

Antiviral Therapy for Neonatal Herpes Simplex Virus: A Cost-Effectiveness Analysis

Stephen T. Mennemeyer, PhD; Louis P. Cyr, PhD; and Richard J. Whitley, MD

Abstract

Each year, about 1,600 infants in the United States are infected with neonatal herpes simplex virus. We conducted a cost-effectiveness analysis of antiviral drug therapy (acyclovir) for three forms of herpes simplex virus infection: skin, ear, and mouth (SEM), central nervous system (CNS), and disseminated multi-organ (DIS) disease. Five levels of patient outcomes were examined (normal, mild, moderate, severe, dead). We obtained information on disease occurrence and survival from clinical trials and historical reviews of untreated newborns. We considered approaches for treating all or any of the forms of the disease and compared them with no use of antiviral drugs. The main measure of effectiveness was lives saved, including those of descendants of survivors. Costs were measured from a societal perspective and included direct medical costs, institutional care, and special education. We used a discount rate of 3% and valued dollars at 1995 levels. We also considered the perspective of a managed care organization. From a societal viewpoint relative to no treatment, antiviral therapy for SEM resulted in a gain of 0.8 lives and a cost reduction of \$78,601 per case. For the treatment of CNS and DIS disease, antiviral therapy saved more lives but at increased cost, with respective marginal costs per additional life saved of \$75,125 and \$46,619. From a managed care perspective, antiviral therapy is more cost-effective than from a societal viewpoint because costs of institutional care and special education are not the responsibility of managed care organizations. Development of at-home therapies will further improve the cost-effectiveness of antiviral therapy for neonatal herpes simplex virus infection.

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Neonatal herpes simplex virus (HSV) infections can cause devastating disease in affected children and disrupt the integrity of the family unit. The incidence of neonatal HSV infections in the United States is estimated at 1,200 to 2,000 cases per year.^{1,3} Without antiviral therapy, neonatal HSV infection has an overall mortality of approximately 50%, with neurologic impairment occurring in most survivors.^{1,4,5} With the introduction of antiviral therapies, such as vidarabine and acyclovir, the mortality rate associated with neonatal HSV infection decreased significantly overall (approximately 20%) and for each severity-based disease category. Although neurologic impairment occurs overall in 33% of surviving neonates for whom follow-up data are available, the severity of the impairment is less than that documented before the availability of therapeutic agents.^{1,6,8} In large part, these beneficial effects have been achieved because antiviral therapy significantly decreases disease progression.^{7,8}

Although the medical advantages of treating several viral diseases have been well documented, the cost savings to society have not been demonstrated to date. We used components of the data from the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) to investigate the costs associated with antiviral treatment of neonatal HSV infection. Costs were divided into three categories: (1) costs related to healthcare, including those associated with the initial medical treatment and follow-up monitoring and treatment over the first 20 years of life; (2) long-term institutional care; and (3) special education during elementary and high school.

... METHODS ...

Data from the NIAID CASG therapeutic trials of neonatal HSV infection provided the foundation for our analyses.⁶⁻⁸ All infants with virologically confirmed disease, regardless of severity, were eligible for enrollment in these therapeutic studies. All protocols

From The School of Public Health (S.T.M.) and Departments of Pediatrics, Microbiology, and Medicine (R.J.W.), University of Alabama at Birmingham, Birmingham, AL, and Cyr-Stat Inc. (L.P.C.), Moncks Corner, SC.

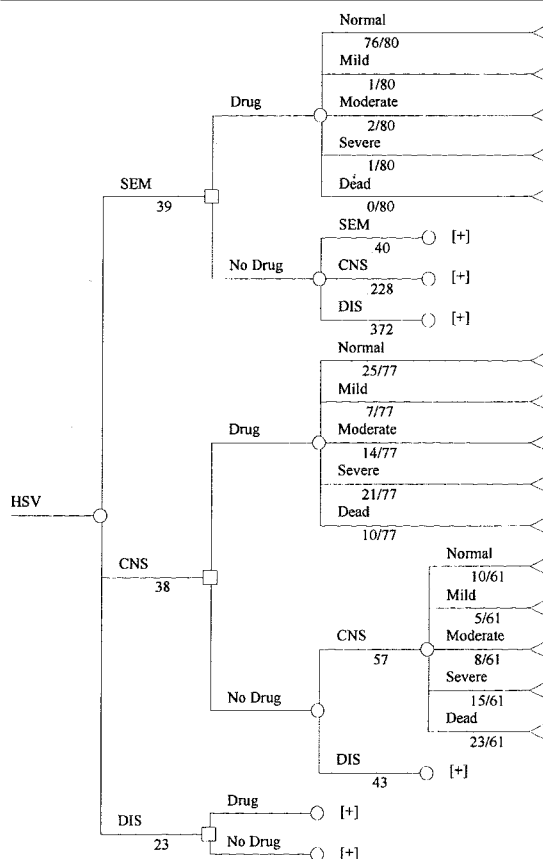
Address correspondence to: Stephen T. Mennemeyer, PhD, University of Alabama at Birmingham, School of Public Health, 1825 University Boulevard B55 MJH, Birmingham, AL 35294-2010.

Table 1. Progression of Herpes Simplex Virus Infection in Untreated Neonates

Initial Classification	Re-classified to:	Final Classification
SEM (39%)	SEM (40%) CNS (23%) DIS (37%)	SEM (15%)
CNS (38%)	CNS (57%) DIS (43%)	CNS (31%)
DIS (23%)	DIS (100%)	DIS (54%)

SEM = skin, ear, and mouth; CNS = central nervous system; DIS = disseminated multiorgan. Authors' calculations based on data from Whitley et al.⁶

Figure 1. Abbreviated Decision Tree for Neonatal Herpes Simplex Virus



A full drawing of this tree would have each incomplete branch (indicated by the plus sign) terminating in the five outcome states, subject to different probabilities. Numbers at each branch are transition probabilities from Tables 1 and 2. Probabilities for the decision analysis were determined by comparing treated patients enrolled in the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group studies with untreated patients in the historical database. HSV = herpes simplex virus; SEM = skin, ear, and mouth; CNS = central nervous system; DIS = disseminated multiorgan.

required informed consent according to the Department of Health and Human Services regulations. Standardized case-record forms and data tapes were available for infected infants as follows: 56 newborns enrolled in a vidarabine (28 cases) versus placebo-(28 cases) controlled study (1974-1979)⁶; 39 newborns enrolled in vidarabine dose-comparison studies (1979-1983)⁷; 202 infants enrolled in a clinical trial comparing vidarabine and acyclovir (1984-1989)⁸; and 54 infants treated in acyclovir dose-comparison studies (1989-1997). Disease classification, progression to more severe forms of disease, and patient outcome (3-year follow-up of survivors) were recorded. In all clinical trials, no statistically significant differences in mortality or morbidity between the vidarabine and acyclovir groups were detected except for drug-associated toxicity. Thus outcome data were pooled, as previously reported.⁹ The infants who received placebo in the placebo-controlled vidarabine trial and an historical database of 235 untreated neonates with known disease classification and outcome were used for comparisons.⁴⁻⁶

Infants with neonatal HSV infection were classified according to the extent of disease and outcome, as previously reported.^{1,4,5,8} Briefly, disease was classified as either localization to the skin, eye, or mouth (SEM), encephalitis or central nervous system involvement (CNS), or disseminated with multiorgan involvement (DIS). Outcome was defined as duration of survival and extent of neurologic impairment and was classified as: (1) normal; (2) mild (minimal functional neurologic damage, such as hemiparesis or recurrent ocular disease); (3) moderate (neurologic damage, including seizure disorder, visual impairment, developmental delay, or learning disabilities); (4) severe (continuous care or institutionalization necessary); or (5) dead (death during neonatal period).

In the NIAID CASG studies,^{5,8} infants who died during the neonatal infection lived an average of 10 days. Among infants surviving the initial infection, those with normal, mild, and moderate outcomes have had a life expectancy equivalent to that of the general US population. Survivors with a severe outcome generally have not lived

past age 19. We used this mortality experience in constructing our cost estimates.

In our analyses, "treated neonates" were those who received either vidarabine or acyclovir therapy in the NIAID CASG clinical trials. "Untreated neonates" were those included in the historical database of 235 untreated newborns with documented HSV infection.

Disease Progression

Disease progression has important implications for cost-effectiveness. Herpes simplex virus infection in infants is classified as one of the three forms—SEM, CNS, or DIS disease. A clinical diagnosis can be made when the infant is first considered for antiviral therapy. Drug treatment stabilizes the patient at the current form of the disease. If no drug treatment is administered, the disease may remain stable but usually becomes worse. Thus some patients with SEM disease may progress to CNS or DIS disease, and some patients with CNS disease may develop DIS disease. After the final form of the disease develops, one of five patient outcomes is possible (ie, normal, mild, moderate, severe, or death). Table 1 shows the progression of disease in untreated neonates from the historical database.⁶ The reported percentages were used to determine the probabilities for the first branch in Figure 1.

Table 2 shows how treated and untreated patients differed in the final outcome of the disease. Comparing treated neonates with those not treated, we found that a larger percentage of treated infants (56% versus 25%) were normal and a smaller percentage (17% versus 47%) had died.¹⁰ The implication for cost analysis is that antiviral drug treatment may be cost-effective if it prevents appreciable numbers of patients from progressing to outcomes that involve higher costs.

Calculating Costs

From a societal viewpoint, treating neonates with HSV infection affects three uses of economic resources—direct medical costs, institutional care, and special education. Direct medical costs are the resources used during the initial hospitalization for the infection and those used to monitor and treat sequelae in later years. We evaluated direct medical costs by comparing the records of the historical cases with those of 93 cases treated with antiviral drugs at the University of Alabama at Birmingham from 1974 to 1989. Based on

this review, we formulated a medical decision model with all costs converted to 1995 dollars.

During our chart review, we found appreciable differences between treated and untreated patients in length of stay and use of the pediatric intensive care unit (PICU) as well as in the costs associated with antiviral drugs and supplies. For SEM patients, PICU days were not required but semi-private room days increased when antiviral therapy was used because patients were kept in the hospital for drug administration. For CNS patients, a combination of PICU and semi-private room days was typical. Antiviral therapy allowed shorter stays in the PICU for patients with less serious outcomes; semi-private room days were about the same with or without antiviral drugs. For DIS patients, antiviral therapy reduced the length of stay in the PICU roughly by half, but semi-private room stays increased for patients with more serious outcomes. Based on this chart review, we used for our decision analysis the average lengths of stay shown in Table 3 for the base case analysis. In the base model, charges were \$555 and \$1,215 per day for semi-private room and PICU care, respectively. The model included charges for pulse oximetry and ventilator services in the PICU at \$300 and \$635 per day, respectively. Charges were converted to costs by assuming that soci-

Table 2. Distribution of Outcomes in Neonates Treated and Not Treated with Antiviral Therapy

	SEM	CNS	DIS	Total (%)
Not Treated				
Normal	35	10	14	59 (25)
Mild	3	5	1	9 (4)
Moderate	13	8	4	25 (11)
Severe	7	15	10	32 (14)
Dead	0	23	87	110 (47)
Total (%)	58 (25)	61 (26)	116 (49)	235 (100)
Treated				
Normal	76	25	13	114 (56)
Mild	1	7	2	10 (5)
Moderate	2	14	1	17 (8)
Severe	1	21	6	28 (14)
Dead	0	10	25	35 (17)
Total (%)	80 (39)	77 (38)	47 (23)	204 (100)

SEM = skin, ear, and mouth; CNS = central nervous system; DIS = disseminated multiorgan

Authors' calculations based on data from Nahmias et al¹ and Whitley et al^{6,10}
Percentages may not add up because of rounding

Table 3. Days of Use of Hospital Ward and Pediatric Intensive Care (PICU) by Neonates Treated and Not Treated with Antiviral Therapy

	SEM	CNS	DIS
Not Treated			
Ward	4	14	7
PICU	0	7	14
Treated			
Ward	10	14	7 - 14
PICU	0	2 - 7	7

Authors' calculations based on data from Nahmias et al⁶ and Whitley et al.⁶⁻¹⁰

ety pays only 74% of hospital charges¹¹ because many payers negotiate discounts.

In addition to the differences in length of stay, treated patients incurred expenses for the antiviral drug and related supplies. The decision model for the base case assumed that expenses involved a 10-day drug regimen of acyclovir with associated use of intravenous fluids and pumps with total charges of \$2,300 per patient.

Antiviral treatment affects the use of institutional care. The base case assumed that all patients with severe outcomes required continuous institutional care in a skilled nursing facility at an annual cost of \$44,205 in 1995 dollars. This figure is based on a survey of 22 families with a child under treatment at the University of Alabama at Birmingham.

Antiviral treatment also affects the need for special education. The base case assumed that all patients with moderate outcomes would require intensive use of special education from ages 5 to 18. Studies have found that special education services typically cost two to three times that of standard public school education.^{12,13} The base case assumed that special education costs in 1995 dollars would be \$8,059 per year more than normal education costs.

Table 4 shows the base case assumptions for all costs—direct medical, institutional care, and special education—from birth to age 20 by patient outcome. Costs differ between treated and untreated patients in the first year for the reasons stated above. In later years, costs depend solely on the patient's outcome. The base case did not consider costs beyond age 20 for two reasons. First, patients with severe outcomes typically die by puberty. The base case allowed their expenses to continue to age 20 to reflect the longest likely lifespan. Second, for normal, mild, and moderate outcomes, it becomes more difficult to distinguish routine health costs from HSV sequelae after adulthood.

Measuring Cost-Effectiveness

The primary measure of cost-effectiveness used in our analysis was cost per year of life saved by antiviral therapy. Cost per year of life saved is measured as: C/X, where C is the incremental change in total resources used when patients receive antiviral drug therapy compared

Table 4. Total Cost by Form and Outcome of Neonatal Herpes Simplex Virus Infection from Birth to Age 20 (1995 Dollars)

Year	SEM				
	Normal	Mild	Moderate	Severe	Dead
1 NT	4,333	5,383	8,680	58,150	3,056
1 T	8,706	9,756	13,056	62,523	20,677
2	221	947	4,396	54,814	0
3	221	1,019	3,372	53,956	0
4	221	1,019	3,372	53,956	0
5	221	1,356	3,709	54,127	0
6-11	221	276	9,569	50,530	0
12-20	221	276	9,569	50,530	0
CNS					
1 NT	22,384	23,368	28,319	78,095	15,726
1 T	15,477	16,733	23,696	75,324	16,984
2	442	947	7,057	56,366	0
3	276	853	6,033	55,507	0
4	276	853	6,033	55,507	0
5	276	1,190	6,259	55,678	0
6-11	221	404	9,569	50,695	0
12-20	221	404	1,510	0	0
DIS					
1 NT	27,758	28,679	34,658	83,057	15,496
1 T	20,085	21,007	28,273	78,933	16,754
2	276	885	7,057	56,476	0
3	276	791	6,198	55,618	0
4	276	791	6,198	55,618	0
5	276	1,128	6,308	55,789	0
6-11	221	404	9,569	50,817	0
12-20	221	404	1,510	0	0

SEM = skin, ear, and mouth; CNS = central nervous system; DIS = disseminated multiorgan; NT = not treated with antiviral drugs; T = treated with antiviral drugs.

with resources used when patients do not receive drug treatment. The term C includes direct medical costs, institutional care, and special education. The term Y measures the benefits associated with antiviral therapy as the expected average change in years of life saved because of the drug intervention. In selecting this measure, we adopted the approach of Hay et al,¹⁴ which allows a comparison of our findings for antiviral therapy with theirs for respiratory syncytial virus immune globulin (RSVIG).

Hay et al¹⁴ reject the approach of measuring lives saved in terms of a quality-adjusted year of life because of the lack of a consensus about the appropriate weights that should be given for pain and disabilities. They argue that this is a sensible approach for evaluating RSVIG because "no studies have demonstrated that RSV infection elevates the risk of experiencing longer term physical damage...." For neonatal HSV, in contrast, extensive evidence indicates that long-term sequelae can be serious, which is why, to precisely measure this problem, we classified patients into five outcome states. Thus our base case may overestimate the value of a life saved for persons with serious sequelae.

To examine alternative measures of life, we performed a sensitivity analysis, which measured quality-adjusted lives saved using the EuroQol scale.¹⁵⁻¹⁷ This scale follows the convention of valuing death at 0 and normal life at 1.0. To apply the scale, our clinical team first rated patients along five dimensions of life: mobility, self-care, usual activity, pain, and anxiety using a scale of 1 (normal) to 3 (very dysfunctional). For example, a normal outcome was rated as [1,1,1,1,1] and a severe outcome was rated [3,3,3,2,2] over the five respective dimensions. These dimensions seemed particularly appropriate for capturing the conditions experienced by persons with HSV infection. Based on a large survey of consumers, the developers of the EuroQol scale devised a formula for weighting the relative importance of these dimensions. We applied the formula to obtain quality-adjusted life-years (QALY) of 1.0, 0.82, 0.52, 0.16, and 0.0, respectively, for the normal, mild, moderate, severe, and dead outcomes. In further sensitivity analyses not reported in this paper, we allowed these values to vary considerably.

Hay et al¹⁴ recognized that when an infant life is saved, lives of succeeding generations are made possible. Our base case followed their assumption that each person produces only one child (ie, replacement fertility) and that this occurs at age 25 into an infinite future. The base case measured lives saved plus the resulting lives saved in future generations. Using a 3% discount rate, this means that saving one life in turn saves a stream of lives with a present value of 0.91. Sensitivity

analyses with quality-adjusted lives assumed that all descendants of normal, mild, and moderate survivors of HSV infection would have normal lives.

A 3% discount rate was used to discount all costs and benefits (ie, years of life saved) into present value equivalents. The 3% rate follows the approach of Hay et al¹⁴ and a recent consensus recommendation.¹⁸⁻²⁰ Sensitivity analyses were done at discount rates of 5% and 10% without changing the essential nature of our findings.

No attention was given to the potential lifetime earnings of patients in the base case analysis. Some authors argue that monetary values for lost life-years should not be imputed in the C term because considerations of future income may be implicit in the denominator Y when the latter is measured in quality-adjusted life-years.¹⁹ Thus double counting of income is avoided by ignoring it in the numerator. A counter argument is that many quality-of-life scales are silent or cursory about income. Thus income could be included without double-counting when the Y term simply measures years of life unweighted for income-related quality. In the base case analysis, we ignored income in keeping with standard practice. This promotes comparison of our results with those of Hay et al¹⁴ and other investigators. In further analyses not reported in this paper, potential earnings from a cost-benefit perspective were examined and results were found consistent with the base case analysis reported here.

Managed Care Perspective

Managed care organizations are responsible for the expenses of direct medical costs for inpatient and outpatient care. They are not responsible for the societal costs of special education or long-term institutionalization. Whether a managed care organization would be concerned with saving the lives of future generations is not clear, because it is not guaranteed that the organization would be successful at marketing to the offspring of their members. Arguably this could be a concern if success in current marketing depended on meeting the concerns of current enrollees about the well-being of their descendants. The existence of fertility services in many managed care organizations attests to the importance of this concern. To explore the cost-effectiveness of antiviral drug therapy from the viewpoint of a narrowly self-interested managed care organization, we performed a sensitivity analysis that ignored the costs of special education and long-term care and that valued only the survival of current enrollees.

... RESULTS ...

The results of a cost-effectiveness analysis using the base case assumptions discussed above are shown in Table 5. When neonatal HSV initially appears in the SEM form, treatment with antiviral drugs is a dominant strategy that saves lives and reduces costs. In the base case, treating an SEM case with antiviral therapy costs \$19,873 and saves 1.9 lives per case (ie, the affected individual plus the discounted stream of all future descendants). No treatment costs an average of \$98,474 and saves only 1.1 lives per case. Thus treat-

ment with antiviral drugs saves \$78,601 and 0.8 lives. Results are favorable but less compelling for treating the more serious forms of HSV infection because additional cost is incurred per additional life saved. For CNS cases, the marginal cost per additional life saved (C/Y) is \$75,125. This happens because not treating the infection costs \$120,859 and saves 0.7 lives per case, while treating the infection costs \$172,808 and saves 1.4 lives per case. For DIS cases, the marginal cost per additional life saved is \$46,619. Here no treatment costs \$69,054 and saves 0.4 lives per case, while treatment costs \$86,714 and saves 0.8 lives per case.

Table 5. Marginal Cost per Additional Life Saved in Neonates Treated and Not Treated with Antiviral Therapy (1995 Dollars)

Strategy	Cost	Marginal Cost (ΔC)	Lives Saved (ΔY)	Marginal Lives Saved (ΔY)	C/Y	$\Delta C/\Delta Y$
SEM						
Drug	\$19,873		1.9		\$10,467	
No drug	\$98,474	\$78,601	1.1	-0.8	\$90,444	Dominated
CNS						
No drug	\$120,859		0.7		\$167,336	
Drug	\$172,808	\$51,950	1.4	0.7	\$122,233	\$75,125
DIS						
No drug	\$69,054		0.4		\$173,045	
Drug	\$86,714	\$17,660	0.8	0.4	\$111,476	\$46,619

SEM = skin, ear, and mouth; CNS = central nervous system; DIS = disseminated multiorgan

Table 6. Marginal Cost per Additional Life Saved in Neonates Treated and Not Treated with Antiviral Therapy (1995 Dollars): Managed Care Perspective*

Strategy	Cost	Marginal Cost (ΔC)	Lives Saved (ΔY)	Marginal Lives Saved (ΔY)	C/Y	$\Delta C/\Delta Y$
SEM						
Drug	\$13,638		1.0		\$13,638	
No drug	\$35,870	\$22,233	0.6	-0.4	\$59,277	Dominated
CNS						
No drug	\$42,717		0.5		\$92,344	
Drug	\$50,858	\$8,141	0.9	0.4	\$58,448	\$19,975
DIS						
Drug	\$32,107		0.5		\$68,592	
No drug	\$32,736	\$629	0.3	-0.2	\$130,942	Dominated

*Lives of future generations not counted.

SEM = skin, ear, and mouth; CNS = central nervous system; DIS = disseminated multiorgan.

In a sensitivity analysis, we increased and decreased the cost of drug treatment by a factor of two to see what might happen under changing market conditions when the patent for acyclovir expires. Only small changes occurred in the results for the base case because the cost of antiviral drugs is only 2% (for DIS disease with a severe outcome) to 12% (for SEM disease with a normal outcome) of the present value of direct healthcare costs.

In performing a sensitivity analysis from a managed care perspective, we found that antiviral drug therapy was a dominant strategy for both initial SEM and DIS cases (Table 6). For CNS cases, antiviral therapy saved more lives at an increased cost. For SEM cases, no treatment cost \$35,870 and saved 0.6 lives per case, while drug therapy cost \$13,638 and saved 1.0 lives per case. For CNS cases, the marginal cost per additional life saved was \$19,975. This is based on a cost of \$42,717 and 0.5 lives saved per case without therapy and a cost of \$50,858 and 0.9 lives saved per case with therapy. For DIS cases, no treatment cost \$32,736 and saved 0.3 lives per case; drug therapy cost \$32,107 and saved 0.5 lives per case. Thus antiviral therapy is more attractive from a managed care perspective than a societal perspective.

Returning to the societal cost perspective, we repeated the analysis with lives valued as QALYs using the weights discussed in the Methods section. Treatment of SEM was again found to be a dominant strategy. Costs were the same as those for the base case in Table 5. Without treatment, an average of 28 QALYs was saved per SEM case; with treatment, 58 QALYs were saved, so that the marginal gain from treatment was 30 QALYs per case treated. For CNS disease, the marginal cost per additional QALY was \$3,016. Without treatment 16 QALYs were saved per CNS case; with treatment 33 QALYs were saved for a gain of 17 QALYs. For DIS disease, the marginal cost per additional QALY was \$1,662. Without treatment, 9 QALYs were saved per DIS case; with treatment 20 QALYs were saved for a gain of 11 QALYs. Thus, when QALYs are used to measure lives saved, we continue to find that treatment of SEM disease reduces costs and saves lives while treatment of CNS and DIS disease saves lives at additional societal cost.

... DISCUSSION ...

Our analysis shows that treating neonatal HSV infection with antiviral drugs can reduce societal costs and save lives when the disease is discovered in the SEM form. When the disease has progressed to the more serious CNS and DIS forms, antiviral therapy involves additional societal cost per additional life

saved of \$75,125 and \$46,619, respectively. These amounts compare favorably with many other health-care interventions. For example, Hay et al¹⁴ report a cost per year of life saved of \$24,305 for RSVIG.

The paradoxical finding that treating SEM disease is more cost-effective than treating CNS disease or DIS disease is explained by the progressive pattern of the illness. When an initial case of SEM is treated, the probability of a normal outcome is 0.95; if the case is not treated, the probability of a normal outcome is only 0.24 (0.40 of cases remaining SEM times 0.60 who have normal outcomes). In contrast, an initial DIS case with treatment has a probability of a normal outcome of 0.27 compared with a probability of 0.12 without treatment. Thus a much larger gain occurs in the probability of a good outcome when the SEM case is treated. Antiviral drug treatment of the more serious CNS and DIS cases produces a gain in lives saved, but only at greater societal expense.

One concern with antiviral treatment of neonatal HSV infection is that it might further the survival of severely disabled persons who would require institutional care or special education. This concern was not found to be true when consideration was given to how antiviral drug therapy inhibits the progression of the disease. Antiviral therapy was found to produce a 3 percentage point decrease in the percentage of cases with moderate outcomes (involving high special education expenses) and no change in the percentage of cases with severe outcomes (involving a short lifespan in institutional care). In the United States, approximately 1,600 neonatal HSV cases occur each year, so a 1 percentage point change is about 16 persons. Antiviral therapy's main effect has been to decrease the percentage of infants who die of HSV infection from 47% to 17% and to increase the percentage who have a normal outcome from 25% to 56%. With antiviral therapy, there was only a 1 percentage increase in the number of cases with mild outcomes, which requires neither special education nor institutional care.

We examined the cost of treating neonatal HSV infection from the perspective of a managed care organization in sensitivity analyses. This was done by ignoring the costs of special education and long-term institutional care and the lives of descendants of HSV patients. We found that antiviral drug therapy was somewhat more attractive to managed care organizations than to society. Treating patients with SEM and DIS disease saved lives and decreased costs, while treating patients with CNS disease involved a cost of \$19,975 per additional life-year saved.

Advances in treatment methods are likely to further reduce the costs of antiviral drug therapy. Our analysis compared two historical cohorts of patients. Home administration of the antiviral drug by parents with the aid of a visiting nurse has the potential to eliminate about a week of hospital expense and thus make antiviral drug therapy a dominant strategy for all forms of HSV disease.

Acknowledgments

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