ARTICLE

Cost-effectiveness Analysis of Herpes Simplex Virus Testing and Treatment Strategies in Febrile Neonates

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Objective: To determine the clinical effectiveness and cost-effectiveness of testing for and empirically treating herpes simplex virus (HSV) infection in neonates with fever aged from birth to 28 days.

Design: Cost-effectiveness analysis.

Setting: Decision model.

Patients: Neonates with fever with no other symptoms and neonates with fever with cerebrospinal fluid (CSF) pleocytosis.

Interventions: Four clinical strategies: (1) HSV testing and empirical treatment while awaiting test results; (2) HSV testing and treatment if test results were positive for HSV or the patient had symptoms of HSV; (3) treatment alone without testing; or (4) no HSV testing or treatment unless the patient exhibited symptoms. The 2 HSV testing methods used were CSF HSV polymerase chain reaction (PCR) and comprehensive evaluation with blood HSV PCR, CSF HSV PCR, and multiple viral cultures.

Main Outcome Measures: Twelve-month survival and quality-adjusted life expectancy with a cost-effectiveness threshold of $100 000 per quality-adjusted life year (QALY) gained.

Results: Clinical strategy 1, when applied in febrile neonates with CSF pleocytosis, saved 17 lives per 10 000 neonates and was cost-effective using CSF HSV PCR testing ($55 652/QALY gained). The cost-effectiveness of applying clinical strategy 1 in all febrile neonates depended on the cost of the CSF HSV PCR, prevalence of disease, and parental preferences for neurodevelopmental outcomes. Clinical strategies using comprehensive HSV testing were not cost-effective in febrile neonates ($368 411/QALY gained) or febrile neonates with CSF pleocytosis ($110 190/QALY gained).

Conclusions: Testing with CSF HSV PCR and empirically treating with acyclovir sodium saves lives and is cost-effective in febrile neonates with CSF pleocytosis. It is not a cost-effective use of health care resources in all febrile neonates.

Arch Pediatr Adolesc Med. 2008;162(7):665-674

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NEONATAL HERPES SIMPLEX virus (HSV) infection is associated with high morbidity and mortality unless identified and treated early. On the basis of previous clinical trials, treatment with the antiviral drug acyclovir sodium is effective and safe and should be initiated early for greatest effect.[1-3] Although there have been important advances in diagnostic technology and therapeutic options during the last 2 decades, there has been little change in the time between onset of symptoms and initiation of treatment because the signs and symptoms are often nonspecific and many days may elapse before test results enable identification of infection.[4-9]

The American Academy of Pediatrics Committee on Infectious Diseases recommends that HSV infection should be considered in "neonates with fever, irritability, and abnormal cerebrospinal fluid (CSF) findings, especially in the presence of seizures."[10] Although frequently absent when the patient is first seen, fever is known not only to be a symptom of HSV infection but also of other viral infections and many bacterial infections.[4,11] Results of a recent investigation indicate that the prevalence of HSV infection is 0.3% in neonates with fever and 1.0% in neonates with fever and CSF pleocytosis.[11]

Given the impetus for early treatment of neonatal HSV and because fever can signal the onset of HSV infection, clinicians may consider initiating acyclovir therapy in all neonates who have fever alone or who have fever and CSF pleocytosis. While it is likely that initiating empirical antiviral therapy in all febrile neonates would increase health care costs, there is no evidence that it will save lives or decrease morbidity from HSV infection. We sought to determine the relative effectiveness and costs of available HSV testing and treatment strategies in febrile neonates through decision analysis and cost-effectiveness analysis.

METHODS

DECISION ANALYSIS MODEL

We developed a decision analysis model (**Figure 1**) to represent the diagnostic and

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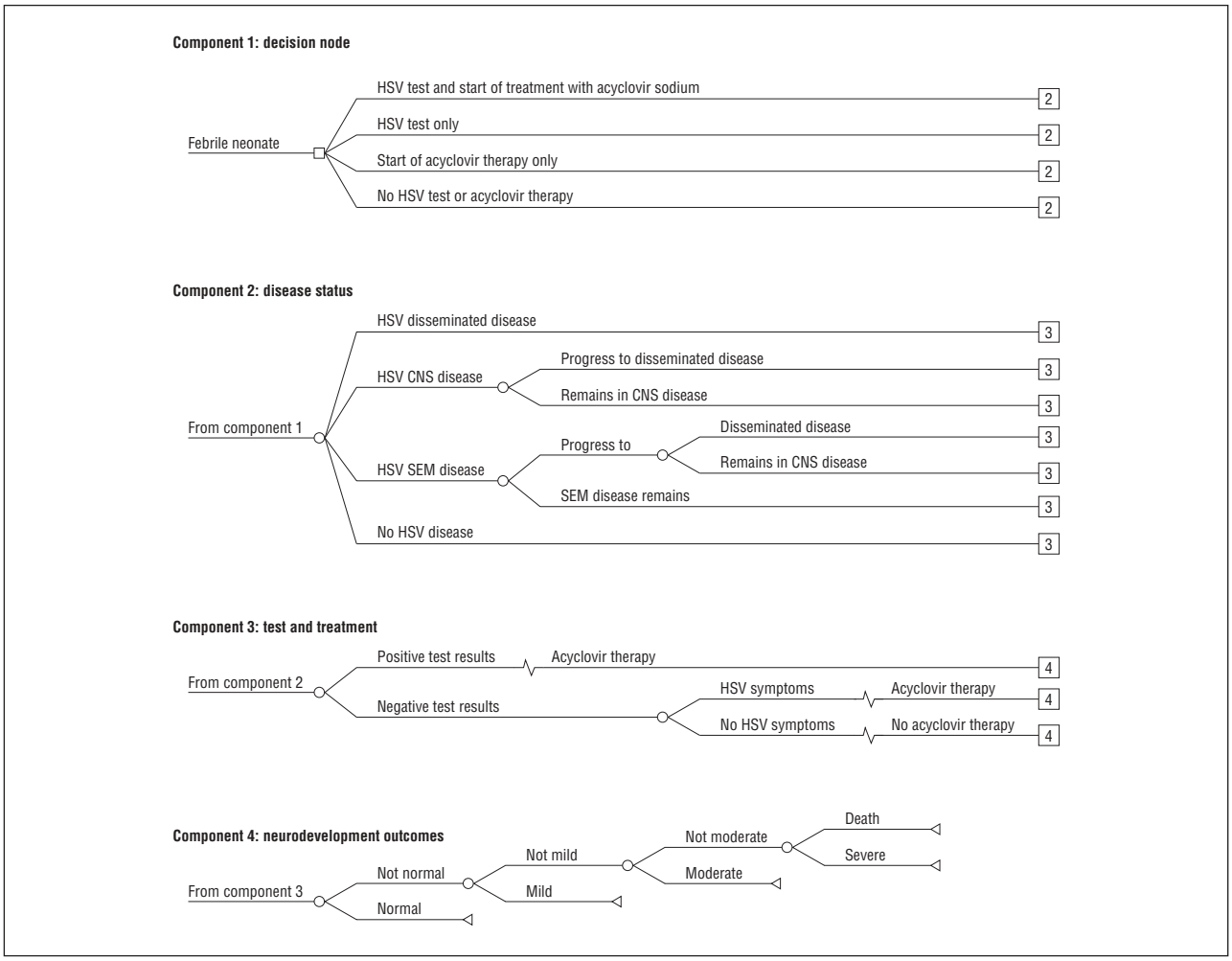

Figure 1. Components of the decision tree used in the cost-effectiveness analysis of herpes simplex virus (HSV) testing and treatment strategies in neonates with fever. CNS represents central nervous system; SEM, skin, eyes, and mouth. For neurodevelopmental outcome; see "Quality-Adjusted Life Expectancies" subsection of the "Methods" section.

therapeutic options available to the physician caring for a neonate with fever. The hypothetical patient was aged from birth to 28 days, with fever (rectal temperature, ≥38°C) and no other signs or symptoms of HSV infection, representing the neonatal population for whom the best HSV testing and treatment strategy is unclear. In accord with standard of care in most institutions, routine evaluation included urinalysis; complete blood cell count; CSF Gram staining and protein and glucose levels; and CSF, blood, and urine bacterial cultures.[12-14] The neonate was then admitted to the hospital and given intravenous antibiotic therapy for a minimum of 48 hours while awaiting bacterial culture results.

We performed a separate analysis for the subgroup of febrile neonates with CSF pleocytosis, defined as CSF with a white blood cell count of more than 20/μL (to convert to $\times 10^9$/L, multiply by 0.001) and more than 1 white blood cell per 500 red blood cells. Cerebrospinal fluid pleocytosis is a known laboratory finding in neonatal HSV infection.[6,7,11]

We considered 4 clinical decision strategies: (1) HSV testing and empirical treatment while awaiting test results, (2) HSV testing and treatment if HSV test results were positive or symptoms and signs of HSV developed, (3) empirical treatment alone without testing, and (4) no HSV testing or treatment unless signs and symptoms of HSV developed.

Treatment of HSV infection was with acyclovir sodium, 60 mg/kg/d intravenously, for 21 days in neonates with disseminated or central nervous system disease or for 14 days in neonates with skin, eyes, and mouth disease.[10] For the purposes of this decision analysis, acyclovir therapy was empirically initiated in hypothetical patients in strategies 1 and 3. Acyclovir therapy was discontinued in strategy 1 if all HSV tests yielded negative results and patients exhibited no symptoms, but was continued to a full treatment course in strategy 3 because tests are less sensitive after the initiation of antiviral therapy. In strategy 2, acyclovir therapy was initiated only if 1 of the HSV tests yielded positive results or if the patient developed symptoms. In strategy 4, acyclovir therapy was initiated only if the hypothetical patient developed symptoms.

Tests for HSV included the isolation of HSV by viral culture and the detection of HSV DNA by polymerase chain reaction (PCR). We analyzed the following 2 testing approaches: (1) detection of HSV DNA in CSF by PCR (CSF HSV PCR) and (2) a comprehensive evaluation including detection of HSV DNA by PCR in blood and CSF, and multiple viral cultures (mouth, nasopharynx, conjunctivae, skin vesicles, rectum/stool, urine, blood, or CSF).[10] Although the clinical strategies using comprehensive testing were likely to be more expensive than and dominated by the PCR testing strategies, we chose to include the comprehensive evaluation because it is recommended by the American Academy of Pediatrics and because we wanted to provide quantification of its relative cost. In keeping with clinical practice, we assumed the absence of neonatal HSV in-

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fection in neonates who remained clinically well, without signs or symptoms of HSV disease, and with negative HSV test results (except in strategy 3, in which no tests were performed).

COST-EFFECTIVENESS ANALYSIS

We performed a cost-effectiveness analysis from the societal perspective, adhering to the reference case scenario recommended by the Panel on Cost-Effectiveness in Health and Medicine.[15]

OUTCOMES

For the cost-effectiveness analysis, we measured effectiveness as (1) 12-month survival and (2) quality-adjusted life expectancy, assuming a normal life expectancy for the average neonate in the United States. We considered strategies with an incremental cost-effectiveness ratio of less than $100 000 to be cost-effective because this threshold has become relatively standard.[16]

ASSUMPTIONS

We assumed that the early initiation of acyclovir therapy would improve patient outcomes by hindering HSV disease progression.[17] We also assumed that there was no HSV resistance to acyclovir therapy.[18]

We assumed that HSV infection in neonates always causes symptomatic disease and that patient symptoms would influence decisions about when to start, continue, or discontinue acyclovir therapy. For example, because HSV can cause such a severe disease, we assumed that acyclovir therapy would be started or continued with any positive test result, even if the patient exhibited no symptoms. Alternatively, we assumed that acyclovir therapy would be discontinued when HSV test results were negative as long as the patient exhibited no symptoms.

Although there may have been competing diseases such as bacterial infection that may have caused continued symptoms, we assumed that these diseases would have been equally distributed across the decision strategies and have no effect on the HSV outcome. We assumed that the cost of these evaluations for competing illnesses would be similar across decision strategies and excluded them from the model.

We assumed that neonates who survived HSV disease either recovered completely or developed residual neurologic and developmental effects. The adverse effects of acyclovir therapy in neonates with HSV include neutropenia (21%) and nephrotoxicity (6%).[1] We excluded from the model acyclovir-induced renal toxicity because it occurs only in patients with comorbid conditions,[1] and acyclovir-induced neutropenia because it is transient and does not have long-term effects on survival and quality of life.[1]

We assumed that hospital stay would not be longer than 48 hours for patients with negative PCR test results and normal findings at clinical examination. For those awaiting culture results, we assumed that the hospital stay would be extended to 72 hours because most cultures would have been positive by that time. We assumed that neonates in strategy 3 (empirical treatment alone without testing) would stay in the hospital for 21 days, the duration of a complete course of HSV therapy.

PROBABILITIES

We conducted a MEDLINE search of English-language articles published between 1966 and 2006 to determine relevant probabilities for use in the decision analysis (**Table 1**). For HSV test accuracy, we included studies regardless of patient age. For the natural history, diagnosis, and treatment of neonatal HSV infection, we included studies if they included neonates with HSV infection and the end point of death. We used commercially available software (Intercooled STATA, version 9.0; StataCorp LLP, College Station, Texas) to calculate confidence intervals from the published literature using exact methods of binomial approximation. If sufficient information was unavailable to estimate confidence intervals, we established the range for sensitivity analysis to include all possible values (ie, 0.00-1.00).

PREVALENCE OF NEONATAL HSV

We used HSV prevalence estimates from a retrospective study of 5817 neonates admitted to Texas Children's Hospital, Houston, of whom 10 had a diagnosis of HSV infection.[11] Of the 960 neonates with fever at presentation, 3 were given a diagnosis of HSV infection, and of the 204 with fever and CSF pleocytosis, 2 were given a diagnosis of HSV infection.

PROGRESSION OF DISEASE

We used the probabilities of disease progression without acyclovir therapy that were originally estimated by Mennemeyer et al[17] from previous studies.

MORTALITY

Mortality data were available for 12 and 24 months of follow-up, respectively, from the published placebo-based antiviral study and acyclovir studies.[1,3] Because there were no deaths in the high-dose acyclovir group between 12 and 24 months of follow-up, we used 12-month mortality for our analysis. In addition, we assumed that the median time to death was 6 days, based on our own data[11] and mortality information from the 2003 Healthcare Cost and Utilization Project Kids' Inpatient Database.[19]

In our analysis, we assumed treatment with high-dose acyclovir. To our knowledge, only 1 previous study reported the results of high-dose acyclovir therapy in a few patients.[1] We used the treatment mortality estimates derived from several studies and summarized in a cost-effectiveness analysis performed by Mennemeyer et al.[17]

TEST CHARACTERISTICS

We estimated the diagnostic accuracy of PCR and viral culture for neonatal HSV from previous studies.[20-25] We found no data about the accuracy of the comprehensive evaluation strategy (blood HSV PCR, CSF HSV PCR, and multiple viral cultures) in identifying HSV infection. In the base-case scenario, we assumed that comprehensive tests had a sensitivity and specificity of 1.00 because any positive test results are considered diagnostic of neonatal HSV, which implies that at least 1 test should yield positive results in any case of neonatal HSV. In the sensitivity analysis, we varied the range of values from 0.95 to 1.00 for both sensitivity and specificity. The CSF PCR is highly specific (0.94-1.00) for HSV infection but has low sensitivity (0.75-0.80) in early disease.[20,21] Later in disease, the sensitivity in central nervous system disease is 0.98 to 1.00.[22-25]

Quality-Adjusted Life Expectancies

We estimated quality-adjusted life expectancies by multiplying preference weights for the various HSV outcomes by the mean life expectancy from the neonatal period; we estimated differences between strategy-specific quality-adjusted life expectancies as quality-adjusted life-years (QALYs) gained. We estimated the likelihood of various patient neurodevelopmental outcomes of HSV infection from available studies as normal, mild (minimal functional neurologic damage such as hemiparesis or recurrent ocular disease, speech delay, or mild motor delay), moderate (neurologic damage including seizure disorder, visual impairment, or developmental delay of less than 3 months), severe (microcephaly, spastic quadriplegia, blindness or chorioretinitis, developmental delay of more than 3 months, or necessity for continuous care or institutionalization), or death.[1-4,17] We considered ranges for these preference weights between

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Table 1. Probabilities, Costs, and Ranges for Cost-effectiveness Analysis

Variable	Baseline Value	Range for Sensitivity Analysis	Source
Prevalence of neonatal HSV			Caviness et al[11]
Fever	0.003	0.001-0.009	
Disseminated HSV disease	0.001	0-0.006	
CNS HSV disease	0.002	0.0-0.008	
SEM HSV disease	0	0-0.004	
Fever and CSF pleocytosis	0.01	0.001-0.04	
Disseminated HSV disease	0	0-0.02	
CNS HSV disease	0.01	0.001-0.04	
SEM HSV disease	0	0-0.02	
Test characteristics			
CSF PCR sensitivity			
Disseminated disease	0.93	0.66-1.00	Kimberlin et al[20]
CNS disease, early	0.75	0.19-0.99	Troendle-Atkins et al[21]
SEM disease	0	0-0.15	Kimberlin et al[20]
CSF PCR specificity	1.00	0.97-1.00	Troendle-Atkins et al[21]
Utilities/preferences			Mennemeyer et al[17]
Normal	1.00	0-1.00	
Mild	0.82	0-1.00	
Moderate	0.52	0-1.00	
Severe	0.16	0-1.00	
Death	0	0-1.00	
12-mo Outcome with acyclovir therapy			Mennemeyer et al[17]
Disseminated disease			
Normal	0.28	0.16-0.43	
Mild	0.04	0.005-0.15	
Moderate	0.02	0.001-0.11	
Severe	0.13	0.048-0.26	
Death	0.53	0.38-0.68	
CNS disease			
Normal	0.32	0.22-0.44	
Mild	0.09	0.04-0.18	
Moderate	0.18	0.10-0.29	
Severe	0.27	0.18-0.39	
Death	0.13	0.06-0.23	
SEM disease			
Normal	0.95	0.88-0.99	
Mild	0.01	0.003-0.07	
Moderate	0.03	0.003-0.09	
Severe	0.013	0.003-0.07	
Death	0	0-0.045	
Disease progression without acyclovir therapy			Whitley et al[3]
SEM disease to CNS disease	0.23	0-1.00	Mennemeyer et al[17]
SEM disease to disseminated disease	0.37	0-1.00	
CNS disease to disseminated disease	0.43	0-1.00	
12-mo Outcome without acyclovir therapy			
Disseminated disease			
Normal	0.12	0.07-0.19	
Mild	0.009	0.002-0.047	
Moderate	0.03	0.009-0.09	
Severe	0.09	0.04-0.15	
Death	0.75	0.66-0.83	
CNS disease			
Normal	0.16	0.08-0.29	
Mild	0.08	0.03-0.18	
Moderate	0.13	0.06-0.24	
Severe	0.25	0.14-0.37	
Death	0.38	0.26-0.51	
SEM disease			
Normal	0.60	0.47-0.73	
Mild	0.05	0.02-0.14	
Moderate	0.22	0.13-0.35	
Severe	0.12	0.049-0.23	
Death	0	0-0.06	

(continued)

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Table 1. Probabilities, Costs, and Ranges for Cost-effectiveness Analysis (cont)

Variable	Baseline Value	Range for Sensitivity Analysis	Source
Cost, $ in 2006			
Test			Present study
CSF HSV PCR	75	50-1000	
Comprehensive HSV	555	300-1000	
Acyclovir sodium therapy, 60 mg/kg/d, IV			Thomson Healthcare[28]
1 Day, assuming 4-kg neonate	108	39-164	
Hospitalization after initial 2 d, $			HCUP Kids' Inpatient Database[19]
1 Extra day awaiting test results	653	602-817	
6 d Before death	15 445	9725-67 924	
14 d for SEM disease	13 075	9767-18 189	
21 d for Disseminated disease and CNS disease	27 997	22 895-34 283	
Cost to care for a disabled child, annual, $			
No disability			
Education	7675	5000-15 000	Chambers et al[29]
Health care[a]	643	500-1000	Newacheck and McManus[30]
Mild disability			
Special education	14 797	10 000-20 000	Chambers et al[29]
Health care[a]	1223	500-2000	Newacheck and McManus[30]
Moderate disability			
Special education	14 797	10 000-20 000	Chambers et al[29]
Health care[a]	2447	2000-3000	Newacheck and McManus[30]
Severe disability			
Institutional care	75 376	56 615-89 775	Chambers et al[29]
Health care[a]	4649	3000-6000	Newacheck and McManus[30]

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; HCUP, Healthcare Cost and Utilization Project; HSV, herpes simplex virus; IV, intravenously; PCR, polymerase chain reaction; SEM, skin, eyes, and mouth.

[a] Future health care costs were excluded from the base-case scenario and included in the sensitivity analysis.

0 and 1 to comprehensively evaluate their effect on treatment decision.

Costs

We incorporated all costs identified as beyond routine care in febrile neonates including HSV-related tests, treatment, and outcomes (Table 1). In 2004, mean life expectancies for neonates was 77.8 years.[26] Costs for routine care included those for the initial 2 days of hospitalization and intravenous antibiotic therapy. We estimated costs in 2006 US dollars updated using the Consumer Price Index for cost data from years before 2006.[27] Cost of treatment included acyclovir sodium, 60 mg/kg/d intravenously, for a neonate weighing 4 kg at the mean US cost of $36.00 (range, $10.00-$60.00) per neonate per day.[28] We derived costs for hospitalization beyond the routine 2 days for febrile neonates from the Healthcare Cost and Utilization Project Kids' Inpatient Database for 2003.[19] We derived from the same data set cost and length of hospital stay for neonates who died in the hospital. If hospitalization was needed beyond the usual 2 days but before 6 weeks of age, we did not estimate costs for a parent to be off of work because we assumed that at least 1 parent would have been off of work to care for the infant during that time.

Following the recommendations of the Panel on Cost-Effectiveness in Health and Medicine, we discounted both costs and outcomes of HSV-related abnormal development and neurologic outcome using a rate of 3% (range, 0%-5%).[15] We included costs related to special education and institutional care as estimated from US data.[29,30] We assumed that patients with severe neurologic outcomes would require institutional care until they died prematurely at age 20 years. We assumed that those with mild or moderate neurologic outcomes would require special education during their school years (age 5-18 years).

Consistent with the recommendations from the Panel on Cost-Effectiveness in Health and Medicine, we excluded future health care costs.[15] Because it was possible that costs related to severe deficits could have affected the outcomes, we included health care costs up to the age of 20 years in the sensitivity analysis. These costs include physician appointments, physical therapy, and transportation to and from appointments, which we estimated from available US data using a cost-to-charge ratio of 0.75.

The threat of litigation may influence clinicians to test and treat for HSV infection in some febrile neonates. However, we did not include these in the analysis because medicolegal costs are considered transfer costs.[31]

Analysis

We used a commercially available software package (TreeAge Pro 2005 Suite; TreeAge Software, Inc, Williamstown, Massachusetts) to construct the decision tree and perform the analyses. We conducted the analyses to determine the best clinical strategy in terms of survival, QALYs gained, and cost-effectiveness in neonates with fever as well as febrile neonates with CSF pleocytosis.

We performed deterministic 1-way sensitivity analyses using ranges of possible values for all estimates (Table 1). We then performed probabilistic sensitivity analyses using Monte Carlo simulation to determine the effect of parameter variability on the cost-effectiveness estimates. We assumed beta distributions for the probability, test accuracy, and preference parameters, and gamma distributions for the cost parameters.[32]

Protection of Human Subjects

The study was approved by the Baylor College of Medicine Institutional Review Board and The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects.

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Table 2. Results of Cost-effectiveness Analysis Using Comprehensive Herpes Simplex Virus Testing

Diagnosis and Treatment Strategy	Total Cost, $ in 2006	Total Effectiveness Survival	Incremental Cost, $ in 2006	Incremental Effectiveness Survival	Incremental Cost-effectiveness Ratio, $/Life Saved
Fever					
No tests or acyclovir therapy	84 476	0.99882	. . .	. . .	. . .
Tests and acyclovir therapy	86 079	0.99918	1603	0.0036	4 451 635
Fever and CSF pleocytosis					
No tests or acyclovir therapy	86 235	0.99703	. . .	. . .	. . .
Tests and acyclovir therapy	88 507	0.99873	2272	0.002	1 336 540

	Total Cost, $ in 2006	QALYs	Incremental Cost, $ in 2006	QALYs	$/QALY Gained
Fever					
No tests or acyclovir therapy	84 476	27.05116	. . .	. . .	. . .
Tests and acyclovir therapy	86 079	27.05551	1603	0.00435	368 411
Fever and CSF pleocytosis					
No tests or acyclovir therapy	86 235	26.9512	. . .	. . .	. . .
Tests and acyclovir therapy	88 507	26.9718	2272	0.02062	110 190

Abbreviations: CSF, cerebrospinal fluid; QALY, quality-adjusted life-year; ellipsis, not applicable.

Table 3. Results of Cost-effectiveness Analysis Using Cerebrospinal Fluid Herpes Simplex Virus Polymerase Chain Reaction

Diagnosis and Treatment Strategy	Total Cost, $ in 2006	Total Effectiveness Survival	Incremental Cost, $ in 2006	Incremental Effectiveness Survival	Incremental Cost-effectiveness Ratio, $/Life Saved
Fever					
No tests or acyclovir therapy	84 475	0.99882	. . .	. . .	. . .
Tests and acyclovir therapy	84 948	0.99918	472	0.00036	1 312 385
Fever and CSF pleocytosis					
No tests or acyclovir therapy	86 233	0.99703	. . .	. . .	. . .
Tests and acyclovir therapy	87 380	0.99873	1148	0.00002	675 023

	Total Cost, $ in 2006	QALYs	Incremental Cost, $ in 2006	QALYs	$/QALY Gained
Fever					
No tests or acyclovir therapy	84 475	27.05116	. . .	. . .	. . .
Tests and acyclovir therapy	84 948	27.05551	472	0.00435	108 611
Fever and CSF pleocytosis					
No tests or acyclovir therapy	86 233	26.9512	. . .	. . .	. . .
Tests and acyclovir therapy	87 380	26.9718	1148	0.02062	55 652

Abbreviations: CSF, cerebrospinal fluid; QALY, quality-adjusted life year; ellipsis, not applicable.

RESULTS

Overall, there was evidence for greater clinical effectiveness in the strategies with empirical acyclovir therapy (strategies 1 [HSV testing and empirical treatment while awaiting test results] and 3 [empirical treatment alone without testing]) than for those with acyclovir therapy administered on the basis of clinical symptoms or positive test results (strategies 2 [HSV testing and treatment if HSV test results were positive or symptoms and signs of HSV developed] and 4 [no HSV testing or treatment unless signs and symptoms of HSV developed]). Strategies 1 and 3 each saved 4 lives for every 10 000 febrile neonates and 17 lives for every 10 000 febrile neonates with CSF pleocytosis (**Tables 2** and **3**). The clinical effectiveness of each strategy did not vary by HSV test type (HSV CSF PCR vs comprehensive tests) because we assumed that treatment would be continued in patients with symptoms despite negative test results or no HSV testing. Using $100 000 per QALY gained as a threshold, only strategy 1 using HSV CSF PCR in febrile neonates with CSF pleocytosis ($55 652 per QALY gained) was cost-effective. Strategies 2 and 3 were dominated because strategy 2 was less effective than strategy 1 and strategy 3 was more expensive than strategy 1.

Strategy 1 was increasingly cost-effective with increasing HSV prevalence for all febrile neonates and febrile neonates with CSF pleocytosis using CSF HSV PCR but not using comprehensive testing (**Table 4**; **Figure 2**). Strategy 1 was also cost-effective through a wide range

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Table 4. Results of Deterministic 1-Way Sensitivity Analyses

Diagnosis	HSV Test	Range of Values for Which the Test and Treatment Strategy Is Cost-effective: HSV Prevalence[a]	Total Hospital Days[b]	Test Cost, $ in 2006[c]	Moderate Outcome Utility[d]	Severe Outcome Utility[e]	Normal After Acyclovir Therapy of CNS Disease, %[f]
Fever	HSV CSF PCR	0.36-100.0	None	0-37	0.62-1.00	0.43-1.00	34.3-100.0
	Comprehensive	None	None	None	None	None	None
Fever and CSF pleocytosis	HSV CSF PCR	0.24-100.0	0-3	0-1000	0.03-1.00	0.00-1.00	23.6-100.0
	Comprehensive	1.15-100.0	0-2	0-340	0.64-1.00	0.48-1.00	34.5-100.0

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; HSV, herpes simplex virus; PCR, polymerase chain reaction.
[a] Base-case 0.31% for all infants with fever and 0.98% for infants with fever and CSF pleocytosis.
[b] Base-case, 2 for PCR testing and 3 for comprehensive testing.
[c] Base-case, $75.00 for PCR testing and $555.00 for comprehensive testing. The entire cost of testing was varied so that the PCR test was the only cost varied for the HSV PCR test strategy, and the entire cost of all tests included in the comprehensive testing was varied for the comprehensive testing strategy.
[d] Base-case, 0.52.
[e] Base-case, 0.16.
[f] Base-case, 32.5%.

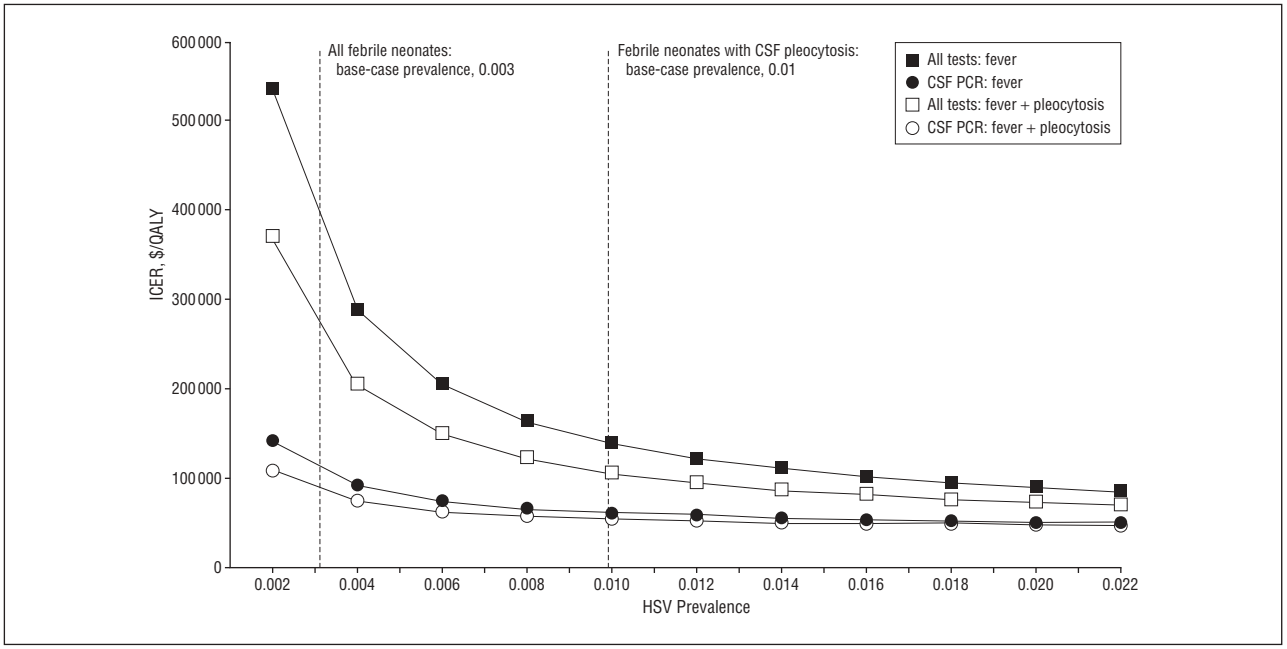

Figure 2. One-way sensitivity analysis of herpes simplex virus (HSV) infection prevalence for the cost-effectiveness of testing and empirically treating HSV in febrile neonates. CSF represents cerebrospinal fluid; ICER, incremental cost-effectiveness ratio; PCR, polymerase chain reaction; QALY, quality-adjusted life-years.

of CSF HSV PCR test costs for febrile neonates with CSF pleocytosis but not for all febrile neonates (Table 4; **Figure 3**). The cost-effectiveness of strategy 1 was sensitive to the moderate and severe utility values: the higher the utility values, the more cost-effective the strategy (Table 4). Likewise, an increasing likelihood for surviving HSV without neurodevelopmental problems was associated with increasing cost-effectiveness of strategy 1 for febrile neonates with CSF pleocytosis, no matter the testing strategy.

The cost-effectiveness was also sensitive to the time required to obtain test results, primarily because we assumed that neonates would remain hospitalized until the results were available (**Figure 4**). For neonates with fever and CSF pleocytosis, strategy 1 with CSF HSV PCR was cost-effective if it was assumed that the results would be available by the end of day 2 (Table 4; Figure 4). It remained cost-effective if it was assumed that the results would be available and the neonate would be discharged from the hospital by the end of day 3 ($86 900/QALY) but not the end of day 4 ($118 100/QALY). For all febrile neonates, strategy 1 with CSF HSV PCR was not cost-effective for 2 days ($108 632/QALY gained) or 3 days ($257 623/QALY gained) of hospitalization.

The results were otherwise robust to the 1-way sensitivity analyses of the remaining variables—test type (CSF HSV PCR or comprehensive evaluation) and accuracy, probability of disease progression with and without acyclovir therapy, morbidity and mortality without treatment, acyclovir therapy costs, future education costs, and discount rates. In addition, the results were robust to the addition of future health care costs.

Monte Carlo simulation indicated that the cost-effectiveness of strategy 1 with HSV CSF PCR for

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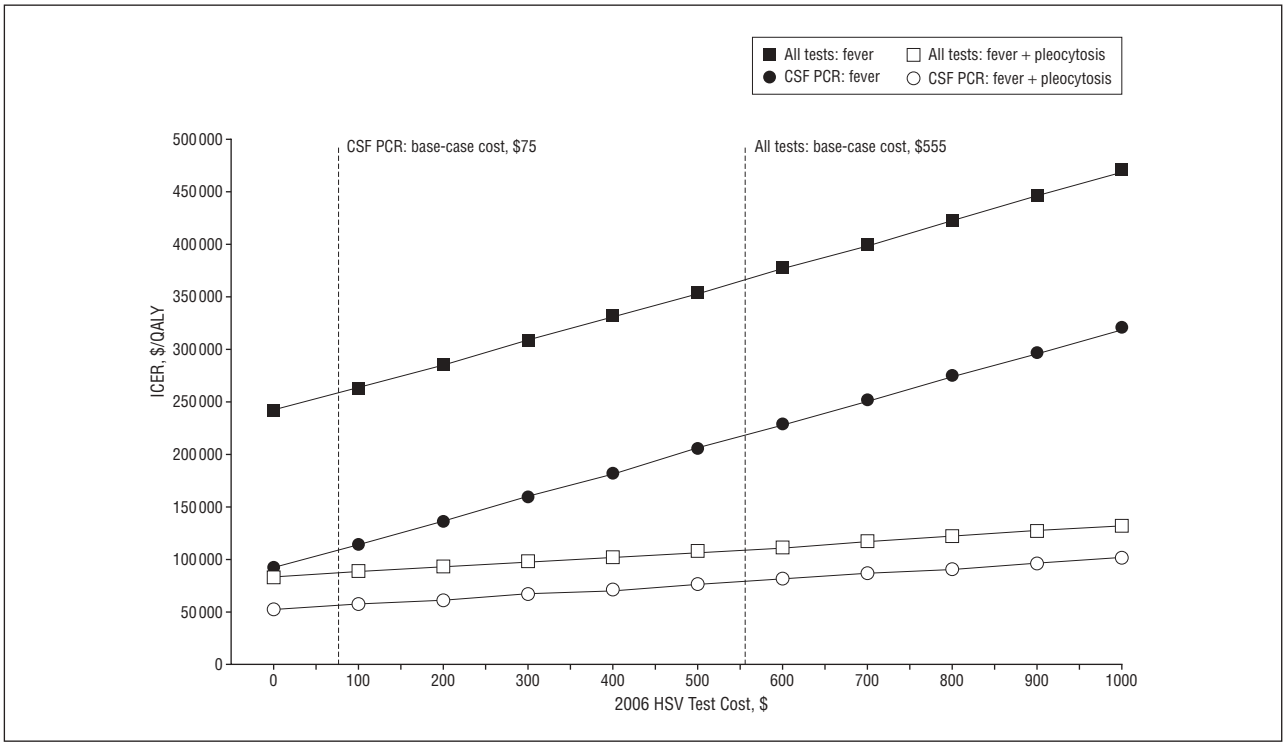

Figure 3. One-way sensitivity analysis of herpes simplex virus (HSV) test cost for the cost-effectiveness of testing and empirically treating HSV in febrile neonates. The entire cost of testing was varied so that the polymerase chain reaction (PCR) was the only cost varied for the HSV PCR test strategy, and the entire cost of all tests included in the comprehensive testing was varied for the comprehensive testing strategy. CSF represents cerebrospinal fluid; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

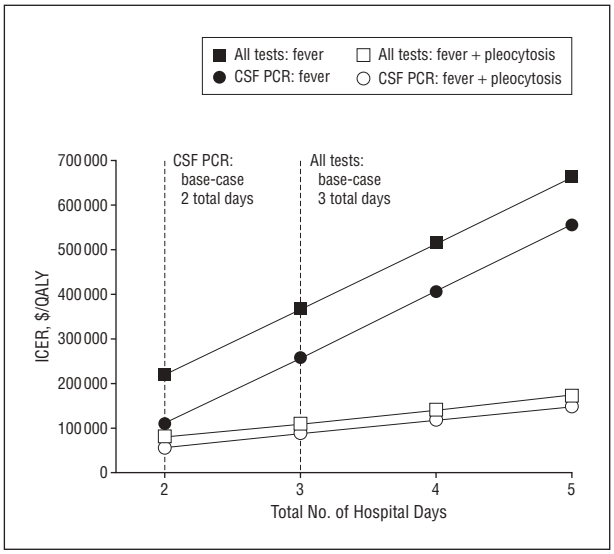

Figure 4. One-way sensitivity analysis of number of hospital days elapsed while awaiting herpes simplex virus (HSV) test results for the cost-effectiveness of testing and empirically treating HSV in febrile neonates. CSF represents cerebrospinal fluid; ICER, incremental cost-effectiveness ratio; PCR, polymerase chain reaction; QALY, quality-adjusted life-years.

febrile neonates with CSF pleocytosis was robust to random variability (**Figure 5**). Given the variability, there was a 59% probability that the strategy would be cost-effective at a $100 000 threshold and a 74% probability at a $200 000 threshold. The probability of being cost-effective was less than 40% in the other 3 groups, indicating that the cost-effectiveness of HSV testing and treatment was sensitive to random variability in those groups.

COMMENT

The results of this study indicate that testing for HSV infection with HSV CSF PCR and empirically administering acyclovir therapy in febrile neonates with CSF pleocytosis is cost-effective. However, it is not cost-effective in all febrile neonates. In addition, although comprehensive testing for HSV (blood HSV PCR, CSF HSV PCR, and multiple viral cultures) is more accurate for identifying HSV infection, the costs associated with comprehensive testing preclude its cost-effectiveness in all febrile neonates and in febrile neonates with CSF pleocytosis.

Given that CSF HSV PCR is relatively insensitive in early central nervous system disease, it is critical that HSV therapeutic decisions be guided by both test results and clinical symptoms. To illustrate this, assuming 10 000 hypothetical febrile neonates with CSF pleocytosis and no other evidence of CNS HSV disease, it is estimated that 0.98% will have HSV infection and 25% (n=25) will have a negative CSF HSV PCR. Further work is needed to improve the sensitivity of testing for neonatal HSV infection without substantially increasing test and hospitalization costs. Potential adjunct tests might include blood HSV PCR, platelet counts, and hepatic enzyme levels, although studies are needed to determine the accuracy of these comprehensive tests in neonatal HSV disease. For now, the clinician should continue acyclovir therapy in neonates with asymptomatic disease with negative HSV test results.

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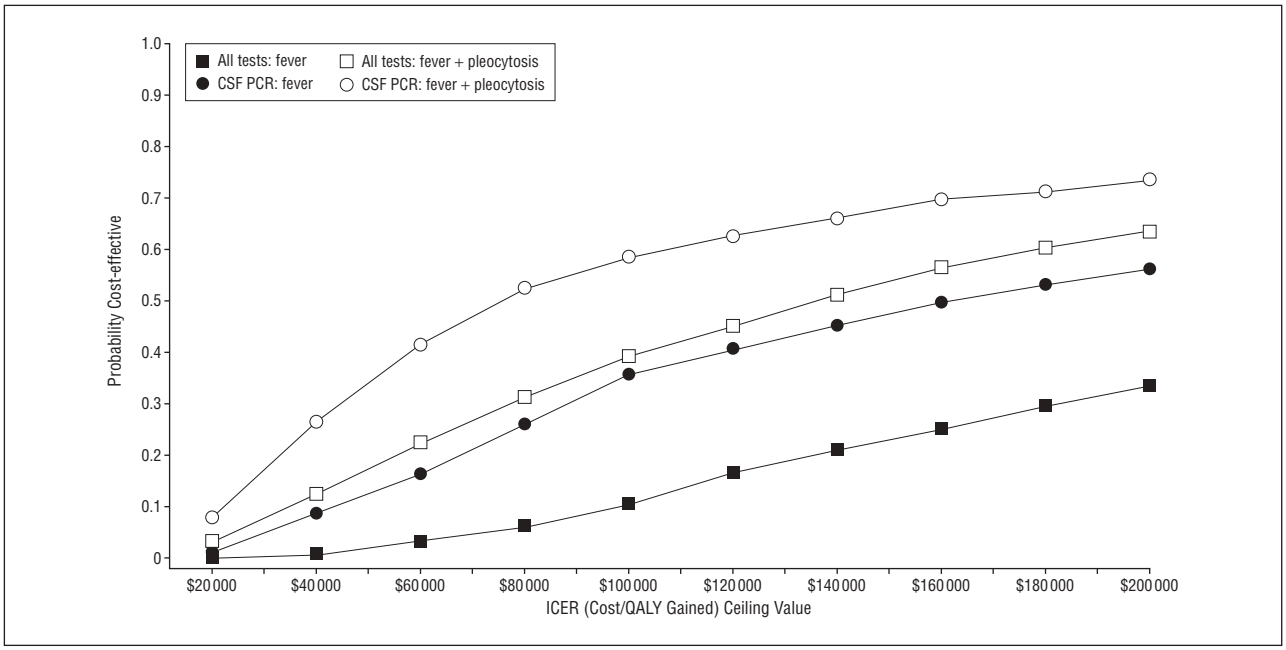

Figure 5. Probabilistic sensitivity analysis: cost-effectiveness acceptability curves. CSF represents cerebrospinal fluid; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

There are certain additional limitations of the study that should be considered by the clinician. In particular, the use of decision analysis required that we make assumptions—for example, that HSV always causes symptomatic disease in neonates and that acyclovir therapy would be continued in neonates with symptomatic disease and negative HSV test results. In addition, estimates such as the time required to obtain HSV test results, HSV test cost, and the cost of hospital stay will be center-specific, which requires that the clinician understand the effect of estimate variations. Ultimately, a randomized controlled trial will be the best way to verify these estimates and decrease methodologic concerns. However, HSV prevalence is so low in febrile neonates that a clinical trial would have to be untenably large, making decision analysis the best feasible option.

There are also limitations specific to this study. Meta-analysis of available studies would have been ideal to assess the effectiveness of acyclovir therapy, but using our inclusion criteria, to our knowledge, there have been only 2 primary studies in neonates.[1,3] In addition, prevalence data were available only from our own center. It is reassuring that the benefits of high-dose acyclovir therapy may be underestimated because the effects of acyclovir therapy on mortality and morbidity were derived from pooled estimates for low, intermediate, and high doses because these were the only ones available in the literature. It is also likely that the economic benefits of interrupting disease progression are underestimated because we excluded differential hospitalization costs based on HSV disease classification.

In addition, it is likely that the estimated benefits would have been greater for the subgroup of febrile neonates with monocytic predominant CSF pleocytosis and negative Gram stain results. However, given that the CSF white blood cell count with differential cell count and Gram stains might be unavailable rapidly at all centers, we chose to target the testing and treatment strategy to CSF pleocytosis in general. It is also likely that there are other clinical features, such as the presence of lethargy, that would further improve the cost-effectiveness of testing and treating empirically for neonatal HSV infection in febrile neonates.

CONCLUSIONS

In febrile neonates with CSF pleocytosis, the strategy of testing with CSF HSV PCR and treating with empirical acyclovir therapy is cost-effective as long as those without disease are discharged by the end of the third day of hospitalization. The cost-effectiveness of testing and treating all febrile neonates depends on the cost of the CSF HSV PCR, the prevalence of disease, and parent preferences for neurologic outcomes. Testing and treatment is not cost-effective using comprehensive testing in all febrile neonates or in febrile neonates with CSF pleocytosis.

Accepted for Publication: December 5, 2007.
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Author Contributions: Dr Caviness had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Caviness and Demmler. *Acquisition of data:* Caviness and Demmler. *Analysis and interpretation of data:* Caviness, Demmler, Swint, and Cantor. *Drafting of the manuscript:* Caviness and Demmler. *Critical revision of the manuscript for important intellectual content:* Caviness, Demmler, Swint, and Cantor. *Statistical*

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analysis: Caviness and Cantor. *Administrative, technical, and material support:* Demmler. *Study supervision:* Demmler, Swint, and Cantor. *Informational support:* Demmler.

Financial Disclosure: None reported.

Funding/Support: This study was supported by internal funds from Baylor College of Medicine.

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