

COMMENTS AND RESPONSES

Treatment of Early Lyme Disease

TO THE EDITOR: Wormser and colleagues (1) reported the results of very short-term (10-day) versus short-term (20-day) antibiotic treatment for patients with early Lyme disease who presented with an erythema migrans rash. Using an on-study analysis, the authors claimed that 84% to 90% of patients had a complete response to one or the other treatment after 30 months of follow-up. These results represent “creative mismanagement” of the study data (2).

Although the study enrolled 180 patients in 3 treatment groups, only 99 patients were evaluable after 30 months of observation, yielding a dropout-plus-exclusion rate of 45% (25% of patients were excluded, and 20% dropped out). Since almost half of the patients were not included in the final analysis of this observational trial, the on-study results are virtually meaningless because the uncounted participants must be considered potential treatment failures (2). Furthermore, an exclusion rate of 25% invalidates the study randomization, and a dropout rate of 20% invalidates the overall study results (2).

In the more appropriate intention-to-treat analysis, which we present in the **Table**, the least stringent response rates (complete response plus partial response) ranged from 49% to 62%, while the most stringent response rates (complete response only) ranged from 44% to 53% at 30 months of follow-up. These results are a far cry from the response rates trumpeted by the authors, and they indicate potential failure of both the short-term and very short-term regimens in a significant number of patients.

An illustrative problem with the analysis was the exclusion of the 5% to 10% of patients who developed a recurrent erythema migrans rash. Although the authors excluded these patients because of the possibility of a new spirochetal infection, a more likely explanation is that the patients had recurrent rashes because of failure of their initial treatment and persistent Lyme disease (3). Thus, manipulation of the study results turned an intention-to-treat failure into an on-study success, and this outcome highlights the problematic data interpretation embraced by the authors. Furthermore, by conservative estimate, at least 41% of patients with early Lyme disease never develop an erythema migrans rash (4). Thus, the study by Wormser and colleagues included only patients whose conditions were easiest to diagnose, making the poor treatment results of short-term therapy even more disappointing.

Over the past 3 years, undertreatment of Lyme disease has become institutionalized in the United States. This unfortunate trend has evolved on the heels of a highly flawed study of chronic Lyme disease therapy (5) and publication of manipulated data from early Lyme disease treatment, as seen in the report by Wormser and colleagues and elsewhere (6). It is time to start using well-designed studies and more appropriate statistics in the analysis of Lyme disease therapy in order to assess the gravity and risk of this protean illness. In contrast to the current national trend, we need to examine longer courses of antibiotics to treat persistent spirochetal infection and obtain better clinical outcomes for patients with Lyme disease (6).

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IN RESPONSE: Stricker and colleagues have “creatively” misread our study, in which 10 days and 20 days of doxycycline treatment were demonstrated to have similar efficacy in patients with erythema migrans. Efficacy was evaluated at 4 different, specific time points (20 days, 3 months, 12 months, and 30 months), as well as at the time of the last visit with the patient, in both an on-study and an intention-to-treat analysis. The sample size estimates were based, as explicitly stated in the manuscript, on the 12-month time point, and were met.

At last patient contact in our intention-to-treat analysis, the complete response rates for the 10-day and 20-day doxycycline groups were nearly identical (83.3% and 86.2%, respectively). The patients who were classified as partial responders had usually mild subjective symptoms, such as intermittent fatigue or arthralgias. “Healthy” control groups of adults without a history of Lyme disease have been found to have similar symptoms at comparable frequencies (1), suggesting that Lyme disease is one of a number of triggers of such symptoms or that our patients’ symptoms were unrelated to their episode of Lyme disease. In either case, the take-home message is that symptoms in early Lyme disease sometimes resolve slowly but will do so at the same rate regardless of whether antibiotic therapy is extended beyond 10 days.

Stricker and colleagues suggest that patients who developed erythema migrans at a different skin location during a subsequent summer, as well as those who did not return for a particular study

Table. Intention-To-Treat Analysis of Short-Term Antibiotic Therapy for Lyme Disease

Patients	Regimen		
	Doxycycline, 10 Days, plus Ceftriaxone	Doxycycline, 10 Days	Doxycycline, 20 Days
At start	60 (100)	61 (100)	59 (100)
At 30 months			
Complete response + partial response	37 (62)	30 (49)	31 (53)
Complete response	32 (53)	28 (46)	26 (44)
Recurrent erythema migrans rash	6 (10)	3 (5)	5 (8)

visit, should have been considered treatment failures. This would not have affected the study findings because the frequency of these events was similar across treatment groups. Erythema migrans, which is found in more than 90% of patients who meet the Centers for Disease Control and Prevention's case definition of Lyme disease if a complete skin examination is performed (2), is, however, not a manifestation of late Lyme disease; it can be recognized as a reinfection because the site of the new tick bite is usually readily identifiable.

There is no scientific evidence to justify prolonged antibiotic therapy for patients with any manifestation of Lyme disease, and our study and that of others (3) should further help to discourage such practice. In addition, antibiotics are no better than placebo in treating patients who carry the label of "chronic Lyme disease," probably because evidence indicates that this entity is not infectious (4). Shorter courses of antibiotic therapy are more convenient for the patient, less expensive, potentially safer, and less likely to promote the emergence of resistant bacteria in the community.

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HIV Survival Benefit Associated with Earlier Antiviral Therapy

TO THE EDITOR: Palella and colleagues (1) found that initiation of antiretroviral therapy (ART) at CD4⁺ cell counts of 0.201 to 0.350 × 10⁹ cells/L was associated with reduced mortality compared

with delayed ART. Their study included patients who were followed from 1994 to 2002, so the results partly reflect the era before widespread use of highly active antiretroviral therapy (HAART). We wonder whether calendar year was accounted for in the models and whether restriction of results to patients with time zero after 1996 affected the findings.

Another relevant point is that patients with CD4 cell counts of 0.201 to 0.350 × 10⁹ cells/L who delayed therapy had a median CD4 cell count of 0.130 × 10⁹ cells/L when they started ART. This is considerably lower than has ever been recommended (2), and cell counts this low are known to be associated with an increased risk for disease progression (3), making Palella and colleagues' study a comparison between early and very late initiation of ART. It would be interesting to see how the results would have differed if patients who did not start ART were censored when their CD4 cell count fell below 0.200 × 10⁹ cells/L and if those who never started ART were not excluded. The current relevance of the difference in the percentages of patients with undetectable viral load who were starting and delaying ART is unclear because fewer than 40% of patients had a viral load below the level of detection. This is considerably lower than the levels observed in cohorts that started therapy with HAART (4). In addition, although Palella and colleagues' results were adjusted for receipt of HAART, we were uncertain how this variable was defined because it was unknown at baseline for those who delayed ART. Even if starting HAART at higher CD4 cell counts has a clinical benefit, the reduction in the risk for clinical progression should be weighed carefully against the risks for treatment failure because of problems with long-term adherence, potential toxicities, and the emergence of resistance.

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IN RESPONSE: We were surprised to see Mocroft and colleagues question our findings of improved survival among treatment initiators with CD4⁺ cell counts above 0.200×10^9 cells/L rather than our suggestion of possible treatment benefit above a CD4⁺ cell count of 0.350×10^9 cells/L. The former is a well-accepted minimum treatment threshold, and the latter is a finding of interest and potential impact.

The calendar time for our observations (1994–2002) included periods before wide availability of HAART. However, numbers did not permit analyses stratifying by calendar time. We presented data on HAART recipients (by definition, those treated after 1995) in our Tables 1 and 2; for both antiretroviral therapy and HAART, groups starting therapy at higher CD4⁺ cell counts had fewer deaths.

Mocroft and colleagues note that treatment delayers in the group with CD4⁺ cell counts of 0.201 to 0.350×10^9 cells/L ultimately initiated antiretroviral therapy at a median CD4⁺ cell count of approximately 0.130×10^9 cells/L, “considerably lower than has ever been recommended,” and ask whether our results would have been different had we censored those who did not initiate antiretroviral therapy once their CD4⁺ cell counts dipped below 0.200×10^9 cells/L. Since, by definition, those who “delayed” therapy in any stratum did start therapy while in a lower CD4⁺ cell stratum, and there was only one lower stratum ($<0.200 \times 10^9$ cells/L), censoring when CD4⁺ cell counts dropped below 0.200×10^9 cells/L would have eliminated all delayers and makes no sense analytically. Those who never received therapy are not included in our Table 2 analyses but, contrary to what Mocroft and colleagues state, were analyzed separately. In addition, to quote from our paper, “despite shorter follow-up, we observed higher mortality rates for all CD4⁺ subgroups when comparing these patients to those who either initiated or delayed ART.”

Mocroft and colleagues also question the relevance of our comparative data on rates of achievement of undetectable viral loads because “fewer than 40% of patients had a viral load below the level of detection,” lower than one would expect in cohorts of HAART recipients. This may represent a misreading. In Table 1, among those with CD4⁺ cell counts of 0.201 to 0.350×10^9 cells/L, 63.8% of those initiating antiretroviral therapy versus 45.8% of treatment delayers achieved undetectable viral loads. Second, these are data from all recipients of antiretroviral therapy, not just HAART recipients. Third, and most important, earlier initiation of antiretroviral therapy was associated with greater likelihood of an undetectable HIV viral load, both in patients with CD4⁺ cell counts of 0.201 to 0.350×10^9 cells/L and in those with CD4⁺ cell counts of 0.351 to 0.500×10^9 cells/L. This finding strongly corroborated the mortality benefit associated with earlier initiation of antiretroviral therapy. We determined receipt of HAART on the basis of retrospective data, so the

question about how this variable was defined if it was unknown at baseline seems to reflect a misunderstanding of our study design.

Last, as covered extensively in our Discussion section, we agree that the HIV clinician must carefully weigh any clinical benefit of earlier initiation of antiretroviral therapy against the possible risks of long-term toxicity, poor adherence, and emergence of viral resistance.

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Itraconazole versus Fluconazole for Antifungal Prophylaxis

TO THE EDITOR: Winston and colleagues (1) reported that itraconazole was more effective than fluconazole for antifungal prophylaxis in recipients of allogeneic hematopoietic stem-cell transplants. We do not agree completely with their conclusion. Two well-designed, double-blind clinical trials showed that fluconazole is beneficial in this population (2, 3). The efficacy of fluconazole was further emphasized by an evidence-based analysis of the literature that involved more than 9000 patients (4). Fluconazole lacks efficacy against *Candida krusei* and *C. glabrata* and particularly against *Aspergillus* species, which pose a major threat late in the post-transplantation period.

Over the years, the rate of invasive fungal infections has increased (5). Such infections are associated with a high mortality rate in the allogeneic setting, especially in patients with severe graft-versus-host disease. The need for antifungal prophylaxis, particularly in the latter group of patients, is obvious. In Winston and colleagues' study, however, crucial risk factors were not matched between groups, which is an important limitation. Besides evaluating feasibility and safety and demonstrating a reduced incidence of invasive fungal infections, a trial of antifungal agents for prophylaxis must also reveal, in our opinion, a significant reduction in the attributable mortality rate (4). To date, only the clinical trials from Goodman and coworkers (3) and Slavin and Marr and associates (2, 6) have done this; Winston and colleagues' trial, although well designed, did not, perhaps in part because of its small sample size.

The pivotal question of attributable mortality remains unresolved for itraconazole. Therefore, we cannot universally conclude that it is more effective than fluconazole for long-term prophylaxis of invasive fungal infections after allogeneic stem-cell transplantation. Larger studies of itraconazole or other antifungal agents that are efficacious not only against yeast but also against filamentous fungal infections remain warranted in this setting.

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TO THE EDITOR: Winston and colleagues (1) showed that studying a relatively small sample of high-risk patients may allow demonstration of a potential difference between prophylactic drugs. However, the results of their study may not be generalizable to patients receiving allogeneic hematopoietic stem-cell transplantation in other institutions with a lower rate of fungal infections. The rate of fungal infections with fluconazole was 2.4% in a recent trial of prophylaxis in allogeneic transplant recipients (2) compared with 25% in Winston and colleagues' trial.

This trial considered empirically treated patients and those who died as "successes." Current diagnostic tests are not sensitive for diagnosis of invasive fungal infections before death (3). Therefore, in Winston and colleagues' study, empirically treated patients and those who died may have had occult invasive fungal disease. Even with autopsy data, it is difficult to distinguish between "fungal-related" mortality and death from other causes in such seriously ill patients. A decrease in "fungal-related" mortality but no difference in overall mortality implies that more patients receiving itraconazole died of non-fungal-related causes, one of which might have been unrecognized drug toxicity.

It may be more clinically relevant to define the primary end point as the incidence of breakthrough invasive fungal infections and all-cause mortality. Patients who received empirical therapy should have been considered as having had failure of prophylaxis, but the numbers of such patients were not given in Winston and colleagues' paper. Regardless, it is important to compare the numbers of these patients between groups. An analysis of Winston and colleagues' trial that considered breakthrough invasive infections and deaths as failures (assuming "fungal-related" deaths were already included as breakthrough infections) would result in 32 failures among 71 patients in the itraconazole group (45.1%) and 33 failures among 67 patients in the fluconazole group (49.3%) (difference, -4.2 percentage points [95% CI, -20.8 to 12.5 percentage points]). This analysis supports the conclusion that the efficacy of itraconazole is similar

but not superior to that of fluconazole for the prophylaxis of fungal infections in patients receiving allogeneic transplants.

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Disclaimer: The opinions expressed in this letter are those of the authors and not necessarily those of the U.S. Food and Drug Administration.

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TO THE EDITOR: Winston and colleagues' data and conclusions (1) should remind us of the problems encountered in the design and reporting of trials of antifungal agents (2). First, it is unclear why blinding of the 2 agents studied was "technologically impossible." Second, even though a multivariable analysis that included graft-versus-host disease showed that itraconazole was still associated with fewer fungal infections than fluconazole, the randomization process could have easily stratified patients by donor type, related versus unrelated, at enrollment. Third, the authors did not mention what percentage of patients in both groups were treated empirically with amphotericin B for suspected fungal infection. Fourth, antifungal prophylactic measures used during the preparative regimens of chemoradiation therapy, such as topical mucosal antifungal agents, were not listed, nor were the prophylactic measures used after day 100 following transplantation. Fifth, the study was designed to show that itraconazole was not inferior to fluconazole but failed to show a significant difference between groups in the incidence of aspergillosis or mortality, including that due to fungal infection, because of the small numbers of patients (3). Sixth, the mean duration of corticosteroid use was not different between groups, but the total cumulative dose of steroids administered was not mentioned.

To put the results of this study in perspective, it may be useful to calculate the number needed to treat for benefit. The absolute risk reduction in invasive fungal infections was 16%, so the number needed to treat for benefit was 1/16%, or 6.25. That is, compared with fluconazole, approximately 6 patients would need to be treated with itraconazole before 1 case of invasive fungal infection could be prevented.

I also wonder whether the authors have data on the incidence of invasive fungal infections in both groups beyond day 180 after trans-

plantation, particularly in patients who developed graft-versus-host disease.

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IN RESPONSE: We do not dispute the efficacy of fluconazole for prevention of *Candida* infections in transplant recipients (1, 2). However, the usefulness of fluconazole for antifungal prophylaxis in recipients of allogeneic hematopoietic stem-cell transplants has recently been compromised by the increasing incidence of *Aspergillus* and certain fluconazole-resistant *Candida* infections. Furthermore, while the Seattle study reported improved long-term survival in patients receiving prophylactic fluconazole after allogeneic hematopoietic stem-cell transplantation (3), these results were not seen in the study by Goodman and colleagues and in other trials of fluconazole prophylaxis (1, 2). It is also uncertain that the improved long-term survival in the Seattle study can be attributed to a reduction of fungal infections by fluconazole administered many years earlier rather than to many other factors and therapeutic interventions. In our study, the favorable trend of a reduction in death from fungal infection in patients taking prophylactic itraconazole probably did not achieve statistical significance because of the study sample size.

Some of the issues of trial design and study end points raised by Drs. Powers and Higgins and Dr. Mossad were discussed in our article. It is not appropriate to compare the low rate of fungal infection with fluconazole prophylaxis in the trial by Van Burik and colleagues (2.4%) (4) and the higher rate of fungal infection with fluconazole in our study (25%). Van Burik and colleagues compared fluconazole with micafungin for antifungal prophylaxis only during the period of neutropenia (18 days) immediately after transplantation in a group that included recipients of autologous as well as allogeneic hematopoietic stem-cell transplants. Recipients of autologous transplants have a considerably lower risk for fungal infection, while the risk for invasive fungal infections among recipients of allogeneic transplants is now much greater after engraftment (usually in association with increased immunosuppression for graft-versus-host disease) than during the early period of neutropenia after transplantation. Similarly, we believe that it is not appropriate to consider all deaths as failure of antifungal prophylaxis. Relapse of malignant disease, graft-versus-host disease, hemorrhage, and other noninfectious factors frequently cause death after hematopoietic stem-cell transplantation and would probably not be affected directly by antifungal prophylaxis. For this reason, studies of anti-infective agents in transplant recipients usually do not use overall mortality as a primary

end point. There was no evidence that any deaths in our study were related to itraconazole toxicity.

Breakthrough fungal infections were more common in patients taking prophylactic fluconazole than in those taking itraconazole (14 of 67 patients [20.8%] vs. 4 of 71 patients [5.6%]; $P = 0.01$). The number of patients receiving empirical amphotericin B ($n = 19$) and the median duration of empirical amphotericin B therapy (8 days) were identical in the 2 study groups. Empirical amphotericin B therapy was most often used during the neutropenic period immediately after transplantation. Since the decision to initiate therapy with empirical amphotericin B is frequently subjective and the duration of therapy is often too short to adequately treat any established fungal infection, we believe that such therapy should not be used as a primary end point.

Because a unique method was used to administer intravenous itraconazole when this study was started and because a very distinctive taste is associated with oral itraconazole solution, blinding was not done. The number of unrelated transplant recipients enrolled in the study was greater than anticipated, but we agree that randomization could have been stratified by donor type. As discussed in our article, a multivariable analysis using donor type and other relevant factors showed that prophylaxis with itraconazole was still associated with fewer invasive fungal infections. The total cumulative dose of corticosteroids, as well as the mean duration of corticosteroid use, was similar for both study groups.

Antifungal prophylaxis was not given during pretransplantation chemoradiation or after day 100 following transplantation. We do not have data on the incidence of any invasive fungal infections beyond day 180. However, at the University of California, Los Angeles, from December 2001 to July 2003, 53 patients who received allogeneic hematopoietic stem-cell transplants also received itraconazole prophylaxis. These patients were at high risk for *Aspergillus* infection (median age was 41 years, 79% had advanced disease, and 89% received high-dose corticosteroids for prevention or treatment of graft-versus-host disease), but none developed *Aspergillus* infection. We note that Dr. Mossad and his colleagues recently reported a similarly low incidence of invasive fungal infections in allogeneic hematopoietic stem-cell transplantation when using an antifungal prophylactic regimen containing itraconazole (5). Thus, we believe that there is sufficient evidence to support the superior efficacy of itraconazole over fluconazole for prevention of *Aspergillus* and other fungal infections resistant to fluconazole but susceptible to itraconazole.

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Suboptimal Monitoring and Dosing of Unfractionated Heparin

TO THE EDITOR: Raschke and colleagues (1) addressed inappropriate dosing of unfractionated heparin in most clinical trials. We recently completed an audit of the use of unfractionated heparin at our institution and discovered many problems besides the lack of correlation of the therapeutic range of activated partial thromboplastin time (aPTT) to an anti-factor Xa heparin level of 0.3 to 0.7 IU/mL.

First, many physicians were not using the recommended weight-based method of delivery with the bolus of 80 U/kg of body weight and the maintenance dosage of 18 U/kg per hour (2). This caused 23.1% of our treated patients to be under the published therapeutic range at 24 hours. Second, our hospital nomogram was outdated, based on the standard nomogram published by Cruickshank and colleagues (3). The therapeutic reference range in the hospital nomogram used by the providers was fixed at an aPTT range of 55 to 95 seconds. This did not correlate with our laboratory's reference range, 70 to 110 seconds at the time of the audit. Thus, our patients were targeted to a subtherapeutic aPTT, albeit unreliable at the time because of lack of correlation to an anti-factor Xa level.

Our institution quickly addressed these problems, and results were favorable on a follow-up audit. Other problems still exist. The recommended method of correlating the range of aPTT to a plasma heparin level by factor Xa inhibition must be done not only with each new aPTT reagent but also with each new lot of unfractionated heparin. This calibration must be done often at our hospital because new heparin lots are ordered every 3 to 6 months. Obtaining plasma samples from the required 30 patients receiving unfractionated heparin is difficult because more and more patients are prescribed low-molecular-weight heparin in favor of unfractionated heparin. We wonder how other institutions are addressing similar obstacles.

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IN RESPONSE: We agree with the comments of Chung and colleagues. We have encountered similar problems and have devised practices for minimizing them. The most important are the development of a close working relationship between interested clinicians and laboratory personnel and proper implementation of standardized heparin order sheets. After years of practice, our coagulation laboratory staff have become adept at calibrating the therapeutic aPTT range for new thromboplastin reagents. We have experienced several major shifts in aPTT therapeutic ranges over the years: Our lowest calibrated range was 46 to 70 seconds, and our highest was 75 to 105 seconds. The calculated aPTT therapeutic range in our hospital is published as part of a preprinted heparin order sheet that is available in all patient care areas. This order sheet incorporates weight-based dosing (1) and has been widely accepted at our institution (2). Whenever the therapeutic range is recalibrated because of a change in reagents, all of the previous order sheets are collected and destroyed, and new ones are distributed. Staff from our coagulation laboratory carry out this procedure on the morning that the new reagent is introduced. It hasn't been necessary to do this more often than once every few years because our laboratory does not change thromboplastin reagents unless there is a compelling reason, and lot-to-lot variation in our reagents has not been significant enough to warrant a change in the heparin order sheets. Over the years, inappropriate aPTT ranges have been introduced into our institution as part of multi-institutional clinical trials. We have declined participation in trials that do not allow participating institutions to use properly calibrated aPTT ranges.

The solution to the problem of maintaining an appropriate therapeutic range for monitoring unfractionated heparin requires a team effort and institutional support. Individual clinicians cannot do all this on their own.

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Eponyms and the Diagnosis of Aortic Regurgitation

TO THE EDITOR: As a “bedside” educator and clinician who frequently refers to eponyms, especially those associated with aortic regurgitation, I very much appreciated the review article by Babu and colleagues (1) on aortic regurgitation and the discrepancy between textbooks and the literature. It has caused me to reassess the value of eponyms on teaching rounds. I would, however, note an error with regard to pulse pressure in Babu and colleagues’ summary statement on the pathophysiologic characteristics of the Corrigan pulse, which was attributed to their reference 35 (2). Their statement read, “A recent investigation found that patients with aortic regurgitation had increased amplitude of the pulse, lower mean arterial pressure, and narrower pulse pressure than normal patients.” The last part of the statement, “narrower pulse pressure than normal patients,” disturbed me because chronic aortic regurgitation almost invariably leads to higher systolic pressure, lower diastolic pressure, and resultant wider pulse pressure. I read the original article by Warnes and colleagues and found that their original experimental observation was as follows: “the pulse pressure was also reduced with elevation (of the wrist). In normal subjects, pulse pressure decreased from an average of 70 mm Hg in the resting position to 61 mm Hg in the vertical position. In those with aortic regurgitation, it decreased from an average of 140 to 125 mm Hg” (2). Therefore, one must conclude that Warnes and colleagues’ study did not show a narrower pulse pressure in patients with aortic regurgitation, but rather confirmed such. It did show that the pulse pressure narrowed with elevation of the wrist but was still significantly wider than that of normal patients, that is, an average of 70 mm Hg in normal patients versus 140 mm Hg in patients with aortic regurgitation.

The authors’ consideration of this matter would be appreciated.

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TO THE EDITOR: We read with interest the article by Babu and colleagues (1) on the value of eponymous signs in the diagnosis of chronic aortic regurgitation. One must be aware of the pitfalls in characterizing physical signs as “poor performers” using evidence-based medicine approaches. Babu and colleagues attempted to validate data on the performance of 4 signs initially described between 1832 and 1909. The signs of Corrigan, Duroziez, Quincke, Traube, and de Musset were probably initially described in syphilis (2). They represent the same hemodynamic phenomenon—a large stroke volume and diastolic vascular collapse—and are often elicited in the same patient (2). The incidences of syphilis and rheumatic fever,

major causes of aortic regurgitation in the past, have since declined (3). Also, echocardiography has made early diagnosis of aortic regurgitation possible. Thus, physicians today are likely to see fewer patients with isolated or severe aortic regurgitation (in whom the eponymous signs are more likely to be elicited), in effect lowering the positive predictive value of these signs. Likelihood ratios, not merely the sensitivity and specificity, are superior indices in describing a physical sign’s diagnostic accuracy (4). For example, a finding with 95% specificity argues conclusively for disease only when the positive likelihood ratio is large. Babu and colleagues did not report likelihood ratios, raising issues about the quality of the evidence they unearthed.

There is concern about suboptimal physical examination skills in the United States, which have been shown to improve only slightly as medical personnel advance through training (5, 6). This being the case, the growing literature on “underperforming” physical signs has the makings of a self-fulfilling prophecy in a milieu that favors excessive use and abuse of medical technology, relegating physical examination to a state of neglected decline.

We agree with Babu and colleagues that physicians must examine the evidence for the usefulness of physical signs. However, debunking physical signs as lacking in evidence without paying attention to the methods used risks erroneously projecting physical examination methods as inept tools. This may impede acquisition of necessary bedside skills by trainee doctors and make them more dependent on technology, triggering a vicious cycle that will probably impair their ability to care for patients while immensely inflating health care costs.

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IN RESPONSE: We agree with Dr. Dermksian that the statement in question was imprecise and could have been more clearly written, as follows: “A recent investigation found that patients with aortic regurgitation had increased amplitude of the pulse, lower mean arterial pressure, and a greater narrowing of pulse pressure on wrist elevation than normal patients.” We are grateful to him for pointing out this

discrepancy and also for his kind comments about our paper as a whole.

Dr. Atkuri and colleagues question the lack of likelihood ratios in our review. It is true that likelihood ratios (which are calculated from sensitivity and specificity) can add valuable information to reports of diagnostic accuracy (1, 2). As we described at length, the vast majority of studies we found relating to the eponymous signs were of low quality and had imprecise estimates of accuracy. It was our view that reporting likelihood ratios generated by using sensitivity and specificity statistics from studies of such questionable quality would be misleading, and therefore we chose not to do so.

Dr. Atkuri and coworkers' assertion that we were "debunking" physical signs without being attentive to methodology is untenable. A major focus of our review was methodology assessment, and the overall process we followed is clearly consistent with widely accepted standards for systematic reviews (3). We also highlighted the point that the lack of evidence in the literature does not prove that these signs are without value. Indeed, we concluded by advocating for further work to clarify the role of these signs in current practice.

We are pleased to note that Dr. Atkuri and colleagues share the concerns originally expressed in our paper about the risks to medical education and practice of an inappropriate reliance on technology. Most of the eponymous signs of aortic regurgitation were identified over a century ago, when disease and treatments had a different flavor. The same can be said of many of the classical signs of physical diagnosis. We now live in an age where technology allows us to virtually dissect a patient in the hunt for disease. Unfortunately, this ability comes at a price, one that patients and society often cannot and should not have to pay. Judicious clinicians, skilled in history taking and physical examination, seek to protect their patients from unwarranted testing, procedures, and costs. Updating and enhancing the literature on bedside diagnosis can only aid their quest.

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Renal Insufficiency and Heart Failure Therapy

TO THE EDITOR: In his excellent review of the treatment of heart failure in patients with renal disease (1), Dr. Shlipak argued convincingly that angiotensin-converting enzyme (ACE) inhibitors are beneficial for this population. He concluded that they can even be used

with care in patients with severe renal insufficiency. Dr. Shlipak appropriately recommended starting with low doses. My concern is the particular agent he suggested: lisinopril. Lisinopril is a long-acting ACE inhibitor that is eliminated primarily by the kidneys. Therefore, in patients with renal dysfunction, its duration of action is extremely long, with a half-life of up to 50 hours (2). Clearly, the duration of undesirable (as well as desirable) effects of this drug (for example, impaired potassium elimination, hypotension, or worsening renal function) may be greatly prolonged in patients with impaired renal function. Because of this, I recommend that in this population ACE inhibitor therapy should be initiated with a short-acting agent, such as captopril, or one that is less dependent on renal elimination, such as fosinopril. Should an undesirable effect develop in a patient taking one of these agents, it will resolve more rapidly than if the patient were taking lisinopril (or another long-acting agent).

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IN RESPONSE: I greatly appreciate Dr. Spital's thoughtful comments on my review and regarding the choice of ACE inhibitor in patients with renal dysfunction. He is correct that fosinopril may be the ideal ACE inhibitor in this setting because it has the greatest hepatobiliary elimination (1, 2). Therefore, if discontinuation is required in response to an adverse event, fosinopril should have a more rapid elimination than other ACE inhibitors. However, because studies have not compared clinical outcomes among the ACE inhibitors, and fosinopril has not been evaluated in a heart failure survival trial, I cannot strongly endorse fosinopril as the optimal ACE inhibitor for patients with heart failure and renal insufficiency. Future studies comparing adverse events in this setting among the various ACE inhibitors would be useful contributions to the literature.

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Mixing Politics and Zen

TO THE EDITOR: Dr. Reinertsen's premise that we must give patients our best if we are to be deserving of their trust (1) is one that

I strongly support. I also agree that the medical community, as a whole, must cop to the charge of failing to fully implement any number of scientifically well-supported clinical guidelines. Dr. Reinertsen's other contentions, however, are primarily political perspectives that he attempts to bolster by wrapping them around patients.

The suggestion I find most troubling in this regard is that the main breach of trust between physicians and patients is that protocols are not widely employed. This proposition concerns me for 2 reasons. The first is that there are any number of reasons for eschewing guidelines (none of which Dr. Reinertsen mentioned) that would be professionally and ethically justified and would thereby, we hope, allow us to maintain patient trust. The second is that there is little evidence that patients as a group know or care about guideline implementation, let alone relate this to their physicians' trustworthiness. This supposition suits entities who bear the perceived cost of failure to implement guidelines or entities with other "axes to grind," however altruistic, who also wish to ally themselves with patients to achieve the political power necessary to accomplish their goals. I object to invoking the good name of patients in support of a cause that patients may or may not support in the manner and to the extent described.

I propose it is more likely that our autonomy is being restricted by the political economics of third-party payers and health care institutions than by patient mistrust generated through our failure to implement guidelines. It seems more likely that patients feel betrayed by physicians and organized medicine because we have abandoned them in their struggle to make sense of this brave new third-party-payer world. While we are having lunch with third-party payers, patients look on, noses pressed against the glass, hoping someone will remember they are there and will give them a voice. If that someone is a third-party payer, politician, or hospital administrator, then that will be the voice they echo. Personally, I would rather hear my patients echo the voice of Osler.

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Reference

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IN RESPONSE: The purpose of my short essay was to place the issue of "using the science we know, reliably," squarely on our professional agenda as physicians by connecting it directly to a strongly held professional value: autonomy. That using the science we know would improve patient outcomes and would also increase the time physicians desperately need to perform the artful custom-crafting of care that each patient requires resonates deeply with another core professional value, that of patient-centered altruism. These are the keywords for an internal professional debate, and perhaps for a much-needed revitalization of medicine. They were not intended to support any external political agenda.

The intensity of interest in these topics (for example, evidence-based medicine and safety) in the external political world is perhaps a symptom of our historic inability to address them within the profession itself. It is in our interests, and our patients' interests, to lead the conversation about how to address these problems, even if we have to confront some cherished values such as our attachment to individual physician autonomy.

I agree with Dr. Horner that patients neither know nor care about implementation of guidelines. What they (and those who claim to represent patients' interests in legislative, regulatory, and payer arenas) do seem to know and care about are unexplained geographic variation in supposedly scientific practices; disturbing safety risks from unreliable, poorly coordinated care processes; and the hurried nature of most physician visits, among other problems. Our professional failure to use guidelines and protocols is but one among many mechanisms through which these results have been produced. The key thrust of my essay was that we should take steps as a profession to address these larger problems, because if we don't do this for ourselves as physicians, someone else will do it to us (if they aren't doing so already). Guidelines aren't the core issue. Effective practice, safety, and the art of medicine—and how these matters are entwined with our attachment to individual physician autonomy—those are the core issues.

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The Cost of Medicine

TO THE EDITOR: On rare occasions, an article will go to the nidos of a problem without even directly addressing it in a formal fashion. "The Cost of Medicine" (1), by Shyam K. Bhat, is a perfect example. In a very personal and reflective manner, Dr. Bhat laid bare the ludicrous nature of medical care in the United States today. Driven by appropriate fear of litigation, physicians are coerced into spending vast sums of money pursuing diagnoses and treatments for the old-elderly, which add little to their longevity or quality of life but detract immeasurably from the resources that could be used to sustain other portions of our populace. The answer to this grotesque misappropriation of resources is to rationally and clearly articulate limits of care to the old-elderly. In the existing political climate, which features adding benefits to an already marginally sustainable Medicare system, this is admittedly a nonsolution. Although no politically viable resolution currently seems tenable, I hope that Dr. Bhat's thoughtful essay can raise our consciousness of this compelling dilemma.

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Reference

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Judging a Confession

TO THE EDITOR: The story told in "Confession" (1)—of an army doctor who destroys the medical record of a wife's miscarriage to

shield it from her cuckolded husband—was troubling. The incident seems to date from decades ago, when a perhaps more paternalistic brand of medicine existed. But it was still wrong.

The problem seems to have arisen because the doctor identified more with the husband than with the patient, his wife. But the doctor's obligation was still to her. Moral issues aside, the record could have become relevant, in case of complications or future gynecologic problems, for example. And, in fact, reasonable alternatives existed. He could have discussed the matter with the woman privately or offered to make her a separate confidential file.

The author stated, "It was, after all, her private matter." But he went on to say, "There were some things I didn't think [the husband] had to see." The contradiction inherent in those statements is why his unilateral decision to discard the medical record was wrong.

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Reference

1. Confession. *Ann Intern Med.* 2003;139:229-30. [PMID: 12899591]

IN RESPONSE: I am pleased that Dr. Feit read my story and took the time to write to the Editor, but she seems to have misunderstood where my sympathies lay. Perhaps the story is unclear.

"There were some things I didn't think Colonel Pennypacker had to see" follows from, rather than contradicts, "It was, after all, her private matter." To spell it out, since I did not (and still do not) know what he knew, I thought it would be destructive to the marriage, and a breach of her privacy, to provide him with incontrovertible evidence of her extramarital sexual activity.

Was it "paternalistic"? Paternalism is now viewed as bad, but *pater* means "father" and a fatherly concern is often viewed as a good thing, even today. Temporally, geographically, and spiritually, 1961, the Army, and Germany were "a long time ago . . . and in another country." My action was prompted by a kind concern for my patient's privacy. I thought I did the right thing. Perhaps I would have acted differently today. I regret that I am not blessed with Dr. Feit's certainty.

H. James Merchant, MD

Note: H. James Merchant, MD, is a pseudonym.

CLINICAL OBSERVATION

Montelukast-Induced Hepatitis

TO THE EDITOR: *Background:* Leukotriene modifiers, commonly used for persistent asthma, are usually well tolerated. Although reports have described elevated liver enzyme levels, hepatitis, and fulminant hepatic failure induced by zafirlukast (1–9) and zileuton (8), clinical trials of montelukast have revealed no liver toxicity (9). We

describe a patient who developed acute hepatitis while receiving montelukast. Discontinuing montelukast therapy led to normalization of all liver function test results except for persistently elevated aminotransferase levels.

Objective: To report what we believe to be the first case of montelukast-induced hepatitis, supplemented by a literature review of leukotriene modifier–induced hepatotoxicity.

Case Report: A 37-year-old woman presented with allergic rhinitis, nasal polyps, and aspirin-sensitive asthma that was inadequately controlled with high-dose inhaled corticosteroids, theophylline, long-acting inhaled β_2 -agonist, allergy immunotherapy, and occasional oral corticosteroid bursts. At presentation, theophylline therapy was stopped and montelukast therapy was started. Before montelukast therapy began, baseline liver function test results were normal. After 3 weeks of montelukast therapy, jaundice, severe pruritus, and nausea developed. The total bilirubin level was 181.3 $\mu\text{mol/L}$ (10.6 mg/dL) (direct, 114 $\mu\text{mol/L}$ [6.7 mg/dL]; indirect, 66.7 $\mu\text{mol/L}$ [3.9 mg/dL]), the alkaline phosphatase level was 231 IU/L (normal, 32 to 92 IU/L), the aspartate aminotransferase level was 123 IU/L (normal, 10 to 40 IU/L), the alanine aminotransferase level was 174 IU/L (normal, 10 to 40 IU/L), and the γ -glutamyltransferase level was 224 IU/L (normal, 5 to 24 IU/L). Results for chest radiography, antineutrophil cytoplasmic antibody and perinuclear antineutrophil cytoplasmic antibody, anti-smooth-muscle antibody, antinuclear antibody, α -fetoprotein, serum protein electrophoresis, and complete blood count (except for an elevated eosinophil count of 8%) were normal. Results of serologic testing for hepatitis A, B, and C viruses were negative. Testing for Epstein–Barr virus suggested past infection. The patient had no history of recent travel or blood transfusions and reported no use of alcohol, intravenous drugs, or cocaine. Montelukast therapy was stopped, and jaundice and pruritus resolved. Bilirubin, alkaline phosphatase, and γ -glutamyltransferase levels normalized over 5 months, but aminotransferase levels remained elevated (2 times the upper limit of normal). Liver biopsy done 14 months after montelukast therapy began revealed mild chronic inflammation in portal areas, without lobular inflammation or fibrosis.

Discussion: Hepatotoxicity has been reported with zileuton (8) and zafirlukast (1–7), but not with montelukast. Preclinical trials (8) revealed elevations in alanine aminotransferase levels of 1.9% in patients receiving zileuton compared with 0.2% in those receiving placebo; 1 reported case of hepatitis with jaundice resolved after therapy was discontinued. A 12-month open-label, randomized, multicenter postmarketing surveillance study of 2458 patients receiving zileuton plus usual care compared with 487 patients receiving usual care alone revealed statistically significantly higher aminotransferase levels (≥ 3 times the upper limit of normal) in the zileuton group (4.6%) than in the usual care group (1.1%) (8). These abnormalities resolved after therapy discontinuation. Most patients were asymptomatic and had elevated liver function test results within 3 months of therapy. No cases of chronic liver failure associated with zileuton have been reported (8).

Controlled clinical trials of zafirlukast have reported elevations of 1 or more liver function test results (7). Premarketing studies showed asymptomatic elevations of liver function test results (2 to 3 times normal) in 1.5% of 4058 patients receiving zafirlukast and 1.1% of 2032 patients receiving placebo (this was not statistically

significant) (2). Eight cases of hepatotoxicity have been reported in patients taking zafirlukast (1, 3–7), including mild to serious elevations in aminotransferase levels, hyperbilirubinemia, and liver failure requiring transplantation. Clinical trials of montelukast showed no significant difference in liver function abnormalities between the montelukast group and the placebo group (2.1% of 1955 montelukast recipients had an increased alanine aminotransferase level vs. 2.0% of 1180 placebo recipients, and 1.6% of montelukast recipients developed self-limited, transient increases in aspartate aminotransferase levels vs. 1.2% of placebo recipients) (9).

To our knowledge, ours is the first reported case of drug-induced hepatitis from montelukast. No pathophysiologic mechanism has been proven to explain our case or the others reported with similar drugs. Immunologically induced hypersensitivity reaction, hepatotoxic metabolites, drug reactions, or unexplained idiosyncratic responses may be involved (1).

Conclusion: Review of all reported cases of leukotriene modifier-induced hepatitis revealed that hepatic toxicity may develop within weeks or as late as 13 months after start of therapy. With the increasing use of these drugs, coupled with monitoring of liver function, more asymptomatic cases may become apparent. Serial liver function testing is recommended for patients receiving zileuton (8) but not for those receiving zafirlukast or montelukast (1, 2, 9). On the basis of our case and literature review, we recommend that liver function be tested within 4 weeks of initiation of therapy with any leukotriene modifier and that testing be repeated at 3, 6, and 12 months.

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Effects of Losartan in Hypertension without Vascular Disease

TO THE EDITOR: In their thorough study, Devereux and colleagues (1) stated, “In other placebo-controlled studies in hypertensive patients, β -blockade or β -blocker–based regimens reduced cardiovascular event rates by 15% to 45%.” They also stated, “the further 19% reduction of the primary end point by losartan in LIFE [Losartan Intervention for Endpoint Reduction in Hypertension] . . . represents incremental benefit beyond the established effects of β -blockade” (1). The authors of the LIFE study stated previously on several occasions that β -blockade in general, or atenolol specifically, reduced event rates in hypertensive patients. Unfortunately, these statements are incorrect—there are no conclusive data showing that atenolol or β -blocker–based therapy reduces heart attacks or strokes in uncomplicated hypertension (2). To the contrary, in the double-blind Dutch TIA [transient ischemic attack] Trial, atenolol, despite lowering blood pressure, did not reduce strokes better than placebo (3). A similar lack of efficacy of atenolol was demonstrated in the double-blind Tenormin after Stroke and TIA (TEST) study in hypertensive patients with established cerebrovascular disease (4). In the Medical Research Council study, neither heart attacks nor strokes were significantly reduced with atenolol when compared with placebo, in contrast to the reduction seen with a thiazide diuretic (5). Thus, 3 independent randomized trials attest to the inefficacy of atenolol-based therapy in reducing cardiovascular, or even more important, cerebrovascular events. In both the Swedish Trial in Old Patients with Hypertension-1 (STOP-1) study and the study by Coope and Warrender (7), which are said to support efficacy of β -blockers, more than two thirds of patients concomitantly received diuretics, and outcome results for the 2 drug classes were never analyzed separately. The wording quoted previously is unfortunate because it has made its way into the annotated prescribing information (8), which is widely distributed to practicing physicians. This document states, “the difference between COZAAR [losartan, Merck & Co., Horsham, Pennsylvania] and atenolol is compelling because there is evidence that atenolol is itself effective (vs. placebo) in reducing cardiovascular events, including stroke in hypertensive patients” (8). This statement is self-serving, untrue, and deceptive. The LIFE study is a landmark trial that has shown distinct benefits of losartan over atenolol. However, atenolol in uncomplicated hypertension has never been shown to reduce morbidity and mortality better than placebo.

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New Case of Acute Hepatitis Following the Consumption of Shou Wu Pian, a Chinese Herbal Product Derived from *Polygonum multiflorum*

TO THE EDITOR: *Background:* Shou Wu Pian (Shenzou-Chinese Medical Centre, Amsterdam, the Netherlands) is a herbal product constituted by powdered root of *Polygonum multiflorum* Thunb (Polygonaceae). It is used in China as a tonic and antiaging remedy. In western countries, it is commonly found in herb shops and grocery stores in Chinatowns.

Two patients with hepatotoxicity related to Shou Wu Pian have been described previously. The first one was a 31-year-old pregnant Chinese woman who had taken the product to treat hair loss (1). She had experienced a similar reaction with a preparation of the same herb about 2 years earlier. The second patient was a 46-year-old Chinese woman whose symptoms began 2 weeks after consumption of Shou Wu Pian to decrease the graying of her hair (2). Anthraquinones, the active ingredients of the product, were thought to cause the hepatotoxicity, but a lack of a purity control on the product limited ability to directly implicate anthraquinones.

Objective: To describe a patient with hepatotoxicity from Shou Wu Pian consumption.

Case Report: A 78-year-old Italian man presented with a 7-day history of jaundice, nausea, abdominal pain, yellow skin, and dark urine. His symptoms started 1 month after consumption of Shou Wu Pian tablets (at the recommended dosage) for a chronic prostatitis syndrome. Physical examination revealed moderate hepatomegaly. Laboratory results were as follows: bilirubin level, 25.5 mg/dL (181.15 μ mol/L); alanine aminotransferase level, 1276 U/L; aspartate aminotransferase level, 1020 U/L; γ -glutamyltranspeptidase level, 393 U/L; and alkaline phosphatase level, 409 U/L. All liver biochemical variables had been normal 6 months earlier. Differential leukocyte count was normal. Serologic and virologic markers for hepatitis A, B, C, and E viruses were negative. Blood samples were negative for hepatitis C virus RNA, hepatitis G virus RNA, cytomegalovirus, and Epstein–Barr virus. Autoimmune, metabolic, or other hepatotoxic causes were excluded. Ultrasonography and magnetic resonance imaging showed no liver or biliary tract damage. Clinical and laboratory measures improved rapidly after the patient discontinued using the herbal product.

Thin-layer chromatography of the product used by the patient excluded substitution of the herbal drug. The anthraquinones content (0.14% w/w), determined by a spectrophotometric method, was

in the range reported by Guigen and colleagues (3). Moreover, the product was microbiologically pure according to the European Pharmacopoeia (4), and the heavy metals content (As, Cd, Cr, Cu, Ni, Pb, Fe, Mn, Zn, Hg) was below the proposed maximum tolerable intake levels (5).

Discussion: In our patient, acute hepatitis occurred a few weeks after he started using Shou Wu Pian for chronic prostatitis, and other causes of hepatitis were excluded. We found no substitution or contamination of the product, which suggests that hepatotoxicity is related to the chemical components of the product and the manner of its use. The major constituents of *P. multiflorum* are polyphenols and anthraquinones. After intestinal metabolism, anthraquinones are transformed in anthrones. These highly reactive substances, when absorbed, can damage the liver (6–9).

Conclusion: Consumption of Shou Wu Pian, an herbal product containing anthraquinones, may cause hepatotoxicity.

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Potential Conflicts of Interest: None disclosed.

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