Lung Cancer Screening
Conundrum or Contumacy?

In this issue of CHEST (see page 329), Jerome Reich, MD, from the Kaiser Foundation Hospitals Center for Health Research, adds his voice to the chorus of epidemiologists who oppose screening for lung cancer (LC) with CT scanning outside of a prospective randomized controlled trial (RCT). He marshals evidence, proposes models to elucidate the medical and economic perils of LC screening, and exhorts clinicians to rally round the “gold standard” of the RCT. The author provides a very complete review of previous screening trials for LC. He discusses the hypothetical reasons for failure of these trials to demonstrate a reduction in population mortality and concludes that overdiagnosis bias (ODB) has been convincingly demonstrated.

Ultimately, Reich’s theory, model, and conclusions are based entirely on indirect and circumstantial evidence. He offers little direct proof that ODB of LC exists. Furthermore, he ignores two clinical series that document very low survival in early stage LC patients who are not treated following diagnosis by screening.1,2 The information from the series by Sobue et al,3 as well as the data from the follow-up study by Flehinger et al2 of prior National Cancer Institute studies, indicates that most patients with small LCs who do not receive surgical resection or other effective treatment die within 5 years. Although this evidence is retrospective, it is very strong. Death is a clear end point.

Reich goes on to postulate that not only are 33% of LCs “pseudodisease” (ie, nonlethal if untreated), but that another 33% are “nonaggressive” in their behavior. This is completely at variance with the data from thousands of clinical series examining this disease. For example, national survival data indicate that only 15% of LC patients survive 5 years.3 Therefore, many patients must die of Reich’s “nonaggressive” LC. Any inferences drawn from such a misguided premise are, of necessity, invalid. Since epidemiologists insist that the RCT is a holy grail, then it is perfectly reasonable to insist that they drop discussion of putative “overdiagnosed” LC until they perform an RTC to demonstrate the existence and frequency of this ephemeral entity. I wish them good luck in finding a suitably compliant institutional review board and study subjects credulous enough to participate in the untreated control arm of their study.

Because resection of pseudodisease provides no benefit, Reich concludes that screening and treatment of early LC will actually result in a reduction in life expectancy. Why? Because the progressive decrease of FEV₁ precipitated by surgery will worsen with age. He postulates that death occurs when FEV₁ falls to 1 L. (This is inaccurate; many such patients will live for years with proper care.) He offers no RCT data to support this conclusion. One benefit of an early diagnosis of LC may be to preserve lung function. It is possible that future research in patients with very small, screen-detected LCs may show that some subsets may be effectively treated by limited resection or radiation therapy rather than by lobectomy.

It is difficult for me to understand how the RCT currently proposed by the National Cancer Institute can nominate chest roentgenogram as one arm, after reading Reich’s scholarly refutation of the value of this test. If one were intellectually and scientifically rigorous, one would have to insist on an RCT of CT scan against current medical practice (ie, diagnose and treat only after symptoms have developed). Could such a study be performed? I personally doubt that it could attract an adequate accrual of patients. Even with sufficient accrual, this RCT will require a minimum of 14 years to complete. During that time, millions will die and technology will change in ways that render current imaging techniques obsolete and the eventual study result meaningless.

Would this RCT be ethical? I do not think so. Randomization of a study subject or patient to a research study demands equipoise. The personal physician must conclude that he does not really know which of the two arms will offer his patient a better chance of survival. Would a reasonable physician make such a conclusion after looking at the data from the Early Lung Cancer Action Project (ELCAP) study, in which 80% of study subjects had LC
detected in stage I. I seriously doubt it. As a former smoker who is at risk of LC death, my personal choice has been to become a study subject as well as a principal investigator in a participating center in the International-ELCAP (I-ELCAP) trial. Furthermore, if I did not have access to this trial, or was otherwise ineligible, I would have requested that the test be performed outside of a study by a skilled radiologic group. I could not, therefore, in good conscience, ask a study subject to risk a 50% chance of randomization to a study arm that was personally unacceptable. I suspect that many judicious clinicians will concur.

Reich also warns that not only will LC screening result in unnecessary deaths, it will also be ruinously expensive. I have addressed this issue in another editorial.5

Because there are so many billions of dollars involved in the implementation of LC screening, it is important to consider whether there are any potential conflicts of interest that might compromise unbiased debate. For example, radiologists and surgeons (like myself) might benefit financially from screening. Governments, medical insurance companies, and managed care organizations (like Kaiser) would be forced to absorb the costs. One major ancillary benefit to payers in an RCT is that any favorable result, and any consequent need to pay for LC screening, would be delayed for many years.

Another very interested third party is the tobacco industry. They recently obtained a favorable verdict in a class action suit in the state of West Virginia that sought to force tobacco companies to pay for CT scan and pulmonary function screening in 250,000 smokers and ex-smokers. They convinced jurors that LC screening, would be delayed for many years.

While Reich is correct in insisting that there are important pitfalls in screening, it is important to put LC screening into a 21st century perspective. The lessons learned from prior screening trials in other organs have been carefully incorporated into the planning of the prospective single-arm I-ELCAP trial that is now in progress at 20 medical centers in the United States and a number of other nations. The I-ELCAP protocol carefully minimizes radiation dosage, maximizes quality control, fosters smoking cessation in study subjects, and incorporates a strict protocol emphasizing demonstrable growth in order to minimize the number of invasive tests and operations. The original ELCAP trial was very successful in all of these areas, and refinements in the protocol make I-ELCAP even better. The research plan of I-ELCAP will provide a definitive answer to the question of whether low-dose, noncontrast, spiral CT scanning will effect a stage shift toward early diagnosis. The overwhelming body of evidence available from hundreds of published surgical series suggests that surgical treatment in very small stage IA non-small cell lung cancer will result in high survival rates and should reduce LC population mortality. Paradoxically, the large scope of this multi-institutional trial also will offer a better opportunity to answer the question of ODB, since it is inevitable that there will be study subjects who are reasonably young and physiologically fit who will opt for no therapy. Careful follow-up in these individuals will provide a definitive answer as to the existence and frequency of pseudodisease LC and nonaggressive LC.

Finally, the performance of prospective single-arm trials does not mutually exclude the performance of large RCTs. There is definitely room for a reasonable difference of opinion over which type of study is superior. What is not acceptable is unwarranted overemphasis on highly theoretical risks while turning a blind eye on the very real carnage caused by LC. What is not acceptable is further pointless delay in implementing life-saving early detection strategies.

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Lung Cancer Screening, Once Again

Lung cancer screening is a frequent visitor to the pages of CHEST, and this issue is no exception. The article by Jerome Reich (see page 329), “Improved Survival and Higher Mortality: The Conundrum of Lung Cancer Screening,” helps to remove some of the mystery behind the theoretical underpinnings of lung cancer screening. In doing so, the article provides a compelling case against the establishment of mass lung cancer screening programs at this point in time, be they with chest radiographs or helical CT scanning.

Randomized controlled trials of lung cancer screening have produced seemingly conflicting findings. These trials have demonstrated increased patient survival but, at the same time, have shown no reduction in lung cancer mortality.1–3 In his article, Dr. Reich addresses how these conditions can legitimately occur at the same time. He also reviews other important issues in lung cancer screening that tend to be overlooked.

The topics discussed by Dr. Reich are not new. The lung cancer literature is replete with articles and editorials positing that it is too soon to establish mass lung cancer screening programs.4–7 So why publish another manuscript? Why did I, a reviewer of Dr. Reich’s article, recommend that it be accepted?

Simply put, there is too much at stake to establish a program of mass lung cancer screening without solid evidence of its benefits. Sadly, the available data8–12 cannot provide irrefutable evidence of a reduction in lung cancer mortality, or even an extension of life, with screening by either chest radiograph or CT scanning. Lung cancer detection, as intuitively appealing as it is, is limited in what it can tell us.

Why is lung cancer detection not enough? The problem with cancer screening, as Dr. Reich points out, is that there is harm that is inherent in the process. There is the very likely possibility of overdiagnosis.4,5 If, by some chance, overdiagnosis did not exist in lung cancer screening, risks would still exist.13 Although the imaging examination itself poses a small immediate threat, the sequela of a positive screening finding (ie, diagnostic evaluation and, if necessary, cancer treatment) can cause trouble. Smoking-related comorbidities (such as heart disease and compromised pulmonary function) make follow-up and treatment even riskier.

Ignoring the financial costs and the strains on the health-care system, it seems, from an ethical perspective, that it would be acceptable to implement mass screening programs at this point in time only if lung cancer screening were, at worst, innocuous. What must be acknowledged is that no mass cancer screening program is ever innocuous; even in the presence of a benefit, there is a guarantee of harm.14 Of course, there is a wide range of harmful effects. At one end, there may be small inconveniences and wasted resources, but on the other end, there may be premature deaths due to complications from undergoing a thoracotomy.

Lung cancer is a horrific disease. Screening proponents and opponents alike agree that something must be done to reduce the burden. It would be unforgivable, however, if a prematurely established lung cancer-screening program resulted in more harm than benefit. Some would contend that such a result is impossible, but Dr. Reich shows us that it could very well happen.

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Quality of Life After Lung Cancer Surgery

A Forgotten Outcome Measure

Currently, surgery is the preferred treatment for resectable lung cancer. Most surgical reports have focused on preoperative risk factors and operative mortality along with long-term survival. Late functional disabilities following surgical resection are not widely reported and may be more important to the patient. There may exist patients in whom potential persistent impairments in functional status would lead them to consider less invasive approaches or alternative treatments. There are many tools available to measure functional status. These can serve as outcome measures and may also be used to guide patient counseling. One such tool, the Short-Form Health Survey (SF-36), was designed to be applicable in a wide range and severity of conditions. Its measures include behavioral functioning, perceived well-being, social and role disability, and personal evaluations of general health. It aims to distinguish role changes attributable to physical limitations from those due to mental conditions.

The utility of the SF-36 in longitudinal studies of patients undergoing total hip arthroplasty, non-small cell lung cancer surgery, and thoracic aortic aneurysm repair have been reported. The SF-36 has been found to be a useful tool in the quantification of patient quality of life. It is brief and has gained general acceptance. More important to the researcher is its well-established reliability and validity in a variety of medical conditions and surgery-specific studies.

For the SF-36 to be useful in assessment of patients with lung cancer, it needs to be sensitive not only to the immediate postoperative physical and emotional consequences of surgery, but should also reflect the effects of uncertainty regarding long-term prognosis. At 6 months and 12 months after surgery, lung cancer patients have reported significantly poorer levels of health perception, physical function, bodily pain, and vitality as compared to their preoperative assessment. It has been found that the physical score of the SF-36 is more sensitive than other measures with which it was compared, but that the psychological score was less sensitive to change. It is often necessary to combine the SF-36 with another tool such as the hospital anxiety and depression scale to better assess both physical and psychological well being of patients with cancer.

In this issue of CHEST (see page 21), Handy and colleagues report their prospective survey of 139 patients undergoing surgical resection for lung cancer. This was a study carried out at three hospitals. They compared functional health status and quality of life using the SF-36 and the quality of life index (QLI). They attempted to stratify outcomes and quality of life following thoracic surgery as a function of preoperative FEV1, 6-min walk distance, diffusing capacity of the lung for carbon monoxide (DLCO), use of chemoradiation, extent of resection, and postoperative complications comparing to age-matched control subjects without lung cancer. The authors found that preoperative functional health status in lung cancer patients is significantly impaired and persisted 6 months following lung resection. They further concluded that impaired DLCO, not FEV1, is a poor prognostic predictor of postoperative quality of life. Although the ability of the preoperative lung to perform gas exchange (DLCO) may in fact be more important than its mechanical behavioral properties (FEV1) in determining surgical results, we would caution against the use of DLCO as the sole preoperative measure of surgical candidacy based on the findings of this group. Traditional surgical literature has suggested poorer surgical prognosis with preoperative FEV1 < 60%, and a preoperative FEV1 < 40% should be considered a contraindication to resection. Handy and colleagues stratified their results into preoperative FEV1 of < 40%, 40 to 79%, and > 79% predicted groups. It would be interesting to see other supportive reports using traditional limits for FEV1 in a similar study.

The implications of the study by Handy and colleagues are many. Where surgeons often consider the probability of survival with regards to preoperative risk factors, patients may be more concerned with the possibility of needing home oxygen, poor exercise tolerance, and inability to perform activities of daily living. Information such as this should be reported in the literature and discussed during preoperative patient counseling. In the setting of surgical treatment for a chronic or potentially incurable disease, quality of life must be considered of prime concern and not forgotten.

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While bleeding remains the most common serious complication of heparin use, heparin is also a common cause of drug-related thrombocytopenia. Heparin-induced thrombocytopenia (HIT) occurs either as an acute, transient, and innocuous phenomenon due to nonimmunologic heparin effects (type I HIT), or as a morbid syndrome that usually occurs after a week of heparin therapy and is associated with platelet activation and a high rate of thromboembolism (type II, commonly termed “HIT”). Heparin-associated thrombocytopenia and heparin-associated thromboembolism with thrombosis are older classifications now folded into the rubric HIT. Thrombocytopenia usually denotes <100×10⁹ platelets per liter. HIT often is described in the context of antiheparin antibodies in patients with >100×10⁹ platelets per liter, if they have a falling platelet count and/or thrombotic events. A decrease in platelets during illness is usually not due to concomitant heparin therapy. Sepsis, disseminated intravascular coagulation, bone marrow suppression by drugs or illness, hypersplenism, or platelet consumption from pulmonary embolism, cardiac bypass, and orthopedic surgery can all decrease platelet counts acutely. HIT has a relatively low incidence of 1 to 3% in patients treated with unfractionated heparin (UFH). When do we need to suspect HIT? In this issue of CHEST (see page 37), we are provided with a study that increases our diagnostic accuracy of HIT. Lubenow and colleagues undertook a retrospective chart review of HIT onset in relation to the start of heparin therapy. They used a database of 119 surgical and medical patients with HIT who were enrolled in a prospective multicenter clinical trial of lepirudin therapy as an alternative anticoagulant. They defined HIT as thrombocytopenia <100×10⁹ platelets per liter in the presence of circulating antiheparin antibodies, whether thrombosis was present or not. Chiefly, they found that HIT is uncommon in the first 5 days of heparin therapy, unless heparin was administered in the preceding 3 months. HIT occurred similarly whether heparin was administered subcutaneously or IV. Heparin-reexposed patients (n=46) had HIT develop at an average of 5 days of therapy (many on day 2), while heparin-naïve patients (n=79) had HIT develop at an average of 12 days (only 6% before day 6). Of the heparin-reexposed patients, only those who received heparin in the past 3 months were likely to get HIT before day 5 of heparin. Most HIT cases from heparin reexposure still occurred “late,” after 5 days of heparin. Few HIT cases involved low-molecular-weight heparin (LMWH). Whether this discrepancy was due to limited use of LMWH at the participating centers or due to the lower immunogenicity of LMWH is unclear. However, the preponderance of HIT cases among UFH-treated patients is consistent with two prospective studies of heparin prophylaxis in orthopedic patients, which revealed significantly less HIT in the LMWH-treated patients compared to those treated with UFH.

How can the study of Lubenow and colleagues help us improve our early diagnosis of HIT? HIT antibody test results may take days. Stopping heparin while awaiting assay results may be unnecessary. Using the findings of Lubenow and colleagues, decreasing platelet counts are likely not due to HIT for a heparin-naïve patient in the first 5 days of heparin treatment for an acute thrombosis. However, deciding whether a patient is heparin naïve may not be simple. Heparin from hemodialysis, IV catheter flushes, and even on heparin-coated central venous catheters can cause HIT. In heparin-naïve patients, platelet monitoring would be of little value before day 5 of heparin, yet should be instituted daily for patients exposed to any heparin in the prior 3 months. If one cannot rule out recent heparin exposure, monitor platelet counts early. The conclusions of this study are consistent with those of another retrospective study of the temporal aspects of HIT with a different definition of thrombocytopenia (>50% fall in platelet count). HIT must be considered in all heparin-treated patients with a significant fall (>30%) in platelet count, even in the absence of thromboembolism or actual thrombocytopenia. While most HIT patients in the lepirudin trial database had <100×10⁹ platelets per liter, thromboembolic events due to HIT in that and other studies clearly can occur with platelet counts in the normal range, yet all such HIT patients had a significant fall in platelet count. The occurrence of thromboembolism in HIT reflects platelet activation, formation of cross-linked platelet aggregates via platelet Fc receptors, platelet microparticle generation, and thrombin activation that occur after specific IgG (or IgM) antibodies bind to a complex of platelet factor 4 and heparin on.
platelet and endothelial surfaces. After heparin therapy is stopped, these antibodies remain and trigger thromboembolic complications in many HIT cases. Thus, therapy of HIT is not just stopping heparin treatment. Anticoagulation may not only be needed for the original indication, but for the high risk of thromboembolism due to HIT antibodies. Clinical benefits and platelet recovery were demonstrated in prospective trials5,11 of alternative anticoagulants in HIT. Based on these studies, consensus guidelines recommend immediate therapy of HIT to limit thrombin generation, either with one of the direct thrombin inhibitors lepirudin5 and argatroban, or the factor Xa inhibitor danaparoid, a desulfated heparinoid.11 Only danaparoid is approved for thromboembolism prevention in patients with previous HIT. LMWH crossreacts with HIT antibodies and should never be used in HIT. All three alternative agents are not reversible, cause bleeding, and have contraindications and pharmacodynamic quirks that mandate involvement of a clinician familiar with their use. The use of warfarin alone during the acute phase of HIT is discouraged, due to reports of thrombosis from warfarin-mediated protein S depletion in the face of ongoing antibody-mediated thrombin generation. Interestingly, HIT antibodies are transient and HIT antibody generation does not involve an anamnestic response. The platelet factor IV heparin enzyme-linked immunosorbent assay remains positive for an average of 3 months, while the heparin-induced platelet activation assay (serotonin release) remains positive after an average of 50 days.8 Reflecting this, Lubenow and colleagues found that subjects with prior HIT who were inadvertently reexposed to heparin after 3 months rarely had early HIT develop; their circulating antibodies had cleared. Nonetheless, all HIT patients should have heparin listed as an allergy, and any future heparin therapy can be done only for compelling indications, only when HIT antibodies disappear, and for as briefly as possible. Substitution of alternative anticoagulants may be safer, though their use for non-HIT indications, only when HIT antibodies disappear, and for as briefly as possible. Urgent administration of an alternative anticoagulant is recommended. We should rarely stop heparin therapy before day 5 in heparin-naïve patients, as we have learned that HIT is unlikely in that group. Avoiding heparin use in routine catheter flushes should prevent some HIT. Future prevention may involve more widespread use of LMWH or alternative anticoagulants in place of UFH. The higher cost of these agents and the low incidence of HIT from UFH therapy limits the appeal of such a strategy. For now, HIT is here to stay.

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Does Splinting From Thoracic Bone Ischemia and Infarction Contribute to the Acute Chest Syndrome in Sickle Cell Disease?

Research into and treatment of sickle cell disease (SSD) have been the province largely of hematologists and pediatricians. With the realization that
pulmonary complications, both acute and chronic, are major causes of morbidity and mortality in patients with this disorder, pulmonary and critical care specialists who treat adults have begun to focus on this disease as well. Mortality rates for patients with sickle cell anemia have declined, with the median age at death being 42 years for men and 48 years for women. Factors leading to increased survival into adulthood include penicillin prophylaxis, Haemophilus influenzae and Streptococcus pneumoniae vaccinations, widespread use of newborn screening programs for early detection, and improvements in parental education. In the Cooperative Study of Sickle Cell Disease, acute chest syndrome (ACS) was the second most common complication, exceeded only by painful vaso-occlusive crisis (VOC), and was the most common condition at the time of death.

SSD is characterized by microvascular occlusions that result in acute and chronic ischemic damage to the lungs, kidneys, spleen, skeleton, skin, and CNS. Hemoglobin S rapidly polymerizes when deoxygenated due to the single substitution of hydrophobic valine for glutamic acid on the β-globin chain. Conditions that promote sickling are high concentrations of S hemoglobin in the RBCs, hypoxia, slow organ transit times, low pH, and cellular dehydration. The S hemoglobin polymers lead to a distortion of the RBC membrane shape (ie, “sickling”) and to a rigidity that retards transit through the microvasculature. In addition to this mechanical obstruction of the microvasculature, increased adhesion of RBCs to the endothelium occurs as a result of increased levels of circulating inflammatory cytokines; microvascular thrombosis; endothelial damage and cellular interactions among the RBCs, WBCs, and endothelial cells. These mechanical and molecular events all contribute to the obstruction of arterioles and to ischemic damage to tissues.

The major acute pulmonary complication of SSD is ACS, although it has been suggested that asthma and pulmonary thromboembolism also occur with increased frequency. ACS has been defined as the presence of a new pulmonary infiltrate (involving at least one complete lung segment, not atelectasis) with chest pain, a temperature of >38.5°C, tachypnea, wheezing, or cough in a patient with SSD. Multiple pathogenetic mechanisms are thought to lead to this syndrome, including fat emboli from infarcted bone, pulmonary infection, atelectasis from splinting due to thoracic pain during VOC, in situ thrombosis, vascular injury due to cell-cell interactions and inflammatory mediators, and thromboemboli (in some cases).

The National Acute Chest Syndrome Study Group reported on 671 episodes of ACS that were treated in 30 centers. Half of the patients were admitted to the hospital for a reason other than ACS, mostly VOC. Clinical findings of patients with ACS developed in a mean of 2.5 days after hospital admission. A specific cause (eg, pulmonary infection or fat embolism) for the ACS was found in 38% of all episodes and in 70% of episodes with complete data. Pulmonary infection, caused by 27 different organisms, was present in 36% of episodes, with Chlamydia, Mycoplasma, and viruses being the three most common pathogens. Fat emboli, with or without infection, were present in 8.8% of patients, pulmonary infarction was inferred in 16% of patients, and in 46% of patients the cause was unknown. Pleural effusions were present in 36% of patients at the time of diagnosis, and in 55% during the hospitalization. Bilobar involvement was typical. Thirteen percent of patients required mechanical ventilation, 11% had neurologic symptoms, and 9% of those >20 years of age died. Children, in contrast to adults, were more likely to present with fever, cough, and wheeze, with upper and middle lobe opacities present on chest radiographs. Adults had more chest pain, limb pain, and dyspnea, with fever and cough occurring in only about 60% of patients. These differences may reflect differences in the relative frequencies of etiology, with children presenting with ACS due to pulmonary infection and adults more commonly presenting with VOC complicated by subsequent fat emboli and ACS. In this sense, pain is a prodrome of the ACS, indicating the need to monitor for and try to prevent its development in those admitted to the hospital for VOC.

The lung plays an important role as the processing site for protecting the arterial circulation and organs from bombardment by sickled cells containing polymerized hemoglobin S. As oxygen loading takes place in the well-ventilated lung, desickling rapidly occurs. It is thought that when thoracic pain is present in a patient experiencing a VOC, splinting leads to regional hypoventilation, hypoxia, and atelectasis, which can cause intravascular in situ sickling in the pulmonary capillaries, leading to lung infarction. When lung dysfunction develops in a patient with VOC, a vicious cycle develops because of the loss of the lung’s role in desickling. Incentive spirometry and pain control should help to prevent these events.

Bellet and colleagues did a prospective, randomized trial of incentive spirometry in 29 patients with SSDs who were hospitalized with acute chest or back pain above the diaphragm. The incidence of thoracic bone infarction (in the ribs, vertebra, or sternum), documented by nuclear bone scan, was 39.5% (15 of 38 hospitalizations). Patients randomized to incentive spirometry took 10 maximal inspirations every 2 h between 8 AM and 10 PM and while awake during
ACS), not the full-blown ACS as defined by the graphic opacities (ie, the mild end of the spectrum of ACS), not the full-blown ACS as defined by the National Acute Chest Syndrome Study Group. Incentive spirometry is now recommended for prophylaxis of ACS in VOC and in the perioperative period.

In this issue of CHEST (see page 43), Needleman and colleagues at the Children’s Hospital at Montefiore (Bronx, NY) provide data that are supportive of the idea that thoracic pain in a VOC leads to ACS, in part due to shallow breathing. This study used respiratory inductive plethysmography (RIP) to evaluate breathing patterns in 25 patients with SSD who were admitted to the Sickie Cell Center Day Hospital for the treatment of VOC. In comparison to those with pain at other sites, the 10 patients with thoracic cage pain had a lower tidal volume (355 vs 505 mL, respectively; p = 0.003) and a higher respiratory rate (23 vs 17 breaths/min, respectively; p = 0.03). After treatment with opiate medication, these differences became insignificant. This study provides additional support for the concept that a low tidal volume-high respiratory rate pattern of breathing (ie, ”splinting”) due to thoracic pain in a patient experiencing a VOC leads to regional hypoventilation, atelectasis, alveolar hypoxia, and subsequent intravascular sickling in the lung, which is part of the pathophysiology of ACS. It also suggests that adequate analgesia is an important part of preventing ACS in those with thoracic pain by allowing larger tidal volumes. Aldrich, an investigator in this study, and colleagues have shown in an animal model that regional hypoxia and/or the resulting vasoconstriction causes the mechanical entrapment of sickle cells, which is reversible with a relief from hypoxia.

There are some inconsistencies in the data that undermine the certainty of the conclusions, although this is likely due to the small study size, an inadequate dose of the opiate, or the use of a suboptimal pain questionnaire. Pain scores and breathing patterns were not significantly changed by opiate administration in the group with chest pain or in the group with pain at other sites, although the baseline differences in tidal volume and respiratory rate between the groups became nonsignificant after pain medication. This weakens the conclusion that the relief of chest pain by opiates leads to a less shallow pattern of breathing. It would be premature to conclude from this study that RIP should be used routinely to monitor breathing patterns in patients with VOC to prevent ACS since this study was not designed to evaluate the impact of RIP on clinical outcomes.

The number of recurrent episodes of ACS, as well as a history of painful VOC with chest pain and asceptic bone necrosis, are the risk factors for sickle cell chronic lung disease. This chronic condition is characterized by pulmonary vascular bed obliteration, smooth muscle hypertrophy, and parenchymal fibrosis. Chest radiographs show reticular changes. Mixed restrictive and obstructive features are seen with reduced FEV1/FVC ratio, total lung capacity, and diffusing capacity. The late stages are characterized by hypoxemia, pulmonary hypertension, and cor pulmonale. This emphasizes the importance of the prevention and treatment of ACS. Rarely, pulmonary hypertension can be due to chronic unresolved large-vessel thromboembolism. Successful pulmonary thromboendarterectomy has been performed in patients with SSD.

The current treatment for patients with ACS includes treatment aimed at the many factors that may contribute to its pathogenesis. The liberal use of fluids to prevent hemoconcentration, supplemental oxygen to reverse sickling, incentive spirometry, and adequate pain control are central elements of treatment. Therapy with antibiotics, including a macrolide or quinolone that is active against atypical pneumonia organisms, should be included in a treatment regimen, although it is clinically difficult to determine which patients with ACS have pneumonia. Some investigators have advocated the routine use of bronchoscopy with BAL for the quantification of fat-laden alveolar macrophages to assess for bone marrow/fat emboli, but this procedure is likely to guide therapy only in selected cases, and its routine use is not indicated. One study found a high proportion of pediatric patients to have plastic bronchitis with bronchial casts, which were removed by lavage and suction with the bronchoscope. Bronchodilators are given to the patient when wheezing or airflow obstruction is present, and some investigators recommend its routine use in all pa-
patients. This is indicated for most patients with ACS, particularly those with moderate or severe hypoxemia, or a worsening clinical course. 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.2–4,10,21,22

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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 may infect the lung. Similarly, the clinician must consider noninfectious etiologies, such as progression of underlying disease, pulmonary edema, treatment-related toxicity, alveolar hemorrhage, and bronchiolitis obliterans organizing pneumonia. The prognosis for immunosuppressed patients with pulmonary complications 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 studies1–3 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 heterogeneous 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 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 withdrawing 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 diagnose 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 indiscriminately.
inately (eg, 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 are in development to allow PCR processing of fluid recovered from BAL.

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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The opinions expressed herein are not to be construed as official and do not reflect the policy of either the Department of the Army or the Department of Defense.

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