Is the More (Intricate) the Better?

To the Editor:

Toraldo and colleagues (December 2005) are to be congratulated on their endeavor to identify daytime variables that are predictive of nocturnal desaturation in COPD patients, a field in which many attempts have failed. However, we think that some points are worth addressing.

First, despite the plethora of data presented by Toraldo et al., it does not greatly contribute to the evidence base of numerous previous articles that the probability for nonapneic desaturation is proportional to the severity of blood gas disturbances and lung function impairment.

Second, we think that an analysis of the possible usefulness of the oxyhemoglobin dissociation curve (ODC) as a predictive tool for nonapneic desaturation in COPD patients could have been included in the discussion. A physiologic decrease of PaO2 during sleep in healthy subjects does not result in significant desaturation because of the plateau in this section of the lung. The decrease of PaO2 in COPD patients frequently combined with an increase in PaCO2 and a decrease in pH, as well as with some specific changes in the biochemistry of hemoglobin (ie, an increase in 2,3-diphosphoglycerate and Po2 corresponding to 50% saturation of hemoglobin) causes a rightward shift of ODC and a displacement of the desaturation point to the steeper slope of the ODC. All of those conditions are prerequisites for significant nocturnal desaturation. We believe that the so-called capacitance coefficients that are a measure of the slope of different parts of the ODC and their “desaturation capacity” may be a promising avenue for the more accurate prediction of the nocturnal desaturation in COPD patients.

Having in mind the major clinical implications of significant nocturnal desaturation, we believe that the authors should comment on these issues.

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The authors hereby declare that they have no conflicts of interest to disclose.

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To the Editor:

We thank Dr. Kostianev et al for contribution of their knowledge in the field addressed by our article (December 2005). We agree that independent predictors of nighttime desaturation in COPD patients useful for clinical applications are still being discussed. Some tests have been proposed: (1) low daytime PaO2 values; (2) reduced sensitivity of respiratory centers to chemical stimuli; (3) serious alteration of pulmonary function test results; (4) a clinical frame of “blue bloaters”; (5) desaturation after physical effort; (6) measurement of carbon dioxide ventilatory response; and (7) awake daytime arterial oxygen saturation (SaO2) values.

Our study used for the first time a cluster analysis in such a prediction. The cluster analysis involves grouping similar objects into distinct, mutually exclusive subsets referred to as clusters. The elements within a cluster have a high degree of “natural association” among themselves, while the clusters are “relatively distinct” from one another. A cluster analysis method, therefore, can be simply defined as a procedure to classify data already used in clinical medicine for patients or patient data classification.

Our data showed that i-cluster analysis was able to detect populations among both “desaturator” and “nondesaturator” COPD patients; desaturator patients were identified not by the percentage of total recording time (TRT) spent in bed with arterial oxygen saturation (SaO2) < 90% alone, but rather by a pattern of percentage of TRT spent in bed with SaO2 < 90% and mean pulmonary artery pressure and PaO2 values, the latter also being predictors of nocturnal desaturation severity. Moreover, cluster analysis was able to identify subgroups of both desaturator and nondesaturator patients with varying degrees of illness.

Kostianev et al identified new biochemical parameters to evaluate oxygen transport using the dissociation curve of human hemoglobin. Sigggaard-Andersen and Sigggaard-Andersen proposed a computer program for calculating and displaying pH and carbon dioxide blood gas data that can be used to predict the oxygen status or acid-base status. Both methods are not simply to be used in clinical medicine for classification of patients. Our contribution is a further clinical/practical approach to clarify such a field opening to further studies on the sleep lung ventilation and oxygen saturation, the chemical control of respiratory function and on response to hypoxic and hypercapnic awake stimuli.

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d-ROMs Test Detects Ceruloplasmin, Not Oxidative Stress

To the Editor:

We read with interest the article by Papageorgiou et al (November 2005) reporting that the measurement of oxidative stress levels with a rapid commercially available method (d-ROMs test; Diacron; Grosseto, Italy) was highly repeatable in the patients studied and may serve as a marker for differentiation between exudates and transudates in clinical practice. Unfortunately, the basic principle of the d-ROMs test is invalid. In this method, overall oxidative stress is measured indirectly by measuring the level of total hydroperoxides. However, the alchilamine used as a chromogen in this method is also a substrate for the ceruloplasmin (ferrooxidase) enzyme, which is abundantly present in serum; the type of buffer used and its pH are more appropriate for ferrooxidase activity. This is borne out by the fact that a significant positive correlation between the assay results and ferroxidase activity has been found (r = 0.911; p < 0.001; n = 100) [Table 1, Fig 6 in the article by Erel2]. Also, this assay is inhibited by sodium azide (Fig 3 in the article by Erel2); no response was observed during copper-induced lipoprotein autooxidation (Fig 8 in the article by Erel2). Also, there were no appropriate linear responses for H2O2, t-butyl hydroperoxide, or cumene hydroperoxide solutions. Further, there was a lack of response during copper-induced lipoprotein autooxidation (Fig 8 in the article by Erel)2.

In a study by Calikoglu et al, it was shown that acute-phase reactants, especially ceruloplasmin, have a high sensitivity, specificity, and area under the receiving operator characteristic curve (92%, 85%, and 0.99, respectively) in the discrimination of exudative pleural effusions. These values are very similar to the findings of Papageorgiou et al (96%, 96%, and 0.99, respectively). Moreover, the significance of the ceruloplasmin values between exudates and transudates (Table 2 in the article by Calikoglu et al) were surprisingly similar to the findings of Papageorgiou et al for these two groups. It is apparent that the results published by Papageorgiou et al essentially reflect ceruloplasmin activity and not oxidative stress.

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REFERENCES


To the Editor:

We appreciate Dr. Harma’s comments regarding our article on oxidative stress levels in pleural effusions as a marker for the differentiation between exudates and transudates.1 The d-ROMs test (Diacron; Grosseto, Italy) may indeed measure ceruloplasmin oxidase activity besides the total level of hydroperoxides, and this is known from the initial study that has validated the d-ROMs method. However, the contribution of ceruloplasmin oxidase activity to the typical change of absorbance at the 505 nm of the d-ROMs test, although not negligible, is relatively small, especially due to the fact that in the d-ROMs method for the serum the sample is 100-fold diluted.2 The same probably applies for the pleural fluid samples, as we have used the same dilutions.

The correlation between ceruloplasmin oxidase activity and the d-ROMs test has not been shown in clinical practice. In hemodialyzed patients, for instance, the d-ROMs values are increased, whereas the ceruloplasmin oxidase activity is reduced.1 Additionally, d-ROMs have been validated in large populations of healthy subjects, alcohol abusers, and in various disease states. Interestingly, d-ROMs are increased in patients undergoing prolonged hyperbaric oxygen treatment and correlate with malondialdehyde levels, another marker of oxidative stress.3 Therefore, the similarities between the diagnostic performance of d-ROMs and ceruloplasmin for the differentiation between exudative and transudative pleural effusions referred by Harma et al are only speculative, and further research is needed in that direction.

In our study, we used d-ROMs as a marker of overall oxidative stress in the pleural fluid, and we concluded that this method is repeatable and represents an excellent marker for the differentiation of exudates and transudates. We believe that further research is needed for the clarification of the mechanisms of...
reactive oxygen metabolites production in the pleural cavity and their role in the pathogenesis of pleural effusions.

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Is Endobronchial Ultrasound Necessary for Transbronchial Lung Biopsy in Solitary Pulmonary Nodule?

To the Editor:

I read the article “Endobronchial Ultrasound-Guided Transbronchial Lung Biopsy in Fluoroscopically Invisible Solitary Pulmonary Nodule” by Herth et al (January 2006)1 with interest. In consideration of the outcomes of this article, several questions arose, as follows:

1. With lesion size being 1.4 to 3.3 cm, why were lesions not seen under fluoroscopy in 54 of 138 patients? Were they entirely indiscernible or somewhat visible?
2. The authors noted that the “suspected area” was approached by a catheter with an ultrasound probe. Was fluoroscopy used in any way during the procedure? Why was the suspected area not investigated initially by obtaining the four to six specimens without endobronchial ultrasound, including cytology?
3. Six apical lesions from both upper lobes were not found to be abnormal by ultrasound. Was this due to the fact that the catheter and ultrasound probe were not able to reach the suspected area?

The design of this study cannot result in any of the following potential recommendations:

1. Replace the conventional method. The new method is better, safer, and more accurate. It should be used in all patients.
2. The new method should be additive to the conventional method. It increased the yield in some circumstances and can be used in selected cases.
3. This new technique is neither able to replace nor to be added to the conventional method.

The technology for diagnosing these lesions has evolved over the past several decades.2–4 The major determining factor for diagnostic yield is whether the sampling device can reach the lesion or get close to it, confirming whether the lesion is reached or not by any means beyond fluoroscopy before sampling is of great interest.5 At least it might have the “ROSE” (rapid on-site cytologic evaluation) effect with lesser specificity.

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DOI: 10.1378/chest.130.4.1277

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5 Welker JA, Alattar M, Gantam S. Repeat needle biopsies combined with clinical observations are safe and accurate in the management of a solitary pulmonary nodule. Cancer 2005; 103:599–607

To the Editor:

We thank Dr. Wang for his thoughtful comments regarding our recent study (January 2006)2 showing the benefit of endobronchial ultrasound guidance for the transthoracic biopsy of solitary pulmonary nodules that are not visible on standard fluoroscopy.

In answer to the questions posed, we offer the following comments: the lesions were not visible at all during the procedure, which is certainly a well-known problem for most bronchoscopists. The suspected area was determined as the most likely lobe and segment from the available static imaging for each patient. Also, the lesions in the upper lobes that Dr. Wang is referring to were not found to be normal but rather could not be...
identified. This may represent a technical problem, as all of those lesions were in the apical segments.

Our article convincingly showed that in this particular circumstance the addition of endobronchial ultrasound to conventional bronchoscopy (not the replacement) can be very helpful and certainly can be recommended. It avoids aborting an otherwise nonpromising bronchoscopy by providing an acceptable yield, does not expose the patient to unnecessary radiation, and is less invasive than primary surgical procedures.

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Is Intensive Insulin Therapy Safe in the Critically Ill?

To the Editor:

Hamdulay et al\(^1\) described two similar cases of severe reversible cardiac depression, temporally related to exposure to chemotherapy agents for the treatment of lymphoma or prior to haploidentical bone marrow transplantation. Both cases required continuous venovenous hemofiltration, which had been reported to result in the reversal of septic shock and hemodynamic improvement over time because of the plasma clearance of myocardial depressant cytokines. It could be argued that the hemodynamic recovery witnessed was not related to insulin-glucose infusion but was explained by time-dependent plasma clearance of inflammatory cytokines because of the earlier initiation of continuous renal replacement therapy.

There are several studies that have indicated that indiscriminate intensive insulin therapy to maintain a blood glucose level at < 6.1 mmol/L (110 mg/dL) can result in attributable mortality. A large randomized controlled trial\(^2\) in patients with acute myocardial infarction reported that insulin therapy at a blood glucose level of 7 mmol/L (126 mg/dL) increased the mortality rate to 8.3% (control mortality rate, 6.6%; \(p < 0.01\)). Murcia et al\(^3\) reported that the cumulative risk for total mortality including cardiovascular mortality and morbidity increased with insulin treatment in diabetic patients with acute myocardial infarction and left ventricular failure. In a recent study by Van den Berghe et al\(^4\), intensive insulin therapy in patients with a short length of stay in the ICU and low severity of illness had a much higher mortality rate (27%) compared to patients receiving conventional insulin therapy (19%) \(\left[\text{relative increase in mortality of } 42\%; \ p = 0.045\right]\). The premature and indiscriminate use of intensive insulin therapy in the ICU, which is based on 2004 recommendations\(^5\) without robust scientific evidence, may have resulted in preventable death across the United States. The early resolution of stressors related to the acute illness and minimizing the iatrogenic interventions that exacerbate hyperglycemia rather than prescribing intensive insulin therapy in critically ill patients is the safest method for improved glycemic control and survival.

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To the Editor:

We thank Dr. Rady on his comments regarding our review on glucose-insulin and potassium infusions in septic shock.\(^1\) However, we disagree on his suggestion that the hemodynamic improvement that occurred in our patients could be attributed to the continuous veno-venous hemofiltration (CVVH).

CVVH has been widely used for the treatment of critically ill patients with acute renal failure, and the effects of CVVH on inflammatory responses have been aggressively investigated.\(^2\)\(^3\) Although circulating inflammatory cytokines were removed by ultrafiltration and adsorption, studies failed to show a decrease in plasma cytokine levels,\(^2\)\(^3\) even with an aggressive high-volume hemofiltration.\(^3\) Having said that, high-volume hemofiltration can significantly improve hemodynamic instability and decrease the vasopressor dose in septic shock patients.\(^6\) Nearly all of our patients with sepsis and renal failure are receiving CVVH, yet such dramatic reductions in

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Correspondence
vasopressor support that we described are unique to the patients in whom we used glucose-insulin-potassium infusion (GIK).

Dr. Rady mentioned that driving glucose to lower levels has been associated with adverse effects on mortality, and therefore therapies that intensively use insulin are to be avoided. It is important to differentiate between the use of GIK as an adjunct to vasopressor in hypodynamic septic shock and the much-discussed tight glucose control in intensive care. Our case reports and literature review make the case that high doses of insulin used in combination with glucose loading may yet have a role in improving hemodynamics. Finally, we agree that GIK should not be used indiscriminately, and further studies to establish its utility as an adjunct to the traditional vasopressors in patients with hypodynamic septic shock should be carried out.

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We conducted a prospective cohort study investigating 108 children for the cause of their chronic cough, using an adult-based approach followed by treatment as appropriate and a defined timeframe to response of 2 weeks, given the placebo and period effect of cough. Dr. Rubin has stated that the pathway used was “radically different” from that used by Irwin and colleagues.3 As we have stated in the article, the pathway has been modified for children as instinctively treating young children will never be the same as treating adults because children cannot tell you they have reflux symptoms as adults can, and, as Dr. Rubin himself states, diagnoses such as cystic fibrosis and tracheomalacia are an “essential part of the evaluation in children.”2 We felt it more important to ensure a thorough and complete investigation of the causes in children than to stringently adhere to the adult protocol, which was designed and tested some decades ago.

We thank Dr. Rubin for highlighting the important new diagnosis of protracted bacterial bronchitis (PBB) but feel it necessary to point out that he has misquoted the diagnostic criteria, which are, in fact, a history of chronic moist cough, the presence of at least a single species of pathogenic bacterial organism at a growth of ≥10^7 cfu/mL, and the resolution of cough with antibiotic therapy in a 2-week period. PBB was not diagnosed based on the presence of increased neutrophils in BAL fluid and was not diagnosed based on the presence of viral or nonpathogenic bacterial organisms. This is a new diagnostic entity, and much is still to be learned about the clinical features, airway inflammatory profile, and causative factors. We look forward to being able to shed further light on this condition in the near future.

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To the Editor:

We thank Dr. Rubin for his kind comments about our study (May 2006),1 which he stated was “one of the most complete studies” of its kind in the pediatric population.2 For readers unfamiliar with the literature on the common symptoms of cough, it is necessary that some points should be clarified, which are summarized in Table 1.

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To the Editor:

I appreciate Dr. Marchant and Chang’s comments on my editorial1 pointing out that although their study2 was an important evaluation of cough in a large number of young children, the protocol that they chose was quite different from that validated in adults as described by Irwin and colleagues.3 They included a number of children with a cough of <8 weeks duration, and more importantly, they did not evaluate for upper airway cough syndrome, asthma, or gastroesophageal reflux as the major diagnosis noted in adults with chronic cough. These were also noted to be common causes of chronic cough in pediatric studies as well.4 Because they chose a radically different approach to the diagnosis, it is impossible to know whether the children in their study had gastroesophageal reflux, asthma, or upper airways cough syndrome. By choosing bronchoscopy as their principal diagnostic test in these patients, the authors determined that 40% of the children had “prolonged bacterial bronchitis” (PBB), although these children did not have increased airway secretions. This is in contradistinction to a report5 that in adults PBB is associated with a large amount of airway secretions. This suggests that the “moist cough” they heard in these children could have been from upper airway secretions in the back of the child’s throat.

These authors are internationally recognized experts regarding the evaluation and treatment of chronic cough in children. I am looking forward to further studies that might better answer the question “Are children with chronic cough really that different from adults?”

Bruce K. Rubin, MEngr, MD, MBA, FCCP
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Table 1—Common Symptoms of Cough*

<table>
<thead>
<tr>
<th>Editorial Comment</th>
<th>Authors’ Clarification of Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>“The authors suggest that FB may be the diagnostic test of choice in evaluating chronic cough in young children”</td>
<td>We wish to clarify that at no time did we suggest or state this. The use of FB in our protocol was to obtain BAL fluid and assess large airway anatomy, but we stated that “we utilized a protocol not widely available and indeed we are not advocating its use . . . .” The utility and limitations of bronchoscopy have also been discussed in the ACCP guidelines for children.4</td>
</tr>
<tr>
<td>“The term moist cough is subjective and carries no physiologic significance”</td>
<td>A discussion on the physiologic significance is available.4 This term has been validated in children, whereby parents were accurate, and it related to the presence of airway secretions seen during bronchoscopy.5 This term has been used widely in the pediatric literature.</td>
</tr>
<tr>
<td>“Results must be replicated in a prospective study of children with a true (&lt;8 weeks duration) chronic cough”</td>
<td>Our study commenced in 2002 when the ACCP guidelines stated “chronic cough of &lt;3 weeks duration.” The new 2006 ACCP clinical practice guidelines in pediatrics define chronic cough as being of &lt;4 weeks duration.6 The reasons for this were discussed in the ACCP guidelines. Irrespective of this, only 15 of 108 children had cough of between 3 and 8 weeks duration on study enrollment.</td>
</tr>
<tr>
<td>“We strongly urged that this supposition (big three causes of cough in adults also common in children) be validated by well-controlled randomized clinical trials”</td>
<td>We agree and have stated so in our article (“ideally an RCT is necessary for assigning treatment effect”), but it should be noted that adult diagnostic algorithms were not evaluated as RCTs.3 Additionally, we used a timeframe for treatment response of 2 weeks, to decrease the placebo and period effects of cough, in combination with methods used in adult studies. Clearly, there are differences in North American and Australian parental expectations. Furthermore, we feel that investigation followed by appropriate therapy has cleaner scientific merit when comparing these approaches. The lack of evidence for the approach suggested by Dr. Rubin is well-documented (see the North American guidelines for GER in children and a Cochrane review on cough and GERD).</td>
</tr>
<tr>
<td>“In North America, where a 1-month course of reflux therapy is thought to be preferable to conducting a pH probe study”</td>
<td>We agree that a placebo-controlled RCT is needed to prove the effectiveness of antibiotic therapy in PBB. Our definition of PBB is based on factors other than the response to antibiotics as described. Follow-up bronchoscopy would be scientifically valuable but is unethical.</td>
</tr>
<tr>
<td>“The ‘response’ to a 2-week course of oral antibiotics should not be considered evidence of PBB without either a follow-up bronchoscopy—or a placebo-controlled arm”</td>
<td>We recruited 95% of the children who presented to our tertiary practice, and thus the study represents the population who presented with chronic cough in Australia, the majority of whom are of preschool age. Should this be different in North America, we look forward to the results of studies there that assess chronic cough in an older pediatric population.</td>
</tr>
<tr>
<td>“Because most of subjects . . . were &lt;3 yr old, these results probably cannot be generalized to the broader pediatric population.”</td>
<td></td>
</tr>
</tbody>
</table>

*FB = fiberoptic bronchoscopy; ACCP = American College of Chest Physicians; RCT = randomized controlled trial; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease.
The author has no conflicts of interest to disclose.

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1 Rubin BK. Pediatricians are not just small internists. Chest 2006; 129:1118-1121

Evaluation of the Causes of Racial Disparity in Surgical Treatment of Early-Stage Lung Cancer

To the Editor:

The idea reported in the article by McCann et al (November 2005)1 that black patients decline surgical treatment for stage 1 and 2 cancers more frequently than their white counterparts requires careful scrutiny. This study should be assessed as an exploration of the ability of physicians to communicate their therapeutic objectives to black patients. Consequently, dynamic variables such as clarity of message, body language, and emphasis could not be captured by retrospective case record analysis. Furthermore, the authors neglected to evaluate the role of physician factors in their observations. This omission is surprising considering that many investigators have shown that physicians asymmetrically employ established standards when caring for black patients.2 McCann et al3 noted that all black patients who were offered surgery by black physicians accepted the procedure. However, this observation was not pursued further. Intriguingly, the authors also noted that elderly black patients declined surgery at an even greater frequency. It would have been interesting if the authors had explored whether this phenomenon correlated with the age, gender, or ethnicity of the advising physician. This line of thought would be in concordance with the notion that physician-patient differences are a causal factor in diverse cases of disparities in care.

The dynamic complexity of the sociocultural universe of modern metropolitan ethnic populations requires more complex communication skills than are required for situations in which the physician and patient are socioculturally more congenent. Uncovering the etiologies of racial disparities calls for innovative research in communication, including visual and audio record analysis as well as physician interviews, to explore the clinical logic behind discrepant care. These approaches would lead to practical solutions toward an important health-care delivery problem.

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Dr. Dube has no conflict of interest to report.

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REFERENCES

To the Editor:

I thank Dr. Dube for his interesting comments about our article.1 He points out that a more complete evaluation of the physician-patient interactions would allow for a better understanding of why black patients declined surgical interventions for lung cancer. I agree with him. In the “Discussion” section of our article, we discussed the fact that prior research2 has shown that black patients seeing white physicians rated their physician’s decision-making style as less participatory. Since the publication of our article, research3 has shown that black patients with lung cancer have less trust in their physicians after the visit despite equivalent trust before the visit. As Dr. Dube points out, a better understanding of the dynamics of physician-patient communication and how they effect the development of trust will be a key factor in improving surgical rates.

Dr. Dube would have us further scrutinize physician demographic data to assess how it impacted decision making. As pointed out in the article,1 we only had three black patients offered surgery by black physicians. All three accepted. Given the small numbers, I am not sure how we could have pursued this further. He also wonders why we did not further evaluate the fact that prior research2 has shown that black patients seeing white physicians rated their physician’s decision-making style as less participatory. Since the publication of our article, research3 has shown that black patients with lung cancer have less trust in their physicians after the visit despite equivalent trust before the visit. As Dr. Dube points out, a better understanding of the dynamics of physician-patient communication and how they effect the development of trust will be a key factor in improving surgical rates.

Our study was retrospective and meant to leverage the ability to review large numbers of cases to begin to evaluate the proximate causes of decreased surgical rates in black patients. We were thus unable to evaluate the physician-patient interaction in depth. Nevertheless, we do feel that our research has provided the insight that we should focus efforts on physician-patient communication as a way to improve surgical rates in black patients with lung cancer. Such efforts would hopefully lead to increased surgical rates and thus decreased mortality from lung cancer in the African-American population.

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Dr. DiGiovine has reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Severe Sepsis Due to Melioidosis

To the Editor:

We would like to comment on the retrospective review of melioidosis by Chan et al in a recent issue of CHEST (November 2005).1 We commend the authors on their work, which reinforces the high mortality rate associated with this infection, particularly in those patients with a critical illness.

Contrary to their assertion that melioidosis in the ICU setting has not previously been described, we have previously published our experience of 42 critically unwell patients with culture-confirmed melioidosis. In our series, we noted a fall in the mortality rate from 95% to 9.5% coincident with the introduction of granulocyte colony-stimulating factor (G-CSF) in patients with septic shock. We also acknowledged that the large fall in the mortality rate that we observed may have been at least partly explained by other potential confounders, including the adoption of a closed intensive care model, the earlier use of antibiotics active against Burkholderia pseudomallei, and more aggressive fluid resuscitation.

We have also demonstrated that pneumonia and biochemical markers of organ dysfunction are generally associated with mortality in patients with melioidosis.3 Studies of melioidosis have been difficult to compare due to the large clinical spectrum of illness and variations in the definitions of “severe melioidosis.” This is reflected in the differences in the rates of bacteremia between studies. However, severe sepsis (as defined by Chan et al1) and septic shock (as defined in our series) represent the group with the highest mortality rate due to melioidosis. The mortality rate that we observed in patients who received G-CSF in our series was lower than that observed by Chan et al1 in a population with a similar severity of illness. Chan et al1 did not differentiate pneumonia with septic shock from pneumonia without septic shock; the Darwin experience suggests that pneumonia with septic shock is associated with an 84% mortality rate.4

We suggest that the measures associated with the fall in mortality at our institution, namely, the use of G-CSF, the routine use of empiric antibiotics for melioidosis, and the use of aggressive fluid resuscitation, should be considered for patients with severe sepsis in melioidosis-endemic areas. We have participated in studies aimed at identifying patients with melioidosis by the use of clinical criteria and rapid diagnostics,5 and we are in the process of conducting a clinical trial of G-CSF for the treatment of severe melioidosis in Thailand.

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Left Ventricular Diastolic Abnormalities in Obese Subjects

To the Editor:

The study by El-Gamal et al (December 2005)1 presented evidence of an association between the degree of dyspnea and both an increased ventilatory drive and reduced static lung volumes. Indeed, weight loss was accompanied by improvement in dyspnea and a reduction in respiratory drive measurements. We would like to comment on one other possible mechanism that was not addressed by the authors explaining the frequent presence of dyspnea in obese patients and the improvement in the degree of such symptoms after weight loss. Left ventricular diastolic dysfunction is a frequent cause of dyspnea. It is commonly present in obese subjects and is correlated with increasing body mass index.2 In obese subjects, weight loss produces an improvement in left ventricular diastolic function that is linked to weight loss-related decreases in left ventricular mass and beneficial alterations in left ventricular loading conditions.3 On the other hand, the authors did not perform polysomnography to rule out obstructive sleep apnea or other sleep disorders, as they acknowledged in the “Discussion” section of their article. It is well-recognized that the vast majority of sleep apnea patients are undiagnosed, and that obstructive sleep apnea is a very common condition affecting obese subjects. This sleep-related disordered breathing has also been independently associated with left ventricular diastolic dysfunction and reduced cardiac response to exercise.4 Weight loss in obese obstructive sleep apnea patients is coupled with an improvement in sleep disorder severity, and the reduction of apneic events has also been associated with subse-
quent improvement in left ventricular diastolic function and hemodynamic response to exercise.4,5

In view of the aforementioned comments, it would be helpful for El-Gamal et al1 to provide data on cardiac function and structure for the patients studied to more precisely understand the possible factors playing a role in the presence of dyspnea and its improvement after weight loss.

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Drs. Arias, Alonso-Fernández, and García-Río have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Respiratory Research Output

To the Editor:

The article by Michalopoulos and Falagas1 (December 2005) draws attention to large-scale research activity in respiratory medicine and to the dominating presence of the United States and western Europe. Contrary to their statement, their article is not the first article to examine respiratory research output. Previous work includes that of Rippon et al,2 who examined world output from 1996 to 2001 and the correlation with disease burden, and García-Río et al,3 who analyzed respiratory medicine output of European Union member states from 1987 to 1998 and compared it with their national products and populations.

The article by Michalopoulos and Falagas4 suffers from two methodologic defects. First, the scientific domain of respiratory medicine is poorly approximated by a set of 30 specialist journals (not listed in the article). We have found that almost three fourths of respiratory medicine research articles are published in general, rather than specialist, journals. They can be identified by means of words in their titles. Failure to apply this method gives a very low recall or sensitivity, and it is likely that some of the 30 journals may generate false-positive results, leading to poor precision or specificity. Indeed, García-Río et al4 commented that their 38 “respiratory” journals also included quite a lot of cardiology research.

Second, there is no comparison given between respiratory medicine and other research output, so we cannot tell whether 49,382 articles in 9 years is an adequate response by researchers to the burden of respiratory disease, too little, or even too much in relation to other diseases. Canada and Oceania (what does this include other than Australia and New Zealand?) apparently perform very well in relation to their wealth. Why is this? Does it reflect the size of the challenge in these countries, top-down decision making, or bottom-up research applications? It would be useful to further analyze the factors leading to superior performance.

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Attention to Doping Controls Required When Prescribing for Athletes

To the Editor:

In their review of exercise-induced bronchoconstriction in athletes, Parsons and Mastronarde1 advocate the use of β₂-agonists and inhaled corticosteroids. Physicians who treat competitive athletes should be aware, however, that athletes competing at national and international levels require a “Therapeutic Use Exemption” for these classes of drug. This is a certificate obtainable from the athlete’s national sports federation or national antidoping agency, which allows their physician to inform the governing body that the athlete requires this treatment. The athlete may then be granted approval to use the drug, and avoid censure if it is unexpectedly found during antidoping tests.2

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Is Bronchoscopy Dangerous in the Pretreatment Workup of Non-small Cell Lung Cancer Patients?

To the Editor:

We read the article by Nakajima et al1 on the possible negative impact of transbronchial lung biopsy (TBBL) on the postsurgical prognosis of non-small cell lung cancer (NSCLC). The authors conclude suggesting that “...a pathologic examination without preoperative bronchoscopy, but through intraoperative incisional biopsy followed by curative surgery, might be beneficial for patients with early-stage lung cancer.” We would like to comment on this.

The TNM staging system of lung cancer includes bronchoscopy in the pretreatment workup on the basis of scientifically well-proved data. Airway examination provides indispensable information on site and size of the tumor (T descriptor), as well as on the presence of synchronous lesions. Gasparini et al2 found synchronous endobronchial visible lesions in 72 of 570 patients (12.6%) being studied for peripheral lesions, and such finding either contraindicated surgery or modified the therapeutic strategy in 35 patients (48.6%). Pierard et al3 submitted 43 NSCLC-operable patients to autofluorescence bronchoscopy and demonstrated synchronous carcinomas in situ or dysplasias in 8 patients (18.6%). Airway examination proves also extremely helpful to identify candidates for sleeve resection of the main bronchus or carina.

Bronchoscopy may also be useful in the definition of the N descriptor through transbronchial needle aspiration (TBNA), which precludes the need for unnecessary diagnostic or therapeutic surgical procedures when it shows malignant cells, due to its extremely high specificity.5,6 A systematic review of 910 TBNA procedures suggested sensitivity and specificity as high as 76% and 96%, respectively. A more recent meta-analysis7 showed that the sensitivity is much lower than previously thought in populations with low prevalence of lymph node metastasis, but it confirmed that the method is highly specific.

In conclusion, pretreatment workup of NSCLC lacking bronchoscopy is incomplete and inaccurate, and it may cause inappropriate therapeutic planning. As for the diagnosis of peripheral lesions, there is no evidence in the literature of tumor implantation in the airway caused by TBLB so far, as the authors state, and we look forward to a prospective randomized trial to reliably assess the effect of TBLB on the postsurgical prognosis of NSCLC.

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Complete Response Following Preoperative Chemotherapy for Resectable Non-small Cell Lung Cancer

To the Editor:

We read with great interest the recent study by Milleron et al1 on the evaluation of complete response (CR) by clinical investigators and an evaluation committee (EC) in patients treated using neoadjuvant chemotherapy for non-small cell lung cancer (NSCLC). The study was carried out using the database of the well-known French randomized trial2 and showed a low sensitivity of CR diagnosis by investigators (31.6%) and EC (15.8%). Specificity, positive and negative predictive values, and accuracy were very high for both investigators and EC, leading to the conclusion that investigator assessment was highly predictive of pathologic CR. Moreover, the study showed that clinical CT scan-based assessment, for both investigators or EC, underestimated the frequency of CR after induction chemotherapy in resected NSCLC.

This study has some methodologic biases that may severely weaken the reported message: (1) a lack of homogeneity in clinical staging: mediastinoscopy or mediastinotomy was not routinely used in IIIA patients to confirm histologic N2 disease before enrolment onto the trial; (2) absence of a homogeneous surgical treatment: in the original article,2 a complete lymph node dissection was performed in 59 patients (40.4%) of the preoperative chemotherapy arm; a lymph node sampling in 56 patients (38.4%), and 31 patients (21.2%) received neither a dissection nor a sampling (calculation based on data from Table 3 of Depierre et al3). Therefore, limitation in their staging technique
and surgical procedure may explain the discrepancy between pathologic CR and investigators and EC.

Surgery should be indicated, when it is reasonably possible, in every case in which an induction therapy has been administered even if an objective clinical response to the therapy has not been evidenced. In fact, the most-used imaging technique (CT scan) hardly distinguishes among neoplastic tissue, fibrosis, and necrosis, and more accurate procedures, such as positron emission tomography scanning, do not reliably predict pathologic response to preoperative chemotherapy in NSCLC in either the primary tumor or the draining lymph nodes. This clinical behavior has been confirmed by the high resectability rate obtained in those patients who were judged to be resectable and then operated on. In conclusion, this study underlines that the radiologic evaluation did not reflect the pathologic staging. In the light of the recent experiences, we think that patients showing a radiologic major response (CR or partial response) after induction treatment for NSCLC should undergo complete surgical resection to eradicate the tumor and to improve survival.

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