

lem. The paucity of information regarding the scale of the missing data affects the appraisal of the potential bias and internal validity of the study.

Mark R. Daley, B.Med.

Royal Prince Alfred Hospital
Sydney 2050, Australia
mark.daley@email.cs.nsw.gov.au

1. Pronovost PJ, Berenholtz SM, Goeschel CA, et al. Creating high reliability in health care organizations. *Health Serv Res* 2006;41:1599-617.

THE AUTHORS REPLY: Large-scale quality-improvement studies are challenging to conduct, and they receive substantially less funding than randomized trials of comparable size. In our study, staff in the 103 participating ICUs did not receive funding to support data collection. Thus, research intended to improve the quality of care must carefully balance the collection of data that are scientifically sound, feasible to collect, and focused on the specific aims of the study.¹

We chose to limit the quantity but not the quality of data collected. It was not feasible to collect data on the organisms cultured or the antibiotics used, as Jenny-Avital suggests. We used standardized though somewhat subjective surveillance rather than clinical definitions of catheter-related bloodstream infections.² However, we believe that potential bias was minimized, because infection-control practitioners who were independent of the ICU teams performed all measurements in their routine manner.

Daley's comments highlight the importance of minimizing and reporting missing data in quality-improvement studies. We made great efforts to minimize information bias and missing data. To garner participation, the ICUs were permitted to choose when to implement the study intervention. The ICUs provided data at varying times,

depending on when they joined the project and started data collection. Forty hospitals implemented the intervention immediately on initiation of the study, which precluded the collection of baseline data. Thus, data were not missing for these ICUs. The results of our sensitivity analysis, which excluded these hospitals, were similar to those of the primary analysis. During the period when each ICU reported data, 30 of 103 ICUs (29%) did not report completely, resulting in missing data for 113 of 2216 potential ICU-months (5%). This level of missing data represents an improvement over a preliminary report conducted before all ICUs had reported their data.³

The need to improve the quality of care is too great and the resources devoted to this effort are too limited to be uncertain about whether quality-improvement interventions actually work. Quality-improvement studies will require more rigor and resources. Since funding for such research has lagged behind funding for basic and clinical research by a factor of more than 100, additional funding will be needed to achieve the goal of improved care. Though our study has helped to advance the science of rigorous quality-improvement studies, more work is needed.

Peter J. Pronovost, M.D., Ph.D.

Dale M. Needham, M.D., Ph.D.

Sean Berenholtz, M.D.

Johns Hopkins University
Baltimore, MD 21205

1. Pronovost P, Wachter R. Proposed standards for quality improvement research and publication: one step forward and two steps back. *Qual Saf Health Care* 2006;15:152-3.

2. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32:470-85.

3. Pronovost PJ, Berenholtz SM, Goeschel CA, et al. Creating high reliability in health care organizations. *Health Serv Res* 2006; 41:1599-617.

Adjuvant Therapy for Early Breast Cancer

TO THE EDITOR: Poole et al. (Nov. 2 issue)¹ conclude that patients with breast cancer benefit from the addition of four cycles of epirubicin to cyclophosphamide, methotrexate, and fluorouracil (CMF) in the adjuvant setting. In contrast to previously published data, the dose intensity of CMF did not seem to play a role.

Patients with breast cancer were included in the study irrespective of age, nodal status, or estrogen-receptor status. The degree of aggressiveness of the chemotherapy was not tailored to the risk of recurrence. The role of tamoxifen could not be evaluated because for many patients, neither hormone-receptor status nor tamoxifen scheduling

was known. In postmenopausal, hormone-receptor-positive patients with breast cancer, tamoxifen has been the standard of care for years, and the addition of chemotherapy has a small effect, if any, on survival.

Serban-Dan Costa, M.D., Ph.D.

Joachim Bischoff, M.D.

Otto-von-Guericke University
39108 Magdeburg, Germany
serban-dan.costa@medizin.uni-magdeburg.de

1. Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *N Engl J Med* 2006;355:1851-62.

Peginterferon and Ribavirin for Hepatitis C

TO THE EDITOR: In their review of peginterferon and ribavirin for the treatment of hepatitis C, Hoofnagle and Seeff (Dec. 7 issue)¹ do not include data on the association between the consumption of alcohol and both treatment response and disease progression. Level-one evidence of the deleterious effects of alcohol on hepatitis C virus (HCV) RNA levels, on the response to treatment, and on disease progression led the National Institutes of Health and the American Gastroenterological Association to issue position statements advising that “abstinence should be recommended before and during antiviral treatment . . . [since] even moderate alcohol consumption can have a deleterious effect on the progression of liver disease in patients with chronic hepatitis C.”^{2,3} Alcohol consumption may explain the marked dichotomy in progression rates that cannot be explained by the HCV genotype.⁴ Knowledge of alcohol’s effects on disease progression should provide reassurance to patients who want to alter the outcome of their disease, particularly since data for nondrinkers show a more benign course than the authors suggest.⁵ At a population level, targeting alcohol consumption may effectively reduce the excess deaths the authors anticipate.

Anne E. Duggan, M.D.

John Hunter Hospital
Newcastle 2310, Australia
anne.duggan@hnehealth.nsw.gov.au

John M. Duggan, M.D.

University of Newcastle
Newcastle 2308, Australia

1. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med* 2006;355:2444-51.
2. National Institutes of Health. National Institutes of Health Consensus Development Conference statement: management of hepatitis C: 2002 — June 10-12, 2002. *Hepatology* 2002;36: Suppl 1:S3-S20.
3. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. *Gastroenterology* 2006;130:231-64.
4. Schiff ER. Hepatitis C and alcohol. *Hepatology* 1997;26: Suppl 1:39S-42S.

5. Pessione F, Degos F, Marcellin P, et al. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *Hepatology* 1998;27:1717-22.

TO THE EDITOR: The article by Hoofnagle and Seeff would have been more informative if it had indicated the relevance of insulin resistance in chronic hepatitis C. Insulin resistance induces interferon resistance by causing the progression of hepatic fibrosis. The mechanism by which insulin resistance promotes the progression of fibrosis includes steatosis, hyperleptinemia, increased production of tumor necrosis factor α , and impaired expression of peroxisome-proliferator-activated receptor γ .¹ Insulin resistance has been found to be a common denominator in patients with difficult-to-treat hepatitis C (including those with the risk factors of cirrhosis, obesity, coinfection with the human immunodeficiency virus [HIV], and black race) and is independently associated with a decreased rate of response to peginterferon plus ribavirin.^{1,2} Whether the addition of insulin-sensitizing agents will improve the response rate remains to be determined.

Nimer Assy, M.D.

Oscar Embon, M.D.

Sieff Hospital
13100 Safed, Israel
assy.n@ziv.health.gov.il

1. Romero-Gomez M. Insulin resistance and hepatitis C. *World J Gastroenterol* 2006;12:7075-80.
2. Romero-Gomez M, Del Mar Vilorio M, Andrade RJ, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005;128:636-41.

TO THE EDITOR: Hoofnagle and Seeff mention that autoimmune diseases are rare side effects of therapy with interferon alfa and ribavirin for hepatitis C, but they do not mention these conditions as possible contraindications. However, the risk