Do No Harm

A cardinal rule in medicine is to “do no harm.” As physicians, we are constantly asking ourselves what the overall risk/benefit ratio is for every therapeutic intervention we consider for our patients. In addition, consideration of any therapeutic modality is based on our knowing the natural history of the condition untreated, with our weighing the advantages vs disadvantages of adding therapeutic interventions (whether medical or surgical). Ricciardi et al report in this issue of CHEST (see page 1218) using echocardiographic parameters to predict an adverse response with an acute trial of nifedipine in patients with primary pulmonary hypertension.

Acute vasodilator testing for patients with primary pulmonary hypertension was first reported in the mid 1970s following favorable experiences with vasodilator therapy for systemic hypertension. With the advent of vasodilators (such as hydralazine), physicians looked to these vasodilators with potential promise for their patients with primary pulmonary hypertension. Unfortunately, several of the earliest experiences with acute vasodilator testing resulted in fatalities using agents with a relatively long half-life, eg, hydralazine, in whom minimal if any active pulmonary vasoreactivity existed, ie, postmortem histopathology revealed severe fixed pulmonary vascular disease with little medial hypertrophy in the pulmonary arterioles. The administration of a relatively long-acting vasodilator in patients with advanced disease resulted in significant systemic vasodilatation with little if any pulmonary vasodilatation and subsequently cardiogenic shock. Based on this early experience, we “stepped back” and readdressed the cardinal rule to “do no harm” in medicine.

Unfortunately, the natural history of primary pulmonary hypertension untreated has a 5-year survival of at best 34%.1 The 5-year survival is most likely < 34% since the National Institutes of Health (NIH) Registry Series included anticoagulation in some patients, which has been demonstrated to improve survival.2,3 as well as calcium channel blockade therapy in some patients (although we do not know from the NIH Registry Series whether or not the patients treated with calcium channel blockade were patients in whom acute pulmonary vasoreactivity existed; chronic calcium channel blockade has only been shown to be efficacious for acute responders).3–5

The standard of care for primary pulmonary hypertension currently includes chronic calcium channel blockade if acute pulmonary vasoreactivity is demonstrated with acute vasodilator testing.3–5 This occurs in approximately 20 to 25% of adults and 40% of children. For the remainder, ie, 75 to 80% of the adults and 60% of the children, continuous IV infusion of prostacyclin is used. Chronic prostacyclin has been shown to improve quality of life, exercise capacity, pulmonary and systemic hemodynamics as well as survival.6 Although patients as well as their physicians prefer oral calcium channel blockade as opposed to IV prostacyclin, the decision needs to be based on safety and efficacy as opposed to a preference for route of administration of the vasodilator agent, ie, oral vs IV.

Ricciardi et al looked at echocardiographic parameters that appear to be useful in predicting who may or may not have an adverse response with acute calcium channel blockade testing. Their data demonstrate that diminished left ventricular size and leftward ventricular septal bowing are associated with systemic arterial hypotension following acute calcium channel blockade testing. The authors recommend using these echocardiographic parameters to select patients for whom a trial of nifedipine should be avoided. Unfortunately, the authors do not present the data for the patients’ acute hemodynamic responses with inhaled nitric oxide or adenosine testing prior to the trial of nifedipine, although they state in their manuscript that 20 of the 23 patients did undergo acute testing with either inhaled nitric oxide or adenosine testing prior to the trial of nifedipine, although they state in their manuscript that 20 of the 23 patients did undergo acute testing with either inhaled nitric oxide or adenosine. The importance of knowing this information is based on several studies demonstrating that acute calcium channel blockade testing is safe if a favorable response occurs with prior administration of IV prostacyclin, inhaled nitric oxide, or IV adenosine.3–5 A positive or favorable acute response is defined as a significant decrease in mean pulmonary artery pressure, as opposed to a decrease in pulmonary vascular resistance only. This is particularly important when using IV prostacyclin...
as the agent for vasodilator testing, since pulmonary vascular resistance decreases in most patients, even if there is not a significant decrease in pulmonary artery pressure. Whether this is due to a positive inotropic effect of prostacyclin increasing cardiac output remains unknown. In our experience, we have only observed systemic arterial hypotension with acute calcium channel blockade testing in patients in whom there was no significant decrease in pulmonary artery pressure with acute testing using IV prostacyclin or inhaled nitric oxide. In the experience of Ricciardi et al with 20 of 23 patients who underwent acute testing with either IV adenosine or inhaled nitric oxide and 22 of 23 patients received a trial of nifedipine, one wonders what the acute response with adenosine or nitric oxide was in the 5 patients in whom systemic arterial hypotension occurred following the first dose of nifedipine (group 1, which also included the 1 patient who was not tested with nifedipine based on the patient’s initial hemodynamic parameters revealing significant right heart failure). If one knew that the acute response with acute testing with adenosine or nitric oxide did not demonstrate a favorable response, one could have predicted a lack of a favorable response with nifedipine testing, thereby avoiding the nifedipine trial with a possible adverse response and serious consequences in this group of patients. Furthermore, one does not know if the two patients who received the trial of nifedipine and were not tested with adenosine or nitric oxide prior to the nifedipine test were in the group that developed systemic hypotension (group 1). It is for these reasons that much has been written in the medical literature strongly recommending acute vasodilator testing with a short-acting potent pulmonary vasodilator, eg, IV prostacyclin, inhaled nitric oxide, or IV adenosine prior to consideration of a trial of calcium channel blockers.3–5

It is not surprising that the authors observed that the association between the echocardiographic variables associated with systemic hypotension following a trial of nifedipine was less significant when controlling for pulmonary vascular resistance. Although pulmonary vascular resistance is a calculated parameter, it correlates (inversely) with acute pulmonary vasoreactivity with acute vasodilator testing using IV prostacyclin.5 A higher pulmonary vascular resistance suggests lack of an acute responsiveness. Unfortunately, the correlation is not 100% accurate; and therefore, unless a patient is in significant right heart failure, we recommend testing an individual patient with a short-acting vasodilator agent, eg, IV prostacyclin, inhaled nitric oxide, or IV adenosine, as opposed to assuming that all patients with right heart failure will only be candidates for chronic IV prostacyclin, as opposed to chronic calcium channel blockade by oral administration.

The authors’ findings remain important and are useful to add to our armamentarium of noninvasive tests assessing the severity of an individual patient’s disease, which is extremely helpful in determining risk/benefit considerations prior to performing invasive procedures such as cardiac catheterization. Previous studies have demonstrated that exercise tests (both the 6-min walk that evaluates exercise endurance, as well as progressive cycle ergometry measuring exercise tolerance)6,7 correlate with severity of disease in patients with primary pulmonary hypertension and the risk of invasive procedures (such as cardiac catheterization) in these high-risk patients. If the authors performed either a 6-min walk or progressive cycle ergometry tests with their patients prior to the trial of nifedipine, it would be interesting to know whether these exercise studies were useful in predicting their results, ie, systemic hypotension following the trial of nifedipine testing. Regardless, Dr. Ricciardi’s study gives us additional information to help us critically weigh risk/benefit concerns as we individualize the evaluation and therapeutic approach for our patients.

Robyn J. Barst, MD
New York, NY

Dr. Barst is Associate Professor of Pediatrics and Medicine at Columbia University College of Physicians and Surgeons, New York, NY.

Correspondence to: Robyn J. Barst, MD, 3959 Broadway BH262N, New York, NY 10032

References
Blood Transfusion
First, Do No Harm!

The earliest documented blood transfusions date back to the mid-17th century.1 However, it was not until the early part of the 20th century that blood transfusion became a mainstay of clinical practice. The value of blood transfusion was essentially unchallenged throughout most of this century. Blood transfusion was looked on as relatively risk free, with benefits so obvious as to make surgery with levels < 10 g/dL unthinkable. It was not until the early 1980s that our transfusion practices began to come under systematic scrutiny.2-4

If blood transfusion was “risk free,” the current intense evaluation of transfusion practice would not be taking place. In the critically ill patient, the risk of a blood transfusion-transmitted infection is not the major concern regarding blood transfusion. What is of more consequence for the critically ill patient is the evidence suggesting that blood transfusion has profound negative effects on the immune system.1,5-7 A variety of immunomodulatory effects associated with blood transfusion have been described, including the following: decreased CD4 and interleukin 2 (IL-2) receptor-positive helper cells; increased CD8 suppressor cells; decreased natural killer cells; increased numbers of B cells; decreased IL-2 production; and increased prostaglandin E2 production. These effects may persist for months or longer.

There is now growing evidence bearing on the potential clinical significance of the immune system effects of blood transfusion. Several studies have suggested that exposure to RBC transfusion increases the risks of recurrence of cancer and the development of postoperative infection.8 Patients who receive allogenic blood transfusions experience increased morbidity, hospital stays, and cost.9 Leukoreduction of transfused RBCs, on the other hand, has been associated with a significant reduction of infection rates following colorectal surgery.10 In the current issue of CHEST (see page 1233), Fransen et al add to the clinical evidence regarding the impact of blood transfusion. These authors demonstrated that intraoperative blood transfusion was associated with an enhanced inflammatory response and increased concentrations of inflammatory mediators. In addition, the administration of allogenic RBCs was associated with increased postoperative morbidity.

It has been difficult to demonstrate a benefit of “routine” transfusion of critically ill patients. Dietrich et al11 studied 32 patients in shock from a variety of causes. After volume resuscitation, increasing hemoglobin levels from 8.3 to 10.5 g/dL did not result in oxygen utilization or the “shock state,” regardless of etiology. Similarly, in a study of septic patients, blood transfusion (hemoglobin 9.6 to 11.6 g/dL) did not affect oxygen uptake, despite significant increase in oxygen delivery.12 These patients were known to have abnormal oxygen uptake by demonstrating increasing oxygen uptake in response to dobutamine. Separate from its immune effects, transfused RBCs, especially during the time period acutely following transfusion, are not “normal.” Storage of RBCs temporarily decreases 2,3-diphosphoglycerate levels, interfering with the ability of RBCs to unload oxygen, and temporarily impairs RBC deformability. In particular, “older” RBCs are a greater problem. Marik and Sibbald,13 in a study of septic patients receiving mechanical ventilation, not only failed to demonstrate acute improvement in oxygen uptake after the transfusion of 3 U of RBCs (hemoglobin 9.0 to 11.9 g/dL), but found that patients receiving “old” transfused blood (> 15 days) developed evidence of splanchic ischemia. A subsequent study employing a rat sepsis model found that while transfusion of “fresh” RBCs acutely increased systemic oxygen uptake, this effect was impaired with transfusion of RBCs stored for 28 days.14

Recently, Hebert et al15 reported the results of a prospective randomized trial comparing a liberal transfusion strategy (hemoglobin 10 to 12 g/dL) to a restrictive transfusion strategy (hemoglobin 7.0 to 9.0 g/dL). These investigators found that the overall in-hospital mortality was significantly lower in the restrictive strategy group, although the 30-day mortality rate was not significantly different. However, in those patients who were less ill (acute physiology and chronic health evaluation < 20) or younger (< 55 years of age), the 30-day mortality rates were significantly lower for the patients in the restrictive transfusion group. There was no difference in mortality between strategies for those patients with cardiac disease.

It is clear that the transfusion of RBCs may not only not help, but may in fact do harm to the critically ill patient. The evidence of the negative effects of allogenic blood suggests that, if possible, routine blood transfusion should be avoided. It is possible that other means to increase hemoglobin levels without blood transfusion, such as erythropoietin, might be of benefit. Erythropoietin therapy, in contrast to blood transfusion, has been shown to improve extractable oxygen in patients undergoing open heart surgery.16 Universal leukocyte reduction of transfused RBCs has been suggested as a means of reducing the toxicity of RBC transfusion.17,18 How...
ever, others have questioned whether the available data at this point supports the considerable expense associated with the universal adoption of this change in transfusion practice. Further work, such as reported in this issue of CHEST, still needs to be done to elucidate the mechanisms responsible for the deleterious effects of RBC transfusion.

Howard L. Corwin, MD, FCCP
Lebanon, NH

Dr. Corwin is Section Chief, Critical Care Medicine, Medical Director, Intensive Care Unit, Dartmouth-Hitchcock Medical Center.

Dr. Corwin receives research support from Ortho Biotech.

Correspondence to: Howard L. Corwin, MD, FCCP, Dartmouth-Hitchcock Medical Center, One Medical Center Dr, Lebanon, NH 03756–401; e-mail: howard.l.corwin@hitchcock.org

References

13 Mark PA, Silhau WJ. Effect of stored-blood donation on oxygen delivery in patients with sepsis. JAMA 1993; 269: 3024–3029

Asthma and Gastroesophageal Reflux Disease

The Truth Is Difficult to Define

In 1892, Sir William Osler1 first observed the association between worsening asthma and a distended stomach. However, it was only since the publication by Kennedy2 in 1962 that attention has focused on the potential causal association between gastroesophageal reflux disease (GERD) and asthma. In the current issue of CHEST (see page 1257), the study by Kiljander and colleagues allows us the opportunity to look at this possible association and to critique the problems inherent in defining its true relationship.

To strengthen the cause-and-effect relationship between GERD and asthma, three criteria should be met. First, patients with GERD should have a higher prevalence of asthma than patients without GERD. This is the case since these reflux symptoms are reported in up to 77% of asthmatics,3 while 32 to 52% of asthmatics have abnormal pH studies.4,5 Additionally, “silent reflux” may be as common as symptomatic reflux, with reports suggesting that 25 to 50% of asthmatics have no reflux complaints but abnormal pH studies.6,7 Second, the pathophysiological mechanisms between GERD and asthma should help explain how the disease processes interact (i.e., esophageal acid should exacerbate asthma). Animal and human studies have shown that GERD can aggravate asthma through several mechanisms, including the following: (1) vagally mediated reflex triggered by acid in the esophagus, (2) heightened bronchial reactivity, and (3) microaspiration of gastric acid resulting in bronchoconstriction.8 Lastly, if GERD causes asthma, then antireflux therapy, either medical or surgical, should improve or even resolve the asthma in many patients. Unfortunately, this is where the causal association begins to fall apart. For example, Field and Sutherland9 recently reviewed 12 studies involving 326 asthma patients whose reflux disease was aggressively treated with medical therapy and could only conclude that “medical antireflux
therapy improves asthma symptoms, may reduce asthma medication used, but has minimal or no effect on lung function.”

I believe that a number of methodologic limitations exist in the currently published literature relating GERD and asthma, which contributes to the confusion in this area. In many of the published studies, there is no attempt to optimize conventional, “standard” therapy for the underlying asthma. Today, this means using daily inhaled corticosteroids. The inadequate use of inhaled corticosteroids is a major treatment shortcoming for many patients with poorly controlled asthma and an important source of variability in the published series. The current study from Finland had patients receiving optimal asthma therapy, including 89% taking inhaled steroids and 91% taking β-sympathomimetic drugs. On the other hand, too-tight control of asthma may not allow a sufficient margin for any new therapy to show improvement, increasing the chances of a false-negative study unless large number of patients are investigated. The authors of the current study believe that this may have been a factor making it difficult to reach a 20% increase in pulmonary function (the definition of a responder) or a statistically significant improvement in asthma symptoms after omeprazole therapy.

A second major limitation in most studies is the lack of an objective assessment of acid suppression while asthmatics are being treated for GERD. The only published study addressing this issue was performed by Harding et al, using serial pH studies in patients treated with the proton pump inhibitor, omeprazole. They found that 73% of patients only required omeprazole at 20 mg/d, but 20% required omeprazole at 40 mg/d, 7% needed 60 mg/d, and one patient was eliminated from the study because her GERD was still not controlled. In the absence of documented control of acid reflux, one cannot conclude that therapy for GERD did not improve the associated asthma. This may explain the overall better efficacy of antireflux surgery in relieving symptoms of asthma. A recent review of 10 surgical studies involving 318 asthmatics with GERD found that 253 patients (80%) had their asthma improved. Of this group, over half were “cured” of their disease (ie, they did not require further asthma medication); many were previously taking oral steroids.

A third limitation is the absence of a control group in some of these studies. Based on data from a variety of experimental anti-inflammatory therapies for chronic steroid-dependent asthma, we know the placebo arm can improve from 20 to 40% simply by participating in a clinical study (ie, the “Hawthorne effect”). A separate control group doubles the number of patients needed and may make recruitment difficult, because patients may not want to risk receiving a placebo for an extended period of time. As done in the current study, a crossover design eliminates these problems. However, this type of design has its own inherent problems, including carryover effect and order effect. Carryover effect implies that active therapy, if given first, may continue to influence the disease even during the placebo phase. As done in this study, this can usually be eliminated by an adequate washout period. On the other hand, an order effect maybe more difficult to control and explain. A review of Figures 1–2 in the study by Kiljander and colleagues suggests that this may have been a factor. In contrast to patients receiving omeprazole first, those receiving placebo for 8 weeks improved their pulmonary symptoms when switched to omeprazole, 40 mg, each morning after a 2-week washout period.

A fourth limitation among many of these studies is that the duration of acid suppression may be too short to predictably show a response in symptoms and pulmonary function tests. As illustrated in Figure 3 of the current study, patients who were regarded as responders showed improvement in their pulmonary symptoms only after several weeks of omeprazole treatment. This is in accordance with several previous medical treatment studies and is further confirmed by the surgical series in which those with longer follow-up usually found improvement in pulmonary function tests. The optimal duration of therapy should be at least 3 months and could even be as long as 6 months, when taking into consideration seasonal variations in asthma.

Finally, predictors need to be identified to help characterize which patients to treat aggressively with antireflux therapy. Harding and colleagues found that responders to omeprazole therapy were characterized by the presence of proximal reflux on pH testing and acid regurgitation into the mouth at least one time per week. These are markers of more severe disease with possible microaspiration. Likewise, the responders in the study by Kiljander and colleagues had greater amounts of total and upright acid reflux on pH testing in comparison to the nonresponders. Other studies have suggested a wide array of predictors, including the presence of nonallergic asthma; difficult-to-control asthma; nocturnal asthma; other respiratory or ear, nose, and throat complaints; and esophagitis healing on medical therapy. However, none of these predictors have systematically been reexamined in an independent study population. Future studies need to be “enriched” with patients who, in all likelihood, have GERD exacerbating their asthma. If this cannot be accomplished, then the prevalence of asthma caused by GERD in the individual studies, rather than the efficacy of the drug treatment, will be the deciding factor in the outcome of these studies.

Many questions remain regarding the relationship...
Cytomegalovirus Prophylaxis With IV Ganciclovir In Lung Transplant Recipients

The Long and the Short of It!

Lung transplantation may prolong survival and improve symptoms for patients with end-stage lung disease. However, many shortcomings plague this procedure, including a lack of donor organs, the need for lifelong immunosuppression, allograft rejection, limited long-term patient survival, the high financial costs of the surgery and subsequent care, and the constant threat of infection. Of the infectious complications, cytomegalovirus (CMV) stands out as an important agent causing significant morbidity and mortality.

The clinical spectrum of CMV includes three manifestations: infection, syndrome, and disease. CMV “infection” is defined by culturing the organism from any body tissue or fluid, while CMV “syndrome” is infection with symptoms. CMV “disease” is characterized by infection associated with symptoms and histologic evidence of tissue invasion. The risk of developing CMV disease depends on the serologic status of both donor and recipient. The greatest risk occurs in recipients who are CMV antibody negative and receive an organ from a CMV antibody-positive donor. Clinical manifestations depend on the site of tissue invasion (ie, lung, GI tract, eye, etc.).

In lung transplant recipients, CMV infection is associated with the development of obliterative bronchiolitis (OB), the pathologic manifestation of chronic allograft rejection. Because OB is the leading cause of long-term morbidity and mortality following lung transplantation, many strategies have...
been proposed to reduce risk factors for this problem. Several prophylactic regimens have been studied to prevent CMV infection. These include IV and oral ganciclovir, IV CMV hyperimmune globulin, and matching CMV-naive recipients with CMV-negative donors.\textsuperscript{4–5} However, the “best” prophylactic strategy in lung transplant recipients remains controversial. Although several studies document the effectiveness of IV ganciclovir in preventing CMV infection following lung transplantation, the appropriate duration of therapy with ganciclovir either as a single agent or in combination with CMV hyperimmune globulin remains unclear. Furthermore, the cost-benefit ratio of prolonged prophylaxis with ganciclovir has not been well described. Most importantly, the impact of CMV prevention on the long-term outcome of lung transplant recipients remains unknown.

In this issue of CHEST (see page 1265), Gerbase and colleagues add to our options by describing the costs and outcomes of long-course ganciclovir in lung transplant recipients. IV ganciclovir was administered for 20 weeks to 22 patients at risk for CMV infection. The course of 20 weeks was chosen to cover the period of maximal immunosuppression. Outcomes included evidence of CMV infection, therapy-related complications, and the overall cost of this treatment. These results were compared to results of previously reported 12-week prophylaxis protocols. As anticipated, the authors found a decreased incidence of CMV infections during the longer course of prophylaxis. This was not associated with significant side effects or complications, and there was no evidence of increased resistance to ganciclovir when the drug was required for subsequent infections. Although this study revealed a decreased incidence of CMV infection with 20 weeks of ganciclovir, the authors were unable to show a cost advantage for this strategy. They noted that the cost of long-duration prophylaxis was higher than the cost of treating the few extra cases of CMV infection prevented by this protocol. The additional costs of treating specific complications associated with this regimen were not presented in the analysis. Although the results of this study are interesting, they must be interpreted with caution since the comparisons were made to other published trials without the benefit of a contemporaneous control group. Thus, we have a therapy that may be clinically efficacious for preventing CMV infection but of unclear financial benefit.

Since CMV infection is associated with the development of OB, it makes intuitive sense that prevention of this infection in lung transplant recipients is important. However, studies to date only show an association of CMV with OB, but not causality. Whether prevention of CMV will ultimately reduce the incidence of OB remains unclear. Furthermore, the cost of this extra therapy in relation to long-term outcome (morbidity and mortality of CMV infection and subsequent development of OB) may not be justified.

So should lung transplant patients at risk for CMV infection receive prophylaxis with IV ganciclovir for 12 or 20 weeks? This question is difficult to answer with a small study from a single center. This and other questions, such as the utility of oral ganciclovir, or the combination of ganciclovir with CMV hyperimmune globulin, will only be answered by prospective clinical trials that enroll sufficient numbers of patients. Given the small number of patients at individual lung transplant programs, large trials are only feasible through multicenter networks. The success of this approach has been demonstrated by other cooperative groups, such as the National Institutes of Health-sponsored ARDS network. Until such collaborations are established in the transplant community and studies are completed, we can only speculate about the best therapies for our patients.

Jonathan B. Orens, MD, FCCP
Baltimore, MD

Dr. Orens is Associate Professor of Medicine, Johns Hopkins Hospital, Division of Pulmonary and Critical Care.
Correspondence to: Jonathan B. Orens, MD, FCCP, Associate Professor of Medicine, Johns Hopkins Hospital, Division of Pulmonary and Critical Care, 600 North Wolfe St, Blalock 910, Baltimore, MD 21287

References

Blood Cultures for Community-Acquired Pneumonia
No Place To Skimp!

In this issue of CHEST (see page 1278), Waterer et al report a provocative retrospective study of the impact of blood cultures on antibiotic prescribing for...
community-acquired pneumonia. Physicians seldom simplified antimicrobial therapy, even when Streptococcus pneumoniae had been isolated from blood cultures, which was the case in 74 of 1,305 patients with community-acquired pneumonia who were admitted to a large private hospital. Waterer et al conclude that “in an era of escalating costs and rationalization of health care,” we should address seriously the issue of whether blood cultures need be obtained in severe community-acquired pneumonia.

Any attempt to reduce the cost of medical care without compromising quality is certainly laudable. However, we lack sufficient data to recommend that blood cultures no longer be obtained for severe community-acquired pneumonia (ie, pneumonia requiring hospitalization). To the contrary, there are compelling reasons to obtain two sets of blood cultures before starting antibiotic therapy.

First, pneumococcal pneumonia is an inappropriate place to begin cost cutting. In the Oregon Plan—a recent, admirable attempt to rank what we do for patients in order of cost-effectiveness and social desirability—antibiotic therapy for pneumococcal pneumonia topped the list, and for good reasons (Ralph Crawshaw, MD; personal communication; July 13, 1999). The cost of two sets of blood cultures from patients with severe pneumonia pales by comparison with other common expenditures in pulmonary and critical care medicine.

Second, and as Waterer et al point out, blood cultures can be invaluable to decision making in individual cases. Two such cases stand out in my own recent memory. One patient seemed to have the ALPS syndrome (alcoholism, leukopenia, and pneumococcal sepsis) until blood cultures disclosed Klebsiella pneumoniae. The other patient was about to undergo lobectomy for cavitary pneumonia with sequestered lung until it was pointed out, since pneumococci had been isolated from blood, that the prognosis for spontaneous resolution was excellent.1 Before abandoning blood cultures, we should determine the number needed to test and its associated cost to identify a single case in which the findings are enormously lifesaving and/or cost saving.

Third, data derived from susceptibility testing on pneumococcal blood isolates are crucially important to medical decision making. As is well-known, S pneumoniae is acquiring resistance not only to penicillin B but also to the newer cephalosporins and fluoroquinolones.2 We need data—not only national, but also regional and local—on pneumococcal susceptibility trends.

Fourth, it is arguable whether simplifying therapy would actually save money in most cases. I have personally championed the continued use of high-dose penicillin G therapy for treatment of pneumococcal pneumonia when the diagnosis is clear-cut, when meningitis is not present, and when the likelihood of a highly resistant strain (minimum inhibitory concentration to penicillin G, > 4 μg/mL) is low.3,4 Yet, as much as I hate to admit it, the actual cost of IV ceftriaxone, 1 g/d, is probably lower than the cost of high-dose IV penicillin G therapy (due to the equipment and personnel costs for administering penicillin G by continuous or frequent intermittent infusion). Physicians’ decisions to “continue what seems to be working” are in some instances understandable.

Fifth, the best chance to reduce costs for severe community-acquired pneumonia hinges less on the choice of antibiotics than reducing the duration of therapy and hospitalization. Unfortunately, for pneumonia, as for most infectious diseases, we lack good data on which to base the length of therapy. We often quip, therefore, that duration of therapy should always resemble a football score: 3, 7, 10, 14, 21, 28, or 42 days. My MEDLINE search for articles on severe pneumococcal pneumonia between 1975 and 1999 using the search phrase “duration of” yielded only one good article: a study from Nigeria in which the average duration of therapy was but 2.54 days. The authors recommended that antibiotics can be stopped when patients have been afebrile for 24 h.5 Supporting this idea, McCormick et al6 concluded recently from a prospective cohort study of 1,185 adult patients that shorter hospital stays did not adversely affect outcomes. These latter authors imply that shortening the duration of hospitalization would not, however, be appropriate for pneumonia of “high-risk” etiology: Staphylococcus aureus or aerobic gram-negative rods. Documenting these high-risk pathogens is yet another indication for blood cultures.

Positive blood cultures remain the “gold standard” (or the “Austrian and Gold standard,” to acknowledge a classic study!) for the diagnosis of pneumococcal pneumonia. Recent data confirm the premier role of the pneumococcus in severe community-acquired pneumonia.8 Waterer et al are to be commended for their provocative study, but the time has not yet come to abandon blood cultures in this disease.

Charles S. Bryan, MD
Columbia, SC

Dr. Bryan is Heyward Gibbes Distinguished Professor of Internal Medicine and Chair, Department of Medicine, University of South Carolina School of Medicine.

Correspondence to: Charles S. Bryan, MD, 2 Medical Park, Suite 502, Columbia, SC 29203; e-mail: cbrryan@richmed.medpark.sc.edu

REFERENCES
1 Yangco BG, Deresinski SC. Necrotizing or cavitating pneumonia due to Streptococcus pneumoniae: report of four cases
Prevention of Ventilator-Associated Pneumonia

Does One Size Fit All?

Ventilator-associated pneumonia (VAP) continues to be a vexing problem in critically ill patients. Estimates of attributable mortality are variable, but increased duration of ventilation is a consistent finding, along with the corresponding increase in hospital days and cost. A major component of the problem is the ineffectiveness of therapy once VAP is diagnosed. Brun-Buisson et al have demonstrated failure rates of 49 to 62% despite the use of standard antibiotic combinations. Given the burden of VAP, both physical and financial, and the difficulties in treatment, prevention strategies would appear to be of paramount importance.

Various strategies have been documented to decrease the risk of VAP. Valles et al demonstrated that the use of specialized endotracheal tubes that allow continuous aspiration of subglottic secretions (CASS) led to a significant decrease in the incidence of VAP. In this issue of CHEST (see page 1339), Kollef et al found a nonsignificant trend toward a decreased incidence of VAP in cardiac surgery patients receiving CASS, although a significant delay in the time to onset of VAP was found. The number of patients needed to treat (NNT) to prevent one VAP episode was 32, compared to a NNT of 7 in the mixed medical surgical population studied by Valles et al. The increased numbers that are needed to have a significant effect raises questions regarding the cost-effectiveness of CASS in a cardiac surgery population, given the cost differential when compared to standard endotracheal tubes. The fact that the majority of pneumonias prevented were Haemophilus influenzae and methicillin-sensitive Staphylococcus aureus, organisms that do not require expensive broad-spectrum therapy and do not have associated excess mortality or prolonged ventilation, also diminishes the cost/benefit ratio of CASS in this population.

This study illustrates the very difficult problem of designing prevention strategies for VAP. Unfortunately, many studies of prevention link all VAPs together, as if pathogenesis and risk factors are the same. The logical extension of that linkage is the assumption that a prevention strategy that works for one group of patients or one group of organisms will be effective for all. Clearly this concept is in error.

The most logical separation of types of VAP is between early-onset VAP (EOP) and late-onset VAP, variously defined with the cutoff between 5 to 7 days of mechanical ventilation. The ability to prevent EOP is clearly greater than that of late-onset VAP. Many of the best-validated strategies for VAP prevention, including CASS, are for EOP. Rather than delaying the presentation of VAP, an alternative explanation for the findings of Kollef et al is that CASS prevented EOP while having no effect on late-onset VAP. This is consistent with other studies of CASS. However, EOP can also be prevented by other strategies, such as by simply administering ventilation with patients in the semirecumbent position, prophylactic short course, high-dose antibiotic therapy, and others. In fact, an equivalent benefit may have occurred in the population studied by Kollef et al, by using a prophylactic antibiotic with greater activity against H influenzae than the ceftazolin that is used in the majority of patients. Unfortunately, while EOP is easier to prevent, the associated benefit is not as clear, because EOP is less likely to be associated with excess mortality and prolonged mechanical ventilation.

Having the ability to prevent late-onset VAP is much more difficult. The pathogenesis is different than EOP. Antibiotic selective pressure and cross infection are themes that are common to late-onset VAPs. Many late-onset VAPs, especially Pseudomonas, occur without preceding oropharyngeal or gastric colonization, the target of many prevention strategies. No prevention strategy has shown a clear-cut benefit for late-onset VAP. The best prevention strategies may actually be an accurate diagnosis of EOP and avoidance of antibiotics as much as possible. While the incidence of VAP may not decrease, the causative organism is less likely to be associated with excess mortality and antibiotic resistance. Barrier precautions should theoretically prevent late-onset VAP, but the benefit in adults has not yet been demonstrated.
A logical strategy is to custom design prevention strategies for the particular patient population and type of pneumonia. In this mechanistic scheme, prevention strategies may vary from institution to institution, ICU to ICU, and patient to patient. For example, because the source of *S. aureus* causing VAP is, frequently, colonization of the nares, prophylactic treatment with mupirocin in at-risk patients makes sense, although not yet proven for VAP as it is for wound infections. Patients at risk for staphylococcal VAP include end-stage renal disease, comatose, or neurosurgical patients, especially if nasal colonization is documented. Because of the association with aspiration, nontraumatic coma patients may benefit from a short course of high-dose antibiotics aimed at neutralizing a bolus of aspirated oropharyngeal secretions, which include anaerobes. Even selective decontamination of the digestive tract may have a place in patients at risk for VAP due to Enterobacteriaceae, either endemically, such as in liver transplant patients, or for epidemic outbreaks.

Nonantibiotic prevention strategies, such as CASS, are even more attractive because they do not risk changing the normal bacterial flora. While easy to recommend but difficult to achieve, shortening the duration of ventilation without increasing the risk of reintubation is one of the few generic recommendations to decrease the risk of VAP in all patient groups. An important rationale for the use of noninvasive ventilation in the subgroup of respiratory failure patients with chronic airflow limitation is the prevention of VAP. Once again, this strategy is most likely to prevent EOP. Given other options to prevent EOP and the lack of benefit in certain groups, CASS makes the most sense in patients who require ventilation in the supine position, such as certain trauma patients, and in patients for whom antibiotics are not indicated.

Given the expense, morbidity, and potential mortality of VAP, it would be easy to assume that prevention of any kind is cost-effective. However, a one-size-fits-all-strategy may be neither effective nor cost-effective. Studies like that of Kollef et al are important contributions to the literature, allowing clinicians to tailor their VAP prevention strategies to the most appropriate fit for their specific practice.

Richard G. Wunderink, MD, FCCP
Memphis, TN

Dr. Wunderink is Associate Director of Clinical Research, Methodist Healthcare Foundation, and Clinical Associate Professor, University of Tennessee, Memphis.

Correspondence to: Richard G. Wunderink, MD, FCCP, Methodist Healthcare Foundation, 1265 Union Ave, 501 Crees Wing, Memphis, TN 38104; e-mail: wunderr@methodisthealth.org

References

1 Wunderink RG. Attributable mortality of ventilator-associated pneumonia. Sepsis 1998; 1:211–221
16 Cottoner FR. Indications for selective decontamination of the digestive tract. Semin Respir Infect 1993; 8:300–307
Husker Days and Fever Nights
Counting Cases of Organic Dust Toxic Syndrome

In 1994, the National Institute for Occupational Safety and Health (NIOSH) issued an “alert” calling for assistance in preventing organic dust toxic syndrome (ODTS).1 At that time, NIOSH estimated that up to 30 to 40% of all heavily exposed United States workers, predominantly in the agricultural sector, might experience ODTS following organic dust inhalation. The NIOSH became concerned, not because ODTS was a new condition arising out of a novel exposure, but because of a growing awareness that this was probably a long-standing but poorly recognized problem. ODTS, a flu-like illness marked by fever, myalgia, and mild cough, is distinct from hypersensitivity pneumonitis (allergic alveolitis) and, importantly, far more common.

But just how common is ODTS? Despite the call for attention to the problem by NIOSH, population-based epidemiologic investigations of this question in the United States have been limited. The study by Sussana Von Essen and colleagues in this issue of CHEST (see page 1452) provides important new information to help us answer this question. Von Essen and colleagues have cleverly surmounted one of the major challenges in studying farmers, a working population that, by its very nature, is typically spread over large geographic areas, thereby limiting easy access. Possible strategies to address this difficulty can include mail-back questionnaires (which are notoriously prone to low-compliance rates in the United States) or telephone surveys, neither of which allows for direct physiologic assessment.

Rather than go to the mountain, Dr. Von Essen chose instead to let the mountain come to her, in the form of “Husker Harvest Days.” By recruiting among the 200,000 attendees at this huge farmer’s fair, she was able to efficiently study nearly 300 persons by both questionnaire and spirometry. Although this was by no means a random sample, she argues convincingly that the subjects did not appear to be in ill health based on the study by Von Essen and colleagues, and, because it was so frequent among the group, it accounted for an attributable risk of 21%, or one in five of the cases identified. One would estimate, therefore, that in a farming population without swine confinement workers, the prevalence of ODTS would be somewhat less (28%), albeit still high.

Handling sorghum or wheat was also associated with ODTS, although marginally so; cough or chest tightness from grain, however, was quite strongly linked to ODTS in the analysis. The grain implicated in the chest tightness was sorghum, a crop that 43% of those studied, has evolved from traditional “pig farming” into a factory-like, enclosed operation that involves high-level exposures to both organic dusts and irritant gases. Doing this type of work doubled the risk of ODTS in the study by Von Essen and colleagues, and, because it was so frequent among the group, it accounted for an attributable risk of 21%, or one in five of the cases identified. One would estimate, therefore, that in a farming population without swine confinement workers, the prevalence of ODTS would be somewhat less (28%), albeit still high.

There are no other United States population-based estimates of ODTS prevalence with which to make comparisons. The earliest epidemiologic studies of this type were carried out by Rask-Anderson2 and Malmberg et al3,4 in central Sweden in the mid-1980s. In one questionnaire sample of 512 farmers, they estimated that 19% of those sampled had had ODTS; in a second, larger sample of 6,267 subjects, they estimated that only 6% met the criteria for the syndrome. In another, smaller Swedish study of 56 vegetable, grain, or swine farmers, 20 other farmers, and 23 urban controls, Carvalheiro et al6 found that 25% of grain or swine farmers, 10% of the other farmers, and < 5% of the controls reported symptoms consistent with ODTS. In 1990, a study among 2,866 Finnish farmers found 14% with ODTS,7 while a 1994 study of 1,577 Swedish sawmill workers estimated that 22% of dust-exposed workers experienced ODTS.8 More recently, a 1998 cross-industry study of 1,032 organic dust-exposed workers in the UK found only 1% with the syndrome.9

One reason accounting for the higher prevalence of ODTS observed in the study by Von Essen and colleagues may be the mix of exposures in the study population and the changing technology of agriculture itself. In particular, “swine confinement work,” as performed by almost 30% of those studied, has evolved from traditional “pig farming” into a factory-like, enclosed operation that involves high-level exposures to both organic dusts and irritant gases. Doing this type of work doubled the risk of ODTS in the study by Von Essen and colleagues, and, because ODTS was a new condition arising out of a novel exposure, therefore sorghum was also likely to have been a major contributor to the high prevalence of ODTS reported and is another important observation from this study.

There is no “gold standard” for surveying ODTS. The definition used by Rask-Anderson2 and Malmberg et al3,4 in their original studies of ODTS prevalence was fairly restrictive, requiring not only fever and chills related to work, but symptoms severe enough to make work difficult or to require bed rest.10 The case defini-
tion used by Von Essen and colleagues (a positive answer to the question “Have you ever had a flu-like illness consisting of fever, aching and tiredness after working on the farm?”) is closer to that used by Carvalheiro et al: “Have you, during the last 2 years, had episodes of influenza-like symptoms (fever, shivering, malaise, cough, tiredness, muscle and joint pains) in connection with dusty work?”

A recent community-based study of 400 pig farmers and 368 rural but nonagricultural controls in the Netherlands compared both definitions.10 By the narrow definition including work impairment or bed rest, only 6% of the pig farmers met the criteria for ODTS. By the broader definition, 26% of the exposed had the syndrome, but 17% of the controls did as well. The 36% prevalence estimate for ODTS reported by Von Essen and colleagues overshoots the true frequency to the extent that the case definition used also picked up the background rate of illnesses that was not work related. Even assuming that 10 to 15% of the illness was misclassified, however, a prevalence of 20 to 25% is still impressive.

The mechanisms underlying ODTS and the interrelationships between this syndrome and other occupational lung diseases associated with organic dust inhalation, including asthma, chronic airway obstruction, and hypersensitivity pneumonitis, are still poorly understood. The shifting terminology that had been used to describe ODTS in the past (including silo-unloader’s disease, pulmonary mycotoxicosis, grain fever, mill fever, and precipitin-negative farmer’s lung1) may have confused clinicians and retarded research efforts. A broader term, inhalation fever, which includes ODTS, polymer fume fever, and metal fume fever under the same rubric, may be more useful insofar as it highlights the similar mechanisms that may link these occupational conditions pathophysiologically.11 A number of human experimental studies have begun to shed light on the inflammatory underpinnings of ODTS.12–17 But epidemiologic investigation has lagged behind, especially in the United States. The study of Von Essen and colleagues is an important step in the right direction.

Paul D. Blanc, MD, MSPH, FCCP
San Francisco, CA

Dr. Blanc is Associate Professor of Medicine at the Division of Occupational and Environmental Medicine, University of California San Francisco.

Correspondence to: Paul D. Blanc, MD, MSPH, FCCP, Division of Occupational and Environmental Medicine, Box 0924, University of California San Francisco, San Francisco, CA 94143-0924; e-mail: blancp@itsa.ucsf.edu

References