ses,[3-5] heterogeneity for mortality between the revised versus the original oximeters was present but sometimes unreported[4,5] (Table S1 in the Supplementary Appendix, available with full text of this letter at NEJM.org). We acknowledge the possibility that post hoc analyses can generate false positive results. However, we believe that the evidence we found suggests that targeting an oxygen-saturation range of 85 to 89% affects disability little but substantially increases avoidable mortality.

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Dexamethasone in Cryptococcal Meningitis

TO THE EDITOR: Beardsley et al. (Feb. 11 issue)[1] report on a randomized clinical trial in which a group of patients with human immunodeficiency virus (HIV)–associated cryptococcal meningitis received adjunctive dexamethasone. This trial clearly showed the disadvantage of glucocorticoid therapy in HIV-infected patients who had primary cryptococcal infections before microbiologic control (i.e., lack of growth in fungal culture after antifungal therapy).

We would like to stress, however, that the results are not necessarily applicable in HIV-negative populations, since the host immune response in central nervous system (CNS) infections is an important effect modifier. Specifically, cryptococcal meningitis that occurs after microbiologic control in patients with other underlying illnesses or persons who were previously healthy is frequently followed by severe intrathecal inflammation.[2] In these patients, adjunctive glucocorticoids may have benefit.[3,4]

Indeed, in an ongoing observational cohort study to evaluate the risks and outcomes of cryptococcal disease among patients without HIV infection (A Prospective Modified Cohort Study of Cryptococcus Infections in People without HIV Infection [CINCH]), 80% of patients who ultimately received glucocorticoids as adjunctive therapy for CNS inflammation after microbiologic control had favorable results in terms of function and survival. Data are lacking from studies to shed light on the underlying pathologic process and more specific immunomodulatory approaches or cerebral edema–reductive approaches to disease management in populations other than an untreated, HIV-positive population with a high fungal burden.

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TO THE EDITOR: The failure of adjunctive dexamethasone to benefit patients with HIV-associated cryptococcal meningitis in the trial reported by Beardsley et al. is probably explained by the well-understood pathologic process of such infections, for which the term "meningitis" is virtually a misnomer. I performed many neuropathological examinations of such patients at autopsy in the era before highly active antiretroviral therapy (HAART) was available, and I found large numbers of organisms in the subarachnoid space and in the perivascular spaces, particularly in the basal ganglia ("flask abscesses"), without any inflammatory responses in those sites or elsewhere in the brain. These observations were confirmed in many descriptions from other centers at that time.

In the absence of inflammation, the beneficial effect of glucocorticoids that characterizes their use in patients with acute bacterial meningitis, for example, has no target. The only potential benefit is in reduction of cerebral edema or in modulation of the immune reconstitution inflammatory syndrome (IRIS), which in fact occurred in only 13 of the 451 patients enrolled in the trial reported by Beardsley et al. Thus, the lack of a benefit from glucocorticoids is not surprising.

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TO THE EDITOR: Beardsley et al. report that the use of adjunctive dexamethasone in patients with HIV-associated cryptococcal meningitis was associated with more adverse events than was placebo. The authors hypothesized that adjunctive glucocorticoids limited disease complications that were caused by resistance to outflow of cerebrospinal fluid (CSF), vasculitis, or increased intracranial pressure arising from brain edema. The rationale for the use of a regimen previously used in patients with uncomplicated tuberculous meningitis[1] is empirical, and it is questionable whether the regimen was adjusted to limit complications of disease that occurred in the first weeks of treatment,[2] albeit glucocorticoid tapering may have reduced the emergence of IRIS.

Dexamethasone reduced opening pressure in the serial lumbar punctures performed. Survival analysis with respect to the score on the Glasgow Coma Scale on admission could indicate whether dexamethasone was beneficial in patients who had a low score, since this score and the CSF opening pressure were the only available data related to increased intracranial pressure and other intracranial pathophysiological features. Since early deaths would be expected to be due to intracranial complications[2] and later events would be expected to be due to complications related to reduced immunologic capacity, analysis of the cause of death would have been necessary in order to achieve a clinically meaningful conclusion.

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THE AUTHORS REPLY: We agree with Panackal et al. that the results of our trial are generalizable only to similar patient populations and in relation to the precise regimen that we tested. Our exploratory analyses showed a heterogeneous treatment effect over time and a hazard ratio in the direction of benefit during the first 3 weeks of treatment; this suggested that a shorter duration of dexamethasone administration might have resulted in a different outcome. Our results should not necessarily preclude further trials of glucocorticoids in different populations or doses. However, we urge caution in the interpretation of cohort studies. Randomized, controlled trials with sufficient follow-up (at least 6 months, since the treatment effect that we identified became more apparent over time) would be required.

Miller suggests that glucocorticoids were doomed to fail because inflammation was not a histologic feature in HIV-associated cryptococcal meningitis in the pre-HAART era. We agree that in such patients there is less histologic evidence of inflammation than in patients with cryptococcal meningitis that is not associated

with HIV. However, granulomatous reactions, lymphocytic infiltration, and elevated levels of CSF proinflammatory cytokines have been described.[1,2] The degree of inflammation in patients who are receiving HAART is unknown but is probably higher than in patients who are not receiving HAART. Our trial was designed to aid decision making at the point of diagnosis. A total of 40% of the patients in our trial were receiving HAART at trial entry. However, we found no benefit of dexamethasone, even in this predefined subgroup analysis. As Miller notes, IRIS occurred infrequently in both trial groups by 6 months (in 6 of 226 patients in the placebo group and in 7 of 224 patients in the dexamethasone group). The low rate of IRIS is interesting; we speculate that it was due to the use of higher doses of antifungal agents (particularly fluconazole) than were typically used in previous cohorts.

Brandt questions the appropriateness of the regimen chosen. We chose the lowest dexamethasone dose used in the trial involving patients with tuberculous meningitis reported on by Thwaites et al. because in that trial patients who received active drug had fewer serious adverse events than patients who received placebo.[3] Among the patients in the trial by Thwaites et al., 18% were infected with HIV and most had profound immunosuppression; no evidence of harm was seen.

Survival in relation to the Glasgow Coma Scale score at admission is provided in Table 2 of our article, and survival in relation to raised intracranial pressure is described in Section 10 of the Supplementary Appendix (available with the full text of our article at NEJM.org). We think that all-cause mortality is the most clinically meaningful end point and that our conclusions are robust.

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Amoxicillin for Severe Acute Malnutrition in Children

TO THE EDITOR: Isanaka and colleagues (Feb. 4 issue)[1] report the results of a double-blind, placebo-controlled trial that showed no benefit from the routine use of amoxicillin in a cohort of children with uncomplicated severe malnutrition in Niger. The authors conclude that amoxicillin may not have a place in the empirical management of uncomplicated severe malnutrition in developing countries. We strongly support the view that antibacterial chemotherapy is not a magic bullet, and we wish to highlight the potential unintended consequences of the mass use of antibacterial agents in this context, including the potential for drug resistance. With the World Health Organization giving a central role to amoxicillin in its essential medicines list,[2] and recent data confirming that the use of antimicrobial agents in childhood is associated with long-lasting shifts in the intestinal microbiome,[3] we call for a shift of emphasis away from the mass administration of antibacterial agents. Instead, ensuring that essential antibacterial agents for the treatment of clinical infections are accessible for all, while sustaining their effectiveness, must remain central to our global approach to managing infections — now and for generations to come.[4]

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