hyponatremia (16). Finally, evidence suggests that bolus infusions of more than 300 mOsm of sodium given over 20 minutes are clinically well tolerated (17), even though the resulting increase in serum sodium significantly exceeds the often-quoted "safe" rate of 0.5 mEq/L/hour. In the absence of preexisting hyponatremia and predisposing comorbidities, there is little evidence to suggest that rapid elevation of serum sodium with HTS during initiation of acute hyperosmolar therapy presents a significant CPM risk for most patients.

This discussion is not intended to be a comprehensive review of hyperosmolar therapy, and interested readers should consult such a publication (18) for additional information and for further references. Additionally, the goal is not to encourage the injudicious use of hyperosmolar therapy, as the modality is not without risk and because the aforementioned side effects, although highly improbable, are not theoretically impossible. Accordingly, consultation with an experienced intensivist, neurologist, or neurosurgeon remains invaluable in the management of patients with elevated ICP, particularly since this represents a rapidly evolving field in which ongoing appraisal of the literature is necessary. Notwithstanding, the preponderance of clinical evidence dispels several antiquated myths associated with hyperosmolar therapy that have persisted for generations within the collective consciousness of the medical community. Changes in individual practice and institutional policies grounded in concerns for patient safety but predicated upon these unsubstantiated myths are long overdue, as appropriate delivery of hyperosmolar therapy reduces morbidity and improves survival among patients with intracranial hypertension.

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Interferon-λ_1 and Viral Wheeze in Asthma: A Gothic Duality?

A recurring theme in Gothic literature is that the human condition is an enigmatic mixture of good and evil. These themes are central in classics such as Robert Louis Stevenson's *Dr. Jekyll and Mr. Hyde*, in which the protagonist begins as a respected pillar of the community, but his darker side becomes evident as the story unfolds. In this issue of the *Journal*, Miller and colleagues (pp. 508–516) suggest that IFN-λ_1, a prototypic antiviral cytokine, may also have an injurious duality (1).

Previous studies have demonstrated that rhinovirus (HRV) infections are closely associated with exacerbations of childhood asthma. Since HRV infections often cause mild or asymptomatic illnesses, this raises questions as to mechanisms that differentiate mild colds from severe episodes of wheezing and shortness of breath in children with asthma. Viral factors could relate to the great diversity among HRVs, which consist of over 150 different types in three species (A, B, and C). In fact, there is some evidence that infections with HRV-C species viruses may be more likely to

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cause wheezing and exacerbations of asthma, while B species viruses may be less likely to do so (2, 3). Environmental risk factors for virus-induced wheeze include exposure to pollutants, and for sensitized children, specific allergens. Finally, host factors that increase the risk of wheezing with HRV and other respiratory viruses include low baseline lung function and individual variations in immunologic responses to infection (4–6).

The role of immunologic factors in determining illness severity has been difficult to ascertain, partly due to the difficulties in sampling the lower airway during virus-induced asthma exacerbations. As a result, most studies have instead sampled the upper airway or blood, assuming that these compartments will provide insight into pulmonary infectious and inflammatory mechanisms. This approach has provided insights, yet no definitive answers, about the nature of viral respiratory infections and their role in acute airway obstruction. Generally, the severity of both upper and lower respiratory illnesses is positively associated with inflammatory indicators, including kinins, cytokines (e.g., IL-1, IL-8, CXCL10), and inflammatory cells (mononuclear cells and neutrophils) in airway secretions (7). Because HRV causes relatively little tissue destruction, even in severe colds, it is assumed that these inflammatory responses are the major contributors to the severity of both upper and lower respiratory illnesses. In contrast, most studies have shown that interferons (IFNs) moderate the severity of viral respiratory infections. Type I IFN includes IFN-α and IFN-β, type II interferon is IFN-γ, and type III interferons include IFN-λ_1, IFN-λ_2, and IFN-λ_3 (also known as IL-29, IL-28A, and IL-28B).

To identify mechanisms of virus-induced wheezing, Miller and colleagues conducted a prospective study comparing children with asthma who presented to clinics with an upper respiratory illness (URI) and wheezing (n = 200) to those who presented with a URI without wheezing (n = 209). The protocol included assessments of viral factors (species, quantity of viral shedding) and immunologic responses (cytokine and interferon levels) in nasal washes. Nearly all eligible children participated in the study, and several findings are noteworthy. Viruses were detected in 82% of the children, and HRVs were most often detected. Infections with HRV compared with other viruses were significantly associated with wheezing illnesses, but the species of HRV or quantity of shedding were similar in wheezing illnesses versus URI. Nasal wash cytokine levels in the wheezing versus URI groups were similar, with the interesting exception of selected interferons. Both IFN-λ_1 and IFN-α were increased in children with wheezing illnesses; however, only IFN-λ_1 was associated with the severity of illness and appeared to mediate the effects of HRV infection on asthma exacerbations. The authors conclude that IFN-λ_1 is uniquely associated with exacerbations of asthma in their study, and suggest that IFN-λ_1 should be considered as a target for prevention or therapy against HRV-associated asthma exacerbations.

In contrast, results from some (8, 9) but not all (10, 11) previous studies have suggested that deficient production of IFN-β and IFN-λ by virus-infected airway epithelial cells could be a key feature of asthma leading to impaired apoptosis of virus-infected cells, increased viral replication, and more severe airway clinical symptoms. Miller and colleagues also cultured airway epithelial cells derived from nasal brushings, and reported that HRV-induced IFN-λ_1 was lower in children with asthma. This represents an interesting duality: HRV-induced IFN-λ_1 secretion from epithelial cells *in vitro* was lower in asthma, but HRV-induced IFN-λ_1 *in vivo* was increased in expression during wheezing illnesses.

The concept that interferons can contribute to illness is familiar to rheumatologists, since chronic IFN-α production has been implicated in the pathogenesis of arthritis and lupus (12). Furthermore, in a mouse model of respiratory viral illness, virus-induced type I interferon production was linked to expression of the high-affinity IgE receptor on lung dendritic cells, which in turn recruit to the airways alternatively activated macrophages that overproduce IL-13 and drive airway inflammation (13). Analysis of patterns of gene expression in children with asthma exacerbations supports the idea that similar mechanisms might be operative in humans (14). These findings suggest that a positive association between overproduction of IFN-λ_1 and airway pathology is plausible.

The study by Miller and colleagues has several limitations, and the authors acknowledge most of these nuances. First, causality cannot be adequately assessed in an observational trial, and it is important to consider the alternative possibility that greater viral replication drives more severe illness and increased interferon responses. The authors measured viral RNA in nasal secretions, and the lack of correlation between viral shedding and wheezing led them to discount this possibility. However, estimation of viral shedding based on a single upper airway sample per illness is not likely to be accurate, and there are technical difficulties in quantitating RNA from the large number of genetically diverse HRVs. These shortcomings cast some doubt on their conclusion. Furthermore, the study did not include routine sampling of nasal secretions, and so asymptomatic colds were not included. Since up 25% of HRV infections are asymptomatic, this is an important consideration in analyzing the relationship between infection, immune responses, and illness severity.

Regardless of these technical limitations, the results of this large and well-designed study are thought provoking, and cast a shadow on the reputation of IFN-λ_1, heretofore a well-respected defender against the ravages of viral respiratory infections in children. Are the effects of this antiviral cytokine more complicated than initially appreciated? Should we be equally suspicious of other pillars of the antiviral community? To resolve these questions, additional studies are needed to more clearly define mechanisms of potential adverse effects of overproduction of IFN-λ_1, and to establish temporal relationships and kinetics of viral replication, IFN responses, and respiratory outcomes. These additional studies, perhaps utilizing experimental inoculation techniques or animal models of viral respiratory infection, should provide the information that is required to decide whether intervention studies to neutralize IFN-λ_1 are truly warranted. The next chapter should be interesting.

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Embracing Physical and Neuropsychological Dysfunction in Acute Lung Injury Survivors: The Time Has Come

Over the last decade, ground-breaking advances have occurred in the management of acute lung injury (ALI), including low tidal volume ventilation and the implementation of a conservative fluid strategy (1, 2). As a result, more patients are surviving ALI. Based on an incidence of 190,000 cases per year and recent case fatality rates as low as 20%, there will be more than 150,000 new ALI survivors annually in the United States alone (3–5). The pulmonary and critical care community has started to focus on understanding and treating post-ICU–related nonpulmonary disorders that occur in the growing number of ALI survivors.

Much of the recent interest in post-ICU consequences has been concentrated on the neuromuscular dysfunction (6). Neuromuscular weakness is common in ALI survivors and unfortunately can persist for years after hospital discharge (7). After 5 years, the median distance walked in 6 minutes by ALI survivors was only 76% of the distance of an age-matched and sex-matched control population, consistent with a persistent reduction in exercise capacity (8). Psychological issues, including symptoms of depression, anxiety, and post-traumatic stress disorder, are also common in ALI survivors (9, 10). Initial studies reported that between 20 and 50% of ALI survivors had symptoms of depression after 1 year (11–13). Risk factors for post-ALI depressive symptoms include obesity, hypoglycemia, alcohol dependence, female sex, younger age, and cognitive dysfunction (14). Symptoms of moderate to severe depression also persist and remain in nearly 20% of ALI survivors after 5 years (15). These 5-year follow-up data suggest that the decrements in quality of life and exercise capacity may have resulted from persistent weakness, as well as a spectrum of neuropsychological impairments in ALI survivors.

In this issue of the *Journal*, Bienvenu and colleagues (pp. 517–524) prospectively followed 186 ALI survivors for 2 years (16). Patients were evaluated at 3, 6, 12, and 24 months after the onset of ALI. Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale, and impaired physical function was defined by having at least two dependencies in instrumental activities of daily living in patients without baseline impairment. The point prevalence of depressive symptoms was 24% at 1 year and 32% at 2 years with an overall cumulative incidence of 40%. The 2-year cumulative incidence of impaired physical function was 66%. The presence of depressive symptoms was independently associated with the development of impaired physical function.

This study provides another excellent picture of long-term outcomes in ALI survivors and adds significantly to our understanding of the complex interactions between physical and neuropsychological impairments. The outstanding follow-up rates and serial data collection reflect the extreme diligence of this research team and depict how post-ICU burden is sustained over time. Most importantly, this study confirms that depressive symptoms are common and persistent in ALI survivors. Healthcare providers who care for patients after ICU discharge should consider screening for symptoms of depression. The methodology of the present study also raises some concern about the interpretation of the results. The Hospital Anxiety and Depression Scale is a screening tool that has been validated to identify the presence of significant depressive symptoms or the risk of actual depression. The persistence of symptoms for more than 21 months suggests that some patients may have actual psychiatric diseases. Qualitative data from individual structured interviews would have been useful to distinguish true major depressive disorders from persistent depressive symptoms in ALI survivors and help understand who may benefit from therapeutic interventions. The investigators also did not collect information regarding the initiation of medical therapy or counseling for depressive symptoms in their cohort of ALI survivors. Some of the temporal variability and reported remissions in the incidence of depressive symptoms may have been related to the initiation of psychological therapies. Previous studies have suggested that decreased exercise capacity in ALI survivors has an impact on neuropsychological impairments (8). In the present study, objective measures of physical dysfunction such as a 6-minute walking test were not reported. It is reasonable to consider that having at least two dependencies in instrumental activities of daily living could result from primary pulmonary dysfunction as well as from other nonpulmonary impairments. These physical–psychological interactions have to be described in detail to design a multimodal intervention that may include both antidepressive therapies and pulmonary and physical rehabilitation. It is also possible that the multiple dependencies in instrumental activities may partially result from depression-related somatization in some ALI survivors.

This study also raises several fundamental questions that should generate future investigations concerning the care of ALI survivors. Some of the variability in the rates of neuromuscular dysfunction

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