Priorities for Lung Transplantation Among Patients With Cystic Fibrosis

To the Editor: In her Editorial accompanying our article1 about prognostic factors for lung transplantation among patients with cystic fibrosis (CF), Dr Maurer2 noted that we did not comment on the survivorship effect of the rate of change in the FEV1%.

We, like others,3-5 initially made the logical assumption that patients with CF who have rapid deterioration of FEV1% would have an increased risk of death. It has been hypothesized that the subset of patients with the most rapid decline in FEV1% would gain a survival benefit from lung transplantation. We created theoretical survival models based on this hypothesis that suggested that we might be able to identify appropriate transplantation candidates several years before the optimal moment for transplantation. This would decrease the number of patients who die while on a waiting list, and optimize the use of donated organs. Unfortunately, none of these models are valid because we also found that the rate of decline in FEV1% is not a significant predictor of survival.6

In our previous work, univariate logistic regression analysis showed that rate of decline of FEV1% predicted was not a significant predictor of survival.6 We now report that, despite the lack of significance, we included the rate of decline of FEV1% predicted in further multivariate analyses because of its clinical appeal. This variable, whether calculated by linear regression or by linear mixed-effects analysis, again was not statistically significant and was excluded in stepwise analysis of variance when FEV1% was also included in candidate models. Because we were initially skeptical of this result, we attempted to use the linear mixed effects model of FEV1% rate of change to predict future FEV1%. We identified 12 477 patients in the CF Foundation Patient Registry with 2 to 5 years of pulmonary function data from 1987 through 1992. We generated linear mixed-effects models of the rate of change of FEV1% for each patient and predicted the change in FEV1% for 1993 through 1997. The Figure shows the complete inability of the FEV1% rate of change to make that prediction.

Because the rate of FEV1% decline was not predictive of survival or even of future FEV1%, as shown here, it was not included in our evaluation of the survival effects of lung transplantation. Based on this additional analysis, we conclude that the rate of decline in FEV1% is not helpful in the selection of patients with CF for lung transplantation.

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Figure. Relationship Between FEV1% Predicted Rate of Change, 1987-1992 and 1993-1997 [N = 12 477]
To the Editor: As a 46-year-old with CF awaiting a lung transplant, I would like to comment on the article by Dr Liou and colleagues. While the study does break new ground in identifying an improved multiparameter technique for estimating remaining life expectancy of adults with CF, I am extremely concerned by the conclusion implying that physicians should consider using the results as a basis for recommending to patients whether they should pursue a lung transplant. The unexamined assumption is that a year of survival with a lung transplant is equivalent to one without a lung transplant.

While I have no problem in evaluating the proposed model as an improved method for estimating life expectancy, I cannot accept the authors’ implication that only those patients falling into group 1, who exhibit improved life expectancy with a lung transplant, should receive one. The authors have used numerous parameters as input to their model for estimating life expectancy, but they use only 1 parameter, years of survival, as a parameter to indicate benefit from lung transplantation. While this may be all that the available database allows, I feel the discussion of the results is sorely lacking in not bringing up the issues of quality of life that accompany a lung transplant. I fear most physicians will not think of it and will base a discussion on whether to proceed with a transplant based solely on years of survival.

I also question the results, since the survival rate of group 1, having a pretransplant 5-year survival expectancy of less than 30%, had about a 63% posttransplant survival, while groups 2 and 3, having pretransplant 5-year survival expectancies of 30% to 50% and 50% to 70%, respectively, each had about a 50% posttransplant survival. One would expect the opposite, the poorest pretransplant group doing the worst posttransplant.

In my experience, physicians often lose sight of the serious toll on the quality of life that end-stage CF takes from a patient on a daily if not hourly basis. It is significant, and years of survival under abnormal conditions are hardly equivalent to years spent enjoying healthy lungs even if they are fewer than without a transplant. As their lungs give out, adults with CF need more sleep, often 10 or 12 hours per day, and they are still exhausted. Therapy requirements increase, adding further pressure to the available hours in a day. People with CF push through the exhaustion in order to retain a job, working when they should be home in bed. Eventually, however, most must give up their jobs, suffering reduced income and often economic hardship for their families. The resulting social isocompatibility and the reduced self-esteem that accompanies loss of one’s career frequently contribute to depression. Lung disease often wipes out a person’s appetite, requiring them to force down food 3 times a day and exist on nutritional supplements or to use a feeding tube to survive, all very unpleasant options. And this doesn’t even include the secondary issues such as battling with one’s providers and insurance companies to correct their numerous billing errors and to ensure appropriate care in this age of fiscal belt-tightening. In short, survival for the sake of survival without a high quality of life cannot come close to comparing with the quality of life available to the transplant recipient. On the other hand, I have met many transplant recipients and they all report their quality of life to be fantastic. Their appetite returns, their lung function is better than it ever has been in their life in many cases, and they are able to work, travel, and vacation with family.

These issues need to be included in a physician’s recommendation to a patient considering a lung transplant. Basing a lung transplant decision solely on years of survival is inappropriate, misleading, and unfair to the patient. I feel that the physician’s ethical obligation is to provide direction to patients that provides for the best overall quality of life.

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In Reply: It is encouraging that Dr Liou and colleagues carefully considered the potential impact of the rate of fall of FEV1% in developing their model for predicting survival in patients with cystic fibrosis. They state that despite a variety of iterations of the model they were unable to find an impact on the survival predictions, and they conclude unequivocally that “the rate of decline in FEV1% is not helpful in the selection of candidates with CF for lung transplantation.” However, they also note that this clinical parameter has been identified as a negative predictor by several other authors. It is important to remember that the model has not yet been validated prospectively in patients with CF who are within their last years of life. The disparity between the model of Liou et al and other published data in predicting 5-year survival likely reflects the different populations studied. Authors who have identified the rate of decrease in FEV1% as an important predictor have generally not looked at the whole population of patients who might be included in a 5-year survival prediction model, but rather at a smaller subset of patients, a “self-selected” group, who are rapidly deteriorating clinically. In this population, the rate of decline of FEV1% might indeed be helpful to caregivers and transplant centers in determining appropriate times to wait-list patients. Whether the addition of this type of parameter to the predictions of the model of Liou et al adds useful information for clinicians will become clear as it is evaluated prospectively.

I understand and empathize with Mr Maish’s comments regarding length vs quality of life. End-stage lung disease, re-
In Reply: We appreciate Mr Maish’s comments about our work and the important issue of quality of life (QOL). We found that only the sickest patients with CF had a survival benefit from lung transplantation. To answer Maish’s specific question, we previously examined the apparent superior survival of transplanted patients from group 1 compared with groups 2 and 3 (Figure 1 in our article) and found no statistical difference.

The greater issue is his concern that physicians might lose sight of the toll that CF has on QOL. The principle primum non nocere (first, do no harm) requires physicians to consider risks before recommending any procedure. Our study provides the first estimate of survival risks and benefits of lung transplantation for patients with CF stratified by predicted survival. We focused on survival because it is an indisputable end point for measuring the benefit of therapy.

We agree, however, that QOL is important, and we are acutely aware of the physical, psychosocial, and economic burdens that CF places on individuals. Several studies show a positive impact of lung transplantation on QOL. However, interpretation of these works requires caution. Some patients evaluated both before and after transplantation experienced no improvement in QOL. In all studies, patients who died shortly after transplantation were not evaluated. The QOL benefit was not uniform, and accurate prediction of individual outcomes is impossible.

A study examining the relationship between predicted survival and QOL would improve the individual estimates of potential QOL benefits from lung transplantation. As we surmised in our article, patients with the poorest predicted survival likely have the poorest QOL. One might assume these patients would reap the greatest QOL benefit from lung transplantation. If true, then transplantation of the sickest patients might maximally improve both survival and QOL.

There may, however, be a group with high predicted survival but poor QOL. Should these patients undergo transplantation? Because the donor organ shortage constrains lung transplantation, preferentially performing lung transplants in patients with potentially improved QOL and longer survival seems wiser than performing transplants in patients with improved QOL but unchanged or decreased survival. If the organ supply should increase, then studies of QOL relative to predicted survival tempered by the known rigors of lung transplantation may help guide the latter group to estimate the potential trade-off between survival and QOL. For now, we agree with Maish that discussions about lung transplantation must include both survival as well as QOL risks and benefits.

In the future, we may want to consider the realistic benefit of transplantation in the remaining group of patients with potentially improved QOL and longer survival.

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In the future, we may want to consider the realistic benefit of transplantation in the remaining group of patients with potentially improved QOL and longer survival.
seromarkers than subsequent enrollees,3 which suggests that on which SFCCC is based had a higher prevalence of HBV may be relevant temporal differences among SFCCC enrollees:

1. Even so, KSHV prevalence in SFCCC actually increased by homosexual men in San Francisco during 1978 through 1985. All of these biases could have obscured an increasing prevalence of KSHV among homosexual men in San Francisco during 1978 through 1985.

2. While this hypothesis is consistent with much of the data, it fails to explain why HHV-8 is much more prevalent in homosexual than in heterosexual men, since deep kissing and oral sex are common in both groups. Nor can differences in HHV-8 prevalence be solely attributed to numbers of sex partners, because even commercial sex workers have a lower prevalence of HHV-8 than do homosexual men. Thus, the higher prevalence of HHV-8 among homosexual men may be related to sexual practices, such as anal sex, that are more prevalent among this population. Several findings of Osmond et al are consistent with this hypothesis.

3. First, HIV-seropositive homosexual men had significantly higher rates of KSHV seroprevalence than did HIV-seronegative subjects. While the seropositive group might have had higher numbers of sex partners, HIV-seropositive subjects are also more likely to have practiced unprotected receptive anal sex, which thus may be an important route of KSHV transmission.

4. Second, as the authors noted, there was limited information about the relationship between specific sexual behaviors and KSHV seroprevalence. The study only identified associations at an ecological level, meaning that an individual’s sexual behavior could not be linked to his HHV-8 status. In addition, HHV-8 seroprevalence was measured at only 2 time points when behavioral data were available (1984-1985 and 1995-1996), so that there were no data to indicate whether KSHV seroprevalence remained constant during the interim. It is possible, for example, that when the prevalence of unprotected receptive anal sex was lowest (1987-1992), KSHV seroprevalence decreased correspondingly. Without additional information, the relative contributions of oral and anal sex in KSHV transmission cannot be determined.

5. Finally, Osmond et al found KSHV seroprevalence to be greater than 25% prior to widespread HIV infection. This important observation makes it clear that HIV is not primarily responsible for differences between homosexual and heterosexual subjects in KSHV prevalence. Thus, other factors, including behaviors such as anal sex, may be responsible for these differences. These factors might best be identified in longitudinal studies of KSHV-discordant, monogamous couples.

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To the Editor: Dr Osmond and colleagues1 noted the lack of consensus as to the route of KSHV transmission in homosexual men. Recent studies1-3 have suggested that KSHV, also known as human herpesvirus 8 (HHV-8), is primarily transmitted among homosexual men through deep kissing or oral sex. While this hypothesis is consistent with much of the data, it fails to explain why HHV-8 is much more prevalent in homosexual than in heterosexual men, since deep kissing and oral sex are common in both groups. Nor can differences in HHV-8 prevalence be solely attributed to numbers of sex partners, because even commercial sex workers have a lower prevalence of HHV-8 than do homosexual men.2 Thus, the higher prevalence of HHV-8 among homosexual men may be related to sexual practices, such as anal sex, that are more prevalent among this population. Several findings of Osmond et al are consistent with this hypothesis.

First, HIV-seropositive homosexual men had significantly higher rates of KSHV seroprevalence than did HIV-seronegative subjects. While the seropositive group might have had higher numbers of sex partners, HIV-seropositive subjects are also more likely to have practiced unprotected receptive anal sex, which thus may be an important route of KSHV transmission.

Second, as the authors noted, there was limited information about the relationship between specific sexual behaviors and KSHV seroprevalence. The study only identified associations at an ecological level, meaning that an individual’s sexual behavior could not be linked to his HHV-8 status. In addition, HHV-8 seroprevalence was measured at only 2 time points when behavioral data were available (1984-1985 and 1995-1996), so that there were no data to indicate whether KSHV seroprevalence remained constant during the interim. It is possible, for example, that when the prevalence of unprotected receptive anal sex was lowest (1987-1992), KSHV seroprevalence decreased correspondingly. Without additional information, the relative contributions of oral and anal sex in KSHV transmission cannot be determined.

Finally, Osmond et al found KSHV seroprevalence to be greater than 25% prior to widespread HIV infection. This important observation makes it clear that HIV is not primarily responsible for differences between homosexual and heterosexual subjects in KSHV prevalence. Thus, other factors, including behaviors such as anal sex, may be responsible for these differences. These factors might best be identified in longitudinal studies of KSHV-discordant, monogamous couples.
which has not yet been observed. Furthermore, the decline in KS prior to HAART has not been explained.

Use of nitrite inhalants should be considered a third factor that is consistent with the unique epidemiology of HIV-associated KS. Homosexual men used “poppers” more commonly than did heterosexuals prior to the AIDS epidemic and use has been declining since. Additional pharmacological and epidemiologic evidence supports the connection of nitrite inhalant use to KS. The decline in the incidence of KS in the United States parallels a similar decrease in the use of nitrite inhalants. The epidemic of HIV-associated KS provides a unique opportunity to decipher the pathogenesis of a malignancy that appears to be multifactorial in origin.

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In Reply: We agree with Dr O’Brien and colleagues that it can often be problematic to infer incidence from prevalence data. As we noted, our data are not inconsistent with some increase in KSHV prevalence with the first wave of HIV infection. Our principal objective in documenting the robust prevalence of KSHV in 1978 in HIV-uninfected men, however, was not to make a strict comparison with 1984 and 1985, but rather to show that KSHV infection was probably not introduced recently in homosexual men. This has implications for understanding KSHV transmission. If acts that are practiced by both homosexuals and heterosexuals, such as kissing, are significant routes of KSHV transmission, KSHV would likely be widespread in heterosexual populations, but actual prevalence estimates range from 0% to 9%. Low prevalence in heterosexual groups despite spread by kissing would be plausible if KSHV were recently introduced, but our data from 1978 do not support this.

O’Brien et al also point out that a closed cohort is a more appropriate study design in which to examine changes in KSHV incidence. Again we agree with the theoretical point but note that the published cohort studies are not in agreement. O’Brien et al9 cite their own cohort analysis and a study by Melbye et al9 as showing declining KSHV incidence, but Goudsmit et al8 report declining HIV incidence and no decline in KSHV incidence during the 1980s. An apparent decline in KSHV incidence early in the follow-up of a closed cohort could be an artifact of serological testing based on a specific but insensitive assay. It is generally acknowledged that the immunofluorescence assay for antibodies against KSHV latency-associated nuclear antigen is an insensitive assay, identifying about 80% of truly infected persons missed on the baseline test as early “seroconverters.” As follow-up time increases, this source of seroconverters would diminish substantially, producing a pattern of declining incidence that is an artifact of the assay characteristics. Our own experience testing longitudinal samples (with the assay used by O’Brien et al9) is similar to that reported by Quinlivan et al7 who found an inconsistent pattern of positive results that make it difficult to determine with confidence when seroconversion occurred. We therefore remain skeptical that published incidence rates from cohort studies have settled the question.

Although we cannot directly infer incidence rates from our cross-sectional data, we believe they are relevant in understanding the relative incidence of HIV and KSHV infections between the 1984 through 1985 and the 1995 through 1996 periods, for which we have identical population-based samples. Restricting comparison to the groups of 25- to 29-year-old subjects, HIV prevalence dropped from 48.6% to 21.9% while KSHV stayed nearly steady at 21.8% and 25.8%. Other explanations are possible, but the most likely explanation for the discrepant patterns of seroprevalence is that the incidence of the 2 viral infections differed in the population of young homosexual men during this period. For example, these men were too young for deaths from AIDS to have had much effect on prevalence. Although we acknowledged that our data do not establish a cause-and-effect relationship, we think the most plausible explanation for the prevalence patterns is that there are significant differences in the way the 2 viruses are transmitted. Finally, we note that O’Brien et al9 found a nearly constant KSHV incidence between 1984 and 1990 (the last year sampled), which is consistent with the constant seroprevalence we found when comparing the period 1984 through 1985 with 1995 through 1996.

We suggested that the difference in seroprevalence patterns could be due to penile-oral intercourse playing a greater role in KSHV than in HIV transmission. Drs Cannon and Pellett note that if KSHV were transmitted by deep kissing and oral sex, it would be common in heterosexuals. We agree with respect to deep kissing but point out that the specific route of transmission in oral sex may be from infected saliva to mucosal cells of the penis, that is, from the receptive to the insertive partner, as the virus is found frequently in saliva but rarely in semen. Hence transmission to female partners would be unlikely to
Letters

To the Editor: Dr Cummings and colleagues found that serum estradiol levels may be useful to identify women who would be most likely to benefit from prophylactic use of raloxifene to prevent breast cancer. Application of their results, however, which used a “sensitive” assay, may not be directly applicable to the commercially available assays for serum estradiol that are generally used in clinical practice. The apparent average value for estradiol in their population of postmenopausal women using this assay was 2.93 pg/mL, which is much lower than the range of 10 to 20 pg/mL used in daily clinical practice. Thus, their results must be adjusted before they can be applied to clinical practice.

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This letter was shown to Dr Cummings and colleagues, who declined to reply.

—Ed.

LETTERS

Measurement of Serum Estradiol

To the Editor: In their Rational Clinical Examination article about temporal arthritis, Drs Smetana and Shmerling suggest that a temporal artery biopsy is important but fail to consider the role of the ophthalmologist. A more rational approach would include a complete ophthalmic examination by an ophthalmologist, neuro-ophthalmologist, or retina specialist. The eye findings could point toward the correct diagnosis (and might suggest other reasons to proceed with the contemplated temporal artery biopsy).

Because many patients with temporal arthritis have ocular manifestations, a complete eye examination is most useful in any patient suspected of having temporal arthritis. When performed in a timely fashion, such an examination, along with evaluation of the erythrocyte sedimentation rate (ESR) and C-reactive protein laboratory tests can allow for a presumptive diagnosis of temporal arthritis. Such a patient can be started on high doses of systemic corticosteroids and a temporal artery biopsy can be scheduled to be performed shortly thereafter to make a definitive diagnosis.

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Value of Ophthalmologic Examination in Diagnosing Temporal Arteritis

To the Editor: In their Rational Clinical Examination article about temporal arthritis, Drs Smetana and Shmerling suggest that a temporal artery biopsy is important but fail to consider the role of the ophthalmologist. A more rational approach would include a complete ophthalmic examination by an ophthalmologist, neuro-ophthalmologist, or retina specialist. The eye findings could point toward the correct diagnosis (and might suggest other reasons to proceed with the contemplated temporal artery biopsy).

Because many patients with temporal arthritis have ocular manifestations, a complete eye examination is most useful in any patient suspected of having temporal arthritis. When performed in a timely fashion, such an examination, along with evaluation of the erythrocyte sedimentation rate (ESR) and C-reactive protein laboratory tests can allow for a presumptive diagnosis of temporal arthritis. Such a patient can be started on high doses of systemic corticosteroids and a temporal artery biopsy can be scheduled to be performed shortly thereafter to make a definitive diagnosis.

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Letters

Drs Haverkos and Kopstein use national surveillance data for the occurrence of KS in patients with AIDS to identify a decline in KS incidence prior to HAART that they believe has not been explained. While we agree that there has been an overall decline in KS incidence in the United States prior to HAART, the more pertinent question is whether there has been a decline in KS incidence among HIV-infected homosexual men (the group at most risk for KSHV infection) who were infected with HIV at different times in the HIV epidemic. If such a decline were seen between men seroconverting for HIV in the early 1980s compared with the late 1980s, this would need to be explained. Veugelers et al found no differences in KS incidence in 407 men who seroconverted for HIV throughout the 1980s. This is consistent with the nearly constant prevalence of KSHV that we found in homosexual men between 1984 and 1995. These data, however, do not rule out a role for other cofactors, such as nitrite use. Indeed, only about half of the men in the San Francisco Men's Health Study who were KSHV and HIV positive developed KS, so there may well be one or more other factors that are important in KS pathogenesis.

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In Reply: The primary purpose of our article was not to determine the incremental value of ophthalmologic examination in the diagnosis of temporal arteritis, but rather to determine the diagnostic value of the history, physical examination, and ESR among patients with suspected temporal arteritis. We agree with Dr Blodi that an ophthalmologic examination may be particularly useful for the subset of patients with suspected temporal arteritis who have visual symptoms at the time of presentation (37% in our review). If clinicians can arrange such evaluation promptly, it is reasonable to request this consultation while awaiting the results of the ESR measurement. However, we do not believe that clinicians should withhold empiric systemic corticosteroid therapy or defer biopsy in patients with a high clinical probability of temporal arteritis (as suggested by multiple typical features or the presence of a high likelihood feature as determined by our review), in order first to obtain the results of an ophthalmologic examination.

Such consultation would be particularly helpful in the absence of compelling clinical features that would suggest temporal arteritis, and when clinicians would thus be more likely to entertain diagnostic evaluation for carotid artery stenosis or other alternate considerations. For example, in a patient with transient visual loss and suspected temporal arteritis whose ESR proves to be normal, the likelihood of temporal arteritis would be sufficiently reduced (likelihood ratio, 0.2) that the physician should consider alternate diagnoses. An ophthalmologic examination would be particularly important in such a case.

We are aware of no evidence to suggest that all patients with suspected temporal arteritis, including those without visual complaints, should receive a complete eye examination as part of the diagnostic strategy. In fact, our review suggests otherwise. The finding of a normal funduscopic examination in such a patient would not alter the likelihood of temporal arteritis. In our review of 745 patients who had a complete funduscopic examination, the negative likelihood ratio for any funduscopic abnormality was 1.0. Likewise the finding of an abnormal funduscopic examination did not substantially increase the likelihood of positive temporal artery biopsy results (positive likelihood ratio, 1.1). Therefore, we find that the risk of potential delay in diagnosis or of institution of appropriate empiric therapy while awaiting temporal artery biopsy would likely outweigh the benefit of ophthalmologic consultation for patients without visual symptoms for whom a clinical suspicion of temporal arteritis exists.

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Obituary Listings of US physicians are no longer published in JAMA. They are now available online on the Web site of the American Medical Association. The listing is now fully searchable and will be updated monthly. The listing can be accessed on the AMA Homepage at http://www.ama-assn.org by clicking on “Physicians and Medical Students,” then “News and Events,” and then “Obituary Listing,” or accessed directly at http://www.ama-assn.org/ama/pub/category/7255.html.