mean arterial pressure, and subsequently, diminished cerebral perfusion. Studies show conflicting results of the effects of PEEP on intracranial pressure (ICP). Hyper-ventilation, long used to cause vasoconstriction and decrease ICP, may induce cerebral ischemia. On the other hand, permissive hypercapnia employed to avoid v-lo-intrauma may increase cerebral blood flow and may lead to elevated ICP. Pulmonary venous air embolism is a rare but potentially serious complication in patients with ARDS who are receiving MV.

Ventilator-associated pneumonia is the most common infectious complication of MV, but patients appear to have an increased risk for eye infections as well.

Neuromuscular dysfunction may complicate MV in critically ill patients. Muscle atrophy is common. Myopathy associated either with critical illness itself or pharmacologic paralysis is well-known. There may be muscle breakdown due to catabolism and anterior horn loss due to hypoxic myelopathy.

Critically ill patients, especially those receiving MV, are at risk for dermatologic complications including pressure ulcers. They are immobile, may have reduced tissue perfusion exacerbated by hypoxemia, and poor nutritional status. All of these factors may contribute to the development of pressure ulcers.

As Mutlu et al point out in their review, and as these further examples illustrate, it is difficult to discern which complications in patients receiving MV are due to the ventilator itself and which are complications associated with critical illness in general. It would be difficult to design human clinical trials to answer these questions. The authors also admit that some of the data remain theoretic or have been demonstrated in animals but not humans and may not necessarily be extrapolated. In fact, a rat model recently was published specifically to study the effects of MV on distant organ systems. A group of rats was ventilated at different tidal volumes, and their hepatic and renal tissues were analyzed. These data, although preliminary, suggest that various ventilator strategies may result in different effects in organs other than the lung.

As pulmonary and critical-care physicians, we understand that the daily use of life-sustaining devices may have unintended consequences. These complications may be indirect and may occur in organ systems distant from the ones for which the mechanical device is intended. Information concerning the pathophysiology is complex, multifactorial, and ever-expanding. There are both cellular and humoral mechanisms as well as inflammatory mediators, including complement and the arachidonic acid cascade. Even a patient with single-system dysfunction who needs these machines requires vigilance in physical and laboratory evaluations to prevent or to diagnose these complications.

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Influenza Pneumonia in Thoracic Organ Transplant Recipients

What Can We Do to Avoid It?

It would seem common sense to assume that the occurrence of influenza pneumonia among thoracic organ transplant recipients would be at least as frequent as in the general population, if not more, because of their immu-
nosuppressed state. Yet, there has been only a handful or so of cases reported.1,2 In this issue of CHEST (see page 1277), Garantziotis et al report on three adult lung transplant recipients who developed influenza pneumonia that was followed, in all patients, by a persistent decline in pulmonary function. This issue is important because more and more data are accumulating to indicate that bronchiolitis obliterans syndrome may occur among lung transplant recipients, not only following cytomegalovirus (CMV) viral respiratory infections but also following non-CMV viral respiratory infections.3,4 In many cases, these were associated with permanent impairment of lung function and death.

The Immunization Practices Advisory Committee of the Centers for Disease Control and Prevention has identified, among others, patients with chronic pulmonary and cardiovascular disease and patients who are immunosuppressed (transplant recipients) to be at increased risk for cardiovascular disease and patients who are immunosuppressed. The Committee recommended immunization of these patients as well as the groups of individuals who may transmit the virus to them. These groups of individuals include physicians, nurses and other health-care personnel in both hospital and outpatient-care settings, employees of chronic-care facilities, providers of home care, and household members of the patient, including children.5 Although vaccination against influenza has been routinely recommended, this practice is not consistent among transplant centers in view of anecdotal reports suggesting that influenza immunization may stimulate rejection by enhancing recipient alloreactivity and linking immunization to mild rejection of the transplanted organ.5,6 Furthermore, and due to the effects of their immunosuppressive medications, transplant recipients may have a diminished antibody response to the influenza vaccine as evident by their lower antibody titers compared to those of otherwise healthy individuals.8,9 However, there have been several studies8,10,11 showing that most of these patients will have an adequate protective antibody titer after one vaccination, and in those patients who have low antibody titers after receiving the vaccine, the level of antibody titer may be improved by booster vaccination.

In the pharmacologically immunosuppressed thoracic organ transplant recipient, the early systemic manifestations of influenza may be abrupt, manifesting as malaise, fever, chills, myalgias, and headache, or they may be completely masked. As the systemic symptoms subside, the respiratory symptoms become more apparent, manifesting as rhinitis, pharyngitis, and cough. Chest complications, although rare, may manifest as tracheobronchitis, or as a localized viral pneumonia, or as diffuse and bilateral pneumonic infiltrates involving the lower lobes more than the upper lobes. Secondary bacterial pneumonia may also develop. In most of these instances, the influenza virus can be isolated from the respiratory tract during the first 2 days of illness. Positive culture results are usually identified within 2 to 3 days, although 2 weeks may be necessary.

In the immunosuppressed transplant recipient, that period of time may represent a golden opportunity where treatment with influenza-specific antiviral agents may be beneficial in order to shorten the duration of the illness and also to decrease the respiratory complications. Therefore, it is imperative that immunosuppressed individuals have access to these medications at or prior to the onset of their symptoms.

Two main classes of chemotherapeutic agents have been available: the M2 matrix protein inhibitors and the neuraminidase inhibitors designed to inhibit influenza neuraminidase, an important surface glycoprotein essential for the replication of type A and type B influenza viruses. The M2 matrix protein inhibitors amantadine and rimantadine are approved for prophylaxis and treatment of influenza A. These agents have limited success due to their underutilization, their lack of activity against influenza B, the rapid development of viral resistance, and their adverse effects.12 The neuraminidase inhibitors zanamivir and oseltamivir are the first class of agents active against both influenza A and influenza B. Both drugs were recently approved for treatment of the uncomplicated acute illness, as they work by inhibiting replication of the virus. Zanamivir is delivered by inhalation because of its low oral bioavailability, whereas oseltamivir is administered by mouth. Because of a broader antiviral spectrum, better tolerance, and less potential for emergence of resistance than is seen with the M2 inhibitors, the neuraminidase inhibitors represent an important advancement in the treatment of influenza.13 Although at present, neither zanamivir nor oseltamivir is approved by the Food and Drug Administration for use as prophylaxis, there have been encouraging data from the United Kingdom in regard to their use in preventing cases of influenza.14 Jefferson et al reviewed the outcome of eight trials that included 1,180 adults who received neuraminidase inhibitors as a preventive measure, and reported that when compared to placebo, these agents were 76% effective in preventing naturally occurring cases of clinically defined influenza, and 60% effective in preventing cases of laboratory-confirmed influenza. In their review, early treatment reduced the severity and duration of influenza symptoms and associated complications.

While vaccination in the transplant population remains the seasonal intervention of choice for prophylaxis, the efficacy, good tolerance, and lack of resistance seen with the neuraminidase inhibitors are likely to make them a valuable adjunct to immunization. When administered together, these agents do not appear to blunt immunogenicity to the vaccine, which is critical, particularly among transplant recipients who may already have a poor antibody response to the vaccine. Neuraminidase inhibitors should also be considered for patients who did not have the chance to receive the vaccine.

Who should then get protection? In our practice, we administer the flu vaccine annually to all patients who are on the waiting list for a transplant, and also to those patients who received a transplant. We recommend annual vaccination of all physicians and other health-care workers who have or will have contact with these two groups of patients. We also recommend administering the vaccine to all of the patients’ household contacts, including their spouses, siblings, children, and others. We advise all of our potential and current transplant recipients to keep a
neuraminidase inhibitor available for use at home, to use it early (within 24 to 48 h) when they develop any flu-like symptoms, and to seek medical attention from their transplant physician if their symptoms persist.

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Pulmonary Artery Catheterization in the ICU/Critical Care Unit

Indications and Contraindications Remain Objectively Undefined

Pulmonary artery catheterization for ICU/critical care unit diagnosis and treatment is used extensively and intensively.1–4 Reviewed several times in CHEST,1–3 a fundamental problem that will not go away is illustrated by two presentations at CHEST 2000, each of which concluded that randomized trials of the pulmonary artery catheter (PAC) are still needed to refine its indications and safety.4,5 Randomized trials of PACs were originally called for >2 decades ago.6

This vital subject is an excellent example of physicians’ problems—scientific, ethical and behavioral7—with any new diagnostic or therapeutic modality beginning with its initial exhibition. Objective proof of efficacy and safety (a low risk/benefit ratio) is needed before wholesale introduction of anything new; mere technical feasibility and animal studies are never sufficient. For new and altered medications, everyone accepts the prospective, randomized, blinded investigation. Equally high standards have not been applied to instrumental methods, while new generations of physicians increasingly rely on them as clinical bedside skills have atrophied.8 (It is probable that some instrumental, especially imaging, modalities may indeed prove superior to many traditional bedside skills; but, sadly, in terms of these skills, we are developing a generation without an umbilical cord).

The case for appropriate studies of the Swan-Ganz PAC has already been made with carefully matched cumulative studies, particularly at the University of Massachusetts2 and University of Virginia.9 In these PAC investigations and in those presented at CHEST 2000,4,5 demonstrations of far poorer net outcomes (mainly greater than expected mortality) ascribed to the PAC strengthens the need, especially in this day of “evidence-based medicine,” for objective trials to determine patients who should and should not have a PAC.

The reasons for the PAC to be investigated thoroughly are not merely those well-known accidents and side effects that are obvious and, mercifully, at a relatively low level for experienced operators. The reasons include the demonstration that indwelling instrumentation of any type changes the recipient physiologically, including responses to cardiocirculatory challenges.6 Unlike the overt complications of PAC, these unmeasured physiologic costs are not obvious. Thus, a compelling additional reason for randomized trials is manifest: if the study groups are comparable at baseline, then the investigation will measure not only what is apparent; its outcome should also reflect the unmeasurable “hidden” variables that, by randomization, should equalize among the study groups. On the ethical side, the argument has been made to randomize the first patient,10 which also applies to “pilot” trials and even technical feasibility trials; it may take twice as long to get an answer, but all trial patients should enter