

Correspondence



Discontinuing Prophylaxis against *Pneumocystis carinii* Pneumonia

To the Editor: In his editorial (Jan. 18 issue)¹ accompanying two studies^{2,3} demonstrating the safety of discontinuing prophylaxis against *Pneumocystis carinii* pneumonia after an antiretroviral therapy–induced rise in the CD4 cell count, Girard writes that other independent risk factors for *P. carinii* pneumonia should be taken into account when one is making this decision. We present a case report that underscores the importance of this recommendation.

A 42-year-old man who was seropositive for the human immunodeficiency virus (HIV) was admitted to the hospital with shortness of breath, fever, and cough. Four years earlier, he had been treated successfully for non-Hodgkin's lymphoma, at which time his CD4 cell count was 7 cells per cubic millimeter. Four months before the current admission, he had stopped primary prophylaxis with trimethoprim–sulfamethoxazole since, as a consequence of antiretroviral therapy, his CD4 cell count had exceeded 200 per cubic millimeter for nearly two years.

At the time of admission, the CD4 cell count was 462 per cubic millimeter (36 percent) and the viral load was 955 copies of HIV RNA per milliliter. Bronchoscopy with biopsy was performed and revealed multiple, noncaseating granulomas; staining with methenamine silver showed scattered *P. carinii* organisms. Treatment with trimethoprim–sulfamethoxazole, without adjunctive corticosteroids, resulted in a gradual improvement in the patient's condition. Since then, prophylaxis against *P. carinii* pneumonia has been continued, and he remains well.

A likely cause of this patient's continued susceptibility to *P. carinii* pneumonia was the additive immunosuppression

associated with the prior non-Hodgkin's lymphoma and the residual immune defects induced by HIV infection — neither of which alone would have predisposed him to *P. carinii* pneumonia. Therefore, although this advice is not formally incorporated into current guidelines for the prevention of opportunistic infections,⁴ clinicians should be cautious about discontinuing prophylaxis against *P. carinii* pneumonia in HIV-infected patients who also have other causes of immunosuppression.

MELISSA A. BENDER, M.D.

PAUL E. SAX, M.D.

Brigham and Women's Hospital
Boston, MA 02115

1. Girard P-M. Discontinuing *Pneumocystis carinii* prophylaxis. *N Engl J Med* 2001;344:222-3.

2. Lopez Bernaldo de Quiros JC, Miro JM, Peña JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. *N Engl J Med* 2001;344:159-67.

3. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. *N Engl J Med* 2001;344:168-74.

4. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep* 1999;48(RR-10):4-7.

To the Editor: We report the cases of a 67-year-old woman and a 68-year-old woman with HIV infection who presented with *P. carinii* pneumonia after the discontinuation of primary prophylaxis after a good response to highly active antiretroviral therapy. Highly active antiretroviral therapy was introduced when the women's CD4 cell counts were 65 and 230 per cubic millimeter, respectively, and the viral load was 110,000 and 55,000 copies of HIV type 1 (HIV-1) RNA per milliliter, respectively. When prophylaxis with trimethoprim–sulfamethoxazole was discontinued, the patients had had fewer than 500 copies of HIV-1 RNA per milliliter and a CD4 cell count of more than 300 cells per cubic millimeter for 23 and 12 months, respectively. *P. carinii* pneumonia occurred three and five months, respectively, after the discontinuation of prophylaxis at a time when each patient had fewer than 500 copies of HIV-1 RNA per milliliter and

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a CD4 cell count of 356 and 345 per cubic millimeter, respectively.

The two patients had had CD4 cell counts of more than 300 per cubic millimeter and a plasma HIV-1 RNA level of less than 500 copies per milliliter for at least one year before prophylaxis was discontinued. The age of these patients might account for the occurrence of *P. carinii* pneumonia. A recent review has emphasized the importance of the age-related decline in T-cell function. In older subjects, the memory T cells include a spectrum of T cells with normal function and hypofunctioning T cells, in contrast to the findings in younger adult control subjects.¹ Old age may be a risk factor for the recurrence of *P. carinii* pneumonia after the discontinuation of prophylaxis.

GWENAËL LE MOAL, M.D.

JEAN-PHILIPPE BREUX, M.D.

FRANCE ROBLOT, M.D.

Centre Hospitalier Universitaire la Milétrie
86021 Poitiers CEDEX, France

1. Castle SC. Clinical relevance of age-related immune dysfunction. *Clin Infect Dis* 2000;31:578-85.

The authors reply:

To the Editor: Bender and Sax describe an HIV-infected patient in whom non-Hodgkin's lymphoma had been previously diagnosed and in whom *P. carinii* pneumonia developed four months after prophylaxis was discontinued, when the CD4 cell count was 462 per cubic millimeter. Non-Hodgkin's lymphomas, as well as other immunosuppressive disorders, including those associated with treatment with corticosteroids, are well-known predisposing factors for *P. carinii* pneumonia even in patients without HIV infection.¹ Prophylaxis against *P. carinii* pneumonia should be discontinued only with caution in HIV-infected patients who also have other immunologic disorders or who are receiving corticosteroids.

Le Moal et al. describe the development of *P. carinii* pneumonia after the discontinuation of primary prophylaxis in two HIV-infected patients whose CD4 cell counts exceeded 300 per cubic millimeter. The recommendations for the use of prophylaxis in patients with CD4 cell counts of less than 200 per cubic millimeter are based mainly on two studies conducted in the 1980s in patients who were not receiving prophylaxis or antiretroviral therapy.^{2,3} In the first study, performed at the Clinical Center of the National Institutes of Health, a new case of *P. carinii* pneumonia was diagnosed in 49 patients between January 1982 and April 1988. In only three of these patients did the pulmonary infection develop while the CD4 cell count exceeded 200 per cubic millimeter.² In the second study, whose participants were drawn from the Multicenter AIDS Cohort Study, less than 0.1 percent of patients who had CD4 cell counts of more than 200 per cubic millimeter had an episode of *P. carinii* pneumonia during the six months after entry, as compared with 8.4 percent of patients with CD4 cell counts of 200 or less per cubic millimeter.³

With the use of these data, the limit of 200 cells per cubic millimeter has been chosen as the level that best predicts the development of *P. carinii* pneumonia and as the threshold for the initiation of prophylaxis. In the same way, we

chose this figure as the limit for discontinuing prophylaxis. It is possible that a few patients will have *P. carinii* pneumonia after the discontinuation of prophylaxis while the CD4 cell count exceeds this limit. However, none of our patients had had *P. carinii* pneumonia after 378 person-years of follow-up. For this reason we consider the cases described by Le Moal et al. to represent an exception, and thus they do not lead us to change our previous recommendations.

JUAN C. LOPEZ BERNALDO DE QUIROS, M.D.

Hospital Universitario Gregorio Marañón
28007 Madrid, Spain

JOSE M. MIRO, M.D.

Hospital Clinic Universitari
08036 Barcelona, Spain

JOSE M. PEÑA, M.D.

Ciudad Sanitaria La Paz
28046 Madrid, Spain

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3. Phair J, Muñoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. *N Engl J Med* 1990;322:161-5.

To the Editor: Drs. Bender and Sax describe a well-documented case of primary *P. carinii* pneumonia in an HIV-infected patient with a high CD4 cell count induced by highly active antiretroviral therapy who had a history of non-Hodgkin's lymphoma associated with severe immunodeficiency. Although this case could be used as a basis to argue for continued use of prophylaxis against *P. carinii* pneumonia in particular clinical circumstances, as was done by Bender and Sax, we think that further documentation is required before a more general revision of the current recommendations is considered,¹ for several reasons.

First, even in patients with previously documented immunodeficiency severe enough to allow *P. carinii* pneumonia to develop, secondary prophylaxis can be discontinued safely in the event of immune reconstitution, as in our study. Second, sporadic cases of *P. carinii* pneumonia occur in patients with CD4 cell counts above the threshold used to consider both instituting² and discontinuing³ prophylaxis. Third, current recommendations already indicate that persons with a history of certain AIDS-defining illnesses (e.g., non-Hodgkin's lymphoma) who do not otherwise meet the criteria (i.e., by virtue of their CD4 cell count or by having a history of oral candidiasis) should be considered for prophylaxis.

The merit of the last recommendation is well illustrated by the case presented by Bender and Sax, which demonstrates that certain HIV-infected patients retain a relative immunodeficiency that is not reflected by the CD4 cell count. More refined measures of specific immunity will be needed to identify such patients; these patients may be the ones to gain further protection from immune-based interventions, such as those that include interleukin-2.⁴ Until such time, in applying the guidelines concerning prophylaxis for HIV-asso-

ciated opportunistic infections, clinicians should continue to use their best clinical judgment in balancing the remaining risk to their patients of the disease they wish to protect them from against the unnecessary cost and potential adverse effects of the prophylactic regimens they are considering discontinuing.

JENS LUNDGREN, M.D.
Hvidovre Hospital
DK-2650 Hvidovre, Denmark

PETER REISS, M.D., PH.D.
Academic Medical Center
NL-1100DD Amsterdam, the Netherlands

BRUNO LEDERGERBER, PH.D.
University Hospital
CD-8091 Zurich, Switzerland

- 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep* 1999;48(RR-10):1-6.
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Hematopoietic Reconstitution by Transplantation of Stem Cells from Bone Marrow or Blood

To the Editor: We have reported a significantly lower rate of relapse of hematologic cancers after allogeneic blood-cell transplantation than after bone marrow transplantation in a double-blind, randomized study.¹ We believe that the reduced rate was due to faster lymphocyte recovery after the transplantation of blood-cell allografts.²

On the basis of these observations, we started using blood cells exclusively for allografts from HLA-matched siblings a few years ago. The data reported by Bensinger et al. (Jan. 18 issue)³ reinforce our position and suggest that a change in general clinical practice is warranted.

SEEMA SINGHAL, M.D.
Northwestern University Medical School
Chicago, IL 60611

RAY POWLES, M.D.
Royal Marsden Hospital
Sutton SM2 5PT, United Kingdom

JAYESH MEHTA, M.D.
Northwestern University Medical School
Chicago, IL 60611

- Powles R, Mehta J, Kulkarni S, et al. Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: a randomised trial. *Lancet* 2000;355:1231-7.

- Powles R, Singhal S, Treleaven J, Kulkarni S, Horton C, Mehta J. Identification of patients who may benefit from prophylactic immunotherapy after bone marrow transplantation for acute myeloid leukemia on the basis of lymphocyte recovery early after transplantation. *Blood* 1998;91:3481-6.
- Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. *N Engl J Med* 2001;344:175-81.

To the Editor: On the basis of their study of the transplantation of allogeneic bone marrow as compared with peripheral-blood stem cells, Bensinger et al. conclude that the risk of graft-versus-host disease (GVHD) is not increased by the use of peripheral-blood stem cells. However, the 95 percent confidence intervals for the hazard ratios for acute and chronic GVHD were reported to be 0.81 to 1.81 and 0.71 to 1.90, respectively, for the peripheral-blood-cell group as compared with the bone marrow group. Therefore, the data do not exclude the possibility that the use of allogeneic peripheral-blood stem cells nearly doubles the risk of both acute and chronic GVHD.

THOMAS R. KLUMPP, M.D.
Fox Chase-Temple University Bone Marrow Transplant Program
Philadelphia, PA 19111

To the Editor: Bensinger et al. do not distinguish between limited and extensive chronic GVHD. This distinction is important because extensive, chronic GVHD has an adverse clinical course.¹ The cumulative incidence of chronic GVHD needs to be reported separately for limited and extensive disease in order for readers to have a better understanding of the data.

HAKAN GOKER, M.D.
Hacettepe University Hospital
06100 Ankara, Turkey

- Sullivan KM. Graft-versus-host disease. In: Thomas ED, Blume KG, Forman SJ, eds. *Hematopoietic cell transplantation*. Malden, Mass.: Blackwell Science, 1999:515-36.

The authors reply:

To the Editor: Our comparison of allogeneic peripheral-blood stem cells with marrow demonstrated improved disease-free survival and suggested a benefit in terms of overall survival in the group that received peripheral-blood stem cells. A subgroup analysis, however, indicated that this benefit was greater in the group of patients with more advanced hematologic cancers than in the group with less advanced cancers, because there were fewer transplant-related deaths and relapses in the former group. Our study was not prospectively designed to detect these differences in survival, so caution must be used in interpreting these results.

Since there was a trend toward a higher incidence of GVHD in the group that received peripheral-blood stem cells, further studies need to be performed to determine whether the benefits of peripheral-blood stem cells outweigh the potentially greater risk of GVHD. Thus, we do not fully agree with Singhal et al. that peripheral blood should be universally used as the preferred source of stem cells in all patients undergoing allogeneic transplantation for hematologic cancers. The trial suggested a trend toward a higher

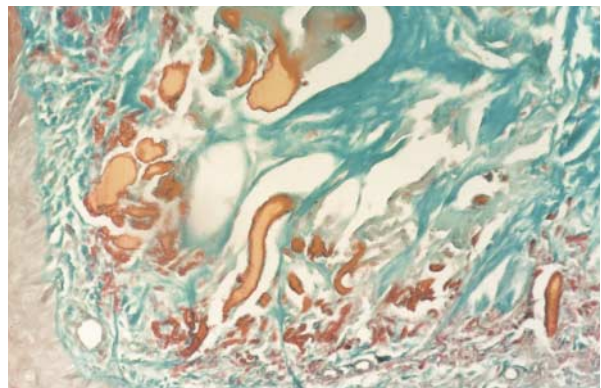
incidence of GVHD in the peripheral-blood–cell group, but with wide 95 percent confidence intervals; we agree with Klumpp that it is possible and perhaps even likely that the use of peripheral-blood stem cells is associated with some increase in the risk of GVHD. We reported only on patients in whom extensive, chronic GVHD developed, since limited, chronic GVHD does not require treatment and is not associated with an adverse clinical outcome.

WILLIAM I. BENSINGER, M.D.
 BARRY STORER, PH.D.
 FREDERICK R. APPELBAUM, M.D.
 Fred Hutchinson Cancer Research Center
 Seattle, WA 98109

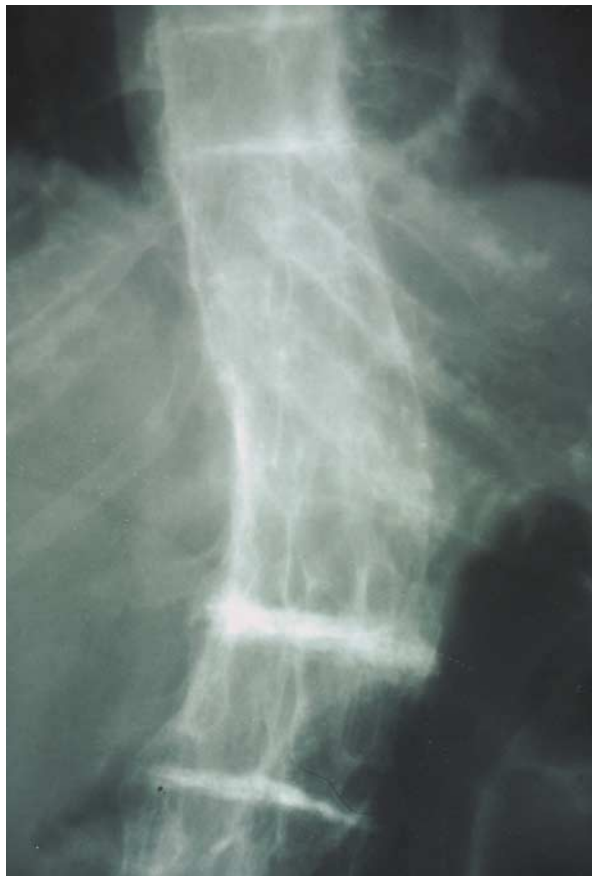
Medical Mystery: The Answer

The medical mystery in the April 5 issue¹ involved an 82-year-old woman with alkaptonuric ochronosis. Alkaptonuria is a rare inherited deficiency of homogentisic acid oxidase, leading to the accumulation of homogentisic acid in various tissues. Ochronosis refers to the characteristic cutaneous and cartilaginous blue-black deposits. This patient had no particular medical history other than a unilateral hip

replacement. The diagnosis of alkaptonuric ochronosis was only established when the patient was 82 years old, at which time she was referred to a dermatologist. The main features of the disorder are cervical arthropathy with intervertebral calcification (Fig. 1A), kyphosis, and ankylosis; yellow-brown dermal deposits of polymerized homogentisic acid (Fig. 1B); cutaneous and subungual ochronosis of the thumb (Fig. 1C);



B



A



C

Figure 1. A Woman with Alkaptonuric Ochronosis.



D



E

urine that turns black after six hours because of oxidation (Fig. 1D); and brown-black pigmentation of the face (Fig. 1E). This patient also had focal dark pigmentation of the sclera. The level of serum β -melanocyte-stimulating hormone was increased by a factor of six as compared with values in controls; there was no other sign of endocrine dysregulation.

ARJEN F. NIKKELS, M.D., PH.D.
GÉRALD E. PIÉRARD, M.D., PH.D.
University of Liège
B-4000 Liège, Belgium

1. Nikkels AF, Piérard GE. A medical mystery. *N Engl J Med* 2001;344:1057.

Editor's note: We received 755 responses to the medical mystery. About 43 percent of the respondents said that the woman had alkaptonuric ochronosis. The next most common explanation, suggested by 23 percent of respondents, was that the patient had melanoma. Another common answer, suggested by 22 percent of respondents, was porphyria or porphyria cutanea tarda. Other responses included paroxysmal nocturnal hemoglobinuria and ingestion of arsenic or silver.

Asthma and the Hygiene Hypothesis

To the Editor: With reference to the review article by Busse and Lemanske on asthma (Feb. 1 issue),¹ we would like to raise the following points. Figure 4 fails to make it clear that several serious diseases, including type 1 diabetes,² are mediated by a type 1 helper-T-cell (Th1) response; for this reason, any immunotherapy aimed at manipulating the helper-T-cell response in favor of a Th1 response may have unwanted effects, such as the development of Th1-mediated diseases. Type 1 diabetes, like atopy, commonly presents early in life, is also rising in incidence in Europe, and is most common in first-born children and children whose families are well off.³⁻⁵ Thus, the epidemiologic features of type 1 diabetes have much in common with those of atopic disease. This evidence contradicts the hypothesis that a change in the balance between Th1 and type 2 helper-T-cell responses is occurring in children.

WENDY J.A. ANDERSON, M.R.C.P.
Antrim Hospital
Antrim BT41 2RL, Northern Ireland

LORNA WATSON, M.R.C.P.
Lothian Health
Edinburgh EH8 6RE, Scotland

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The authors reply:

To the Editor: We greatly appreciate the comments of Anderson and Watson regarding the "hygiene hypothesis" and the parallel increases in incidence noted for atopic asthma and type 1 diabetes. The contribution of the hygiene hypothesis to our understanding of allergic diseases and asthma continues to be both supported and challenged by epidemiologic data and in vitro observations. The figure depicting this hypothesis in our review article was purposely drawn to emphasize the importance of a balance between Th1 and Th2 cytokine responses. We agree entirely that early interventions aimed at stimulating the immune response to be dominated by Th1 cells might create more problems than they would solve.

With regard to type 1 diabetes in children, recent studies have shown that preschool day-care attendance, a proxy measure for infectious disease in childhood, is inversely associated with the incidence of type 1 diabetes.¹ Similar correlations have been noted for childhood asthma.² These parallel trends do not necessarily contradict the hypothesis that a change in the balance between Th1 and Th2 responses is occurring in children. The explanation for these findings according to the hygiene hypothesis would be that frequent

childhood infections may stimulate Th1 responses in a way that corrects any underlying imbalance between Th1 and Th2 in children destined for atopy, without “pushing” the immune system too far in the opposite direction, thereby leading to the preferential Th1 response of diabetes.^{3,4} It will require further study to resolve this debate, but the hygiene hypothesis provides a new perspective on mechanisms of asthma and allergic diseases, as well as potential treatments.

ROBERT F. LEMANSKE, JR., M.D.
WILLIAM W. BUSSE, M.D.

University of Wisconsin—Madison Medical School
Madison, WI 53792

1. EURODIAB Substudy 2 Study Group. Infections and vaccinations as risk factors for childhood type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. *Diabetologia* 2000;43:47-53.
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Low Back Pain

To the Editor: The informative review of the evaluation and treatment of low back pain in primary care by Deyo and Weinstein (Feb. 1 issue)¹ bypassed electrodiagnostic testing (by electromyography), one of the most common diagnostic procedures. Electrodiagnostic testing, which has been available for more than 50 years, has been largely swept aside in the rush for more visually interesting imaging studies. But long before the Agency for Health Care Policy and Research (AHCPR)² existed, a large study that used surgical findings as a standard established that electromyography was better than the physical examination and equal to or better than myelography in detecting disk herniations.³ Myelography has not been surpassed in sensitivity; it has only been replaced. Modern research has refined electromyographic techniques and thus has better defined their sensitivity and specificity.^{4,5}

Since, unlike magnetic resonance imaging (MRI), electromyography of the low back has rare and well-defined false positives and since it has a sensitivity similar to that of MRI, has been associated with no clinically significant complications for half a century, and has perhaps half the cost of MRI, it is reasonable for primary care clinicians not to order an advanced imaging study unless the results of electromyography are positive. Electromyography might miss the rare spinal tumor that is not detected by plain-film radiography and that does not affect the nerve root, but it detects plexus lesions, nerve compressions, and types of polyneuropathy that commonly mimic radiculopathy. Spinal imaging strikes out here.

ANDREW J. HAIG, M.D.
AGNES WALLBOM, M.D.

University of Michigan
Ann Arbor, MI 48108

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To the Editor: Deyo and Weinstein tend to minimize the value of chiropractic adjustments. In addition, I disagree with the authors' recommendation that patients should wait three weeks before being treated. In the real world, patients want to get back to work and to functioning as usual in much less time than three weeks. Most studies have shown that early motion, which chiropractic adjustment helps to achieve, is the best way to restore normal function. There is no good reason to wait, when earlier treatment leads to a more positive outcome for a patient. Time is money, and since studies have shown that chiropractic care can restore function in patients with acute, uncomplicated back pain, that care should begin immediately. There have been few studies of chiropractic care for sciatica. However, after 15 years of practice, I can say that it is effective in reducing pain and restoring function in patients with sciatica. Finally, chiropractors believe that MRI for back pain is overused. Unless a patient has obvious neurologic signs that would necessitate immediate back surgery and if other pathologic processes have been ruled out by thorough history taking and examination, there is no good reason to order an MRI. The best course of action is to start conservative care to restore normal structure and function.

PETER G. HILL, D.C.

Boston Copley Square Chiropractic
Boston, MA 02116

The authors reply:

To the Editor: Haig and Wallbom discuss electrophysiological testing. Outside of large urban areas, this important diagnostic technique is less available than imaging tests; its diagnostic accuracy remains less certain than that of modern imaging studies. The optimal sequence of tests remains unclear. We agree with the evidence-based guidelines sponsored by the AHCPR, which concluded that electrophysiological testing is unnecessary if a diagnosis of radiculopathy is obvious and specific on clinical observation or if the patient has acute low back pain alone. We also agree that needle electromyography may be useful in assessing nerve-root dysfunction in patients with leg pain that lasts longer than four weeks, if the presence of nerve-root dysfunction is uncertain on physical examination. We agree that sensory evoked potentials may be useful in assessing possible spinal stenosis or myelopathy.¹ As with most other diagnostic tests, the guideline panel considered that there was only limited, research-based evidence in support of these conclusions. If a patient has clear-cut radiculopathy, imaging tests are valuable both to confirm its cause and to plan surgery, since the anatomical features must be delineated — a task that electrophysiological testing cannot perform.

Dr. Hill believes that we have minimized the value of spinal manipulation. However, randomized clinical trials have

failed to show that spinal manipulation has a significant advantage over conventional physical therapy or medications with regard to absenteeism from work, days of limited activity, or days of bed rest.^{2,3} Shekelle and colleagues⁴ concluded that there was insufficient evidence to demonstrate the efficacy of spinal manipulation among patients with radiculopathy, a conclusion echoed by the AHCPR guidelines.¹ We are unaware of newer studies that would reverse that conclusion. However, we certainly agree that MRI for back pain is overused.

RICHARD A. DEYO, M.D., M.P.H.
University of Washington
Seattle, WA 98195

JAMES N. WEINSTEIN, D.O.
Dartmouth Medical School
Hanover, NH 03755

1. Bigos S, Bowyer O, Braen G, et al. Acute low back pain problems in adults. Clinical practice guideline. No. 14. Washington, D.C.: Government Printing Office, December 1994. (AHCPR publication no. 95-0642.)
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Lamivudine in the Treatment of Polyarteritis Nodosa Associated with Acute Hepatitis B

To the Editor: There is no consensus on the optimal treatment of polyarteritis nodosa associated with hepatitis B virus (HBV) infection. The potential risk of accelerating viral replication complicates the use of corticosteroids and cytotoxic agents. Benefit from the combined use of plasmapheresis, corticosteroids, and antiviral agents has been reported previously.¹ We describe a patient with HBV-associated polyarteritis nodosa who was treated with this approach.

A 39-year-old woman was transferred to our hospital in December 1999 for the treatment of vasculitis. In September 1999, she had presented with a diffuse pruritic rash, polyarticular symmetric arthritis, abdominal pain, and constitutional symptoms. Because the results of her liver-function tests were abnormal (Table 1), she underwent cholecystectomy for suspected acute cholecystitis. Histopathological examination of the gallbladder revealed vasculitis involving medium-sized arteries that was consistent with the presence of polyarteritis nodosa. The patient was treated with oral prednisone (1 mg per kilogram of body weight) until left footdrop developed, and she was then transferred to our hospital.

On admission to our hospital, the patient had decreased sensation in the distal parts of her lower extremities and left footdrop. Findings on laboratory examinations were consistent with the presence of acute HBV infection (Table 1).

TABLE 1. RESULTS OF LABORATORY TESTS.*

VARIABLE	OCT.–NOV. 1999†	DEC. 1999	FEB. 2000	OCT. 2000
Aspartate aminotransferase — U/liter	60	21	65	16
Normal range‡	0–60	2–35	2–35	2–35
Alanine aminotransferase — U/liter	109	17	52	20
Normal range‡	0–63	0–45	0–45	0–45
Hepatitis B surface antigen	Positive	Positive	Positive	Negative
Antibody against hepatitis B surface antigen	NA	Negative	Negative	Positive
Hepatitis B early antigen	NA	Positive	Negative	Negative
Antibody against hepatitis B early antigen	NA	Negative	Negative	Positive
Antibody (IgM plus IgG) against hepatitis B core antigen	NA	Positive	Positive	Positive
Antibody (IgM) against hepatitis B core antigen	NA	Positive	Negative	Indeterminate
Hepatitis B virus DNA§	Positive (1.7 billion copies/ml)	Positive (300,000 copies/ml)	Positive (150,000 copies/ml)	Negative (<0.01 pg/ml)
Erythrocyte sedimentation rate — mm/hr	44	33	1	0
Normal range	0–20	0–20	0–20	0–20
C-reactive protein — mg/dl	NA	1.6	0.5	<0.1
Normal range		0–0.6	0–0.6	0–0.6
Cryoglobulins, antineutrophil cytoplasmic antibody, antinuclear antibody, rheumatoid factor	Negative	Negative	Negative	NA

*NA denotes not available.

†During this period the patient also had an elevated alkaline phosphatase level (268 U per liter; normal range, 50 to 180) and direct bilirubin level (0.5 mg per deciliter; normal range, 0 to 0.4).

‡The normal range varies from laboratory to laboratory.

§The levels were measured with use of a polymerase-chain-reaction assay for which the reference value is less than 0.01 pg per milliliter and 1 pg equals 150,000 copies.

Electromyography revealed mononeuritis multiplex in the lower extremities. The patient began to receive plasmapheresis three times per week, 100 mg of lamivudine per day, and prednisone, which was slowly tapered. In February 2000, she had a transient elevation in her liver aminotransferase levels (Table 1), consistent with the occurrence of hepatitis B early antigen seroconversion.² Since her condition was clinically stable, the frequency of plasmapheresis was decreased, and it was then discontinued four weeks later. From February 2000 to September 2000, she continued to receive low-dose prednisone (<10 mg per day, which was tapered). Treatment with lamivudine (100 mg per day) was continued, and in October 2000 the patient's HBV infection was serologically resolved while her condition was clinically stable (Table 1).

Lamivudine has been shown in a randomized, prospective study to be effective for the treatment of chronic HBV infection,³ and a case report suggests it may also be effective for acute HBV infection.⁴ In our patient, who had life-threatening vasculitis associated with acute HBV infection, corticosteroids and plasmapheresis were used to control the acute manifestations of the vasculitis. Lamivudine, a nucleoside analogue, was used to suppress viral replication and the integration of viral DNA into the hepatocytes. With the use

of this regimen and without any cytotoxic drugs, the patient had no further complications of vasculitis. In addition, effective immunity against HBV developed and the viral infection was cleared. The use of antiviral agents for the treatment of vasculitis associated with HBV infection warrants further study.

SAMARDEEP GUPTA, M.D.

CYRUS PIRAKA, M.D.

MICHELE JAFFE, M.D.

University of Michigan
Ann Arbor, MI 48109-0358

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