


**Response**

*To the Editor:*

We thank Dr Medford for his insightful comments regarding our study evaluating the characteristics and survival of patients with autoimmune-featured interstitial lung disease (AIF-ILD). These patients had signs or symptoms and serologic test results suggestive of autoimmunity but did not meet the criteria for a defined connective tissue disease. Although survival for all patients with AIF-ILD was comparable to patients with idiopathic pulmonary fibrosis, the subgroup of patients with AIF-ILD and an antinuclear antibody (ANA) titer ≥ 1:1,280 had improved survival. As Dr Medford noted, nonspecific interstitial pneumonia patterns, which are generally associated with improved outcomes, were seen more commonly in the subgroup of patients with AIF-ILD and high ANA titers. Nonetheless, the majority of patients with AIF-ILD and high ANA titers had a usual interstitial pneumonia pattern on CT scan and lung biopsy (59% and 73%, respectively), suggesting that radiographic and histopathologic patterns may not fully account for the differences in survival. The small number of patients with AIF-ILD and high ANA titers precluded subgroup analysis to determine the impact of radiographic and histopathologic patterns on survival. Our results underscore the significance of performing a systematic evaluation for autoimmune features in patients with interstitial lung disease regardless of radiographic and pathologic patterns, as patients with usual interstitial pneumonia may meet the criteria for AIF-ILD. More importantly, the presence of elevated ANA titers may have prognostic value.

Evaluation for underlying autoimmune disease may evolve as newer autoantibodies are discovered, as in the case of the antisyntethase syndrome. As Dr Medford suggests, this may also be true for patients with AIF-ILD and high ANA titers. Until then, we believe that it is crucial to evaluate for and recognize the subgroup of patients with AIF-ILD so that additional studies of their disease course, predictors of survival, and response to therapy can be performed.

We hypothesize that there is a spectrum of autoimmunity in interstitial lung disease and that the presence of autoimmunity may impact both response to treatment and survival. Current diagnostic criteria for AIF-ILD rely on clinical characteristics, some of which are nonspecific. As a result, AIF-ILD encompasses a heterogeneous group of patients: Some may have a clinical course similar to patients with idiopathic pulmonary fibrosis, while others may have a course similar to patients with connective tissue diseases. Additional studies of the molecular differences related to autoimmunity for patients with interstitial lung diseases may lead to the development of additional criteria that can be used to objectively distinguish between these subgroups of patients.

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**REFERENCES**


**Sepsis, Lactate, and Oxygen Supply Dependence**

*To the Editor:*

I read with great interest the Point/Counterpoint Editorials of Jones and Rivers et al in CHEST (December 2011). A central supposition of both, however, is that sepsis/septic shock is a condition in which oxygen consumption is dependent on oxygen delivery (DO2). Studies suggesting such were discounted in the 1990s as (measurement) artifact of mathematical coupling. Although nitric oxide-mediated microvascular dysregulation is certainly a feature of septic shock, data are not so conclusive that tissue-level DO2/oxygen consumption mismatch contributes to tissue dysxia/hypoxia or lactic acidosis (LA). Nobody would argue that patients with severe hypotension during septic shock may have some LA resulting from hypoxia (when/if extraction fractions exceed around 60%), but LA often persists after resuscitation. And both debaters agree that generation of LA in sepsis is complex, if not completely understood.

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What if LA is a marker of dysmetabolism more than tissue hypoxia in septic shock? Data from the 1980s may support such a concept. Then the underlying theoretical presumption for treating the macrocirculation using LA as a marker of “success” is ill founded. Even the landmark study by Rivers et al does not provide conclusive evidence that patients who received an intervention benefited because hypoxia was attenuated; with postresuscitation central vein saturations averaging 66% (control group) and 77% (intervention group), patients were nowhere near critical oxygen extraction (ie, central vein saturations of 40%).

The intervention included a complex algorithm of titrated treatments, including fluids, vasoactive agents, inotropes, and blood, all designed to augment DO2. But the protocol also suggested that these patients were transferred to “the first available inpatient bed,” whereas control subjects were admitted “as soon as possible.” Time-to-transfer is not reported, but it is plausible that the observed differences resulted from (1) the DO2-driven interventions, (2) type 1 error (we are still awaiting confirmatory studies), (3) earlier transfer to units with better nursing ratios/proficiency, and/or (4) some other intervention bias.

Do not get me wrong: It would be foolhardy not to embrace earliest-possible administration of syndrome-targeted antibiotics, refilling of the circulation, and source drainage when necessary. It is only common sense. But the prevalent presumptions that outcomes are impacted by manipulation of DO2 (beyond rudimentary resuscitation), that central venous oxygen saturation (beyond very low values) can help guide therapy, and that LA fluxes are necessarily tied to DO2 in sepsis are not proven, at least not to my satisfaction. None of these theoretical nuances in any way reduces the importance of Dr Rivers’ work, which has driven health-care systems and clinicians to treat patients who are septic with the same vigilance and rigor brought to other treatment-time-sensitive illnesses.

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Response

To the Editor:

I thank Dr Manthous for his interest in the recently published Point/Counterpoint Editorials. A large portion of his letter addresses concepts and critiques of the trial by Rivers et al, which I will leave to Dr Rivers to address. Dr Manthous does, however, raise the point that lactic acidosis is not a marker of tissue-level hypoxia. As stated in my Point Editorial, elevated lactate levels reflect the total picture of energy metabolism in the acutely stressed patient with sepsis. Both anaerobic and aerobic processes contribute to lactate production in sepsis. Thus, as opposed to central venous oxygen saturation, which is a rudimentary indicator of only the balance between oxygen supply and demand, lactate clearance biologically reflects more of the general homeostasis of the host and provides more meaningful data about the overall adequacy of the resuscitative processes. I take issue with Dr Manthous’s assertion that treating the macrocirculation using lactic acidosis as a marker of success is ill founded. Human and controlled animal studies alike have consistently shown that impaired oxygen transfer at any point from the lungs to the nicotinamide adenine dinucleotide oxidase enzyme will cause lactic acidosis, and clearing lactate levels almost always signifies improvement in host oxygen use. As such, lactate clearance as a choice of a resuscitative end point in sepsis is supported by high-quality human and animal data and can assist clinicians in their bedside care of this disease.

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