Use of the Polymerase Chain Reaction in the Diagnosis of Herpes Simplex Encephalitis: A Decision Analysis Model*

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PURPOSE: To evaluate the utility of an assay based on a polymerase chain reaction (PCR) of cerebrospinal fluid in the management of patients with suspected herpes simplex encephalitis.

METHODS: A decision model was constructed and used to compare a PCR-based approach with empiric therapy. Inputs required by the model included the sensitivity (96%) and specificity (99%) of PCR (derived from review of the literature), the prevalence of herpes simplex encephalitis (5%, based on the actual prevalence at Barnes Hospital among patients treated empirically with acyclovir), the outcomes for patients with and without herpes simplex encephalitis (derived from clinical studies of the Collaborative Antiviral Study Group and the actual experience at Barnes Hospital), and the average duration of empiric acyclovir therapy for patients with possible herpes simplex encephalitis (5.3 days based on actual experience at Barnes Hospital).

RESULTS: Using these input values, the decision model predicted better outcomes with empiric therapy. However, low rates of inappropriate discontinuation of empiric therapy in patients with herpes simplex encephalitis or improved diagnosis and outcome resulting from a negative PCR assay result in patients without herpes simplex encephalitis led to better outcomes with the PCR-based approach. The PCR-based approach was associated with 9.2 fewer doses of acyclovir per patient.

CONCLUSION: Based on the decision model using conservative assumptions, a PCR-based approach can yield better outcomes and reduced acyclovir use compared with empiric therapy. **Am J Med. 1998;105:287–295.** ©1998 by Excerpta Medica, Inc.

Although herpes simplex encephalitis is the most common form of sporadic viral encephalitis, it is still a rare disease, with an estimated incidence of 1 in 250,000 to 1 in 500,000 persons per year (1). Acyclovir is effective in reducing the morbidity and mortality associated with the disease (2). Typically, viral cultures of the cerebrospinal fluid from patients with herpes simplex encephalitis are negative. Thus, until recently, laboratory diagnosis during the acute illness required a brain biopsy. However, the use of brain biopsy for this purpose has been controversial (3). Because acyclovir therapy is safe, the drug is widely used on an empiric basis for patients with findings suggestive of herpes simplex encephalitis. This approach results in many more patients being treated than the actual number with the disease.

Recently, the polymerase chain reaction (PCR) has been used successfully to detect herpes simplex virus DNA in the cerebrospinal fluid of patients with herpes simplex encephalitis (4–20). Consequently, PCR has generated intense interest as a relatively noninvasive test for the disease. A commercial PCR assay is not available, but local assays are performed by several university-affiliated laboratories as well as some commercial laboratories. Despite its increasing use, the role of PCR in the evaluation of patients with suspected herpes simplex encephalitis has not been subjected to critical analysis. We used decision analysis techniques to understand the role of PCR in making clinical decisions when the diagnosis of herpes simplex encephalitis is suspected, and we have developed suggestions for its use.

METHODS

Decision Model

The decision model that we employed is shown in Figure 1. The structure of the model is based on those previously used for brain biopsy in the management of patients with suspected herpes simplex encephalitis (21–23). We used the model to compare two approaches, both of which included initiating therapy with acyclovir while awaiting the results of diagnostic tests. In strategy 1, the PCR-based approach, a PCR assay was performed on cerebrospinal fluid and acyclovir was discontinued if the PCR was negative. Patients with a positive PCR received a 14-day course of therapy. In strategy 2, empiric therapy, acyclovir was continued for 14 days unless an alternative diagnosis was established, in which case it was discontinued. This approach was based on the clinical practice that was widespread at Barnes Hospital (St. Louis, Missouri) during the study period.

The model required the following inputs: the sensitivity and specificity of PCR for the diagnosis of herpes sim-

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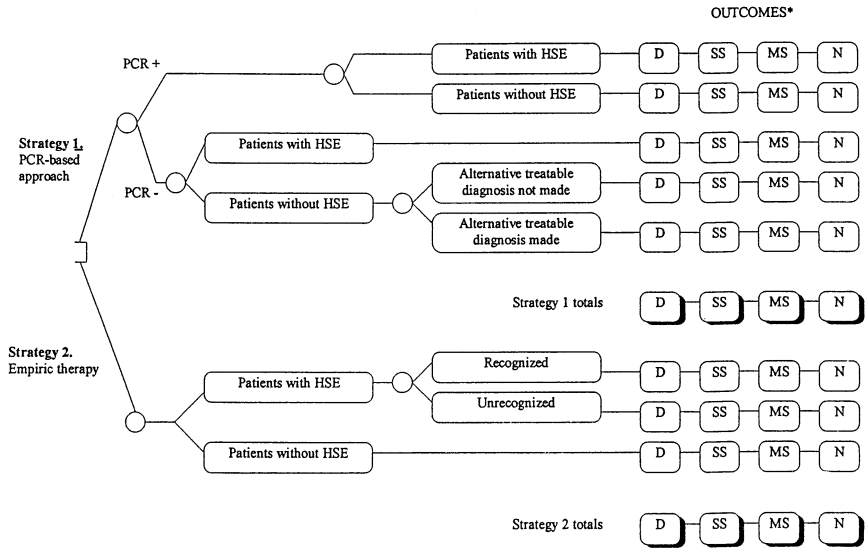

Figure 1. Decision model comparing a polymerase chain reaction (PCR)-based approach and empiric therapy for the management of patients with suspected herpes simplex encephalitis. HSE = herpes simplex encephalitis; D = death; SS = severe sequelae; MS = moderate sequelae; N = normal or return to baseline.

plex encephalitis, the prevalence of herpes simplex encephalitis in the population under study (patients started empirically on acyclovir therapy for suspected herpes simplex encephalitis), outcomes of treatment for patients with and without herpes simplex encephalitis, and the average duration of empiric therapy (Table 1). We used the model to examine the effect of changing two baseline assumptions: (1) that not all patients with herpes simplex encephalitis managed with empiric therapy would receive a full course of acyclovir (because another diagnosis was

Table 1. Values and Sources of Inputs Used in the Decision Model

Input	Value	Source
Prevalence of herpes simplex encephalitis among patients started empirically on acyclovir	5%	Experience at Barnes Hospital 1993–1995
Sensitivity of the PCR assay	0.96	Review of the literature (4–20, 24, 25)
Specificity of the PCR assay	0.99	Review of the literature (4–20, 24, 25)
Duration of empiric treatment with acyclovir for suspected herpes simplex encephalitis	5.3 days	Experience at Barnes Hospital 1993–1995
Outcome probabilities of patients with herpes simplex encephalitis treated with a full course of acyclovir		Collaborative Antiviral Study Group (21)
Death	0.19	
Severe sequelae	0.34	
Moderate sequelae	0.09	
Normal or minor sequelae	0.38	
Outcome probabilities of patients with herpes simplex encephalitis not treated with acyclovir		Collaborative Antiviral Study Group (21)
Death	0.70	
Severe sequelae	0.10	
Moderate sequelae	0.05	
Normal or minor sequelae	0.15	
Outcome probabilities of patients without herpes simplex encephalitis		Experience at Barnes Hospital 1993–1995
Death	0.19	
Severe sequelae	0.21	
Moderate sequelae	0.19	
Normal or minor sequelae	0.41	

PCR = polymerase chain reaction.

Table 2. Studies Used to Determine the Sensitivity and Specificity of PCR for Herpes Simplex Encephalitis

	Number of Subjects	Herpes Encephalitis Present (n = 160)		Herpes Encephalitis Not Present (n = 416)	
		PCR+	PCR−	PCR+	PCR−
Lakeman et al (20)	101	53	1	3	44
Aurelius et al (5)	130	41	2	0	87
Rozenberg et al (8)	65	27	1	0	37
Kessler et al (16)	123	16	0	0	107
Klapper et al (6)	22	9	1	0	12
Puchammer-Stockl et al (7)	20	4	1	0	15
Troendle-Atkins et al (11)	115	3	1	0	111
Total	576	153	7	3	413

PCR = polymerase chain reaction.

mistakenly made and the empiric therapy was discontinued); and (2) that in patients managed according to the PCR-based approach, a negative PCR in some patients without herpes simplex encephalitis would result in a better outcome than if PCR had not been performed (because the negative result made it more likely that the correct diagnosis would be recognized).

Sensitivity and Specificity of PCR for Herpes Simplex Encephalitis

To estimate the sensitivity and specificity of PCR for the diagnosis of herpes simplex encephalitis, we reviewed all published studies dealing with PCR for establishing this diagnosis. We included studies that met the following criteria: (1) the analytic sensitivity of the PCR assay (number of copies of viral genome detectable) was provided; (2) controls were performed to rule out the presence of PCR inhibitors in the specimen; (3) the PCR results were compared with an appropriate "gold standard" (brain biopsy or intrathecal production of herpes simplex virus antibodies); (4) specimens from patients without herpes simplex encephalitis were included; and (5) the subjects were not included in a previous or subsequent study. Specimens from patients with neonatal herpes simplex infection were excluded.

Nineteen studies were reviewed (4–20,24,25). Of these, four were not included because duplication of patients could not be excluded (4,12,13,18), six because comparison with a gold standard was not provided (9,10,14,15,17,24), and two because specimens from patients without herpes simplex encephalitis were not included (19,25). The relation between PCR and the findings in the gold standard test is shown in Table 2. Based on these results, we estimated that sensitivity of PCR for the diagnosis of herpes simplex encephalitis was 96% (153 of 160), with a specificity of 99% (413 of 416).

Prevalence of Herpes Simplex Encephalitis

We determined the prevalence of herpes simplex encephalitis in patients treated for that diagnosis at Barnes Hospital during the study period of July 1993 to June 1995. We used pharmacy data and the laboratory information system to create a list of all patients who received intravenous acyclovir during the study period (n = 606) who also had a lumbar puncture performed within 48 hours of starting the drug (n = 102). The hospital records of these patients were reviewed, and all those in whom acyclovir was started for possible herpes simplex encephalitis were identified (n = 80). Only 4 patients were judged to have had herpes simplex encephalitis based on the presence of a compatible clinical syndrome accompanied by a positive diagnostic test (intrathecal production of herpes simplex virus-specific antibodies, or PCR performed on cerebrospinal fluid). None of these 4 patients had a brain biopsy, which was performed in only 3 of the remaining 76 patients. The alternative diagnoses assigned that served as the basis for discontinuing acyclovir in those 76 patients are shown in Table 3. Approximately half of these diagnoses were considered presumptive based on clinical and radiologic findings.

Patient Outcomes

The outcomes for patients with herpes simplex encephalitis with and without acyclovir treatment were based on results from the Collaborative Antiviral Study Group clinical trials of acyclovir and adenosine arabinoside (2,26). In those trials, patient outcomes were classified into one of four categories: (1) dead; (2) severe neurologic sequelae (institutionalization or continuous home care required); (3) moderate sequelae (able to perform at gainful level even though hampered by neurologic deficits); or (4) none or minor (back to baseline). For pa-

Table 3. Alternative Diagnoses Used as the Basis for Discontinuing Acyclovir in 76 Patients with Suspected Herpes Simplex Encephalitis

Alternative Diagnosis	n	(%)
Metabolic or anoxic encephalopathy	9	(12)
Cerebrovascular accident	8	(11)
Drug toxicity (including alcohol)	8	(11)
Aseptic meningitis*	7	(9)
Bacterial meningitis/brain abscess	7	(9)
HIV encephalopathy	6	(8)
Psychiatric conditions	5	(7)
Disseminated infection	4	(5)
Seizure disorder	4	(5)
Lupus cerebritis	3	(4)
Cytomegalovirus encephalitis (in HIV positive patients)	2	(3)
Tuberculosis of the central nervous system	2	(3)
Carcinomatous meningitis	2	(3)
Cryptococcal meningitis	1	(1)
Other†	8	(11)

* PCR for herpes simplex virus was performed on 5 patients and was negative in all 5.

† Migraine (1), multiple sclerosis (1), trauma (1), papillary mucinosis (1), systemic vasculitis (1), undiagnosed encephalitis (2), left hospital against medical advice (1).

PCR = polymerase chain reaction; HIV = human immunodeficiency virus.

tients without herpes simplex encephalitis, we derived outcomes by reviewing the records of the 76 patients at Barnes Hospital started on acyclovir for possible herpes simplex encephalitis who were later given other diagnoses. The outcomes were classified in the same categories as above, using the patient's condition at the time of hospital discharge. Since acyclovir would not be expected to alter the outcome in patients without herpes simplex encephalitis, the same outcomes were used for patients without herpes simplex encephalitis whether or not they received acyclovir.

Other outcomes were used to examine the effect of changes in baseline assumptions. For patients who were managed with empiric therapy who had herpes simplex encephalitis that was not recognized and who were therefore mistakenly assigned an alternative diagnosis (causing acyclovir to be discontinued before a full course was given), we assigned rates of death and severe sequelae that were equal to the mean of the rates for patients with herpes simplex encephalitis who did or did not receive full courses of acyclovir (2,26). For patients managed under the PCR-based approach who did not have herpes simplex encephalitis but whose outcomes were improved because a negative PCR result led to the establishment of another treatable diagnosis, we assigned rates of death and severe sequelae equal to one half the rates for patients without herpes simplex encephalitis.

Acyclovir Usage

We also compared the effect of each approach on acyclovir usage. For the patients managed according to the PCR-based approach, we assumed that therapy would be continued until the results of the PCR assay were available. For those patients with a positive PCR, total acyclovir usage was estimated as 42 doses per patient (3 doses per day for 14 days) (2). For patients with a negative PCR, total acyclovir usage was estimated as 6 doses per patient, based on an average 2-day turnaround time for PCR testing, currently performed 3 times per week in the St. Louis Children's Hospital Virology Laboratory. For patients managed with empiric therapy, acyclovir usage was estimated as 42 doses per patient for those with herpes simplex encephalitis. For patients without herpes simplex encephalitis, acyclovir usage was estimated as 16 doses per patient, based on the average duration of 5.3 days of acyclovir therapy for the 76 patients at Barnes Hospital who were started on acyclovir but later assigned an alternative diagnosis. (Only 2 of those 76 patients received a 14-day course.) The duration of empiric therapy may have been affected by PCR results, since the test was used in 43 cases. In 2 patients, a negative PCR result was listed as the basis for discontinuing acyclovir therapy. The effect of the availability of PCR during the study period on the estimates used in the model would most likely be to decrease the average duration of acyclovir usage in patients managed by the empiric therapy approach. We assumed that patients weighed an average of 70 kg, an acyclovir dose of 10 mg/kg per dose every 8 hours, and a charge to pharmacy of $78 per gram for acyclovir, equivalent to $54.60 per dose.

Sensitivity Analysis

The effect of changes in the input parameters was examined by changing each parameter through its range of interest while holding other parameters constant at the value used in the base model.

Bayesian Analysis

Using the values of sensitivity and specificity estimated as described above, we calculated the predictive values for positive and negative PCR results at three different pretest probabilities. A pretest probability of 5% was selected because it was the prevalence in this study. A pretest probability of 35% was used because it approximated the 34% prevalence of herpes simplex encephalitis in patients who had a brain biopsy in a previous clinical trial (21). A pretest probability of 60% was included to represent a situation in which the likelihood of herpes simplex encephalitis was very high. Pretest and posttests odds after a positive and negative PCR were also estimated (27).

Table 4. Results of the Decision Model Comparing Outcomes in a Theoretical Population of 10,000 Patients

	Outcomes (Numbers of Patients)				Total Doses of Acyclovir (per Patient)
	Deaths	Severe	Moderate	Normal	
PCR-based approach (strategy 1)	1,910	2,160	1,850	4,080	8.08
Empiric therapy (strategy 2)	1,900	2,165	1,850	4,085	17.30
PCR-based approach with the assumption that an alternative treatable diagnosis is established in 1% of the cases without herpes simplex encephalitis	1,901	2,150	1,858	4,090	8.07
Empiric therapy with the assumption that 10% of patients with herpes simplex encephalitis are not recognized as having that disease	1,913	2,159	1,849	4,079	17.17

PCR = polymerase chain reaction.

Software

The decision model analyses were performed using Excel version 5.0 for the MacIntosh (Microsoft Corporation, Redmond, Washington).

RESULTS

Decision Model

We compared the outcomes of 10,000 hypothetical patients with suspected herpes simplex encephalitis managed according to the PCR-based approach or with empiric therapy. We first carried out a baseline analysis, using the input values in Table 1. We assumed that with empiric therapy, all patients with herpes simplex encephalitis would be correctly recognized and would receive a full course of acyclovir, and that in the PCR-based approach, a negative PCR would have no beneficial effect on the outcome of patients without herpes simplex encephalitis. Under these assumptions, the model predicted a slight excess of bad outcomes (the sum of deaths and patients having severe sequelae) in patients managed under the PCR-based approach (Table 4). Because the PCR test had a sensitivity of only 96%, 4% of patients with herpes simplex encephalitis managed according to the PCR-based approach did not receive a full course of acyclovir, compared with 100% of patients with herpes simplex encephalitis using the empiric therapy approach. The PCR-based approach was associated with 9.2 fewer doses of acyclovir treatment per patient, corresponding to $502 per patient.

A limitation of the baseline model is the assumption that all patients with herpes simplex encephalitis managed with empiric therapy would receive a full course of acyclovir. In our review at Barnes Hospital, however, only 3% of patients treated empirically received a full course. Thus, we investigated the effect of accounting for the possibility that alternative diagnoses would be mistakenly assigned to some patients with herpes simplex encephalitis, leading to premature discontinuation of acyclovir therapy. We found that a rate of misdiagnosis in patients with herpes simplex encephalitis of 8% or greater shifted the results of the model so that fewer bad outcomes would occur with the PCR-based approach (Figure 2A).

A second limitation of the baseline model is that a negative PCR result does not change the likelihood of establishing a correct alternative treatable diagnosis in patients without herpes simplex encephalitis who were managed according to the PCR-based approach. Assuming that establishing an alternative treatable diagnosis would reduce the rates of death and severe sequelae by one half among patients without herpes simplex encephalitis, we found that establishment of an alternative treatable diagnosis in 0.3% or more of these patients, would result in fewer bad outcomes with the PCR-based approach (Figure 2B).

Sensitivity Analysis

When we varied the prevalence of herpes simplex encephalitis from 0% to 100%, we found a strong effect of prevalence on the difference in bad outcomes and in the doses of acyclovir saved (Figure 3A). At a prevalence of 5%, there were 5 more bad outcomes with the PCR-based approach, and 9.2 doses of acyclovir were saved per patient. In contrast, at a prevalence of 60%, there were 64 more bad outcomes with the PCR-based approach, and 4.7 doses of acyclovir were saved per patient.

Increasing the sensitivity of the PCR assay was associated with a decrease in the excess bad outcomes that occurred with the PCR-based approach, but had little effect on doses of acyclovir saved (Figure 3B). In contrast, increasing the specificity had no effect on the difference in patient outcomes under the two strategies, but was associated with more doses of acyclovir saved by the PCR-based approach (Figure 3C). Changing the proportion of bad outcomes occurring in patients with herpes simplex encephalitis treated with acyclovir had little effect on overall outcome and no effect on doses of acyclovir saved (Figure 3D).

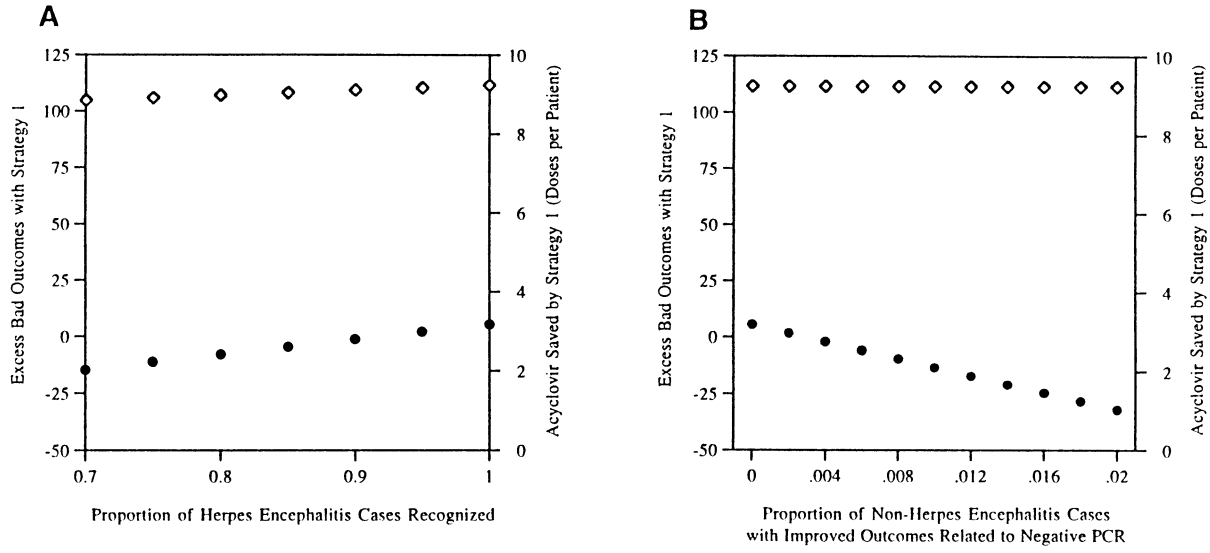

Figure 2. One-way sensitivity analyses. **A**. Effects of changing the proportion of cases of herpes simplex encephalitis that are correctly recognized in patients managed with empiric therapy. **B.** Effects of changing the proportion of non-herpes simplex encephalitis cases managed according to the polymerase chain reaction (PCR)-based approach in whom a negative PCR result leads to an alternative treatable diagnosis. In each panel, the **filled circles** show the excess bad outcomes with strategy 1 of a PCR-based approach (a negative number means fewer bad outcomes with the PCR-based approach), and the **open diamonds** show doses of acyclovir saved.

Bayesian Analysis

In a patient with a pretest probability of 0.05 (odds of 0.05), a positive PCR was associated with a posttest probability of 0.835 (odds of 5.1), while a negative test was associated with a posttest probability of 0.002 (odds of 0.002). For a patient with a pretest probability of 0.35 (odds of 0.54), a positive test corresponded to a posttest probability of 0.98 (odds of 51), while a negative test was associated with a posttest probability of 0.02 (odds of 0.02), not effectively ruling out the diagnosis. In a patient with a high pretest probability (0.6) and odds (1.5) of herpes simplex encephalitis, a positive PCR resulted in a posttest probability of 0.99 (odds of 142); a negative PCR would not rule out the diagnosis (probability of 0.06; odds of 0.06).

DISCUSSION

Polymerase chain reaction testing can detect herpes simplex virus DNA in the cerebrospinal fluid of patients with acute herpes simplex encephalitis (4–20), and thus is attractive as a relatively noninvasive diagnostic test that can provide rapid laboratory confirmation of this important diagnosis. Although brain biopsy has been advocated for the evaluation of patients with suspected herpes simplex encephalitis (21), our findings at Barnes Hospital suggest that empiric therapy with acyclovir without laboratory confirmation is more widely used. Therefore, in our decision model, we compared a PCR-based approach with empiric therapy that corresponds to current practice. Under very conservative assumptions, the PCR-based approach provided better outcomes, and in addition, resulted in substantially less acyclovir use.

Not surprisingly, under the baseline assumptions, the decision model showed better outcomes when empiric therapy was used. This is because all patients managed according to that approach received a full course of acyclovir. This leads to appropriate treatment for all patients with herpes simplex encephalitis, but also results in unnecessary acyclovir treatment for the much larger number of patients with other diagnoses. Obviously, any approach that uses acyclovir treatment in less than 100% of patients with herpes simplex encephalitis would yield worse outcomes in this simplified model.

However, the approach to patients with suspected herpes simplex encephalitis that was widespread at Barnes Hospital during the study period differed from the empiric therapy used in the baseline model. In clinical practice, patients with possible herpes simplex encephalitis were started on acyclovir therapy, which was discontinued when an alternative diagnosis was established. Empiric therapy was discontinued before a full course of treatment in most patients in whom it had been started, with an average duration of therapy of 5.3 days. As that approach does not include any specific diagnostic tests for herpes simplex encephalitis, the diagnosis will likely not be recognized in some patients with the disease, in whom empiric therapy will have been discontinued inappropriately. Without information on the outcomes of patients with herpes simplex encephalitis who receive a par-

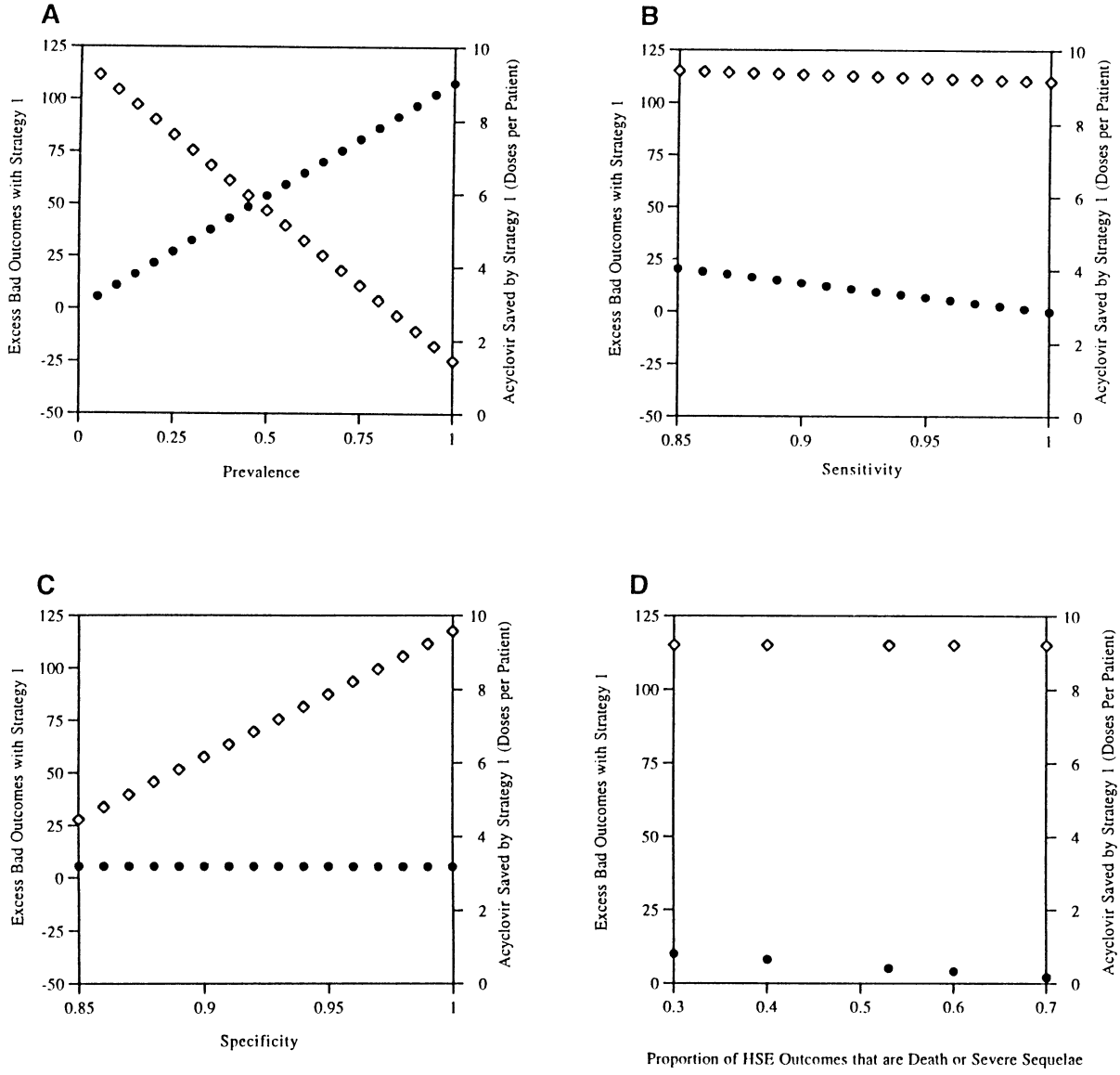

Figure 3. One-way sensitivity analyses. Effects of changes in prevalence of herpes simplex encephalitis (**A**); sensitivity (**B**) or specificity (**C**) of polymerase chain reaction (PCR) assay; and proportion of herpes simplex encephalitis cases treated with acyclovir for which the outcome is death or severe sequelae (**D**). In each panel, the **filled circles** show the excess bad outcomes with strategy 1 of a PCR-based approach (a negative number means fewer bad outcomes with the PCR-based approach), and the **open diamonds** show doses of acyclovir saved.

tial course of acyclovir, we assumed that partial treatment would reduce bad outcomes midway between full treatment and no treatment, as seen in clinical trials (2,26). The model revealed that if the diagnosis of herpes simplex encephalitis was missed in 8% or more of patients with the disease who were managed according to the modified empiric therapy approach, outcomes would be better for patients managed according to the PCR-based approach.

The possibility that negative PCR results may lead to better outcomes for patients without herpes simplex encephalitis also matters. This is because most patients started on acyclovir for possible herpes simplex encephalitis do not have the disease (5% prevalence in the present study), meaning that factors affecting the prognosis of the 95% of patients without herpes simplex encephalitis will have a large effect on the overall outcome of the model. Assuming that establishing an alternative treatable diagnosis would lead to a 50% reduction in the chance of a bad outcome in those patients, overall outcomes would be improved if an alternative treatable diagnosis could be established in only 0.3% of patients without herpes simplex encephalitis. This finding is consistent with an earlier decision analysis that compared an approach based on brain biopsy with a pure empiric ther-

apy approach (21). In that study, the advantage of brain biopsy resulted from better outcomes in patients in whom an alternative diagnosis was established by the biopsy.

Other factors not included in the model also favor an approach that uses a diagnostic test to limit the number of patients treated with acyclovir. The model did not consider, for example, any adverse effects of acyclovir, such as renal or neurologic toxicity. Any adverse effects would favor the PCR-based approach because it involves less use of the drug. Another factor favoring a selective approach is that increased drug use might encourage the emergence of strains of herpes simplex virus that are resistant to acyclovir.

The findings of the decision model can be combined with an assessment of the likelihood that a patient has herpes simplex encephalitis to develop recommendations for the use of PCR in patient management. We recommend starting therapy with intravenous acyclovir in all patients in whom the diagnosis of herpes simplex encephalitis is being seriously considered, while awaiting the results of diagnostic tests. The initial assessment should include neurologic examination directed at the detection of a focal neurologic process, examination of cerebrospinal fluid, and neuroimaging (computed tomography or preferably magnetic resonance imaging) to investigate the presence of temporal lobe involvement and to search for other diagnoses. Herpes simplex encephalitis is highly likely if the patient's illness involves the acute or subacute onset of disordered mentation, evidence of a focal neurologic process based on either neurologic examination or neuroimaging scans, and a lymphocytic pleocytosis in the cerebrospinal fluid. In these patients, a full course of acyclovir should be given, regardless of the results of PCR, unless another diagnosis is firmly established. The rationale is that if these patients are assumed to have a prior probability of herpes simplex of 0.35 to 0.60 (21,22), the posttest probability of herpes simplex encephalitis with a negative PCR is 0.02 to 0.06, which we consider unacceptably high for discontinuing therapy. When these clinical findings are not present, a negative PCR result may be used as the basis for discontinuing acyclovir. Here, the rationale is that with a prior probability of 0.05, the posttest probability of herpes-simplex with a negative PCR is only 0.002. The risk model described by Soong et al (21) shows that clinical findings can be used to estimate the likelihood of herpes simplex encephalitis. (That study did not include data from computed tomography or magnetic resonance imaging since those techniques were not available when the patients were evaluated.)

These considerations apply only when the PCR assay being used has a suitably high sensitivity. The study of Lakeman et al (20), in which PCR results were compared with brain biopsy findings, suggests a standard for PCR assays used in the diagnosis of herpes simplex encephalitis. In that study, in which the sensitivity of PCR was 98%, the PCR assay used was capable of detecting 20 copies of a plasmid containing the target DNA.

In summary, PCR is a powerful technique for the diagnosis of herpes simplex encephalitis, with a sensitivity estimated at 96%. Our decision analysis suggests that, if used as an adjunct to careful clinical assessment, PCR can be used to achieve good patient outcomes and can help avoid overuse of acyclovir. Its proper use can be cost saving, since the savings from decreased acyclovir use are greater than the cost of the assay (current charges are approximately $200). It must be emphasized that although increasingly used, PCR assays for herpes simplex DNA are not currently standardized, and test performance may vary among laboratories. Achieving standardization of PCR assays remains an important priority.

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