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Magic bullets and surrogate biomarkers circa 2009*

Matthew J. Delano, MD, PhD and **Lyle L. Moldawer, PhD**
Department of Surgery, University of Florida, College of Medicine, Gainesville, FL

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With the discovery almost 25 years ago that administration of tumor necrosis factor-α could produce shock and tissue injury similar to severe sepsis, the fundamental role for cytokines in experimental sepsis was established (1, 2) The dramatic improvement in survival, first seen in mice and then confirmed in primates with bacteremic shock, produced simply by inhibiting a single cytokine (3, 4), resulted in unbridled optimism that sepsis mortality in hospitalized patients could be dramatically reduced. This outlook pervaded the collective conscious for well over two decades, spawned a sundry of biological inhibitors, tested in a multitude of human clinical trials, all with the goal of recapitulating the survival benefit imparted by these “magic bullets” in preclinical animal models (5). Unfortunately, these efforts consumed an enormous amount of energy and financial resources, and demonstrated only minimal benefit to the treatment of human sepsis. Fortunately, the past decade has been spent in self-evaluation (some might also say self-denial), asking why such therapies have not yielded the clinic successes observed with preclinical models. Only now are we beginning to understand the complexity of human sepsis and the limits of our preclinical models (6).

In this issue of *Critical Care Medicine*, Osuchowski and co-workers (7) argue that although most antisepsis therapies, in general, and anticytokine therapies, in particular, have failed in severe sepsis clinical trials, the challenge has been to prospectively identify individuals who might benefit from such therapies (5). There is little disagreement that what we call “severe sepsis” is presently so poorly defined that our study populations are too broadly heterogenous to optimize drug efficacy. There is a strong precedent to suggest that anti-inflammatory therapies, in general, and anticytokine therapies, in particular, are most effective in the sickest individuals at the highest risk(s) of mortality. In a large meta-analysis including both preclinical and clinical studies, Eichacker et al (8) demonstrated a linear relationship between anti-inflammatory drug efficacy and overall mortality in the placebo groups. How then do we better identify prospectively those patients with severe sepsis who may benefit from such targeted therapies? Do surrogate biomarkers exist that can prospectively identify individuals who would benefit from such therapies?

*See also p. 1567.

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Osuchowski et al has previously shown that even individual outbred mice subjected to a reproducible cecal ligation and puncture manifest a broad range of survival responses, but mortality could be predicted by their early circulating inter-leukin (IL)-6 concentration (9, 10). In this report, the investigators use the same stratification system to demonstrate that only mice predicted to die based on their IL-6 concentration responded favorably to goal-directed early supraphysiologic dexamethisone. In a 21st century landscape tainted by the history of earlier failed therapeutic interdiction (11), the authors should be applauded for their demonstration that early stratification based on circulating IL-6 levels can guide corticosteroid therapy to improve survival. Equally important, the authors demonstrate that the entire septic mouse cohort and the cohort of mice predicted to survive based on their plasma IL-6 concentrations gained no survival benefit from corticosteroid therapy. Thus, the authors have emphasized the challenges and shortcomings of past trials aimed at empirical treatment of poorly defined, heterogenous septic cohorts (5, 11).

Although the authors have provided convincing evidence that targeted therapies based on IL-6 concentrations can identify cohorts that might benefit from steroid therapies in a murine model of polymicrobial peritonitis, a number of perplexing questions remain. These studies were performed in a model of generalized peritonitis; however, different findings have been witnessed in a murine pneumonia model. Li et al (12) reported that corticosteroid therapies were broadly beneficial in a murine *Escherichia coli* model, regardless of the severity of the initial infection, and the steroids significantly lowered the plasma IL-6 concentrations across the board.

These latter findings are again different than those observed by Osuchowski and co-workers (6). In this report, the authors hypothesized that septic mice succumb to an early overwhelming systemic inflammatory response, which the authors believe may be ameliorated by strategic corticosteroid administration. Surprising was the fact that although early targeted corticosteroid therapy improved outcome, it had little impact on the circulating levels of IL-6, tumor necrosis factor-α, IL-1β, IL-2, macrophage inflammatory protein-1α, macrophage inflammatory protein-2, keratinocyte-derived cytokine, and monocyte chemoattractant protein-1, all bona fide inflammatory mediators, many with prognostic value in themselves. In addition, no significant reduction was observed on circulating numbers of neutrophils, platelets, or lymphocytes as is a common effect of corticosteroids and was observed earlier (13).

Although the authors present a rational, well-considered approach to use IL-6 as a prognosticator that highly predicts early mortality in their model, and a potential 29% survival benefit from cortico-steroids, the fact remains that individual animal models are rather poor surrogates for human sepsis (5, 11, 14, 15). Even though the cecal ligation and puncture model was used to replicate human peritoneal sepsis (and to many represents the “gold standard”), there are numerous intangibles such as preexisting comorbidities, age, continuous fluid resuscitation, nutritional support, guided antibiotic therapy, and operative intervention that make human sepsis more complex, and routinely difficult to replicate in mice (16). Juxtaposed with the murine vs. human sepsis conundrum stands the mortality disparity between the cecal ligation and puncture model, which was 50% across the board and 90% in the group that showed benefit, compared with an overall mortality of

approximately 25% in humans (14, 17, 18). It would be interesting to know whether a more modest (LD_{20}) model of murine sepsis (19) would yield as strong a sensitivity and specificity index for predicting 48-hour mortality, and whether the mice predicted to die would experience as great an improvement in survival from steroids. In a large clinical trial in severe sepsis with anti-tumor necrosis factor therapies using plasma IL-6 as an entry criterion, the study showed an 11% relative reduction in morbidity ($p = 0.041$) with anti-tumor necrosis factor antibodies in patients with elevated IL-6 concentrations (20). In patients with an elevated IL-6 level, placebo mortality was nearly 48%. It should be noted, however, that a smaller earlier study could not confirm these results (21).

Considering the current state-of-the-art medical care, and evidence-based protocol-driven practices employed in most tertiary referral centers, the dilemma experienced by practicing clinicians is not to improve 50% but to prevent 20% mortality. This translates into a higher cost in man hours and financial resources per percentage point of survival gained (5, 18). Indeed, the ability to predict, based on IL-6 responses or some other surrogate marker, which subjects will succumb early to sepsis would be invaluable; however, given the variable etiology of sepsis and the individuals experiencing the syndrome, early identification is unfortunately dependent on multiple circumstances that typically remain far from clinician control, and difficult to summarize with a single biological prognosticator (14).

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