patients. The simple transfusion of RBCs that are depleted of leukocytes and matched for Rh, C, E, and Kell antigens results in improved oxygenation with reduced alloimmunization and seems the equal of exchange transfusion. This is indicated for most patients with reduced alloimmunization and seems the equal of exchange transfusion. This is indicated for most patients with reduced alloimmunization and seems the equal of exchange transfusion.

Therapy with corticosteroids and nitric oxide may be helpful during ACS, and patients with recurrent bouts of VOC or ACS may benefit from hydroxyurea or bone marrow transplantation.

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**The Quick and the Dead**

The Importance of Rapid Evaluation of Infiltrates in the Immunocompromised Patient

The development of pulmonary infiltrates in an immunocompromised patient remains a difficult diagnostic challenge. The differential diagnosis for pulmonary processes in this population is broad and includes both infectious and noninfectious causes. In addition to bacteria, fungi, viruses, mycobacteria, and protozoa, the lung is a target organ for fat embolism. The prognosis for immunosuppressed patients with pulmonary complications of sickle cell disease is grim, irrespective of the factors leading to the altered immune status. For example, in subjects who require mechanical ventilation (MV) following hematopoietic stem cell transplantation (HSCT), multiple studies document that mortality rates exceed 50%. Nonetheless, utilization of immunosuppression is expanding, with increasing numbers of both solid-
organ transplants and HSCTs performed annually. Similarly, therapies for hematologic malignancies are also becoming more aggressive. Particularly frustrating for physicians who care for these patients is the fact that many of the patients are young and have undergone aggressive interventions in hopes of a cure.

In this issue of CHEST (see page 253), Rano and colleagues report the results of a prospective study of a heterogenous population of immunosuppressed patients; these subjects underwent an extensive evaluation to determine the cause of their pulmonary infiltrates. The authors noted that three factors predicted mortality: severity of illness as measured by the APACHE (acute physiology and chronic health evaluation) II score, the need for MV, and the delay in establishing a specific diagnosis. Methodologically, the study was sound in that it was prospective, focused on a consecutive series of patients, and had a large sample size. Nearly one fourth of the patients had noninfectious pulmonary complications. Moreover, most prior studies in this area have examined outcomes in homogenous populations, while Rano et al studied individuals who were immunosuppressed as a result of solid-organ transplantation, HSCT, or chemotherapy for hematologic malignancy. They also performed a rigorous multivariate analysis to control for the impact of many confounders that may affect mortality in this setting.

MV has previously been demonstrated to portend a poor prognosis in the immunosuppressed patient. In HSCT, some advocate withholding care if the patient requires MV and has other organ failures. MV may represent an aspect of severity of illness not captured by the APACHE II scoring system. In other words, patients needing MV are simply more ill than similar patients matched for general severity-of-illness scoring tools. MV may, though, be directly injurious through increasing the risk for nosocomial pneumonia. Supporting this possibility, two randomized trials in immunocompromised subjects with respiratory failure found those treated with noninvasive ventilation (NIV) had better outcomes than those undergoing MV. In light of these studies of NIV, the findings of Rano and colleagues underscore the need to avoid MV if possible in these patients.

As with the need for MV, multiple retrospective analyses in immunosuppressed patients indicate that higher APACHE II scores predict mortality. In an earlier series of subjects admitted to the ICUs following autologous HSCT, no patient with an APACHE II score > 29 survived. In patients with leukemia, Kress et al reported near-universal mortality in persons with high APACHE II scores. Taken alone, the significance of the APACHE II score is limited. Few would advocate either withholding or withdrawing care based solely on the APACHE II score or any severity-of-illness score computed at the time of ICU admission. As a rule, severity-of-illness scoring systems are created from large databases that contain diverse types of patients. As such, extrapolating a specific mortality risk to a particular patient is fraught with difficulty. The APACHE II score, however, may be useful when considered in light of other clinical variables, such as need for MV, prognosis from underlying disease, and response to therapy after several days of aggressive care.

The most significant finding by Rano et al, however, is the implication of delay in diagnosis in terms of risk for mortality. In subjects in whom there was a > 5-day delay in identification of the cause of the pulmonary infiltrates, the risk of death increased independently by more than threefold. One might expect that this reflects the fact that noninfectious disease states would be more difficult to diagnosis or that certain patients were too ill to tolerate fiberoptic bronchoscopy (FOB). As the authors explain, though, the delay results from neither of these factors. To date, the evidence implicating diagnostic delay as a risk factor for mortality has been limited. Some investigators have reported that obtaining a specific diagnosis does not alter mortality in these persons. Other researchers have reached different conclusions. More specifically, in immunosuppressed individuals, early diagnosis of both viral and fungal infections has been shown to decrease mortality.

The impact of diagnostic delay on mortality is an important emerging general theme in the care of seriously ill patients, particularly as it affects the adequacy of initial therapy. In cases of bacteremia, inappropriate antibiotic selections increase the risk of death nearly sevenfold. Given the difficulty with making antibiotic selections in light of growing resistance, some advocate adopting practice guidelines and critical pathways to improve outcomes. For example, reliance on a practice guideline for treatment of ventilator-associated pneumonia improves both the probability that initial antibiotic choices are adequate, and overall outcomes. In light of the range of possible etiologies explaining the development of pulmonary infiltrates in the immunosuppressed, however, one cannot assume that initial therapeutic decisions will be correct unless an attempt is made to obtain a specific diagnosis. Similarly, developing a practice guideline to aid in therapeutic choices would be difficult for this group of patients—many of the agents one would rely on for treatment either have significant toxicity (eg, amphotericin B) or may worsen mortality if used indiscrimi-
inately (e.g., high-dose corticosteroids). Thus, one would be hesitant to employ such therapies empirically.

What then should the clinician do when faced with an immunosuppressed patient with pulmonary infiltrates? Given the conflicting pressures and risks, physicians should adopt a strategy that involves both invasive and noninvasive testing (Fig 1). Serologic testing will become an increasingly important component of this approach as polymerase chain reaction (PCR) technologies improve and allow the rapid identification of fungal and viral pathogens. Early use of CT scans in this setting to investigate unexplained fever also show promise as a tool for the expeditious diagnosis of pulmonary processes. Finally, FOB will remain an important diagnostic test in this population. Although controversy exists regarding the role of FOB in the diagnosis of ventilator-associated pneumonia, its value in immunosuppressed patients is more evident. Multiple investigators have shown that in immunosuppressed patients, FOB allows diagnosis of many conditions that otherwise would have been missed. Similarly, tests in development to allow PCR processing of fluid recovered from BAL. In turn, this will aid in identification of organisms such as Aspergillus fumigatus and Pneumocystis carinii. In summary, our approach to these patients must not only be thorough but prompt if we hope to improve on the significant mortality burden that accompanies the development of pulmonary infiltrates in the immunosuppressed patient.

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