studies (9, 10). Other antiviral treatments are scarce: ribavirin may be used in severe RSV and paramyxovirus infections, and cidofovir in adenovirus infections, particularly in immunocompromised hosts, but proof of efficacy remains elusive (11, 12). Drugs against rhinovirus and others are under development, but are not yet available (13). The treatment of patients having developed severe pneumonia with a specific antiviral treatment is thus far from becoming the standard of care, but this is now due to the lack of drugs and no longer to the lack of appropriate diagnostic procedures.

In conclusion, undoubtedly viral infection of the respiratory tract may be associated with and/or cause exacerbation of chronic lung disease (14) or serious lower respiratory tract complications including viral pneumonia, and probably in a much larger proportion of patients than commonly thought, particularly if immunosuppression or other conditions are present (8). Choi and coauthors contribute to the knowledge and understanding of the etiology of severe pneumonia including HCAP. This could provide hints to design studies to limit antibiotic overuse (a key issue not addressed in the study) and to better control hospital transmission of viral agents. However, many unresolved questions still remain, the main one being the direct therapeutic consequences due to the absence of a specific antiviral agent for most of these infections. Progress in clinical microbiology has surpassed antiviral drug development, but the time has come for clinicians to use these diagnostic tools to impact their clinical management and to be prepared for future progress in the field.

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Trajectories of Recovery and Dysfunction after Acute Illness, with Implications for Clinical Trial Design

After more than a decade of rigorous empirical work, it is increasingly accepted that long-term outcomes after critical illness are an important problem—not only clinically meaningful for patients, but scientifically fecund for understanding basic biology (1). Many—but by no means all—of our patients who survive critical illness will have important new deficits in their brain or muscle function. Many of these injuries will be new, although there will also be some acute recognition of chronic problems (2, 3). To design a randomized controlled trial of therapies to improve these long-term outcomes, we need an appropriately defined patient population, a biologically plausible intervention, and a clinically meaningful endpoint. In this issue of the *Journal*, Woon and colleagues (pp. 333–340) provide important and provocative new data to inform our choice of endpoint (4).

To understand why these results are so interesting, we need to make explicit the mental models of post-ICU trajectory that we usually only reference implicitly. Why could so many of us read the report by Schweickert and colleagues of a difference in *hospital discharge* location after early mobilization, and yet confidently use such data to justify this intervention for all patients to improve *long-term* outcomes (5)? I suggest that it is because those results resonated with our implicit mental model, shown in Figure 1 as the Big Hit. In a Big Hit trajectory, patients have an acute loss of function during their critical illness, from which

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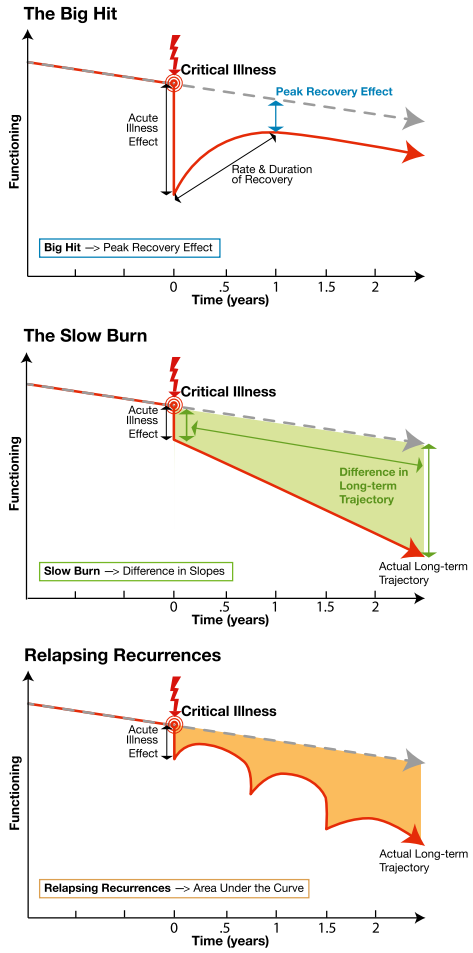

Figure 1. Prototypical trajectories of recovery. The *upper gray line* extending past critical illness is the counterfactual trajectory of functioning that would have occurred, had the patient not developed critical illness.

they may gradually recover. After acute illness, it appears that peak recovery is 1–2 years after initial injury for physical functioning (6–8). Nonetheless, we expect a relatively smooth trajectory after the initial deficit. Key questions after a Big Hit are how we can reduce the depth of the initial functional loss, improve the slope of functional recovery, and minimize the residual deficits.

Woon and colleagues test the hypothesis that individual patients' cognitive function at discharge would be strongly predictive of 6-month cognitive function, as we might expect from a Big Hit trajectory. If this hypothesis were correct, the authors would thereby validate a short-term, readily obtained measure that could serve as a surrogate endpoint for a longer-term outcome. Such a validation would let us target postdischarge cognitive rehabilitation to a subset of patients, increasing cost effectiveness of any intervention; it would let us more appropriately counsel families about prognosis. To test this hypothesis, they assembled a cohort of 70 consecutive patients with few comorbidities from the Shock Trauma and Respiratory Intensive Care Units at LDS Hospital and Intermountain Medical Center. Ten patients died, and seven were lost to follow-up, leaving a respectable 53 patients who underwent cognitive screening at hospital discharge.

Contrary to the Big Hit hypothesis, and to this author's great surprise, they found that discharge cognitive function simply was not associated with 6-month cognitive function. This was true for either of two well-accepted short assessments of cognitive function. This was not a case of marginal *P* values and not-quite-significant findings. There were very substantial levels of disagreement. Consider their results in Table 3 when using an MMSR cut-off of 27, which is simply a 2 × 2 table of cognitive function at discharge versus cognitive function at 6 months.

Eight patients were not cognitively impaired at discharge and still not impaired 6 months later. These are the patients who do well after critical illness, and Rubenfeld has tirelessly argued that we should not forget that these patients exist (9). Eighteen patients were cognitively impaired at discharge and again at 6 months. These are the patients on whom the long-term outcomes literature has focused, those who get knocked down and stay down.

Fifteen patients left the hospital with cognitive impairment but had recovered by 6 months out. Our Big Hit model fully expects patients in this category—indeed, one of our goals in changing ICU practice and providing postdischarge therapy is precisely to increase the number of patients in this "recovered" category. This study was too small to determine what characteristics of these patients led to their recovery, but such a study is certainly worth undertaking. There may be much that we can learn from those patients who recover on their own; in other fields, this is known as the study of "positive deviants." In particular, we need to know: what had the patients, their caregivers, or their medical team figured out that may be generalizable and testable in a broader population?

The disturbing cases are the 12 patients who left the hospital unimpaired by assessment, but who were significantly cognitively impaired at 6-month follow-up. There are three possible explanations for this large group. Least interesting, this might all be measurement error, but that seems unlikely given the well-established assessment tools used. Alternatively, perhaps these patients all happened to get another really bad injury after leaving the hospital; we cannot rule that out. More likely is that these patients were not on a Big Hit trajectory. Two other trajectories are possible, as shown in Figure 1, and well-described in other illnesses. In a Slow Burn trajectory, the patients are sent off on a new path of persistent more rapid decline, as diabetes increases atherosclerosis. In a Relapsing Recurrent trajectory—common in multiple sclerosis or chronic obstructive pulmonary disease—patients have a disease with acute exacerbations and then partial recovery. Some scholars have even argued that relapsing recurrence is the best model for posthospitalization disability, although there is no scientific consensus on that interpretation (10).

With only two data points for each patient, we cannot distinguish Slow Burns from Relapsing Recurrences. But these 12 patients' declines are inconsistent with a Big Hit. Importantly, there are multiple credible biological and psychosocial mechanisms for such accumulating decrement pathways. These include a prolonged inflammatory milieu (11, 12), microglial cell activation (13), an inactivity/loss-of-function spiral, self-imposed restriction of life activities and mobility (14), and the adoption of a sick role.

As with any study, the article by Woon and coworkers has limitations. Because of idiosyncrasies in their recruiting and enrollment criteria, we do not know the relative frequencies of each trajectory. Certainly this work needs to be confirmed in a broader population. A replication using precisely the same instruments at discharge and follow-up would be nice, but the instruments used in the article are well established and credibly measure the same underlying construct.

This leaves us with an urgent need to carefully map the trajectories of injury and recovery for specific critical illnesses. We need to know the relative frequencies of different illness trajectories because they imply different endpoints for ICU trials interested in long-term patient-centered outcomes—regardless of whether the trials specifically target long-term outcomes. For patients on a Big Hit trajectory, a clinical trial should examine the change in absolute level of function at maximal recovery. In contrast, for

patients on a Slow Burn trajectory, there is no single time point at which that difference should be measured—instead a clinical trial should seek to change the trajectory of decline. For patients on a Relapsing Recurrence trajectory, a clinical trial should seek to maximize the number of impairment-free months. These are fundamental differences in trial design that call for an empirical grounding rather than guesswork. The present work by Woon and colleagues is an important step in the right direction, as it emphasizes how many assumptions we have been making and how much more data we truly need.

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Making It Personal: Using Genomics to Predict Pulmonary Hypertension in Sickle Cell Disease

In this issue of the *Journal*, Desai and colleagues (pp. 359–368) attempt to use genomic-based methods to enhance screening patients with sickle cell disease (SCD) for the presence of pulmonary hypertension (PH) (1). This work contributes significantly to this rapidly evolving field and may help provide insights into disease pathogenesis.

Despite treatment advances over the past 20–30 years, patients with SCD have an average mortality in the fifth decade with pulmonary complications being the major cause of death (2). Much work has been done over the past decade to gain a greater understanding of the prevalence and natural history of PH in this population. Although not diagnostic of PH, an elevated tricuspid regurgitant jet velocity (TRV) by Doppler-echocardiography consistent with risk for PH occurs in approximately 30% of hemoglobin-SS and 10–25% of hemoglobin-SC adults and is an independent risk factor for mortality (3, 4). PH, diagnosed by right heart catheterization, occurs in 6–11% of hemoglobin-SS adults. Approximately 40–50% of patients with PH have pulmonary arterial hypertension (PAH), and the rest have pulmonary venous hypertension (PVH), primarily related to diastolic dysfunction (5–7). PH, regardless of etiology, is also an independent risk factor for mortality in SCD (7), supporting the notion that echocardiographic screening is an effective screening tool. However, the high false-positive rate of echocardiography suggests that other noninvasive screening tests are needed to better risk stratify patients with SCD prior to right heart catheterization (6).

The clinical heterogeneity observed in SCD despite the shared genetic hemoglobinopathy suggests that extra-erythrocytic factors play an important role in disease modulation. Over the past decade, a body of literature has emerged that supports the concept that other genetic modifiers of this disease exist. Large-scale genetic studies of patients with SCD have identified single-nucleotide polymorphisms (SNPs) in *VCAM1*, *KL*, and genes within the transforming growth factor (TGF)-β signaling pathway as being associated with different vascular complications of SCD, including an elevated TRV (8). Microarrays of peripheral blood mononuclear cells (PBMCs) from patients with SCD have demonstrated an antioxidant and proinflammatory phenotype when compared with normal volunteers, suggesting a dysregulation of each of these pathways in SCD (9). This is the first study to date that attempts to link SNP data with mRNA expression in circulating blood cells of patients with SCD with a specific clinical phenotype. In the present study, examination