placebo group received subsequent life-extending therapy at the time of data cutoff. At that time, of the 251 patients in the placebo group who had not received subsequent life-extending therapy, 24% continued to receive placebo, 19% received other therapies, and 43% died before receiving any subsequent therapy. We would suggest that the timing of chemotherapy in such patients has not been shown to affect survival and that the post-progression treatment experience of our study patients reflects the standard of care.

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Brain Abscess

TO THE EDITOR: In their review article, Brouwer et al. (July 31 issue)[1] suggest the use of vancomycin for the treatment of brain abscesses caused by methicillin-resistant *Staphylococcus aureus* (MRSA). However, regarding this choice, there are some concerns that should be considered.

First, vancomycin has poor cerebrospinal fluid (CSF) penetration when administered at a standard dose; thus, larger doses should be administered to achieve adequate CSF levels. However, high vancomycin serum concentrations are independently associated with nephrotoxicity.[2] Second, dexamethasone, used for the management of brain edema, can substantially reduce the penetration of vancomycin into CSF.[3] Third, infections caused by MRSA strains with high minimum inhibitory concentrations of vancomycin have been associated with increased treatment failure and mortality when vancomycin is used empirically.[4]

Here, we pose the question of whether it is time to review the current approach to antibiotic therapy. We believe that, as first-line empirical treatment for brain abscesses caused by MRSA, newer antibiotic agents, such as linezolid, that achieve higher CSF levels than those observed with vancomycin should be used.[5] Although interindividual variability has been reported, an increasing number of reports have shown the efficacy of linezolid for the treatment of brain abscesses.

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TO THE EDITOR: In their review article, Brouwer and colleagues recommend the standard four-drug regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) for the treatment of brain abscesses due to *Mycobacterium tuberculosis*. This recommendation is in accordance with current guidelines[1]; nevertheless, it must be noted that although this regimen has been studied extensively in patients with respiratory tuberculosis, there is a scarcity of data regarding its use for the treatment of brain abscesses.

Pharmacokinetic studies[2] have shown that the CSF penetration of ethambutol is poor, with negligible concentrations in patients without meningitis. In contrast, fluoroquinolones, which have good activity against *M. tuberculosis*, reach CSF levels well above the minimum inhibitory con-

centrations,[3,4] although an unequivocal benefit in tuberculous meningitis has not been proved.[5]

Available pharmacokinetic data should induce some caution in recommending the use of ethambutol for the treatment of tuberculosis of the central nervous system and should discourage the use of low doses of ethambutol (15 mg per kilogram of body weight). However, the use of fluoroquinolones in combination with isoniazid, rifampin, and pyrazinamide may deserve consideration in the treatment of this severe condition.

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TO THE EDITOR: The article by Brouwer et al. mentions several causes of brain abscesses but does not include paracoccidioidomycosis. This fungal disease is the most common systemic endemic mycosis in Central America and South America (but with increasing incidence in Europe and North America) and is the eighth highest cause of death (1.45 deaths per 1 million inhabitants per year) from chronic infectious disease in Brazil.[1,2]

The prevalence of central nervous system involvement in paracoccidioidomycosis (neuroparacoccidioidomycosis) is approximately 10% and can reach 36% with more aggressive use of neuroimaging.[3] However, it is frequently underrecognized and underreported. Neuroparacoccidioidomycosis presents as brain lesions (abscess, granuloma, nodule, or cyst) in 90% of cases and as meningitis in 10%, is associated with a striking mortality of 44%, and causes substantial sequelae in approximately half the survivors.[3,4] Consequently, this fungal disease should be considered in patients with brain abscess, especially in those with concomitant oral lesions, microstomia, skin ulcerations, diffuse pulmonary infiltrates, or adrenal abnormalities (Fig. 1).[1,3,4] This high clinical suspicion may allow early diagnosis and treatment, possibly reducing mortality and sequelae.

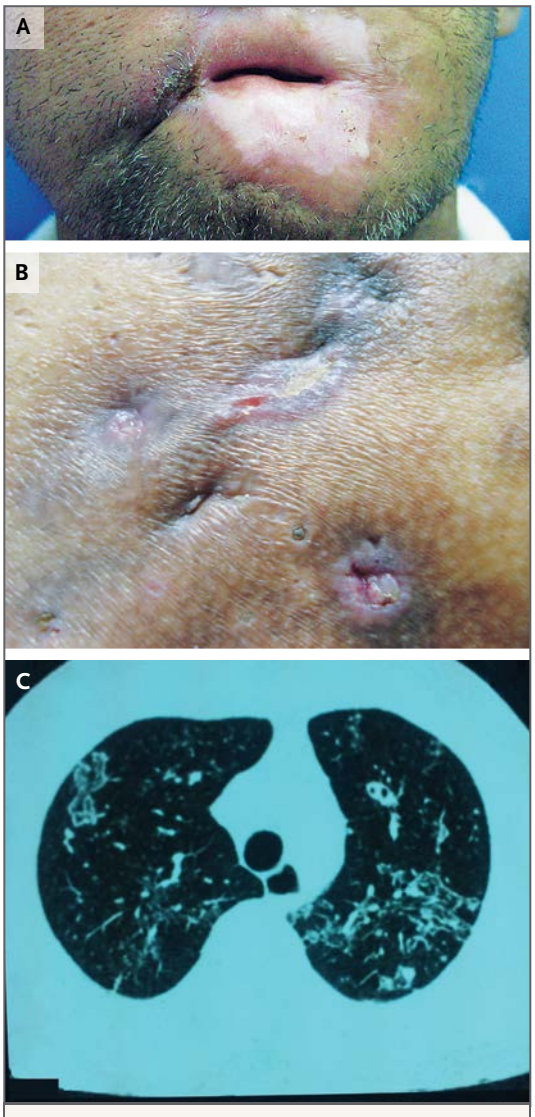

Figure 1. Possible Concomitant Findings in Patients with Neuroparacoccidioidomycosis.
Panel A shows microstomia, Panel B skin ulcerations, and Panel C pulmonary infiltrates (reversed halo sign).

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THE AUTHORS REPLY: We agree with the concern regarding vancomycin penetration into the CSF, although a study has shown that the administration of high doses of intravenous vancomycin (60 mg per kilogram per day as a continuous infusion, after a loading dose of 15 mg per kilogram), even with the concomitant administration of dexamethasone, in patients with bacterial meningitis led to adequate CSF concentrations (7.9 μg per milliliter),[1] suggesting that the decreased penetration can be overcome with the administration of appropriate parenteral doses.

With regard to the penetration of vancomycin into brain abscesses, there are limited data. In one case report in a patient with an *S. aureus*–associated brain abscess, simultaneous measurements of vancomycin concentrations in serum and brain-abscess fluid were obtained 1 hour after the intravenous administration of a 500-mg dose. Vancomycin levels obtained from the brain-abscess fluid before and during operative removal of the abscess were 15 μg per milliliter and 18 μg per milliliter, respectively; the serum vancomycin level was 21 μg per milliliter.[2] Pending further data, we continue to recommend treatment of brain abscesses caused by MRSA with vancomycin. However, careful monitoring of these patients is critical, and we agree that salvage therapy with relatively new agents (such as linezolid or daptomycin) should be used in patients with brain abscesses caused by MRSA strains who do not have a response or who have an elevated minimum inhibitory concentration of vancomycin.

The advised standard four-drug treatment regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) for tuberculous brain abscesses is recommended in the current World Health Organization guidelines for tuberculosis of the central nervous system. Despite the excellent penetration of moxifloxacin into the CSF, a survival benefit with that drug in tuberculous meningitis has not been shown.[3] Levofloxacin is currently being evaluated in a randomized, controlled trial involving patients with tuberculous meningitis.[4] If this study shows benefits with levofloxacin, it would seem prudent to incorporate this agent into the treatment regimen for tuberculous brain abscesses.

In a recent meta-analysis that included 9699 patients with brain abscess, fungi comprised only a minority of cases (1.4%),[5] and paracoccidioidomycosis was rarely reported as an etiologic agent. However, we agree that neuroparacoccidioidomycosis should be strongly considered, in the appropriate clinical setting, as a cause of brain abscess in inhabitants of, and travelers from, regions in which this disease is endemic.

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