small numbers of patients and by relatively short study intervals. Nonetheless, longer intervals of follow-up in open trials have also yielded variable outcomes.\(^6,^8\) Study design varied with some investigators using formal prestudy or initialization phases. Outcome, however, neither appeared to depend on whether the design was parallel or crossover nor on whether prestudy phases were used. Other factors may have influenced patient response, including variations in conventional therapy and patient compliance. Although all patients appeared to have had trials of more conventional “steroid-sparing” therapy, there was no uniformity between the studies as to the therapies and doses maintained throughout the study. Also, variable patient severity, airway inflammation, and nature of illness may influence patient response. Considerable inter-study variability existed among patients in their response to methotrexate. Factors such as degree of reversible airflow obstruction, duration of steroid-dependent asthma, extrinsic characteristic of asthma, or other features may have influenced outcome in individual patients.

Despite the uncertainties raised by the differing outcomes in the above studies, pertinent observations can be made. First, adjuvant treatment with methotrexate may have a steroid-sparing effect in asthma, but beneficial therapeutic responses are not consistently seen. Second, the incidence of significant side effects with methotrexate therapy in asthma appears to be infrequent. The uncertain efficacy of methotrexate in patients with steroid-dependent asthma, however, should be weighed against reports suggesting a possible risk of infectious complications such as *Pneumocystis carinii* pneumonia in patients taking both steroids and methotrexate\(^5,^7,^8\) and the rare but potentially severe hazard of occult cirrhosis with long-term methotrexate therapy.\(^9\)

The current standard of care for severe chronic asthma should remain the use of conventional therapies as recommended in a recent expert panel report.\(^10\) This care should include patient and family education, the use of daily patient diaries, regular peak flow monitoring, the development of a patient-provider partnership, and close follow-up to assess the patient’s response to therapy and whether the desired outcomes are being achieved. The data now available indicate that methotrexate is not the panacea for steroid-dependent asthma. While methotrexate may be advantageous in select patients, there remains no substitute for frequent, careful, and attentive patient care.

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**Diagnosis of *Pneumocystis carinii* Pneumonia**

**How Invasive?**

In the years preceding the current epidemic of HIV, *Pneumocystis carinii* was a relatively rare clinical pathogen. *Pneumocystis carinii* pneumonia (PCP) was, as it is now, an opportunistic infection which occurred in immunosuppressed patients. At that time, it was commonly accepted that PCP required an invasive procedure, usually open lung biopsy, for definitive diagnosis.\(^1\) This was in part based on the knowledge that, in patients dying of this infection, organisms appeared to be limited to the alveolar space and did not extend appreciably out of this compartment. Further, noninvasive procedures in sporadic cases failed to yield a diagnosis. Although not evaluated in a large series, sputum examination was consistently reported to be of no diagnostic value.

The HIV epidemic necessitated a re-evaluation of Pneumocystis diagnosis. Clinicians discovered at the outset of the epidemic that open lung biopsy was

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unnecessary for the diagnosis of PCP in the HIV-positive patient. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy were as effective and associated with less morbidity. Subsequent studies have established, in turn, that bronchoscopy with bronchoalveolar lavage alone is virtually as sensitive as bronchoscopy with both lavage and transbronchial biopsy. Thus, we now understand that PCP cases can be detected with bronchoalveolar lavage performed at bronchoscopy.

The ever increasing population of HIV-positive patients and the frequency of PCP in this population have prompted a search for even less invasive diagnostic methods which may also be more cost effective. Sputum induction and nonbronchoscopic lavage are two such methods. Sputum induction was initially demonstrated to be a sensitive procedure that obviated the need for bronchoscopy in a large number of patients. However, some centers had difficulty reproducing these initial promising results. What has become clear from these studies is that the interest and the experience of the examiner play a large role, as do the sputum-induction protocol and the staining method for Pneumocystis, in the sensitivity of this technique. In large centers that have experience with sputum induction, many invasive procedures can be avoided, with substantial cost and comfort benefit to the patient. This may not be the case for smaller centers with less experience, suggesting that there is still a need for alternative strategies for the diagnosis of PCP. Catheter lavage was first evaluated in intubated and ventilated patients and was found to be sensitive and safe. However, this method of diagnosis has the disadvantage that it is only applicable to a subset of patients, namely those who are intubated.

In this issue of Chest (see page 816), Bustamante and Levy report a study in which they have attempted to extend the utility of catheter lavage to nonintubated patients. They employed a coudé catheter for nonbronchoscopic bronchoalveolar lavage. They have compared their results with the coudé catheter to results with sputum induction in the same patients. Coudé catheter lavage, in their hands, is a safe procedure in which the catheter can be placed by a nonspecialist or even a nonphysician and yields a good sample of lower respiratory tract lining fluid to analyze for Pneumocystis. They found sputum induction to be a very insensitive test for PCP (less than 10 percent). This is in contrast to most reports which suggest that in 50 percent of patients or better, PCP can be detected by sputum induction. The authors attribute the low sensitivity of sputum induction in their study to the low frequency of Pneumocystis in their population. However, the number of a nonproductive or an inadequate sputum induction was very high, and most patients with sputum-negative/lavage-positive samples were in this group. Thus, a more vigorous attempt at sputum induction might have yielded a higher sensitivity for this method of diagnosis. Another difficulty with assessing this report was the lack of a denominator in the study. There was no "gold standard," such as bronchoscopy, that catheter bronchoalveolar lavage was compared to, although the authors do imply that no cases were missed by this technique.

A major issue with catheter lavage is safety. The authors report a single incident of gastric intubation with emesis and aspiration early in the development of their technique. The course of this patient was relatively uncomplicated, but the incident does raise a cautionary flag. The remarkable safety of bronchoscopy is, in part, a function of direct visualization of the field of interest. Intuitively, one could thus argue that a blind catheter lavage would be more likely to be associated with complications.

More than a decade of experience with PCP in HIV-positive patients has revealed that noninvasive or minimally invasive procedures are diagnostic for many patients. Transbronchial biopsy is uncommonly needed, and open lung biopsy is unnecessary. In centers with a particular interest and the expertise afforded by large numbers of patients, sputum induction can reduce the need for more invasive procedures by 75 percent. In settings where less expertise with induced sputum is available, bronchoscopically directed bronchoalveolar lavage is currently the procedure of choice. Bustamante and Levy provide us with new information that the coudé catheter lavage may be a safe alternative that is less costly, and perhaps, more comfortable for the patient. However, many questions remain. How safe is this procedure when performed on a larger scale or exclusively by nonphysician operators? How does the sensitivity of this procedure compare to bronchoscopic bronchoalveolar lavage? Should coudé catheter lavage be performed in large centers in those patients who are not diagnosed by sputum induction? The ultimate clinical role of coudé catheter lavage in the evaluation of possible PCP in HIV-positive patients will depend on the answers to questions such as these.

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High-Frequency Ventilation in Acute Pediatric Respiratory Failure

Mortality in pediatric patients with severe acute respiratory failure remains high, ranging from 60\(^1\) to 92\(^2\) percent. Animal studies comparing conventional and high-frequency ventilation (HFV) in the management of acute lung injury show that HFV can improve gas exchange and survival and reduce the occurrence of barotrauma.\(^3,4\) The results of “rescue” studies in humans are encouraging,\(^5,6\) but two large controlled clinical trials failed to show that HFV could improve outcome when compared with continued use of conventional ventilation.

Carlton and coworkers\(^7\) randomized 309 adults with acute lung injury to conventional ventilation (n = 157) or high-frequency jet ventilation (n = 152). A significantly higher percentage of patients treated with high-frequency jet ventilation met successful ventilation criteria (88 vs 76 percent, p<0.05), but there were no differences between the two groups with respect to survival or the number of days spent in the intensive care unit. The HIFI Study Group\(^8\) randomized 673 neonates with respiratory distress syndrome to high-frequency oscillation (n = 327) or conventional ventilation (n = 346). Survival, the average number of days spent on mechanical ventilation, and the occurrence of chronic lung disease were similar in both treatment groups. High-frequency oscillation was associated with an increase in the incidence of intracranial hemorrhage and periventricular leukoencephalomalacia. It is reasonable to ask why there is still interest in the use of HFV.

First, the data from animal experiments are compelling. Explanations for the contradictory findings between the human and animal studies are most likely related to (1) the timing of HFV initiation and (2) the heterogeneity of the human population.

In animal models of acute lung injury, the immediate application of HFV reduces barotrauma when compared with the continued use of conventional ventilation.\(^3,4\) Later “rescue” use of HFV is not as effective.\(^9\) Most human studies have evaluated the relatively late use of HFV. To achieve the dramatic results demonstrated in animal experiments, it may be that HFV intervention must be initiated early. In this October issue of Chest (1993; 104; 216-21), the study by Rosenberg et al supports this conjecture. Children who survived on HFV were treated earlier in their disease progression than children who died. When compared with nonsurvivors, survivors had a better initial response to HFV, suggesting that they had greater pulmonary reserve and less lung injury. Similar observations have been reported in neonates.\(^10\)

The second important difference between animal studies and human studies is the heterogeneity of human diseases. Animal experiments are conducted under precisely controlled conditions, and great effort is made to produce a consistent degree of lung injury. Human experiments are never so controlled. Factors such as age, diagnosis, duration of illness, immune response, cardiac function, and infection can have a profound effect on outcome and response to ventilator changes. In neonates, HFV appears to be most useful in the management of diffuse disease processes like hyaline membrane disease, pneumonia, and adult respiratory distress syndrome.\(^3\) High-frequency ventilation is less effective in patchy lung diseases, such as meconium aspiration syndrome.\(^11\) Most of the data on pediatric patients have been collected on patients with adult respiratory distress syndrome. In this setting, HFV appears to be an effective method for applying a high mean airway pressure to recruit lung volume and improve oxygenation without compromising ventilation or cardiac output. The use of HFV in pediatric patients with airway disease and/or patchy lung disease may not be as effective. In this setting, the time constant of the respiratory system is relatively long, and the propensity for gas trapping is high. The use of HFV in these patients may increase gas trapping. Future clinical studies must correct for these confounding variables and apply disease-specific ventilator strategies if they are to be successful.

Another confounding variable is the application of different types of HFV in the same study. As Rosenberg et al suggest, the outcome in patients managed with high-frequency flow interruption was not as good as in those treated with high-frequency oscillation. There are three types of high frequency ventilators: jets, flow