Tissue Plasminogen Activator and DNase in Empyema

TO THE EDITOR: Rahman and colleagues (Aug. 11 issue)¹ found improved fluid drainage in patients with pleural infections and a reduced frequency of surgical referral and duration of hospital stay after combined therapy with intrapleural tissue plasminogen activator (t-PA) and DNase. In pleural effusions, the viscosity correlates with the concentrations of albumin, protein, and lactate dehydrogenase.²,³ In an experimental model, the peak in lactate dehydrogenase levels occurs about 12 hours after the peak in numbers of inflammatory cells in the pleural fluid.⁴ Hence, antibiotic treatment before randomization might have had an influence on the pleural inflammatory response and consequently on the results. Can the authors provide information about antibiotic treatment before randomization and chest-tube drainage?

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TO THE EDITOR: In the Second Multicenter Intrapleural Sepsis Trial (MIST2), Rahman and colleagues found that in patients with pleural infection, the combination of t-PA and DNase improves the drainage of pleural fluid, leading to a reduction in hospital stay and the need for surgery. They stated that 91% of patients had evidence of loculation, which was assessed with the use of plain radiographs in approximately four of five of the patients in the study. In using radiographs for the assessment of loculation, the authors probably included a heterogeneous population with patients in different phases of empyema at the time of treatment, which may have had an effect on their measured outcomes.² Had the authors performed a more comprehensive analysis of pleural fluid images, they might have been able to gather data about the relationship between imaging of empyema and outcomes.

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THE AUTHORS REPLY: Bachmayer suggests that the administration of antibiotic therapy before randomization may have influenced the pleural inflammatory response and postulates that this may affect fluid viscosity and hence the trial results. Although experimental data (as cited by Bachmayer) suggest that fluid viscosity may be associated with inflammatory cell populations, these findings have not been correlated with important clinical outcomes. Details of the antibiotic therapy administered in MIST2 are provided in the Supplementary Appendix (available with the full text of the article at NEJM.org), and there were no differences between groups in the number of antibiotics used, the length of antibiotic treatment, or the baseline level of lactate dehydrogenase in pleural fluid. Even if fluid viscosity had been influenced by prior antibiotic treatment, the treatment groups were likely to be balanced in this regard, which means that the treatment should not have influenced the study result.

Simons and colleagues comment on the assessment of loculation in MIST2. The clinical significance of pleural fluid loculation and stage of empyema remains uncertain. There are as yet no robust data to suggest that outcome in pleural infection is correlated with earlier radiographic parameters, with a previous study showing no association between baseline radiographic findings and outcome.³ Addressing this question was not our primary focus in this study, and we therefore adopted a pragmatic approach to
loculation scoring, in which it was not possible to perform computed tomographic (CT) imaging for all participants. However, we believe the loculation scoring conducted to be robust, with all radiographs scored by two independent readers who were in 100% agreement on the presence of radiologic loculation. The definition used for loculation was the presence of pleural fluid or pleural thickening that was not distributed in accordance with gravity, and the radiographs were taken with the patient in an erect position. Among those patients for whom there was no evidence of loculation on chest radiography (59 of 210 patients, or 28%) and for whom a CT scan was available (41 of 59 patients, or 69%), 98% (40 of 41) had evidence of loculation on CT.

In our trial, the loculation scores measured on chest radiography were balanced among treatment groups at baseline; it therefore seems unlikely that imbalance at baseline went undetected. We agree that specific studies are required to address the relationship between imaging parameters and important clinical outcomes. Such studies, using data from this trial and detailed scoring of CT scans, are now in progress.

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


Chimeric Antigen Receptor–Modified T Cells in CLL

**TO THE EDITOR:** Porter et al. (Aug. 25 issue) report that chimeric antigen receptor–modified T cells proliferated and survived after infusion in a patient with chronic lymphoid leukemia, and they exerted potent antitumor activity. However, the authors did not analyze the clonal structure and lentiviral integration site of chimeric antigen receptor–modified T cells that proliferated and survived in vivo. The study methods detailed the collection of polyclonal autologous T cells, transduction with a viral vector, and infusion of cells back into the patient. Therefore, the in vivo, expanded, chimeric antigen receptor–modified T-cell population could be monoclonal, oligoclonal, or polyclonal in nature. Insertional activation-related events resulting from lentiviral transduction might contribute to the CD137-enhanced proliferation of chimeric antigen receptor–modified T cells. Thus, the analysis of the clonality and integration site might provide insights into the unique biologic mechanisms, in addition to the potential adverse effects of this therapy.

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**TO THE EDITOR:** Porter et al. describe the treatment of a patient with autologous T cells that were genetically modified to recognize the B-cell antigen CD19. This article confirms many findings of our December 2010 article, which described a patient with advanced follicular lymphoma whom we treated with chemotherapy followed by an infusion of T cells expressing an anti-CD19 chimeric antigen receptor (CART19). A dramatic partial remission lasting 10 months was achieved in our patient. He was retreated on our protocol and was in an ongoing partial remission 26 months after the original treatment. In addition, both normal and malignant B-lineage cells were completely eradicated from the blood and bone marrow in our patient for 36 weeks. Similarly to the patient described by Porter and coworkers, hypogammaglobulinemia developed in our patient. We have treated a total of 11 patients in two different clinical trials of CART19. Adoptive transfer of T cells genetically modified...