

a bridge too far to interpret the present findings as relevant for early asthma recognition.

The study by Latzin and coworkers is the first that prospectively links elevated FE_{NO} in early infancy to later development of respiratory symptoms. Their findings are of great interest and a major stimulus for the study of the interaction between early-life exposures and genetic background of the child with early-onset asthma, using exhaled markers of airway disease. Confirmation of the findings in larger groups and development of sensitive and robust techniques to assess FE_{NO} and other markers of airway inflammation in exhaled air or exhaled breath condensate are needed. Also, studies with a longer follow-up are necessary to ascertain the long-term outcome. Finally, the added value of FE_{NO} compared with other well-established risk factors for asthma should be addressed. Prospective FE_{NO} -typing of infants, followed by the development of well-targeted early treatment and prevention strategies before the onset of clinical disease, is an attractive perspective indeed.

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Relative Adrenal Insufficiency in the ICU: Can We at Least Make the Diagnosis?

The use of corticosteroids for patients with septic shock has long been controversial. As early as 1950, small studies suggested a potential benefit of corticosteroids in the setting of suppurative streptococcal infection (1). In 1976, one clinical trial found a dramatic reduction in mortality for patients with bacteremic septic shock treated with high dose corticosteroids (2), but a larger subsequent trial did not (3). To reconcile these disparate results, a large multicentered trial was conducted in which patients received methylprednisolone or placebo within two hours of meeting study criteria. Not only did corticosteroids not confer benefit, but a trend toward increased mortality was observed (4).

In the late 1990s the concept of relative adrenal insufficiency (RAI) in septic shock emerged. While absolute adrenal insufficiency in the setting of septic shock appears rare (5, 6), a lack of adrenocortical reserve, as determined by an inadequate re-

sponse to synthetic corticotropin stimulation, is both common and associated with increased mortality (5, 7, 8). Extrapolating from these observations, Annane and colleagues undertook a randomized placebo-controlled trial of low-dose hydrocortisone and fludrocortisone replacement therapy in patients with septic shock (9). Patients were also tested for RAI, defined as an increase in serum cortisol less than 9 $\mu\text{g}/\text{dl}$ after stimulation with 250 μg of synthetic corticotropin. When analyzed by intention to treat, there was no difference in overall mortality between the groups receiving steroid replacement or placebo. By *post hoc* analysis, in the subset of patients meeting the predefined definition of RAI, adrenal replacement therapy did decrease 28-d, ICU, and hospital mortality.

This trial no doubt resurrected the use of steroids for patients with septic shock by many clinicians, but it again stoked the fires of controversy. Importantly, survival benefit has yet to be

confirmed. Equally controversial is the ability to actually make a diagnosis of RAI in patients with septic shock. If baseline levels of cortisol under conditions of extreme stress are very low, does not this alone signal RAI, quite apart from a failure to increase levels with exogenous stimulation? If baseline levels are high, are measures of further stimulation relevant? Was the corticotropin test the best for classification, when it yields a diagnosis of RAI in approximately 75% of all patients with septic shock (9)? What of the potential for failure to diagnose secondary adrenal insufficiency with the corticotropin test? Would a more thorough test of the hypothalamic pituitary adrenal axis—such as insulin tolerance or metyrapone testing—better identify RAI? As critically ill patients frequently develop hypoproteinemia and more than 90% of circulating cortisol is protein-bound, can we rely on judgments made by measuring total serum cortisol levels in the critically ill? (10). Finally, what is the level of cortisol in the tissues during critical illness and how do serum levels—basal or provocative—indicate the true glucocorticoid status of individual organs and tissues?

In this issue of the *Journal*, Dr. Annane and colleagues (pp. 1319–1326) go a long way toward answering these questions and concerns (11). Using the overnight metyrapone test—sensitive to the detection of both primary and secondary adrenal insufficiency—as a “gold standard,” they confirm that diminished adrenocortical reserve is indeed common among patients with severe septic shock, occurring in approximately 60%. In addition, they validate both the corticotropin test and absolute cut-offs for both free and total cortisol levels to define RAI. The strongest predictors of adrenal insufficiency were baseline total cortisol level less than 10 $\mu\text{g}/\text{dl}$, baseline free cortisol level less than 0.8 $\mu\text{g}/\text{dl}$, or a change in cortisol after corticotropin stimulation less than 9 $\mu\text{g}/\text{dl}$ (total cortisol) or 2 $\mu\text{g}/\text{dl}$ (free cortisol). Conversely, adrenal function was most likely to be intact when the corticotropin-stimulated total cortisol level was greater than 44 $\mu\text{g}/\text{dl}$ or when the change after corticotropin was greater than 17 $\mu\text{g}/\text{dl}$.

As centers have debated over how best to spend precious resources on diagnostic tests, many have questioned the utility of using random cortisol levels or free cortisol levels in attempting to diagnose adrenal insufficiency. Free cortisol performed no better than total cortisol for any diagnostic parameter, rendering unnecessary the extra expenditure for free cortisol levels. The best predictor of adrenal insufficiency was the presence of baseline cortisol $< 10 \mu\text{g}/\text{dl}$ or delta cortisol $< 9 \mu\text{g}/\text{dl}$, with a specificity of 96%, positive predictive value of 94%, and positive likelihood ratio of over 10.

Several surprises emerge from this study. It was shown that 12.5% of patients with septic shock had absolute adrenal insufficiency as defined by a baseline total cortisol level below 10 $\mu\text{g}/\text{dl}$. This rate is approximately four times higher than has been reported in the past (5), and lends credence to the usefulness of baseline cortisol levels done routinely as part of a corticotropin test. Even more surprising, the vast majority (71%) of patients with severe septic shock with adrenal insufficiency were found to have secondary, as opposed to primary, adrenal insufficiency as determined by the metyrapone test. While this constitutes the first report of metyrapone testing in critically ill patients, the distinctly different patterns for the patients without septic shock but who were critically ill as compared with patients with septic shock suggests a specific interplay between the physiology of sepsis and the activity of the hypothalamic pituitary adrenal axis. Hypothalamic pituitary dysfunction is also believed to underlie the “euthyroid sick” and “eugonadal sick” syndromes observed in critical illness (12); however, whereas treatment of RAI in sepsis apparently impacts outcomes, treatment of thyroid or gonadal hypofunction—given the limits of our present knowl-

edge—does not. Potential mechanisms for this neuroendocrine insufficiency may include sepsis-induced hypothalamic or pituitary apoptosis (13), or depletion of adrenocorticotrophic hormone (ACTH) brain stores in the face of persistently high demands, a condition akin to vasopressin depletion in patients with septic shock (14).

The present study does not address treatment of relative adrenal insufficiency, and thus cannot diffuse the remaining controversy regarding the size of treatment effect or the necessity of fludrocortisone. We await the results of a large multicenter trial, the Corticosteroid Therapy of Septic Shock (CORTICUS) trial, which is anticipated to enroll 800 patients and could validate the mortality benefit of steroids in ACTH nonresponders in septic shock (15, 16). In the meantime, we have at least been provided an elegant algorithmic approach to the diagnosis of RAI in severe sepsis and septic shock, a necessary starting point for all rational treatment decisions.

NOTE: Metyrapone is no longer available in the United States, so these studies will be difficult to replicate here.

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Rhinovirus Infections More Than a Common Cold

Rhinoviruses, single-stranded RNA viruses from the Picornaviridae family, are responsible for the majority of common colds. Perhaps more importantly, viral infections trigger the great majority of asthma exacerbations, and rhinoviruses account for two-thirds of these (1). A recent study detected rhinoviruses in 82% of children admitted to an emergency room for acute asthma (2). Rhinovirus infection has also been associated with nearly half of all chronic obstructive pulmonary disease (COPD) exacerbations (3). In addition, evidence has emerged that rhinoviruses are the most common cause of wheezing illness in the first year of life, and rhinovirus-induced wheezing illness in the first year of life is the strongest predictor of subsequent third-year wheezing (4).

The precise mechanism by which rhinoviruses induce exacerbations of airway disease is unknown. Because rhinovirus replication is optimal at 33°–35°C, infections were once thought to be restricted to upper airway tissues. Until recently, rhinoviruses had not been reliably cultured from lower airway secretions. However, rhinoviruses can replicate in lower airway cells even at core temperature, although greater viral yields are obtained at cooler temperatures (5). Also, temperatures of the large airways are 33°–35°C during resting breathing at room temperature (6). Thus, conditions in the lower airways may be permissive for rhinovirus replication. After experimental infection, rhinovirus RNA has been detected in lower airway secretions and epithelial cells (7, 8), and rhinovirus capsid protein has been found in airway epithelial cells, albeit sporadically (9). Together these findings suggest that rhinoviruses can grow in the lower airways, although the extent of rhinovirus replication in these locations is unknown.

It is conceivable that certain individuals are more susceptible to rhinovirus infection and its complications. Compared with normal volunteers, adults with asthma have increased susceptibility to rhinovirus infection both *in vitro* (10, 11) and *in vivo* (12). The mechanisms of this increased susceptibility are just beginning to be understood and relate to impaired innate immune responses (10, 11). A recent study examining the persistence of rhinovirus RNA after asthma exacerbation in children showed that RNA was detectable in 44% of patients 6 weeks after infection, and exacerbations with persistent virus were more severe (2). These data suggest that individuals with asthma possess increased susceptibility to rhinovirus infections. The possibility that host factors contribute to rhinovirus susceptibility merits investigation.

In this issue of the *Journal* (pp. 1392–1399), Kaiser and colleagues (13) describe an immunosuppressed lung transplant recipient who was chronically infected for 13 months with a single rhinovirus strain. Despite retransplantation, 5 of 12 subsequent bronchoalveolar lavage specimens were positive for rhinovirus by cell culture, and the patient died of progressive respiratory failure. Rhinovirus-positive cells were detected in the lung parenchyma by immunohistochemistry. Sequencing of the viral protein 1 capsid glycoprotein and a portion of the 5' noncoding region confirmed persistence of the same rhinovirus strain, which was serologically closely related to serotypes 64 and 94. An additional

prospective study of 68 lung transplant recipients showed persistent rhinovirus infection for many months in two additional patients, one of whom also died of respiratory failure; the other appeared to clear the virus after 8 months, and this was accompanied by resolution of clinical illness.

Why is this report important? This article has obvious ramifications for the growing number of patients undergoing bone marrow and solid organ transplant patients, in whom opportunistic infection with viruses, bacteria, fungi, and parasites is common. Although Kaiser and coworkers (13) did not identify gross histologic modification of the lung parenchyma, the persistence of single strains of rhinovirus accompanied by persistent clinical symptoms, combined with progressive respiratory failure in two of three patients, suggests that rhinoviruses can cause clinically significant, chronic lower respiratory tract infections in immunosuppressed patients. Respiratory syncytial virus, influenza viruses, and parainfluenza viruses have all been reported to cause serious lower respiratory tract infections in immunocompromised hosts, and human metapneumovirus has recently been added to this list (14). Specific antiviral therapies are available for influenza viruses and are in development for each of the others; thus, early diagnosis will be essential for optimal management of these serious infections. In appropriate situations, diagnostic tests for rhinoviruses are therefore clearly warranted and efforts to hasten development of antiviral agents are urgently needed.

The report by Kaiser and colleagues (13) ends once and for all the argument that rhinoviruses cannot infect the lower airways. Although interesting new data suggest that rhinoviruses may induce proinflammatory responses in lung cells independent of viral replication (15), replication is almost certainly required for a maximal response. However, until the present report, which includes positive bronchoalveolar cultures and lung immunohistochemistry, incontrovertible evidence of rhinoviral replication in the lung in the setting of spontaneous infection has been lacking. This report informs our understanding of the mechanisms underlying rhinovirus-induced exacerbations of asthma and COPD.

Although transplant patients are clearly different from most patients with chronic airway disease, the data presented by Kaiser and colleagues (13) are consistent with the notion that immune defects predispose patients to rhinovirus infection. Indeed, it has been shown that peripheral blood monocytes from patients with asthma have a deficient type II interferon- γ response to rhinovirus (16). More recently, bronchial epithelial cells isolated from patients with asthma have been demonstrated to have an incomplete innate immune response to rhinovirus infection, with deficient type I interferon- β and type III interferon- λ production (10, 11). It remains unclear whether the observed alterations in immune responses represent intrinsic defects specific to patients with asthma, or whether they may be associated with chronic airway inflammation and are therefore present in other diseases, such as COPD. These exciting new data raise the possibility that patients with asthma and other patients with chronic airway disease are unusually susceptible to rhinovirus infection, leading