along with their 95% confidence limits of normal. Using the latter methodology recommended by the American Thoracic Society and European Respiratory Society guidelines, we avoided this overestimation, as illustrated in Figure 1. The original GOLD document’s expert opinion of using a fixed ratio to diagnose COPD, intended as a tool for classifying and managing COPD, unfortunately has proliferated into widespread use as an all-encompassing method for interpreting spirometry for all diseases.

Dr. Madan and colleagues also recommended that before adopting the FEV1/FVC ratio for common use, it should be validated using other radiographic and clinical assessments. But what if this is the more sensitive measurement? Without concomitant emphysema, a CT scan would appear normal unless air trapping was sufficient to cause a mosaic pattern. Clinically, subjects with milder forms of diseases such as diabetes or hypertension can remain asymptomatic for years. Hansen et al.4 clearly showed the association of smoking to a reduction in this ratio. Our study supported this relationship. In 1984, Morris et al.5 and the Intermountain Thoracic Society advocated using this ratio and its lower limit of normal to identify mild/mild/mild obstruction. Short of pathologic correlation with lung biopsies, large patient databases may be the most sensitive way to identify mild physiologic differences between groups. We are not advocating that the FEV1/FVC replace the FEV1/FVC ratio, but rather feel it may have an important complimentary role in identifying milder disease. In response to the opinion that the term lung injury should be restricted to the diagnosis of ARDS, we used these words in the same context as our pathology colleagues who routinely use this phrase to describe damage to the lungs no matter what the cause, including ARDS.

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Pneumocystis Pneumonia Following Rituximab

To the Editor:

We read with interest the article by Martin-Garrido et al.1 in a recent issue of CHEST (July 2013) that described a series of 30 cases of Pneumocystis pneumonia at the Mayo Clinic between 1998 and 2011 in association with rituximab. Three cases within this series were associated solely with rituximab (with the remaining 27 cases also associated with steroids, chemotherapy, or both, which are known risk factors). It is noteworthy that in all three cases, the diagnosis was made solely on the basis of polymerase chain reaction (PCR) testing compared with only 12 of the remaining 27 cases. Although this difference is not statistically significant, it raises the question of whether these three cases could have been false-positive diagnoses due to colonization by Pneumocystis.

The performance of the PCR assay used in this study was previously described at the same institution.2 In that publication, 27 immunosuppressed patients were found to have a positive PCR result with normal direct fluorescent microscopy examination findings. Among these, only 84% were considered to have definite or probable Pneumocystis pneumonia. This report found no PCR positivity among 102 immunocompetent patients, suggesting that the rate of Pneumocystis colonization may be higher among immunosuppressed patients.

Given the high volume of complex cases evaluated at the Mayo Clinic, three cases over a 14-year span may represent a very low false-positive rate. Prior to concluding that rituximab alone may predispose to Pneumocystis pneumonia, it would be useful to know the details of these three cases.

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**Response**

To the Editor:

I thank Dr Farkas and colleagues for their interest in our study on the potential risks of developing *Pneumocystis* pneumonia (PCP) in patients with compromised immune systems receiving rituximab.¹ The letter raises the important question about whether the three patients reported in the case series might actually represent colonization rather than PCP. This question arose because the cases were detected by polymerase chain reaction (PCR) assay. We believe that these cases represent true PCP rather than colonization; thus, further clarification is needed.

Many PCR assays reported in the literature amplify mitochondrial DNA sequences.² Hence, they amplify multicopy *Pneumocystis* target genes, significantly heightening detection sensitivity. In addition, these assays often rely on nested PCR approaches where the initial amplification products are subsequently reamplified, yielding even greater sensitivity.³ Indeed, such approaches may be overly sensitive for many routine clinical applications. Accordingly, previously reported PCR assay approaches are known to detect *Pneumocystis* colonization in addition to invasive infections.⁴ However, the *Pneumocystis* PCR assay used in our clinical microbiology laboratory has unique features that circumvent many of these issues.⁵ To address the issues of colonization, we use a diagnostic *Pneumocystis* PCR assay that uses a single-copy target gene from *Pneumocystis jirovecii*, namely *pjcdc2*.⁶ We also perform quantitative amplification with real-time PCR and do not reamplify the reaction products with nested PCR.³ With this PCR assay, we have observed an increase (approximately 7%) in total diagnostic sensitivity over smeared stains alone. In addition, in now >200 consecutive cases without clinical evidence of infection, we have not detected a PCR signal. Hence, the assay used in this study was specifically designed to detect PCP rather than colonization.² On this basis, our laboratory now routinely uses this PCR assay rather than microscopic examination for the diagnosis of *Pneumocystis* infection. Moreover, it must be noted that the patients in the current report had active lung infiltration as well as signs and symptoms of infection. In each patient, there was no evidence of any other significant alternative organism, despite routine comprehensive culture, antigen detection, and molecular diagnostic assays performed to rigorously detect typical and atypical bacteria, viruses, and other fungi. Thus, in all three patients, the clinical evidence pointed to active PCP rather than to colonization.

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**Recovery of Consciousness After Head Injury**

To the Editor:

Luce¹ is to be commended for his excellent review on chronic disorders of consciousness following coma that recently published in *CHEST* (October 2013). Nevertheless, we wish to point out that, in our opinion, the author is inaccurate in stating that “coma following TBI [traumatic brain injury] usually is manifested pathologically by diffuse axonal injury, which also is called traumatic injury, involving the cerebral cortices and brain stem.”²

The mechanisms involved in TBI and coma are actually complex and often multifactorial. Focal lesions (extradural and subdural hematomas, intraparenchymal hematomas and contusions), diffuse lesions (swelling, diffuse axonal injury [DAI], posttraumatic subarachnoid hemorrhage), and biochemical derangements can act as independent or associated causes of coma after TBI. The variety

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