The authors reply: Caputo and colleagues agree with us that short-acting benzodiazepines are the cornerstone for treating patients with the alcohol withdrawal syndrome. They suggest that we ought to have included sodium oxybate (the sodium salt of γ-hydroxybutyric acid [GHB]) among the alternative therapies. Sodium oxybate is approved for the treatment of the alcohol withdrawal syndrome in Italy and Austria and for the treatment of narcolepsy in the United States.1 In addition to space constraints, we did not include sodium oxybate among the potential alternative treatments, mainly because of its potential for abuse and its adverse-effect profile.2 In addition to the references cited by Caputo and colleagues, a recent article published after our manuscript went to press reported pooled data from 3436 patients with alcohol dependence and a pharmacovigilance database involving more than 260,000 patients with alcohol dependence who had been treated with sodium oxybate with very few adverse side effects and only a few cases of abuse.1 In a review article published 20 years ago in the Journal, another Italian researcher argued for the inclusion of GHB as a potential treatment for the alcohol withdrawal syndrome and for relapse prevention.3 We believe that benzodiazepines are the drug of choice and that sodium oxybate could be considered, at best, as an option for treatment when other established medications are not appropriate.

Rathi and colleagues share their perspective on the treatment of alcoholic hepatitis. This is a matter that we did not discuss in our article because we believed it was beyond its scope. We agree with Rathi and colleagues that there is a need for exploration of new therapies beyond glucocorticoids and pentoxifylline, given that, as we noted in our article, patients with alcoholic hepatitis have a poor prognosis and very few patients will eventually benefit from liver transplantation.

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Since publication of their article, the authors report no further potential conflict of interest.

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Antibody-Mediated Rejection of Solid-Organ Allografts

To the Editor: The comprehensive review article by Loupy and Lefaucheur (Sept. 20 issue)1 on antibody-mediated rejection describes major advances in understanding the pathophysiological process and diagnosis of antibody-mediated rejection, but successful treatment is still limited to the acute forms of antibody-mediated rejection.2 Allograft loss eventually occurs in the majority of patients in whom true pathogenic donor-specific anti-HLA antibodies develop.3 This is frustrating for both clinicians and patients because even treatments administered at early stages of the disease are not effective. It is quite obvious that the best strategy to minimize the risk of donor-specific antibodies is to improve the level of HLA matching between the donor and recipient.4 This point was omitted in the article.

Recent studies suggest that molecular HLA eplet matching could reduce the risk of the development of donor-specific antibodies.5 Since class II rather than class I donor-specific antibodies are associated with chronic antibody-mediated rejection, this strategy to achieve HLA class II molecular matching appears to be feasible. The
challenge is to find out how to integrate such a strategy into the current algorithms for solid-organ allocation.

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TO THE EDITOR: In the review article by Loupy and Lefaucheur, the assertion that antibodies are a major cause of acute and chronic rejection of solid-organ allografts is not substantiated. Aside from rare cases of hyperacute or accelerated rejection in HLA-sensitized patients, a causal relationship between antibodies and rejection has not been established.

“Antibody-mediated rejection,” as described by Loupy and Lefaucheur, occurs more commonly in association with or after cellular rejection than in isolation. It is frequently diagnosed in the absence of circulating donor-specific anti-HLA antibodies or evidence of antibody binding to graft tissue. The histologic criteria used to infer the presence of antibodies, including C4d, are not specific. In a study of heart transplantation, even when antibody binding was detected histologically, it was associated with graft dysfunction in fewer than 5% of patients. Antibody-targeting therapies do not reverse “antibody-mediated rejection,” and in anecdotal cases in which improvement was observed, the effect of therapy on nonhumoral immunity could not be ruled out. Finally, in studies in animals, the absence of antibodies has not been shown to prevent lesions associated with “antibody-mediated rejection.” Therefore, the term “antibody-mediated rejection” should be used with caution until scientific causation is established. Mislabeling could misguide scientific investigations and trigger unwarranted interventions.

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THE AUTHORS REPLY: In reply to Cruzado: our review article focused on recent insights regarding the diagnosis and clinical presentation of antibody-mediated rejection and the resulting clinically actionable biomarkers for monitoring and therapeutic follow-up of patients who receive transplants. The potential for new allocation policies aimed at reducing the incidence of allograft rejection, including HLA matching at the eplet level, is an interesting but complex subject that would require a dedicated overall review to be fully addressed. Moreover, the feasibility of such precise HLA matching in the time-sensitive, real-world setting of current allocation logistics remains to be developed.

We strongly disagree with the comments by Lakkis et al., since antibody-mediated rejection exists as a clinical entity primarily caused by circulating donor-specific anti-HLA antibodies. Although anti-HLA antibodies have been linked to a spectrum of pathogenicity, robust data from numerous clinical and basic studies published in the past three decades provide support for the
causality of anti-HLA antibodies in antibody-mediated rejection. Many criteria for evidence of causation as applied to antibody-mediated rejection have been met, including the strength of the effect size, consistency and reproducibility, specificity, a strong biologic gradient, a dose-dependent effect, additional biologic plausibility, and experimental models in animals that indicate causation (Table 1).  

In our review article, the definition of antibody-mediated rejection in kidney, lung, heart, liver, and pancreas transplantation was consistent with that used by the Banff classification of kidney allograft rejection and the classification of the International Society for Heart and Lung Transplantation. Beyond providing a standardized nomenclature, these classifications base the diagnosis of antibody-mediated rejection on a combination of several markers (antibodies, pathological and immunochemical features, and gene expression) that are directly derived from the evidence described above. Regarding the comment on antibody-negative antibody-mediated rejection, these phenotypes are far less frequent in clinical practice than those related to HLA antibodies and do not rule out the presence of other non-HLA pathogenic antibodies. Finally, the experience of clinicians who treat patients with antibody-mediated rejection as well as results published in the recent literature are not in line with the assertion by Lakkis and colleagues regarding an “anecdotal” efficacy of antibody-targeting therapies. These findings indicate that more than two thirds of patients with active antibody-mediated rejection after kidney transplantation have had a response to antibody-targeting treatment leading to allograft survival.
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Since publication of their article, the authors report no further potential conflict of interest.

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