CORRESPONDENCE

Cutaneous Miliary Tuberculosis in the AIDS Era

SIR—A recent review of cutaneous miliary tuberculosis in the AIDS era [1] emphasized the importance of having a high index of suspicion for this condition in HIV-positive patients with skin lesions and advanced immunodeficiency. However, the authors were able to identify only five such cases in the literature, in addition to the case they reported. In a prospective study, ongoing since October 1994, we have identified only one case of cutaneous tuberculosis among nearly 400 patients with biopsy-confirmed or culture-confirmed tuberculosis; 47% of these patients were HIV-positive. In view of the rarity of cutaneous tuberculosis and the fact that skin biopsy is not usually necessary to make a diagnosis of disseminated tuberculosis, we believe that skin biopsy should be performed primarily to exclude other causes of skin conditions in patients with advanced HIV disease, as the following case report illustrates.

A 48-year-old HIV-infected heterosexual man who had no history of use of illegal substances but who had received treatment for two previous episodes of tuberculosis presented with chronic pathogen-negative diarrhea, colicky abdominal pain, weight loss, fever, and dark maculopapular lesions on his hands. The CD4 cell count was 3×10^6/L, and a chest roentgenogram showed fibrocystic changes in the right upper lobe and possible mediastinal adenopathy.

An ultrasonogram of the abdomen showed adenopathy in the epigastrium. No sputum was obtained, but a blood culture for mycobacteria with use of the radiometric system (BACTEC; Becton Dickinson, Sparks, MD) was negative. Examination of a duodenal biopsy specimen obtained by endoscopy revealed cryptosporidia. One of the skin lesions was biopsied to exclude Kaposi's sarcoma, and the specimen was sent for a routine mycobacterial culture. A diagnosis of disseminated tuberculosis was made on the basis of the patient's clinical presentation and the presence of adenopathy; he was discharged and received antituberculous therapy as an outpatient. *Mycobacterium tuberculosis* was cultured from the skin biopsy specimen 2 weeks later.

While cutaneous manifestations are common in the HIV-positive population in Cape Town, South Africa, few lesions are biopsied, so we may have missed other cases of cutaneous miliary tuberculosis. However, as was true for our patient, the diagnosis of disseminated tuberculosis is usually evident on clinical grounds; cultures are performed to confirm the diagnosis and to exclude drug resistance. Although the positive culture of the skin biopsy specimen confirmed the diagnosis for our patient, the result was unexpected; if the result had been negative, treatment would have been continued. Similarly, in the case reported by Libraty and Byrd, the patient's risk factors and presentation, apart from the short history of symptoms, were suggestive of disseminated tuberculosis. Further, the positive culture result for the skin biopsy specimen became available after acid-fast bacilli had been seen on examination of bronchoalveolar lavage fluid and bone marrow biopsy specimens.

In conclusion, our own experience and that of other investigators [2] is that an HIV-related diagnosis of extrapulmonary tuberculosis can usually be made without performing a skin biopsy. Notwithstanding the findings in two recent reports [3, 4], in most cases it would be more appropriate to use procedures with documented high diagnostic yield, e.g., lymph node biopsy [5], than to perform a skin biopsy. Isolated instances of positive skin biopsy specimens must be weighed against the large number of negative skin biopsy specimens if the recommendations of Libraty and Byrd are followed.

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Cutaneous Miliary Tuberculosis in a Patient Infected with Human Immunodeficiency Virus

SIR—Libraty and Byrd [1] recently described a case of cutaneous miliary tuberculosis in an HIV-positive patient and reviewed the published cases of cutaneous miliary tuberculosis among patients with AIDS [1]. The authors claimed that only six cases (including their own case) have been reported so far. However, they did not mention two cases of cutaneous miliary tuberculosis due to multidrug-resistant *Mycobacterium tuberculosis* in patients with AIDS, which we described previously [2]. Since the publication of our report in October 1995, we have diagnosed a further case of cutaneous miliary tuberculosis, also known as tuberculosis cutis miliaris disseminata (TCMD).

A 38-year-old man with an 8-year history of intravenous drug abuse who was receiving methadone maintenance therapy presented with a 1-week history of high fever (temperature, 40°C), chills, a nonproductive cough, epigastric pain, and dysphagia. He had been aware of his HIV seropositivity for 3 months. He was not receiving any antiretroviral therapy or prophylaxis for *Pneumocystis carinii* pneumonia.

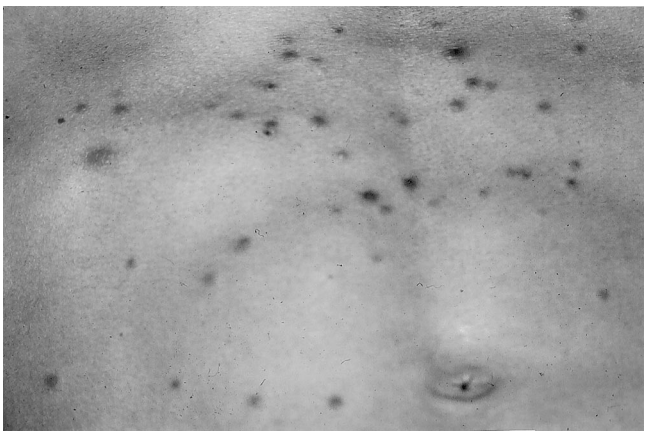

Figure 1. Maculopapular skin eruption in a patient with cutaneous miliary tuberculosis.

Laboratory examinations at the time of admission showed the following values: WBCs, 2,020/mm^3 (72% neutrophils, 24% lymphocytes, and 4% monocytes); hemoglobin, 10 g/dL; RBCs, 5.0×10^{12}/L (mean corpuscular volume, 63 fL); platelets, 46,000/mm^3; CD4 cell count, 2/mm^3; serum urea nitrogen, 112 mg/dL; creatinine, 1.4 mg/dL; aspartate aminotransferase, 777 U/L; alanine aminotransferase, 228 U/L, with a normal bilirubin value; lactate dehydrogenase, 6,520 U/L; and creatine phosphokinase, 1,754 U/L. Findings on a chest radiograph were normal. An ultrasonogram of the abdomen showed hepatomegaly with multiple small hypoechogenic lesions and four solid areas in the right lobe (largest area, 2 cm in diameter) and splenomegaly with multiple pinpoint hyperechogenic lesions. Esophagogastroduodenoscopy revealed a large ulcer (5×6 cm) without protruding edges in the last portion of the esophagus. Multiple blood cultures were performed.

On the second hospital day, the patient developed a diffuse maculopapular skin eruption (figure 1) involving the trunk, abdomen, arms, and legs. He complained of myalgias and severe dysphagia and was confused. A serum cryptococcal antigen test was negative. A skin biopsy was performed, and because of the similarity between the cutaneous lesions and those in the cases of TCMD that we had already seen, we decided to start antituberculous therapy (iv rifampin, isoniazid, and ethambutol at standard doses) plus iv therapy with amikacin (1 g/d). An ophthalmologic evaluation showed yellow choroidal lesions in the right eye that were also compatible with a diagnosis of miliary tuberculosis. Five days later, histological examination of the skin biopsy specimen showed focal areas of necrosis containing multiple acid-fast bacilli. *M. tuberculosis* subsequently grew from cultures of blood and cultures of the skin biopsy specimen. The isolated strain was resistant to isoniazid.

The clinical condition of the patient rapidly improved. His fever disappeared 5 days after the antituberculous therapy was begun, and liver-function test results returned to normal 7 days later. The cutaneous lesions completely disappeared 2 weeks later, and an abdominal ultrasonogram obtained 5 weeks after the first one was obtained showed nearly complete regression of the lesions. The patient was discharged in good health 6 weeks after admission.

Cutaneous miliary tuberculosis is still an uncommon disease, even in the setting of HIV infection, but in recent years the incidence of this form of tuberculosis seems to be increasing. Therefore, when multiple papulovesicular skin lesions are present in a severely ill patient, this condition should be clinically suspected. We agree with Libraty and Byrd that the absence of a miliary pattern on a chest radiograph should not lead to exclusion of the diagnosis of TCMD, since none of our three patients presented with this radiographic picture. The finding of typical choroidal tubercles on ophthalmologic examination could be helpful in supporting the diagnosis of TCMD before the results of histological and microbiological examination of a skin biopsy specimen are available.

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Reply

SIR—Antinori et al. [1] note that they have reported two cases of cutaneous miliary tuberculosis in patients with AIDS that were not included in our review [2]. Furthermore, they present another case that adds to the growing literature on tuberculosis cutis miliaris disseminata in patients with AIDS. We apologize for our oversight and concur with their observations and conclusions.

Hudson et al. point out that they have observed only one case of cutaneous tuberculosis in almost 400 HIV-seropositive patients with tuberculosis. The rarity of cutaneous miliary tuberculosis in HIV-seronegative adults has been well established over the past century. Although cutaneous miliary tuberculosis is obviously not a common entity, its prevalence among HIV-seropositive patients would appear to be higher than among HIV-seronegative patients, as evidenced by the continuing case reports submitted by us [2], Franca et al. [3], Oliva et al. [4], and Antinori et al. [1]. Even a prevalence of 0.5% among HIV-seropositive individuals with tuberculosis would bear out this statement. As mentioned in our article, the occurrence of disseminated cutaneous tuberculosis, like other extrapulmonary manifestations of tuberculosis, simply reflects the stage of HIV disease and consequent cell-mediated immune defects.

We agree that biopsy of cutaneous lesions is not generally the crux of the diagnosis of disseminated tuberculosis in HIV-seropositive patients; when disseminated tuberculosis is suspected, empiri-

cal therapy may be warranted. However, even when tuberculosis is suspected, a primary goal should be to obtain adequate clinical specimens for culture and susceptibility testing of *Mycobacterium tuberculosis* isolates. This is especially true in the HIV era, given the ability of *M. tuberculosis* to rapidly spread in the population of HIV-infected patients and the concomitant potential for outbreaks of drug-resistant tuberculosis.

Contrary to the assertion of Hudson et al. that skin biopsy is of little value in the treatment of disseminated tuberculosis, the case that they describe precisely illustrates the potential value of skin biopsy. What if their patient's condition had not improved with therapy and/or the organism was drug-resistant? Without the results of culture of the specimen, Hudson et al. would have had to have administered empirical tuberculosis therapy for an organism of unknown drug susceptibility. In fact, Antinori et al. [1] described multidrug-resistant tuberculosis, and skin biopsy culture in another case revealed an isoniazid-resistant organism.

We thus reiterate our position that, in selected cases, biopsy of papular lesions can provide a simple and easily accessible method for diagnostic confirmation and culture when disseminated tuberculosis is suspected. As demonstrated in our review, if papular lesions are due to disseminated or miliary tuberculosis, the acid-fast smear should be positive. Biopsy of papular lesions provides another tool in the diagnostic armamentarium for HIV-seropositive patients with suspected disseminated tuberculosis.

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Cerebrospinal Fluid–Shunt Infection Due to *Corynebacterium striatum*

SIR—We read with interest the report by Weiss et al. [1] concerning *Corynebacterium striatum* meningitis. We report three cases of CSF-shunt infections due to *C. striatum;* all cases occurred in children.

A 20-month-old male underwent removal of a ventriculoperitoneal (VP) shunt because of presumed infection. Cultures of CSF and cultures of the shunt itself were sterile, and a new shunt was inserted after 5 days. After insertion of the shunt, the infant was febrile and irritable, and cultures of CSF obtained from the shunt yielded *C. striatum.* The shunt was removed and cultures of CSF obtained intraoperatively as well as culture of the VP shunt yielded *C. striatum.* A new VP shunt was inserted after 10 days of treatment with vancomycin administered both intravenously and intrathecally.

A 13-month-old female with Joubert's syndrome was admitted to our institution because of ascites; her VP shunt was removed, and an external ventricular drain (EVD) was inserted. Cultures of CSF, VP-shunt tubing, and peritoneal fluid were sterile. A new VP shunt was inserted 13 days later, and culture of the EVD tip yielded *Moraxella catarrhalis* and *C. striatum.* Over the next 3 days, the infant was intermittently pyrexial, and cultures of two CSF samples obtained from the shunt yielded *M. catarrhalis* and *C. striatum.* She was treated with chloramphenicol and became afebrile; however, two subsequent CSF cultures yielded pure growth of *C. striatum.* Consequently, the shunt was removed, and cultures of CSF obtained intraoperatively, as well as cultures of the shunt tip, yielded *C. striatum.* A new shunt was inserted after 2 weeks of treatment with chloramphenicol.

A 6-year-old female was treated for *Staphylococcus aureus* infection of her VP shunt. When the new shunt was inserted, a culture of the removed EVD tip yielded *C. striatum,* as did cultures of two CSF samples obtained from the shunt on subsequent days. The child was drowsy and intermittently pyrexial, and treatment with chloramphenicol was instituted. The shunt was removed, and cultures of the ventricular and abdominal ends yielded *C. striatum.* During the next 2 weeks, two additional operations were required to replace nonfunctioning EVDs. Cultures of CSF samples obtained after the second procedure yielded *S. aureus,* and the treatment regimen was changed to iv flucloxacillin. The patient was afebrile; however, cultures of CSF samples yielded *S. aureus* and *C. striatum.* The child was then treated with iv and intrathecal vancomycin. Cultures of CSF remained sterile over the next 2 weeks, and a new VP shunt was inserted.

The isolates were identified by use of the API-Coryne System (bioMérieux, Marcy-l'Etoile, France), and all isolates had the same profile. All three isolates were resistant to penicillin and erythromycin and susceptible to cephradine, chloramphenicol, and vancomycin on disk-diffusion testing. Susceptibility to tetracycline and rifampin varied between the isolates.

Corynebacterium species are responsible for a small proportion of VP-shunt infections; however *C. striatum* has not been implicated to date. To our knowledge, there have been no previous reports of invasive disease due to *C. striatum* in children. A number of reported *C. striatum* infections have been associated with prosthetic devices. Weiss et al. [1] describe a case with a CSF drain in situ, and in their literature review, they cite reports of central-venous-catheter infections, pacemaker-associated endocarditis, and peritonitis associated with continuous ambulatory peritoneal dialysis. Another report describes endocarditis in a patient with a ventriculoatrial shunt [2].

Person-to-person transmission of *C. striatum* has been documented [3]. The three patients described in the present report were treated on the same ward, and the admission dates for the latter two

patients overlapped. Further molecular typing would be required to determine if isolates from all three patients were indistinguishable and to exclude the possibility of nosocomial transmission. It appears that the latter two patients acquired their *C. striatum* infections from colonized EVDs, thus emphasizing the potential role of *C. striatum* in the development of CNS infections, particularly in individuals with prosthetic devices.

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Ganciclovir Therapy for Severe Cytomegalovirus Infection in Immunocompetent Patients

SIR—In a review of severe cytomegalovirus (CMV) infections in immunocompetent patients [1], Eddleston et al. recommended early institution of ganciclovir therapy. This recommendation is based on the ''historically poor prognosis'' of this disease, which was noted in 34 published cases of severe CMV infection that occurred in previously healthy individuals and in seven reports in which ganciclovir or foscarnet therapy ''was perceived as being effective'' in similar, otherwise immunocompetent patients with severe CMV disease [1]. Eddleston et al. acknowledge that ''the manufacturer warns that ganciclovir should not be used in immunocompetent persons since the drug is highly toxic and there currently are insufficient data to establish safety and efficacy in such patients'' [2]. However, they cite only myelosuppression and renal impairment as potential worrisome toxicities.

Eddleston et al. [1] failed to mention one of the most worrisome potential toxicities of ganciclovir when it is administered to immunocompetent patients, i.e., the risk of permanent infertility and of teratogenesis. In the manufacturer's package insert for ganciclovir, the following specific warnings regarding these two risks are included: ''Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses. Although data in humans have not been obtained regarding this effect, it is considered probable that ganciclovir at the recommended doses causes temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur. Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment . . .'' [3].

Severe CMV disease is a rare occurrence in immunocompetent patients; in fact, it is so rare, its natural history is uncertain. Any potential benefit of treatment is speculative. On the basis of the anecdotal data presented by Eddleston et al. [1], there is no evidence that antiviral treatment of CMV neurological disease might be beneficial. On the other hand, a comparison of the anecdotes of visceral CMV disease treated or not treated with ganciclovir suggests that treatment with ganciclovir might result in a survival advantage. However, the treated cases were all reported between 1992 and 1996, while all the untreated cases were reported earlier [1]. Thus, other factors related to advances in medical care, rather than CMV-specific antiviral therapy, might account for a temporal change in survival outcome.

In summary, ganciclovir may cause permanent sterility and may be teratogenic. Clinicians considering the use of ganciclovir in immunocompetent patients with reproductive potential should be aware of these risks and of the lack of compelling data supporting efficacy of the drug in this patient population. If specific treatment for CMV infection must be given to an immunocompetent patient who does have reproductive potential, then foscarnet (which does not adversely affect fertility and general reproductive performance in laboratory animals) might be a more appropriate choice [4].

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Reply

SIR—We thank Jacobson for pointing out the possible toxic effect of ganciclovir on the male and female reproductive systems. We agree that these side effects, as with all potential side effects, should be borne in mind and discussed with the patient before ganciclovir is administered.

However, we did not ''recommend early insitution of ganciclovir therapy for immunocompetent patients with severe cytomegalovirus (CMV) disease,'' as stated by Jacobson. Instead, our review [1] suggested only that specific antiviral treatment be considered and emphasized the following points: (1) CMV infection in immunocompetent individuals may be severe, and in the worst cases, rapidly fatal. (2) In recent years, improved outcomes have coincided with the use of specific antiviral agents. This finding suggests that such drugs *may* be valuable for severely ill patients. (3) Fortunately, severe manifestations are very rare complications of CMV infection. It is therefore unlikely that high-quality clinical trials will be performed to assess the efficacy and toxicity of specific antiviral drugs in patients with these manifestations. In the absence of such trials, we are forced to make use of the best data available, and it is this data that we have presented in our paper.

The expected benefit of any treatment must be balanced against potential side effects. Severe CMV infection may prove fatal. We therefore believe that early administration of specific antiviral agents must be considered for patients with this CMV disease as soon as the severe nature of the infection is apparent. Although the possibility of future reproductive difficulties should be borne in mind before the decision to give ganciclovir is made, this decision must be balanced against the possibility of immediate benefit to a patient with life-threatening disease.

We are happy that Jacobson's analysis of the presented data agrees with our own. We also agree that recommendations for treatment of CMV infections should be based on the results of high-quality, randomized clinical trials. Unfortunately, no such data are available or are likely to become available in the near future. Instead, we must make the best use of the data that are available to us, even if they are based only on 34 case reports.

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Antibiotic Therapy for Foot Infections in Diabetics

SIR—McKinnon et al. [1] recently concluded that ampicillin/sulbactam was more cost-effective than imipenem/cilastatin for the treatment of limb-threatening foot infections in diabetic patients; this conclusion was based on a retrospective analysis of a clinical trial that was not designed to assess economic end points [2]. A number of methodological limitations of the study led us to question the authors' conclusions. We have three primary criticisms: (1) a number of cost components that are important to institutions were not accounted for in the analysis; (2) the clinical study upon which the economic analyses were based was underpowered with regard to outcomes that would tend to be important cost-drivers in an economic analysis; and (3) by using the institutional perspective, the authors overlooked quality of life and other issues that are likely to be important to patients and physicians. While a complete economic analysis needs to be conducted to draw conclusions about the cost-effectiveness of the two treatment approaches, the three methodological limitations of the current analysis bias the results in favor of treatment with ampicillin/sulbactam, making it difficult to draw meaningful conclusions from the economic data presented by McKinnon et al. [1].

With respect to inadequate accounting of institutional cost, the authors used an average hospital per diem for the economic analysis and failed to account for differences in institutional costs that occur as a result of days in an intensive care unit, procedures, and surgeries. Although McKinnon et al. [1] observed a shorter mean ($\pm$ SD) length of stay when ampicillin/sulbactam, rather than imipenem/cilastatin, was used (i.e., 13 $\pm$ 6.5 days vs. 15 $\pm$ 8.6 days), the shorter length of stay may have resulted from the fact that more early surgical amputations were performed in the ampicillin/sulbactam group. Amputation was undertaken before the day-5 assessment for 16 (48%) of the 33 patients treated with ampicillin/sulbactam and for six (21%) of the 28 patients treated with imipenem/cilastatin who required the procedure. The increased rate of early surgical amputation among the patients treated with ampicillin/sulbactam may partly reflect poor response to the study medication. Indeed, clinical improvement due to study medication before amputation was noted for 12 (36%) of 33 patients treated with ampicillin/sulbactam vs. 17 (61%) of 28 patients treated with imipenem/cilastatin ($P = .10$).

Across the total population, 69% of the patients treated with ampicillin/sulbactam required amputation, and three of these patients underwent below-the-knee procedures, whereas 58% of the patients treated with imipenem/cilastatin required amputation, and only one underwent a below-the-knee procedure. In contrast, vascular reconstruction procedures were more common among the patients treated with imipenem/cilastatin. The costs of these and other procedures performed for the patients were not adequately reflected in an overall per-diem hospital cost. McKinnon et al. [1] also failed to account for the costs of follow-up treatment by excluding recurrent episodes of infection that occurred following initial successful treatment. During an average follow-up period of ~1 year, freedom from recurrence of infection at the original site was documented for 27 (56%) of the 48 episodes treated with ampicillin/sulbactam vs. 33 (69%) of the 48 episodes treated with imipenem/cilastatin.

The study of clinical end points was underpowered. As pointed out above, treatment with imipenem/cilastatin resulted in a 16% reduction in the amputation rate over that observed after treatment with ampicillin/sulbactam. While the study from which these results were drawn was underpowered for detecting a statistical significance of this important end point, the economic and quality-of-life implications of the results can be substantial. The study by Grayson et al. [2] generated an important hypothesis that treatment with imipenem/cilastatin, rather than ampicillin/sulbactam, may obviate the need for amputation.

Is the perspective of the analysis correct? Society, and most important, patients, may well accept a marginal increase in the

costs of treatment in exchange for the incremental benefits of fewer amputations, even if many are foot sparing. It is not clear that the perspective offered by McKinnon et al. [1], which placed no value on fewer amputations, would be taken at most institutions. Conclusions about the cost-effectiveness of ampicillin/sulbactam vs. imipenem/cilastatin for treatment of diabetic foot infections must await a more comprehensive analysis that includes all costs and consequences of the two treatment regimens.

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Reply

SIR—We appreciate the interest that Hu et al. have shown in our study, and we welcome the opportunity to respond to their methodological concerns. We accept the criticism of our use of mean hospital per diem to model hospitalization costs but disagree with the assertion of bias. The allegation that the shorter length of stay for the patients treated with ampicillin/sulbactam vs. those treated with imipenem/cilastatin may have been the result of early amputations in the ampicillin/sulbactam group and that this reflects poor response is speculation. In fact, antibiotic failure did not result in any amputations. As stated in the original manuscript, foot-sparing amputation reflects an aggressive approach to the treatment of osteomyelitis [1].

The first criticism of Hu et al. selectively points out several raw number differences that purport to favor treatment with ampicillin/sulbactam, while ignoring other differences, such as the incidence of osteomyelitis, which occurred in 68% of the patients treated with ampicillin/sulbactam vs. 56% of the patients treated with imipenem/cilastatin. In fact, the comparisons mentioned in the first criticism are not statistically different and should not be interpreted as such.

The second criticism also focuses on a nonsignificant difference in data and contains further inaccurate speculation regarding amputations. Amputations were performed because of the presence of osteomyelitis but rarely because of ischemia; these procedures were not related to antibiotic efficacy. Thus, the hypothesis presented by Hu et al. is not supported by the data. It should be recognized that limb-sparing procedures (performed only when necessary) that maintain ambulation are consistent with a general treatment goal [2].

Societal perspective is usually advocated by economists as the preferred viewpoint of an economic analysis [3]. Indeed, this is a comforting perspective from a health care practitioner's position, as it evaluates what should be done for patients. However, several practical considerations limit its application. How does one determine the value to society of a person who is retired or otherwise not gainfully employed? Another concern with the societal perspective is that it does not help health care providers determine what can be done for patients within the constraint of limited resources. A recent study found that the incremental cost associated with choosing tissue plasminogen activator over streptokinase as thrombolytic therapy for patients with acute myocardial infarctions was $32,678 per year of life saved, a societal-based figure that is considered cost-effective [4].

The question remains as to whether society will reimburse an institution where tissue plasminogen activator is used in place of streptokinase. With regard to the treatment of diabetic patients with foot infections, it has previously been determined that the overwhelming majority of health care costs are related to hospital care [2]. For these and other reasons, we consider it logical and appropriate to have conducted our economic analysis from the institutional perspective. Thus, 1-year postdischarge data are not pertinent to this analysis.

Hu et al. propose that our methods favor treatment with ampicillin/sulbactam by not accounting for the costs of specific surgeries and procedures. The implication that there is an incremental economic benefit associated with performing a vascular surgery procedure as opposed to an amputation is not supported by data. In a review of the local representative costs, we found that digital amputation costs less than one-third as much as a vascular reconstructive procedure, a finding corroborated by other investigators [2]. Regardless of the relative costs, these specific procedures were performed for disease-based rather than drug-based reasons.

We certainly hold the view that quality of life is important. In fact, the corresponding author (J.A.P.) has attempted on numerous occasions to add a health-related quality-of-life (HRQOL) component to clinical and economic studies of investigational antibiotics. Without exception, the pharmaceutical industry has failed to support this attempt. The reasoning has varied surrounding the theme that, for patients with acute diseases, quality of life will not drive short-term decisions. Perhaps Hu et al. have the means to support such a study, and we encourage them to do so. We do not agree that a HRQOL assessment would change the results to favor treatment with imipenem/cilastatin. As there were more serious side effects in the imipenem/cilastatin group that led to increased duration of hospitalization, we would not expect to find improved quality of life among the patients treated with imipenem/cilastatin.

Finally, as hospital-based practitioners, we would not term a $3,000-per-patient difference a marginal increase.

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Cutaneous Infection Caused by *Mycobacterium gordonae* in a Human Immunodeficiency Virus–Infected Patient Receiving Antimycobacterial Treatment

SIR—With the onset of the AIDS pandemic and the emergence of a broad range of diseases in immunocompromised patients, there is renewed interest in mycobacterial diseases. In particular, various manifestations of the new aspects of typical mycobacterial infections as well as novel pathologies due to atypical mycobacteria previously considered nonpathogenic have been recently reported [1–5]. In 1996, two interesting papers published in *Clinical Infectious Diseases* underscored cutaneous involvement of mycobacterial infections, either by *Mycobacterium vaccae* [4] or by *Mycobacterium tuberculosis* [5]. *Mycobacterium gordonae,* usually considered a nonpathogenic commensal, has been recognized as a pathogen in immunocompromised patients [1, 2]. Herein we report the case of an HIV-infected patient who developed a cutaneous infection due to *M. gordonae* while she was being treated with antimycobacterial agents.

A 29-year-old, HIV-infected, previously drug-addicted woman who had remained healthy until October 1994 presented to our outpatient department with fever and cough productive of sputum. At the time of these symptoms, her $CD4^+$ cell count was 7/μL, and she had been receiving primary prophylaxis for *Pneumocystis carinii* infection with trimethoprim-sulfamethoxazole; she refused treatment with antiretroviral drugs. A chest radiograph showed a perihilar lesion of the left upper lobe. A bronchoaveolar lavage fluid specimen was obtained, and a culture of this specimen was positive for *M. tuberculosis.* Therefore, a regimen of isoniazid, rifampin, pyrazinamide, and ethambutol was instituted.

During this therapy, her clinical condition improved slightly, until December 1994, when pyrazinamide therapy was discontinued because of gastric intolerance. In January 1995, because of her poor clinical picture and because a chest radiograph showed that her condition was worsening, her antituberculous therapy was changed to isoniazid, rifampin, ethambutol, and ciprofloxacin. In September 1995, the therapy was suspended for 15 days because of the sudden onset of jaundice. Subsequently, upon normalization of liver function, rifampin and ethambutol therapy was discontinued and treatment with clofazimine was introduced. At this time, however, nodular pruriginous cutaneous lesions appeared on her face and arms. Evaluation of a skin biopsy specimen showed gigantocellular, acid-fast-bacilli–negative granulomas. Cutaneous dissemination of tuberculosis was suspected; however, mycobacterial cultures of blood, sputum, and stool were consistently negative. The result of an *M. tuberculosis*–specific PCR assay of skin specimens, amplifying the IS6110 region, was negative, whereas the result of our other reaction, based on the amplification of the 65-kD genomic fragment present in the *Mycobacterium* species, was positive. A final diagnosis was proposed after 20 days on the basis of culture isolation and typing with DNA probes (Gen-Probe Accura-probe, San Diego) that demonstrated presence of an *M. gordonae* strain. The mycobacterial susceptibility pattern suggested resistance to isoniazid, streptomycin, and rifampin.

Because of the appearance and the persistence of the *M. gordonae* skin lesion, despite the current therapy with antimycobacterial agents, treatment was changed from isoniazid to ethambutol. One week later, the cutaneous lesions began to resolve, and after 30 days, the lesions had disappeared completely. Findings on the chest radiograph were normal, and there were no signs or symptoms of mycobacterial infection. After 10 months of follow-up evaluations, there was no recurrence of mycobacterial infection, and after 12 months, the antituberculous treatment was discontinued altogether.

Recent reports demonstrate the potential for and the importance of cutaneous mycobacterial involvement [1–5]. Disseminated skin lesions that appear during acute infection in AIDS patients have been attributed to *M. tuberculosis* [5]. Moreover, atypical mycobacteria generally considered nonpathogenic (e.g., *M. vaccae*) have been implicated in the etiology of cutaneous diseases in immunocompromised patients [4]. *M. gordonae* infection is unusual among HIV-negative individuals, and antituberculous drugs are rarely used, even in instances in which the disease has localized to various organs [1, 2]. Recently, *M. gordonae* was isolated from sputum and bone marrow specimens in AIDS patients [2, 3]. In the present report, we describe what is, to our knowledge, the first case of cutaneous disease due to *M. gordonae* in an HIV-infected patient, emphasizing the need to consider atypical mycobacteria as potential pathogens in immunocompromised patients.

Because of the previous diagnosis of pulmonary tuberculosis, in this patient our attention was initially directed toward a possible recurrence of tuberculous infection with cutaneous involvement; we did not immediately consider the possibility of a new, different mycobacterial infection. Our experience with this case has illuminated the need for an efficient and accurate method for the diagnosis of mycobacterial infections in immunocompromised patients, given that these patients may be infected by atypical and unusual mycobacteria usually considered nonpathogenic. PCR has proven useful as a diagnostic tool for the exclusion of tuberculous relapse, allowing consideration of the possibility of a nontuberculous infection. Once again, the importance of developing sensitive PCRs that could differentiate rapidly between several mycobacterial species has been demonstrated. The need for diagnostic specificity is underscored by the therapeutic choices that must be made in the presence of infections caused by various species of mycobacteria. Even for our patient, the therapeutic regimen appeared inadequate, and thus a change in therapy, driven by a specific diagnosis of *M. gordonae* infection, was indicated.

In conclusion, the present report demonstrates the importance of considering the possibility of cutaneous lesions due to unusual mycobacteria in HIV-infected patients and the need for sensitive and specific diagnostic assays.

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Coagulase-Negative *Staphylococcus* Species as Unusual Causes of Infection

SIR—Although the utility of the precise identification of all coagulase-negative *Staphylococcus* species in the clinical laboratory has not met with universal agreement [1, 2], commercial kits and automated systems have provided virtually every diagnostic laboratory the ability to identify a number of *Staphylococcus* species that would be otherwise unidentifiable in routine laboratory practice.

We read with interest the report by Mastroianni et al. [3], in which they describe the first reported case of primary septic arthritis caused by *Staphylococcus cohnii* in a patient with AIDS. These authors have also reported the first case of a pancreatic pseudocyst resulting from infection due to *Staphylococcus xylosus* in an HIV-infected patient [4]. However, although, in both instances, the focus of interest is clearly the uncommon nature of the *Staphylococcus* species involved, no information was provided in either case about how these unusual species were identified. Because any extensive identification based on taxonomically relevant phenotypic and molecular characteristics would probably have been stated explicitly, it appears that the species were identified by use of a commercially available kit or automated system.

Commercial biochemical test systems can identify a number of the *Staphylococcus* species with an estimated accuracy of 70% to >90% [1, 2]. For the identification of certain species, however, accuracy may diminish considerably in the absence of additional tests (e.g., coagulase production or novobiocin resistance) [1, 2, 5]. Our institute often receives *Staphylococcus* strains that have been isolated in clinical and veterinary diagnostic laboratories in Italy and tentatively identified by use of rapid commercial systems; our facility confirms the identification by use of extensive phenotypic and molecular characterization. In our experience, misidentifications are common with the use of these commercial systems, especially for minor coagulase-negative species, and in most instances pass unnoticed. During the last 3 years, only one of the three isolates received by our institution as *S. cohnii* and only two of the three received as *S. xylosus* were confirmed; the two isolates misidentified as *S. cohnii* were actually *Staphylococcus epidermidis* and *Staphylococcus capitis,* and the isolate misidentified as *S. xylosus* was appropriately identified as *Staphylococcus aureus.*

Furthermore, the *S. xylosus* isolate, the subject of one [4] of the two reports by Mastroianni et al., was said to be resistant to vancomycin. This finding, noted incidentally in the report, does not support the identification of the isolate as *S. xylosus,* given that, among the coagulase-negative *Staphylococcus* species, resistance to glycopeptides (usually to teicoplanin rather than to vancomycin) has been documented thus far with certainity only in strains of *Staphylococcus haemolyticus* and *S. epidermidis* [6]. On the other hand, vancomycin resistance in a clinical isolate of *S. xylosus,* if confirmed, is probably of even greater interest than the isolation of this species from a particular infection site.

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Reply

SIR—We read with interest the report by Varaldo and Biavasco concerning coagulase-negative *Staphylococcus* species as unusual causes of infection. The authors raise objections to our previous reports in which we describe one case of septic arthritis caused by *Staphylococcus cohnii* [1] and one case of pancreatic pseudocyst due to *Staphylococcus xylosus* [2] in two HIV-infected patients. The basis for the authors' objections was that extensive information was not provided with respect to the microbiological method used to identify these microorganisms. Drs. Varaldo and Biavasco's statements, ''commercial biochemical test systems can identify a number of the *Staphylococcus* species with an estimated accuracy of 70% to >90%'', and ''for the identification of certain species, however, accuracy may diminish considerably in the absence of additional tests (e.g., coagulase production or novobiocin resistance),'' are appropriate.

In the two cases referred to by Varaldo and Biavasco, species of coagulase-negative staphylococci (CONS) were identified (i.e., *S. xylosus* and *S. cohnii*) by use of the Sceptor Numerical Identification System for Aerobic Gram-Positive Bacteria MIC/ID (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD), the coagulase test (Sclavo Diagnostic SRL-SALCOM, Italy), and the Pastorex Staph-Plus (Sanofi-Pasteur, Paris) and on the basis of the morphology of aged (>5 day) colonies, gram-stain morphology, and novobiocin resistance.

The isolates were subjected to antimicrobial susceptibility testing by use of the broth microdilution method according to the procedures outlined by the National Committee for Clinical Laboratory Standards. Although misidentification of CONS may be frequent in the microbiological laboratory and other species of CONS may produce biochemical reactions similar to those of *S. cohnii* and *S. xylosus,* as noted by Varaldo and Biavasco, there are some key characteristics, determinable by simple laboratory techniques, that are sufficiently discriminatory and, thus, adequate for the differentiation of these species. The more common distinguishing biochemical characteristics of *S. cohnii, Staphylococcus epidermidis,* and *Staphylococcus capitis* and conventional biochemical tests for identification of *S. xylosus* and *Staphylococcus aureus* are presented in tables 1 and 2. A coagulase-negative *Staphylococcus* isolate can be identified presumptively as ''*S. cohnii*'' if the Voges-Proskauer test of acetoin production from glucose, a test for polimixin B susceptibility, a test for urease and arginine production; and acid production from sucrose, lactose, xylose or arabinose, turanose, and melezitose, and nitrate reduction are negative; and if a test for novobiocin resistance is positive. Generally, failure to ferment sucrose and turanose is typical for *S. cohnii. S. xylosus* strains are coagulase-negative, nonhemolytic, and novobiocin resistant. In addition, these strains are phosphatase and urease positive and produce acid aerobically from mannitol, sucrose, trehalose, mannose, xylose, fructose, arabinose, maltose, and lactose. These strains do not, however, metabolize ribose and xylitol.

Table 1. Distinguishing biochemical characteristics of *Staphylococcus cohnii, Staphylococcus epidermidis,* and *Staphylococcus capitis*.

Characteristic	*S. cohnii*	*S. epidermidis*	*S. capitis*
Novobiocin	+	−	−
Micrococcus screen	+	+	+
Polimyxin B	−	+	−
Saccarose	−	+	−
Nitrate reduction	−	+	+/−
Voges-Proskauer	−	+	−
Arginine	−	−/+	+
Urease	−	+	−

NOTE. + = >90% positive; − = negative; +/− = >90% strains weakly postive.

Table 2. Distinguishing biochemical characteristics of *Staphylococcus xylosus* and *Staphylococcus aureus*.

Characteristic	*S. xylosus*	*S. aureus*
Coagulase	−	+
Novobiocin	+	−
Polimyxin B	−	+
Saccarose	+	+
Trehalose	+	+
Mannitol	+	+
Mannose	+	+
Xylose	+	−
Maltose	+	+
β-glucoronidase	+	−
Agglutination	−	+

NOTE. + = positive; − = negative.

Several different methods may be used for the detection of infection due to CONS; these methods include biotyping, antibiotic susceptibility pattern analysis, serological typing, phage typing, slime-production detection, protein-profile analysis, immunoblot fingerprinting, and DNA typing; however, application of these methods is particularly suited to the epidemiological study of CONS isolates. In fact, prompt distinction between different *Staphylococcus* species by use of phenotypic-trait study and molecular analysis aids in the determination of the epidemiological patterns of these organisms. Recently, we reported that *S. cohnii* is an uncommon pathogen in our hospital, occurring at low frequency but associated with high morbidity [3–4].

We believe that microbiological laboratories should be encouraged to identify infection caused by CONS by use of appropriate methods in order to establish the importance of different CONS isolates, and to report such strains so that the incidence can be defined more accurately. We agree with the observation of Varaldo and Biavasco that vancomycin resistance in the reported strain of *S. xylosus* would be of greater interest than the isolation of this *Staphylococcus* species itself. However, we note that resistance to vancomycin was reported in error; our strain was in fact susceptible to vancomycin and resistant to clarithromycin.

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Herpes Simplex Virus Hepatitis

SIR—I read with interest the recent report by Kaufman et al. concerning herpes simplex virus hepatitis [1]. Although I appreciate being reminded of this clinical entity, I wondered how the authors performed their literature review. They cited a number of reports that included 52 patients; however, their literature review did not appear to be complete. For example, my files (which are not that extensive) contain two reports about herpes simplex virus hepatitis (one on patients with solid-organ transplants [2] and one on patients with marrow transplants [3]), neither of which was included in their literature review.

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Induction of Antiphospholipid Autoantibody During Cytomegalovirus Infection

SIR—We would like to add to the report by Labarca et al. [1], who described an association between cytomegalovirus (CMV) infection and antiphospholipid syndrome. We have looked at the production and possible mechanisms of induction of antiphospholipid autoantibodies during viral infections, including those caused by hepatitis and dengue viruses [2]. We suggest potential pathways that may account for the increased serum concentration of these antibodies in patients with CMV infection.

First, it has been reported that autoantibodies to specific antigens can be generated when viral proteins combine with antigens. Presumably, the viral-host complexes become immunogenic; these virally induced specific antibodies have been shown for DNA as well as phospholipids [3, 4]

Second, there is evidence that phospholipid-binding proteins such as B_2-glycoprotein I annexins are involved in the attachment of viruses, including CMV and hepatitis B, to their cellular targets by complexing with viral phospholipids [2, 5]. During this process the induction of antiphospholipid autoantibodies (the immunogen expressed as viral phospholipid-host protein) may be seen as an event secondary to the cellular binding and entry of viruses.

Third, the accelerated cell death, or apoptosis, associated with a viral infection will be accompanied by the externalization of anionic phospholipids, particularly phosphatidylserine, in the apoptotic cell membrane [6]. The activation of antiphospholipid autoantibody synthesis in this situation could be involved in the immunoclearance of the dead cells [6, 7].

Investigators recently demonstrated that CMV infection of smooth muscle cells increases the uptake of oxidized low-density lipoprotein and may thus play a role in the development of atheroma [8]. The findings that elevated antiphospholipid autoantibody levels are also linked with a greater frequency of myocardial infarctions and that antiphospholipid autoantibodies also cross-react with oxidized low-density lipoprotein [9] imply a link and overlapping mechanisms between CMV infection and antiphospholipid antibody induction. However, whether CMV-activated antiphospholipid autoantibodies are definitely pathogenic or merely an immunologic result of the viral infection remains to be established [2, 10].

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Reply

SIR—We appreciate the interest of Cheng and Khairullah in our case report about antiphospholipid syndrome related to acute cytomegalovirus (CMV) infection in an immunocompetent host [1]. Prieto et al. showed strong evidence that hepatitis C virus (HCV) infection is associated with the presence of antiphospholipid autoantibodies and a high incidence of thrombotic disorders in this group of patients [2]. Therefore, there is growing evidence that antiphospholipid autoantibodies related to viral infections could be pathogenic and are not only an epiphenomenon. However, there is some evidence that enveloped virus could have some procoagulant activities. For example, it has been shown that the CMV surface contains the necessary procoagulant phospholipid for coagulation enzyme complex assembly [3].

In addition, patients with cirrhosis secondary to HCV infection and thrombosis could have other procoagulant alterations that explain the thrombotic problems [4]. In this sense, the hypothesis of Cheng and Khairullah about probable pathways for anticardiolipin induction during viral infections should be considered and explored. Further studies to define the pathogenic role of anticardiolipin antibodies in relation to various infections are warranted.

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Isolated Detection of Cryptococcal Polysaccharide Antigen in Patients with Cryptococcosis

SIR—Manfredi et al. recently highlighted the importance of CSF cryptococcal antigen assay for the early diagnosis of cryptococcosis in patients with AIDS [1]. However, the isolated detection of cryptococcal polysaccharide in CSF is not a new finding. In our series from northern India [2], cryptococcal meningitis was diagnosed in 11 patients by use of isolated cryptococcal antigen assay (Crypto-LA test; International Biological Labs, Cranbury, NJ). Simultaneous efforts to isolate *Cryptococcus neoformans* from the same CSF samples were unsuccessful. The antigen titer was >8 in all 11 cases. Ten patients presented with symptoms and signs of chronic meningitis. The remaining patient had no signs of meningeal involvement and presented with pyrexia of unknown origin. Six of 11 patients were immunocompromised because of underlying illness, but none of the patients had AIDS.

Because of the known specificity of cryptococcal antigen assay, antifungal therapy was instituted for all of the patients, eight of whom responded well. The other three patients died of their illnesses. One patient was autopsied, and yeast cells with capsules were identified in meningeal tissue. The cross-reaction of *Trichosporon* antigen and *Cryptococcus* antigen is known [3]. However, the rarity of disseminated trichosporon infection in northern India led us to believe that all of these patients had cryptococcosis; this could even be confirmed by autopsy in one case. Therefore, cryptococcal antigen assay should be included as part of the routine diagnostic protocol for all patients with chronic meningitis.

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Reply

SIR—Chakrabarti and Gupta present important observations regarding isolated detection of the polysaccharide antigen of *Cryptococcus neoformans* from the CSF of 11 non-HIV-infected patients with CNS cryptococcosis in northern India, although in three of 11 cases, direct microscopic study of the CSF revealed the organism [1]. Unfortunately, at the time that we submitted our report [2], we were not aware of Chakrabarti and Gupta's report [1]; the journal in which their study was published is not available in our country and is not cited in the major international indexes.

The testing of serum and CSF for cryptococcal antigen is used increasingly as a highly sensitive and specific screening technique for high-risk immunocompromised patients, most specifically those with advanced AIDS [3, 4]. Although the presence of cryptococcal antigenemia without detection of fungi from any site represents an emerging issue because of repeated observations [3] (Powderly [4] already stated in 1993 that isolated cryptococcal antigenemia should be regarded as a ''new clinical entity''), an early diagnosis of CNS cryptococcosis made solely on the grounds of CNS positivity for antigen remains rare [1, 2], although it should be carefully considered in the management of this opportunistic infection, whose early recognition may be hampered by mild and atypical clinical features and slow progression.

The data reported by Chakrabarti and Gupta are largely consistent with ours and above all underline that isolated CSF antigen detection may occur both in patients with an immunosuppressive disease other than HIV infection and in persons without apparent immunodeficiency [1]. Moreover, although the majority of patients with isolated antigenemia do not seem to develop CNS disease or disseminated disease after administration of appropriate antimycotics [3], a potentially severe course characterized a significant percentage of reported cases in both of the series discussed [1, 2], regardless of concurrent HIV disease and despite correct and timely antifungal therapy. Finally, it is unfortunate that Chakrabarti and Gupta did not report details concerning prior antifungal therapy in their patients [1], a situation that might support emerging isolated antigen detection [2–4].

From a practical point of view, cryptococcal antigen assay performed on either serum or CSF or on other body fluids that is positive should suggest further diagnostic evaluation and prompt the immediate institution of systemic antifungal treatment [2–4]. In fact, this finding appears undoubtedly associated with active infection [1–4] and probably represents an early sign of disease, often preceding a disseminated, potentially life-threatening illness [1, 2]. Both patient series [1, 2] confirm that antigen screening of immunocompromised patients or other individuals at risk for cryptococcosis may provide a valuable diagnostic tool, leading to early and reliable identification of this opportunistic fungal disease and indirectly ameliorating the prognosis and outcome. Further observations are needed to provide insight into the natural history and evolution of cryptococcosis that is recognized initially (or solely) by isolated antigen detection, and to devise guidelines for appropriate treatment of this condition.

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Thrombotic Thrombocytopenic Purpura and Cytomegalovirus Infection in an Immunocompetent Adult

SIR—We read with interest the recent article on severe cytomegalovirus (CMV) infection in immunocompetent patients by Eddleston et al. [1]. On rare occasions, CMV infection may also give rise to thrombotic microangiopathy [2]. Recently, we treated a patient with thrombotic thrombocytopenic purpura (TTP) that arose during the course of a primary CMV infection; to our knowledge, this is the first case of TTP reported in a CMV-infected patient.

A 30-year-old woman was referred to our hospital because of purpura, fever (temperature, 39°C), and jaundice. Two days before presentation, she had noticed the appearance of purpuric lesions on her feet that spread to her thighs. There were no other clinical signs on admission.

Blood test results were consistent with mechanical hemolytic anemia and included the following: hemoglobin, 75 g/L; haptoglobin, markedly decreased; schistocytes, 8%; direct antiglobulin test, negative; total bilirubin, 55 mg/L (unconjugated, 34 mg/L); platelets, 10×10^9/L; WBCs, 11.6×10^9/L (neutrophils, 55%; lymphocytes, 30%; and no atypical forms). There were no hemocoagulation abnormalities. Renal function was not altered. Results of blood chemistry evaluation revealed evidence of hepatic cytolysis: aspartate aminotransferase (AST), 136 IU/L; alanine aminotransferase (ALT), 154 IU/L (normal values <30 IU/L). The alkaline phosphatase level was 176 IU/L (normal level, 20–80 IU/L), and the γ-glutamyl transpeptidase level was 327 IU/L (normal level, <37 IU/L). Blood and urine cultures were negative.

Several hours after hospitalization, the patient experienced a rapid onset of confusion with decreased alertness, which prompted her transfer to intensive care. Clinical examination revealed bilateral Babinski's sign. A CT of the cranium did not show evidence of intracranial hemorrhage. Given that these neurological symptoms arose in the context of fever associated with mechanical hemolytic anemia and thrombocytopenia, they were suggestive of TTP.

A treatment regimen consisting of high-dose corticosteroids together with blood plasma transfusions led to rapid improvement in the patient's condition in a few days (based on clinical and laboratory evaluations). An ELISA revealed IgM antibodies to CMV and the progressive appearance of IgG antibodies (initial level, 2 IU/L, increasing to 700 IU/L 8 months later). There was also evidence of CMV in the patient's urine. Testing for antigen pp65 was not performed. In view of these results, treatment with foscarnet was administered secondarily for 3 weeks despite the improvement in the patient's condition, as already demonstrated on clinical and hematologic examination.

Eight months later the patient was symptom free, and only evidence of slight hepatic cytolysis persisted (AST level, 56 IU/L; ALT level, 118 IU/L). Serological tests for hepatitis A, B, and C and the immunologic work-up remained negative. Examination of a liver biopsy specimen showed a few inflammatory lesions of the portal spaces and fragmented and agglutinated erythrocytes in the sinusoids; results of histochemical evaluation for CMV were negative.

TTP is a disorder that can be classified among thrombotic microangiopathies along with hemolytic uremic syndrome (HUS). In TTP, microangiopathic hemolytic anemia is associated with schistocytosis, thrombocytopenia, and neurological dysfunction (often with fever and renal involvement) [3]. TTP has been described as occurring in the setting of viral infections, principally HIV and, more rarely, human T-lymphotropic virus type 1 [4]. From a pathophysiologic standpoint, TTP results from damage to vascular endothelial cells and platelet aggregation, leading to the formation of arteriolar microthrombi in different organs, predominately the kidney and brain [5]. CMV is known to have an affinity for the vascular endothelium [6], and endothelial-cell lesions linked to viral replication might thus give rise to TTP.

The prognosis of TTP in the absence of treatment is poor, with death often occurring in days or weeks [5]. Treatment generally consists of corticosteroids and plasma transfusions [7]. Such management led to our patient's rapid recovery.

The present case of TTP and another case involving HUS [2] probably justify systematic searching for an underlying primary CMV infection in patients with thrombotic microangiopathies.

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Central Nervous System Infections with Nontuberculous Mycobacteria

SIR—We read with interest the article by Flor et al. [1] describing two cases of *Mycobacterium avium* complex (MAC) meningitis and the article by Smith et al. [2] reporting a fatal case of *Mycobacterium fortuitum* meningitis in a patient with AIDS. We recently published a comprehensive review of CNS infections due to all species of nontuberculous mycobacteria that included meningitis, encephalitis, and brain or spinal cord abscesses [3]. We believe that each of us was responding to an apparent increase in these diseases in recent years.

We identified 56 cases of MAC disease of the CNS (48 of the patients had AIDS). Most of these patients had meningitis or meningoencephalitis. Two of the patients without AIDS had brain abscesses, and on the basis of postmortem or brain biopsy examinations, nine were described as having encephalitis without evident meningeal disease. Six of nine patients with *Mycobacterium kansasii* disease of the CNS had AIDS. Two of these patients had abscesses without evident meningitis. Seven cases of *M. fortuitum* CNS disease were identified, including two cases (one case of ventriculitis and one case of brain abscess) not included in the review by Smith et al. [2]. Five of these patients had meningitis, three had abscesses of the CNS, and one each had subdural empyema and ventriculitis. Four of six patients with adequate histories had infections associated with trauma or surgery, and one each had otitis media and mastoiditis. Four additional case reports of CNS infection due to *Mycobacterium gordonae, Mycobacterium genavense,* and *Mycobacterium terrae* were identified [3].

Thus, with the reports of CNS disease due to MAC [1] and *M. fortuitum* [2], there have been a total of at least 79 reported cases of CNS disease, including meningitis, encephalitis, and brain abscess, due to nontuberculous mycobacteria. As the epidemic of HIV infection and the application of immunosuppressive treatments expand, we may anticipate further occurrences of these uncommon infections, with involvement of the brain itself, as well as the meninges.

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