

Prevention of Herpes Simplex Virus Eye Disease

A Cost-effectiveness Analysis

David R. Lairson, PhD; Charles E. Begley, PhD; Thomas F. Reynolds, MS; Kirk R. Wilhelmus, MD, MPH

Objectives: To estimate the cost of treating herpes simplex virus (HSV) eye disease, and to evaluate the incremental cost-effectiveness of chronic suppressive antiviral prophylaxis for reducing ocular HSV recurrences.

Methods: An economic decision-tree model was used on follow-up data from 703 patients with prior ocular HSV disease who were enrolled in a Herpetic Eye Disease Study multicenter clinical trial that evaluated the prolonged use of oral acyclovir. Costs were based on wholesale drug prices, Medicare fees, and national health surveys. Incremental cost-effectiveness ratios for all patients and for patients with prior stromal keratitis were calculated as the additional net cost of acyclovir prophylaxis compared with the number of cases of ocular herpes prevented during 12 months. One- and 2-way sensitivity analyses evaluated the effect of different treatment costs and recurrence risks.

Results: Approximately \$17.7 million is expended annually to treat the estimated 59 000 new and recurrent episodes of HSV eye disease occurring among 29 000 individuals each year in the United States. Chronic suppressive oral acyclovir costs \$8532 per ocular HSV episode averted. The incremental cost per infection averted would decline by up to 51% if antiviral prophylaxis were more effective and by up to 87% if patients had a higher recurrence risk. Targeting prophylaxis to patients with a history of stromal keratitis is not more cost-effective than providing oral acyclovir for patients with any prior HSV eye disease.

Conclusions: Herpetic eye disease is costly to treat and prevent. Because prophylactic oral acyclovir is not a cost-effective option for all patients with previous HSV eye disease, therapeutic decisions must be made on a case-by-case basis.

Arch Ophthalmol. 2003;121:108-112

HERPES SIMPLEX virus (HSV) of the eye affects more than 400 000 people in the United States.¹ Each additional ocular episode and its sequelae can have an increasing personal, social, and financial burden. A randomized, placebo-controlled clinical trial demonstrated that twice-daily oral acyclovir reduced the incidence of ocular HSV recurrences during 1 year in participants with a history of herpetic eye disease.²

*For editorial comment
see page 115*

The preventive effect of acyclovir has potential economic benefits.³ Although the cost-benefit ratio for the chemoprevention of recurrent genital herpes among otherwise healthy individuals is uncertain,^{4,5} oral acyclovir suppression is cost-effective for pregnant women^{6,7} and immunocompromised patients. The cost savings in preventing recurrent ocular herpes have not been previously demonstrated. Therefore, we conducted an economic evaluation of antiviral

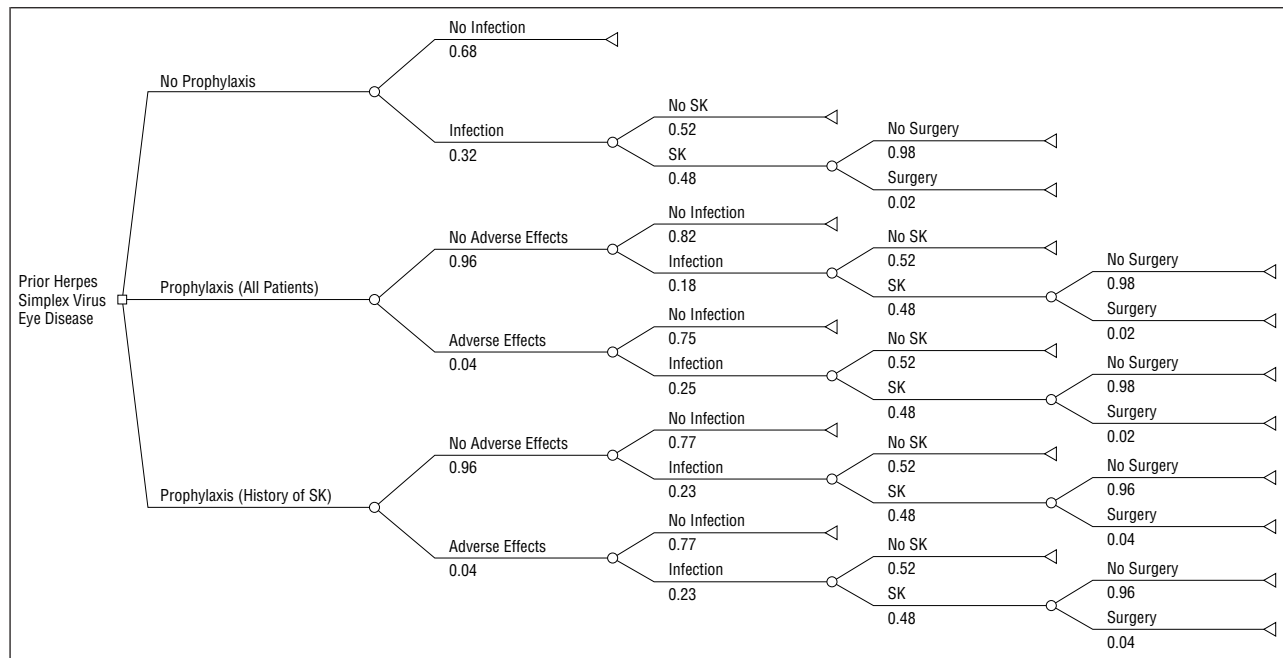
prophylaxis for preventing ocular HSV recurrences compared with no preventive treatment. Using information on the direct and indirect expenses associated with recurrent ocular disease and the cost and effect of oral acyclovir during 1 year, we derived an incremental cost-effectiveness ratio for preventing ocular recurrences among patients with herpetic eye disease. Because individuals with prior stromal keratitis are at increased risk of developing more severe disease,⁸ we also determined whether the cost-effectiveness of prophylaxis targeted to these patients was substantially different.

METHODS

MODEL FOR REFERENCE CASE

A decision-tree model was constructed to compare the direct costs, indirect costs, and the number of cases of recurrent ocular herpes during a 12-month period among immunocompetent patients who had ocular HSV disease in the preceding year (**Figure**). The reference-case analysis compared 3 strategies: no prophylaxis, twice-daily use of 400 mg of oral acy-

From the School of Public Health, University of Texas Health Science Center at Houston (Drs Lairson and Begley and Mr Reynolds), and the Department of Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston (Dr Wilhelmus).



Decision-tree model for 1 year of follow-up following randomization to receive oral acyclovir prophylaxis, for subjects with and without a history of stromal keratitis (SK), or no chemoprophylaxis.

clovir for all patients, and twice-daily use of 400 mg of oral acyclovir for patients with a history of stromal keratitis. The probabilities associated with alternative outcomes and medical care utilization of the major strategies were obtained from the Acyclovir Prevention Trial of the Herpetic Eye Disease Study (HEDS),⁹ supported by cooperative agreements with the National Eye Institute of the National Institutes of Health (Bethesda, Md). The trial was conducted at 74 clinical sites and was overseen by an independent data and safety monitoring committee.

The health benefit is the number of recurrent infections prevented during 12 months of treatment. The incremental cost-effectiveness ratio, evaluated against the no intervention option, is the additional net cost of the acyclovir prophylactic strategy divided by the total number of cases of ocular herpes prevented. Net cost is the intervention cost minus the disease cost averted. We calculated the incremental cost-effectiveness of prophylaxis with acyclovir by comparing the first and second strategies and the second and third strategies. The analysis was conducted from the perspectives of payers and patients. Costs and benefits were undiscounted because of the 1-year follow-up.¹⁰

BENEFITS

The 1-year cumulative probability of recurrent ocular HSV disease decreased by a relative risk reduction of 45% in the randomized controlled trial, from 32% among placebo-treated patients to 19% among patients with a history of ocular HSV disease who received oral acyclovir.² No serious adverse effects were associated with oral acyclovir, although 4% of patients discontinued treatment because of an adverse reaction. One half of adverse effects were gastrointestinal, 10% were rashes, and others included dizziness, weight gain, headache, fatigue, sexual dysfunction, memory loss, anxiety, tinnitus, and hair loss. We assumed that persons developing an adverse effect stopped taking the drug within the first 30 days. The 1-year cumulative probability of recurrent stromal keratitis among 337 (48%) of 703 trial patients who had a history of prior stromal keratitis decreased by a relative risk reduction of 43% in the trial, from 28% in the placebo

group to 14% in the acyclovir group.¹¹ Of 703 trial patients, 10 (1.4%) underwent corneal transplantation during the follow-up period; 8 patients with no ocular recurrence (5 in the control group and 3 in the acyclovir group) and 2 with an ocular recurrence (1 keratoplasty in each group) received transplants.

COSTS

The direct costs of prevention include the cost of acyclovir and physician services to monitor use of acyclovir, net of the direct cost averted because of fewer infections, drug cost, physician office visits, and surgical costs for treating herpetic eye disease (**Table 1**). The clinical trial used brand-name Zovirax 200-mg capsules (GlaxoSmithKline, Research Triangle Park, NC). Because of recent pharmaceutical developments, this analysis was based on the cost of generic acyclovir administered as one 400-mg tablet twice daily. The generic drug cost was estimated by the mean wholesale price quoted by leading suppliers, as published in the drug topics *Red Book*.¹² Drug cost for treating a recurrent eye infection was based on the mean wholesale price for topical antiviral, corticosteroid, and cycloplegic medications. The cost of physician services for drug monitoring was based on 2001 Medicare payments for initial and continuing visits for eye care. The physician cost of treatment for an eye infection is similarly based on the Medicare payment for an initial visit.¹⁴ The cost of corneal surgery was based on a prior study¹³ and validated with eye-bank charges, facility fees, and professional service fees in the Houston, Tex, area. Utilization of physician services, patient travel, and corneal surgery associated with chemoprophylaxis and treatment for recurrent infections were derived from the HEDS clinical trial.

Indirect costs of prevention included the patient's lost work and leisure; transport and time for travel, waiting, and examination for monitoring acyclovir; and the net of the same indirect costs averted because of fewer infections plus less surgery (**Table 2**). The value of a patient's time spent traveling to care, waiting for care, and receiving care were each calculated separately. The ZIP codes of clinics and patients were entered into the Web-based MapQuest program¹⁵ to derive distances and time traveling to care. Travel time was valued using the mean wage rates of full-time workers in 2001 collected in the Current Popu-

Table 1. Direct Costs Associated With Herpetic Eye Disease

Variable	Best Estimate (Range)	Source(s)
Cost per day of acyclovir, \$	4.24 (3.78-5.22)	Red Book, ¹² 2001
No. of days taking acyclovir per year		
Persons with no adverse effects	365	Assumption, HEDS trial
Persons with adverse effects	30	Assumption, HEDS trial
Cost of initial visit for acyclovir, \$	71.16	Medicare Fee Schedule
Cost of follow-up visit for acyclovir, \$	60.83	Medicare Fee Schedule
No. of follow-up visits for acyclovir		
Patients without adverse effects	3.2	HEDS Trial
Patients with adverse effects	1.0	HEDS Trial
Cost of visits for infection, \$	60.83	Medicare Fee Schedule
No. of visits per epithelial keratitis episode, control group	2.5 (2.3-4.0)*	HEDS Trial
No. of epithelial keratitis episodes, given at least 1, control group	1.2 (1.0-1.2)*	HEDS Trial
Cost of medication per stromal keratitis episode, \$†	134.00 (100-147)*	Red Book, ¹² 2001
Cost of medication per epithelial keratitis episode, \$‡	87.31 (56-92)§	Red Book, ¹² 2001
No. of visits per stromal keratitis episode, control group	3.0 (2.0-3.0)*	HEDS Trial
No. of stromal keratitis episodes, given at least 1, control group	1.7 (1.0-1.7)*	HEDS Trial
Cost of corneal surgery, \$	11 945	Estimate ¹³

Abbreviation: HEDS, Herpetic Eye Disease Study.

*Range is across mean values for the study groups.

†One bottle each of 7.5 mL of 1% trifluridine, 15 mL of 1% prednisolone phosphate, and 5 mL of 0.25% scopolamine hydrobromide.

‡One bottle of 7.5 mL of 1% trifluridine.

§Range is across pharmaceutical company prices.

||The 1996 estimate was inflated to 2001, according to the medical care component of the Consumer Price Index.

Table 2. Indirect Costs Associated With Herpetic Eye Disease

Variable	Best Estimate (Range)	Source
Cost of time per minute, \$	0.28	Current Population Survey
Cost per mile of travel, \$	0.33	Internal Revenue Service
Roundtrip miles per visit for acyclovir	33.7 (2.6-115)	HEDS trial, mean
Roundtrip travel minutes per visit for acyclovir	68 (8-302)	HEDS trial, mean
Wait plus examination minutes per visit for acyclovir	45 (10-165)	Medical Expenditure Survey
Cost per lost work or leisure day, \$	118.80	Current Population Survey
Lost days per visit for acyclovir	0.5	Assumption
Roundtrip miles per visit for ocular recurrence	33.7 (2.6-115)	HEDS trial, mean
Roundtrip travel minutes per visit for ocular recurrence	68 (8-302)	HEDS trial, mean
Wait plus examination minutes per visit for ocular recurrence	60 (10-180)	Medical Expenditure Survey
Lost work or leisure days per visit for ocular recurrence	1	Assumption
Lost work or leisure days per keratoplasty	3	Assumption

Abbreviation: HEDS, Herpetic Eye Disease Study.

Table 3. Cost-effectiveness Analysis of Oral Acyclovir Prophylaxis*

Strategy	Cost, \$	Incremental Cost, \$	Effect†	Incremental Effect	Cost-effectiveness, \$	Incremental Cost-effectiveness, \$
Including Indirect Costs						
No prophylaxis	299	...	0.461	...	649	...
Acyclovir, all patients	2304	2005	0.226	0.235	10 195	8532
Acyclovir, patients with prior stromal keratitis	2329	25	0.272	-0.046	8549	Dominated
Excluding Indirect Costs						
No prophylaxis	189	...	0.461	...	411	...
Acyclovir, all patients	1837	1647	0.226	0.235	8128	7009
Acyclovir, patients with prior stromal keratitis	1852	15	0.272	-0.046	6800	Dominated

*Ellipses indicate not applicable.

†No. of cases of ocular herpes simplex virus per person.

lation Survey.¹⁶ The time spent waiting for care and receiving care was based on the most recent data available from the Medical Expenditure Panel Survey.¹⁷ Average wages for all workers were used to estimate the value of lost occupational time. We assumed that patients missed half a day of work or leisure in accessing care associated with acyclovir treatment, 1 day for treatment of recurrent infections, and 3 days for corneal surgery. Average wages were used to value each day that was lost.

SENSITIVITY ANALYSIS

The analysis was run including and excluding indirect costs to isolate the effect of direct patient costs on the incremental cost-effectiveness of the prevention strategy. One-way sensitivity analysis was done for the daily cost of acyclovir, the probability of infection in the control and treatment groups, and the probability of surgery given the occurrence of stromal kera-

titis. The cost of acyclovir was varied from zero to the highest current price listed in the *Red Book*. The probability of infection for the treatment group was varied from 0 to 0.19, the point estimate obtained in the HEDS trial. The probability of infection in the control group was varied from 1 to 0.32, the point estimate obtained in the HEDS trial. Two-way sensitivity analysis was done for the probability of infection in the control and treatment groups to examine how estimates vary as the risk of infection changes from the trial values to the most favorable scenario for the intervention. The probability of corneal surgery, a costly but infrequently used service, was varied from 0 to 0.04 to determine whether surgery is an important factor when rates are relatively high.^{1,18}

RESULTS

COSTS

By combining the direct (Table 1) and indirect (Table 2) costs associated with HSV eye disease, a mean of \$299 is expended to treat each episode (Table 3). Extending the annual expenditure associated with herpetic eye disease to the US population at risk was estimated from a population-based cohort study in one northern US community. If the directly age- and sex-adjusted incidence of 20.7 (95% confidence interval [CI], 18.3-23.1) episodes per 100 000 person-years found in Rochester, Minn, from 1950 through 1982¹ is extrapolated to the current US population of 286.7 million people,¹⁹ then 59 350 (95% CI, 52 470 to 66 230) new and recurrent episodes occurred during the current year in the United States. Thus, an estimated \$17745650 (95% CI, \$15688530 to \$19802770) is being spent annually on direct and indirect costs for all ocular HSV episodes. If prolonged oral acyclovir prophylaxis is used for all patients with an ocular HSV episode occurring during the prior year, then 1-year costs increase to \$2305 (Table 3). Based on the experience of 151 patients in Rochester with new or recurrent HSV eye disease per 1.5 million person-years,¹ 28 860 people in the United States would be expected to develop herpetic eye disease this year. Treatment and prevention costs for this group would be \$66 522 300 per year.

COST-EFFECTIVENESS ANALYSIS

Compared with nonprophylaxis for HSV ocular disease, the incremental cost-effectiveness ratio of the acyclovir strategy for all persons with a recent history of HSV was \$8532 per ocular HSV infection averted. The strategy of prophylaxis for only those persons with a history of stromal keratitis was dominated by the acyclovir for all patients strategy. The targeted strategy was slightly more costly and less effective (Table 3). Similar results were obtained when the analysis was restricted to direct costs.

SENSITIVITY ANALYSIS

The results of the analysis were most sensitive to the probability of infection in the treatment and control groups. As the probability of infection in the control group rises from the value observed in the HEDS trial to the upper limit, the cost of prevention declines rapidly to \$1127 per infection averted (Table 4). As the probability of infection in the

Table 4. Sensitivity Analyses

Variable	Incremental Cost per Ocular HSV Episode Averted, \$	
	Total Cost	Direct Cost Only
Probability of ocular HSV recurrence		
Control group		
0.32	8532	7009
0.49	3848	3224
0.66	2328	1996
0.83	1576	1388
1.00	1127	1025
Acyclovir group (all patients)		
0.00	4161	3482
0.045	4809	4005
0.09	5662	4693
0.135	6831	5638
0.18	8532	7009
Probability of ocular HSV recurrence		
Control group/acyclovir group		
1.00/0.00	864	814
0.66/0.09	1947	1690
0.32/0.18	8532	7009
Probability of corneal surgery, given		
SK infection		
0.00	8703	7170
0.01	8620	7092
0.02	8532	7009
0.03	8453	6936
0.04	8369	6858
Cost of daily dose of acyclovir, \$		
0.00	2188	666
1.30	4142	2620
2.61	6096	4574
3.92	8050	6527
5.22	10 004	8481

Abbreviations: HSV, herpes simplex virus; SK, stromal keratitis.

treatment group falls to zero, the incremental cost per infection averted decreases to \$4161. A 2-way sensitivity analysis of probability of infection in the treatment and control groups shows that under the most favorable conditions, 100% probability of infection in the control group and none in the treatment group, the incremental cost-effectiveness ratio would be about \$800 compared with about \$8500 when the probabilities obtained in the HEDS trial are applied. The incremental cost per infection averted is not sensitive to the relevant range in the probability of corneal surgery given a stromal keratitis recurrence. Varying the price of acyclovir from the highest current wholesale price to zero changes the incremental cost per infection averted from more than \$10000 to \$2188.

COMMENT

Acyclovir is clinically safe and effective in reducing the recurrence risk of ocular HSV disease for patients who had ocular HSV disease during the preceding year. From an economic viewpoint, prolonged oral acyclovir is a relatively expensive preventive strategy. The estimated cost of treating infections among those in the control group was \$299 compared with a mean cost for prophylaxis and treatment of \$2304 in the acyclovir group.²⁰ Lacking a metric to convert the outcome measure to quality-adjusted life-years, our conclusion rests on the apparent high incremental cost of the intervention relative to actual eye disease episodes.^{21,22}

Whether patients or health agencies would be willing to pay \$8500 per ocular infection averted is an open question because many recurrent episodes are mild, short-term, and relatively inexpensive to treat.

Our findings provide a reasonable estimate of the costs involved in treating and monitoring herpetic eye disease in the United States. We used the risk estimates for ocular recurrences that were found in a multicenter trial. Costs were based on representative estimates from widely used sources, although the indirect cost estimates of time lost relied on expert opinion and the cost of surgery was based on local data. Travel time and costs were estimated from a subset of patients in the HEDS trial by measuring the distance from their residence to the trial clinic, although these distances may overstate the travel required by patients because many would likely use a local provider.

An important limitation of this study is that the influence of HSV eye disease on vision was not incorporated into the cost estimates. Visual loss from herpetic eye disease entails human and socioeconomic costs. Residual corneal scarring occurs in 22% to 24% of patients with recurrent HSV keratitis,^{1,18} often as a consequence of HSV stromal keratitis.^{23,24} After resolution of ocular inflammation, visual acuity of the affected eye is worse than 20/100 in 3% to 12% of patients.^{1,18,23-26} Even if vision in the other eye is good, quality of life is adversely affected regardless of severity of visual loss in the poorer eye.²⁰ Whether the possible prevention of visual loss offsets the relative expense of chronic suppressive antiviral prophylaxis is a difficult judgment. Although it is not a cost-effective option for all patients with previous HSV eye disease, prophylactic oral acyclovir may be appropriate for patients with sight-threatening recurrences, frequent episodes, or other reasons for reduced quality of life due to ocular herpes.

A related shortcoming of our study is the 1-year period, and, therefore, our inability to track long-term consequences of recurrent ocular infections. Prolonged follow-up would permit direct observation of the cumulative effect of recurrent infections on vision loss and associated quality of life. Extending the analysis over several years is unlikely to change the basic conclusion because the annual cost of prophylaxis is not likely to diminish and there is no reason to believe the infection rates would change over time, although the consequences may be more serious for some patients.

Besides assessing safety and efficacy, clinical trials should examine the personal and societal costs of new interventions. Economic analyses can be done before, during, and after large clinical trials are conducted. Examination of the cost of eye disease relative to the cost of prevention combined with a threshold analysis of intervention efficacy may be warranted *ex ante* when considering large-scale clinical trials.²⁷ If a pharmacoeconomic analysis suggests that an intervention is cost-effective under the range of effectiveness uncertainty, then a randomized trial may be justified. A cost-effectiveness study could be conducted alongside many clinical trials in ophthalmology to guide the collection of socioeconomic data, including quality-of-life information, in order to conduct *ex post* monetary evaluations that may help guide national eye care policy.

Submitted for publication April 16, 2002; final revision received September 5, 2002; accepted September 23, 2002.

This study was supported by grant U10 EY 09687-05 from the National Eye Institute, National Institutes of Health, and Research to Prevent Blindness, Inc, New York, NY. The HEDS Coordinating Center at the Jaeb Center for Health Research, Tampa, Fla, provided the HEDS data set for the analysis.

Corresponding author and reprints: David R. Lairson, PhD, Professor of Economics, Department of Management and Policy Sciences, University of Texas Health Science Center at Houston, 1200 Herman Pressler St, Houston, TX 77030 (e-mail: dlairson@sph.uth.tmc.edu).

REFERENCES

1. Liesegang TJ, Melton LJ III, Daly PJ, Ilstrup DM. Epidemiology of ocular herpes simplex: incidence in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol*. 1989;107:1155-1159.
2. Herpetic Eye Disease Study Group. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. *N Engl J Med*. 1998;339:300-306.
3. Drummond M, Backhouse M. Assessing the economic benefits of antiherpes therapy. *J Med Virol*. 1993;suppl 1:51-57.
4. Engel JP. Long-term suppression of genital herpes. *JAMA*. 1998;280:928-929.
5. Handsfield HH, Stone KM, Wasserheit JN. Prevention agenda for genital herpes. *Sex Transm Dis*. 1999;26:228-231.
6. Randolph AG, Hartshorn RM, Washington AE. Acyclovir prophylaxis in late pregnancy to prevent neonatal herpes: a cost-effectiveness analysis. *Obstet Gynecol*. 1996;88:603-610.
7. Scott LL, Alexander J. Cost-effectiveness of acyclovir suppression to prevent recurrent genital herpes in term pregnancy. *Am J Perinatol*. 1998;15:57-62.
8. Herpetic Eye Disease Study Group. Predictors of recurrent herpes simplex virus keratitis. *Cornea*. 2001;20:123-128.
9. Herpetic Eye Disease Study Group. *Manual of Operations*. Springfield, Va: National Technical Information Service; 1994. Accession No. PB97-112999.
10. Gold MR. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.
11. Herpetic Eye Disease Study Group. Oral acyclovir for herpes simplex virus eye disease. *Arch Ophthalmol*. 2000;118:1030-1036.
12. Medical Economics Co. *Red Book*. Montvale, NJ: Medical Economics Co; 2001.
13. McDonnell P. Empirical or culture-guided therapy for microbial keratitis? A plea for data. *Arch Ophthalmol*. 1996;114:84-87.
14. Centers for Medicare & Medicaid Services. National Physician Fee Schedule [database online]. Available at: <http://cms.hhs.gov/physicians/pfs/>. Accessed September 4, 2001.
15. MapQuest.com, Inc, and Navigation Technologies. MapQuest Web site. Available at: <http://www.mapquest.com>. Accessed September 2001 to December 2001.
16. Bureau of Labor Statistics, US Department of Labor. Current Population Survey. Available at: <http://www.bls.census.gov/cps/cpsmain.htm>. Accessed September 17-20, 2001.
17. Medical Expenditure Panel Survey [database on CD-ROM]. Rockville, Md: US Dept of Health and Human Services, Agency for Healthcare Research and Quality; 1997.
18. Wilhelmus KR, Coster DJ, Donovan HC, Falcon MG, Jones BR. Prognostic indicators of herpetic keratitis: analysis of a 5-year observation period after corneal ulceration. *Arch Ophthalmol*. 1981;99:1578-1582.
19. US Census Bureau. US POPClock projection. Available at: <http://www.census.gov>. Accessed January 2002.
20. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol*. 2000;118:47-51.
21. Kerlikowske K, Salzman P, Phillips KA, Cauley JA, Cummings SR. Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. *JAMA*. 1999;282:2156-2163.
22. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J*. 1992;146:473-481.
23. Barron BA, Gee L, Hauck WW, et al. Herpetic Eye Disease Study: a controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology*. 1994;101:1871-1882.
24. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic Eye Disease Study: a controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology*. 1994;101:1883-1896.
25. Norn MS. Dendritic (herpetic) keratitis, I: incidence-seasonal variation-recurrence rate-visual impairment-therapy. *Acta Ophthalmol (Copenh)*. 1970;48:91-107.
26. Claoue C, De Cock R. The spectrum of herpes simplex virus disease of the anterior segment in the 1990s. *Acta Ophthalmol Scand*. 1996;74:407-410.
27. Phillips CV. The economics of "more research is needed." *Int J Epidemiol*. 2001;30:771-776.