sulin resistance. What are the signaling pathways activated or inhibited by RBP4 that could affect insulin action? Do increased RBP4 levels cause or result from reductions in GLUT4 levels? Is genetic variation in the RBP4 gene associated with variation in the risk of insulin resistance or type 2 diabetes? Does the administration of a synthetic retinoid such as fenretinide, an agent that reduces the serum RBP4 level and total-body retinol levels, improve insulin sensitivity in humans?

The study by Graham et al. should prompt investigations to address these and other questions to define the biologic action of RBP4 in relation to insulin resistance and diabetes. Whatever the outcome of these investigations, it will take new approaches such as those used by Graham et al. to identify unanticipated mechanisms underlying type 2 diabetes and to identify better treatments for this disease.

Dr. Polonsky reports serving as a member of the scientific advisory board and holding equity in Amylin Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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Fluid-Management Strategies in Acute Lung Injury — Liberal, Conservative, or Both?

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One of the factorial assessments carried out in the Fluids and Catheters Treatment Trial (FACTT) conducted by the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, the results of which are reported by Wiedemann et al. in this issue of the *Journal*,[1] was to determine whether a conservative or a liberal strategy of fluid management was more effective in patients with established acute lung injury. Although there was no difference in mortality at 60 days between the two treatment groups, patients in the group treated according to a conservative strategy of fluid management had significantly improved lung function and central nervous system function and a decreased need for sedation, mechanical ventilation, and intensive care. These salutary effects were achieved without an increase in the frequency of nonpulmonary organ failure or shock. This trial provides guidance on fluid management in critically ill patients.

The lungs provide a unique clinical window on the evolution of critical illness. Acute lung injury results from a direct or indirect inflammatory insult that has characteristic radiographic features and functional changes. The lungs, and their function, reflect the dynamic balance between the primary insult and pathogenic mechanisms responsible for the outcome of organ dysfunction, death, or recovery (Fig. 1). In 1942, Cuthbertson described this metabolic response as the "ebb and flow" of shock[2]: "During the ebb-phase or pre-resuscitation phase, there is low cardiac output, poor tissue perfusion, and a cold and clammy patient." In this phase, there is an intense avidity for sodium and water that is a response to a decrease in intravascular volume. Vasoregulatory and myocardial dysfunction, increased metabolic demands, and impaired systemic oxygen use may also be present. These hemodynamic perturbations create global tissue hypoxia, which contributes to inflammation[3] and early respiratory decompensation.[4] The presence of these processes and their interactions provide the rationale for the use of strategies of comprehensive hemodynamic optimization in the intensive care unit (ICU).[5,6]

In another randomized, controlled clinical trial involving patients in the early phase of systemic inflammation,[6] my hospital applied a strategy of comprehensive hemodynamic optimization[5] on the patient's arrival at the emergency department. This strategy was applied during the first six hours after the patient was admitted to the hospital and before admission to the ICU. Some observers have

regarded this approach as "aggressive fluid resuscitation." Although significantly more fluid was given to these patients than to those in the control group during the first six hours after arrival at the hospital, the amount of fluid administered during the first three days was essentially the same in the two groups. The use of our strategy was associated with a significant reduction in morbidity, mortality, interlukin-8 levels, and the need for mechanical ventilation.[7] Thus, the timing of the titration of fluid administration (that is, during the ebb phase) after disease presentation has important effects on the pathogenesis of inflammation, therapy, and mortality.

Cuthbertson observed that "during the flow phase, which is a staccato affair, the patient struggles to break from the grip of the ebb-phase, which lasts about 3 days. Upon entering the flow-phase, the swollen patient has an increased cardiac output, normal tissue perfusion where diuresis occurs, and body weight falls steadily." Bone et al. described this as the stage in which the balance between proinflammatory and anti-inflammatory mediators reaches homeostasis and there is no longer a need to continue aggressive hemodynamic support and fluid therapy.[8] At the same point, the factors driving systemic conservation of water and sodium attenuate, and there is a mobilization of extravascular fluid.

Although these phases have been pathogenically well described, the clinical landmark that separates the ebb phase from the flow phase is frequently indistinct and complex. In patients with acute lung injury in the established phase, an increase in lung water is due to changes in the direct permeability of the capillaries of the lung and systemic influences on water balance.[9,10] If manipulation of the fluid balance is not performed, pulmonary edema, cardiovascular complications, respiratory insufficiency, and continuation of the need for ventilator support can result. Therefore, conservative fluid strategies, perhaps even with the use of diuretic provocation, along with appropriate caution to preserve organ perfusion and avoid metabolic derangement, are therapeutically sound.

In the trial conducted by Wiedemann et al., the manipulation of fluid management was isolated as a controlled intervention. Because the transition from the ebb phase to the flow phase may be indistinct, the timing of the initiation of conservative strategies of fluid management is very important. In this trial, the therapy was started on average 43 hours after admission to the ICU and 24 hours after the establishment of acute lung injury. Most of the patients in the study already had nearly optimized hemodynamics (i.e., volume-replete intravascular space and hyperdynamic circulation with a cardiac index ranging from 4.2 to 4.3 liters per minute per

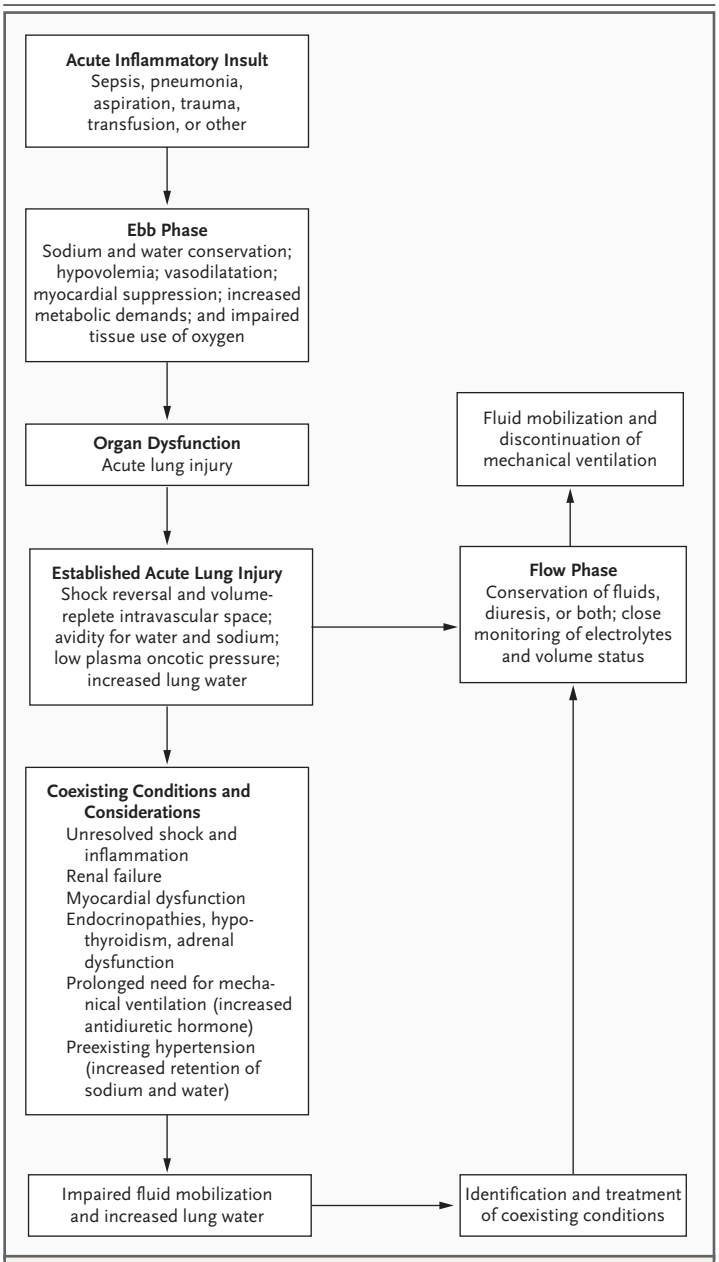

Figure 1. Factors Influencing Fluid Management in Acute Lung Injury.

square meter at baseline) and thus were homogenous in this respect. Because patients whose condition required dialysis and those with overt renal failure were excluded from the trial, it was possible to introduce conservative strategies of fluid management into the care of patients who were less vulnerable to the negative consequences of intravascular volume depletion and diuretic therapy.[11] When the strategies of fluid management were compared according to whether the patients were or were not in shock at baseline, the benefits of a conservative strategy were less robust. The increase within 0.3 day in cardiovascular-failure–free days in the group treated with the liberal strategy, as compared with those treated with the conservative strategy, suggests that caution should be used in applying a conservative strategy of fluid management during the resuscitation, or ebb, phase.

The protocol used in this trial is not identical with standard practice. In order to generalize these results and avoid mitigating the salutary findings, multiple variables must be considered when applying a conservative approach to fluid management.[12] The exclusion of patients receiving hemodialysis and those with overt renal insufficiency or heart failure, and the relatively young age of the patients included in the study — approximately 50 years of age — make this trial a departure from the reality that many clinicians face in the treatment of patients with acute lung injury. The clinician must also make an accurate clinical assessment of the flow phase while paying particular attention to the untoward complications that may occur with the institution of conservative strategies of fluid management and active diuresis.

Fluid may be a friend when appropriately titrated during the resuscitation, or ebb, phase of acute lung injury. However, excess fluid becomes an enemy when it is no longer physiologically needed. Conservative fluid management during the established phase of acute lung injury is just as important as titrated liberal administration during the acute phase of the inciting insult. There are important benefits to the goal-directed administration and the removal of fluid during the appropriate phases. In contrast to what is true in politics, in fluid management of acute lung injury, it is OK to be both liberal and conservative.

Dr. Rivers reports having received fees for service on advisory boards or consulting fees from Biosite, Lilly, Hutchinson Technology, Chiron, and Edward Lifesciences; lecture fees from Phillips, Eisai Pharmaceuticals, and Edwards Lifesciences; and research support from Hutchinson Technology. No other potential conflict of interest relevant to this article was reported.

This article was published at www.nejm.org on May 21, 2006.

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