sul in 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.

From the Department of Medicine, Washington University School of Medicine, St. Louis.


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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, interleukin-8 levels, and the need for mechanical ventilation. 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. 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. 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
square meter at baseline) and thus were homoge-
ous 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.\textsuperscript{11} When the strategies of fluid manage-
ment 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 cardiovas-
cular-failure–free days in the group treated with
the liberal strategy, as compared with those treat-
ed with the conservative strategy, suggests that
cautions should be used in applying a conservative
strategy of fluid management during the resus-
citation, 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.\textsuperscript{12} The exclusion of patients receiv-
ing hemodialysis and those with overt renal in-
sufficiency 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 cli-
nicians 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 ti-
trated 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 in-
jury, it is OK to be both liberal and conservative.

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From the Departments of Emergency Medicine and Surgery,
Henry Ford Hospital, and the Department of Emergency Medicine
and Surgery, Wayne State University School of Medicine — both
in Detroit.

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