derived from published studies. The sources searched, the inclusion criteria, and the methods used to derive the estimates for the model were discussed. The main clinical parameters included the prevalence of neonatal HSV-related diseases, the sensitivity of the diagnostic tests for HSV disease, and mortality at 12 months with and without acyclovir therapy.
Monetary benefit and utility valuations:
The utility weights were derived from published studies.

Measure of benefit:
The measures of benefit were survival and quality-adjusted life-years (QALYs).

Cost data:
The direct cost categories were those for diagnostic tests and acyclovir treatment, hospitalisation costs, and special education and institutional care costs due to HSV-associated developmental health problems. Only the summary costs, from the published literature, were reported. The costs were adjusted for inflation and reported, in US dollars ($), for the price year of 2006. An annual discount rate of 3% was applied.

Analysis of uncertainty:
A probabilistic sensitivity analysis was conducted by means of Monte Carlo simulations. The type of distribution that was assumed was stated. In addition, deterministic one-way sensitivity analyses were conducted on all the model parameters and their ranges were reported.

Results
An incremental analysis was performed. The results were presented for both neonates with fever alone and those with fever and CSF pleocytosis. Overall, the strategies which included empirical acyclovir treatment were found to be more effective than those strategies in which acyclovir was initiated only after a positive test result or after the appearance of HSV symptoms.

At a cost-effectiveness threshold of $100,000 per QALY gained, strategy one (HSV testing and empirical treatment whilst awaiting test results), with CSF PCR test, was cost-effective compared with strategy four (no testing and no treatment), yielding an incremental cost per QALY gained of $55,652 for infants with fever and CSF pleocytosis.

The cost-effectiveness of strategy one was sensitive to utility values for moderate and severe neurodevelopmental HSV-related outcomes, and to the time that elapsed until the test results were received. Strategies two and three, with CSF PCR testing, were dominated (more costly and less effective).

All the strategies for fever alone produced incremental cost-effectiveness ratios above the threshold of $100,000 per QALY.

The sensitivity analysis showed that these findings were sensitive to the time taken to obtain the test results. Generally the findings were fairly robust to variations in the one-way sensitivity analyses, Further probabilistic sensitivity analysis demonstrated that strategy one was generally robust to random variability.

Authors’ conclusions
The authors concluded that testing with CSF HSV PCR combined with empirical treatment with acyclovir sodium constituted a cost-effective strategy only for febrile neonates with CSF pleocytosis.

CRD commentary
Interventions:
The strategies compared were clearly reported including the treatment dosage. The four strategies appear to have included all the relevant test and treat options.

Effectiveness/benefits:
The effectiveness data were derived from published studies. Some details of the literature search and inclusion criteria were not reported. As only one database was searched to identify the relevant literature and the full review methods were not reported this review does not appear to have been systematic, although it does appear to have been comprehensive. In addition, no quality assessment of the literature was reported making it impossible to comment on the validity of the primary studies. However, the baseline values and ranges were presented for all input parameters and extensive deterministic and probabilistic sensitivity analyses were conducted.
Costs:
Although the perspective was societal, productivity losses were not included. Despite this limitation, the costing was
detailed and transparently reported. Once again, baseline values and ranges were presented and extensive sensitivity
analyses were conducted. Further, adjustments for inflation, discounting and the price year were reported, facilitating
the revaluation of the results in future years.

Analysis and results:
The model structure was presented graphically along with the modelling assumptions. The analysis seems to have been
appropriate, including the distributional assumptions made to allow the probabilistic analysis to be completed. All the
relevant details and the results were adequately reported including the presentation of a cost-effectiveness acceptability
curve. The authors commented on the low quality and appropriateness of the evidence used to derive the estimates of
effectiveness and correctly acknowledged this as one of the major limitations to their study.

Concluding remarks:
Despite some limitations to the clinical data, a reasonably transparent analysis was presented and the results are likely to
have reflected the available evidence.

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