end points and workload and that evaluates the cost-effectiveness of closed-loop glucose control would be, in our view, important.³

Marchand provides a critical appraisal of our work. The glucose target range that we applied was based on national and international guidelines and consensus for the treatment of inpatients receiving noncritical care (the American Diabetes Association and the Endocrine Society) at the time that our trial was conceived. The consensus statement to which Marchand refers was developed by experts in the context of outpatient care but not inpatient care,⁴ the latter typically involving an older and more vulnerable population in need of more attention to hypoglycemia prevention. We suggest that the consensus statement has only limited scope with respect to our trial. We maintain that the glucose target range that we chose was appropriate given that our trial involved inpatients.

The consensus statement supports the use of the coefficient of variation (a metric relative to the mean) but also mentions that the use of the standard deviation may be beneficial.⁴ The coefficient of variation was prioritized by the experts on the basis of statistical considerations. It is well documented that the mean glucose level and the standard deviation are interlinked. This does not apply to the coefficient of variation. However, there is no evidence that the coefficient of variation is more clinically relevant than the standard deviation for the assessment of glucose variability, and further investigations are warranted to resolve the issue. On the basis of these considerations, it is our opinion that the observed differences in the standard deviation within a single day and the coefficient of variation between days reflect lower glycemic variability in the closed-loop group than in the group of patients who received conventional insulin therapy.

Lia Bally, Ph.D.
University Hospital Bern
Bern, Switzerland

Hood Thabit, Ph.D.
Manchester University Hospitals NHS Foundation
Manchester, United Kingdom

Roman Hovorka, Ph.D.
University of Cambridge
Cambridge, United Kingdom
rh347@cam.ac.uk

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**Procalcitonin-Guided Antibiotic Use**

**To the Editor:** The null result for the use of procalcitonin level to guide the prescription of antibiotics, reported by Huang et al. (July 19 issue),¹ is incongruent with our experience as an early emergency department (ED) adopter. Rapid procalcitonin assays have been ordered for more than 4000 patients since 2014. The ability of procalcitonin to differentiate viral from bacterial infections is most helpful when there is uncertainty as to whether a diagnosis of bronchitis or pneumonia should be made.²,⁴ Since both conditions often have viral causes, the results of a procalcitonin assay, if used as a guide, have the potential to substantially reduce ED antibiotic prescribing.⁵ Unfortunately, less than half of the trial participants had these diagnoses. For bronchitis, procalcitonin guidance was followed in most cases, yielding a 14.8% reduction in ED antibiotic prescribing.¹ Conversely, in patients with pneumonia, the procalcitonin result was almost universally disregarded (77.7% of patients had a negative result on the procalcitonin assay, yet 71.9% received antibiotics).¹ Simply put, clinicians did not trust procalcitonin even among a cohort of patients in which the majority had a Pneumonia Severity Index (PSI) score indicating low risk (with 60% having PSI Class I or II pneumonia), a factor that attenuated the observed 4.4% reduction in
ED antibiotic prescribing for pneumonia.\textsuperscript{1} Future work should focus on the usefulness and implementation of the procalcitonin assay for patients in whom pneumonia is suspected.

Michael S. Pulia, M.D.
Lucas T. Schulz, Pharm.D.
Barry C. Fox, M.D.
University of Wisconsin—Madison
Madison, WI
mspulia@medicine.wisc.edu

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TO THE EDITOR: Huang et al. evaluated the implementation of procalcitonin guidance for the management of lower respiratory tract infections. Implementation of rapid molecular diagnostics for infectious disease is suggested to incorporate both diagnostic and antimicrobial stewardship,\textsuperscript{1} but implementation in the absence of an antimicrobial stewardship program (ASP) may fail to provide a clinical benefit.\textsuperscript{2} In the intervention group, even though 746 of 808 patients (92.3\%) had an initial procalcitonin level that suggested antibiotics were not necessary, 34.1\% and 57.0\% of patients received antibiotics in the ED and by day 30, respectively. This observation suggests an opportunity for an ASP to provide real-time feedback on the interpretation of procalcitonin assays and the decision to discontinue antibiotics. Although we agree that the adherence to protocol exercised in trials such as ProHOSP (Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections)\textsuperscript{3} is not feasible in the real world, active ASP involvement, including the use of prospective audit and feedback, is possible, and we have had success with this strategy.\textsuperscript{4} Thus, the conclusion drawn should not be that procalcitonin is not useful but rather that its introduction in the absence of adequate ASP support may lead it to fall short of the desired outcome.

Derek N. Bremmer, Pharm.D.
Nathan R. Shively, M.D.
Thomas L. Walsh, M.D.
Allegheny General Hospital
Pittsburgh, PA
derek.bremmer@ahn.org

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more than 90% of the procalcitonin values were within ranges that “discouraged” or “strongly discouraged” antibiotic use, yet the majority of patients still received antibiotics, suggesting that stewardship support and training regarding the use of procalcitonin were inadequate.

Brad Spellberg, M.D.
Los Angeles County and University of Southern California Medical Center
Los Angeles, CA
bspellberg@dhs.lacounty.gov

Neil Gaffin, M.D.
Ridgewood Infectious Diseases Associates
Ridgewood, NJ

No potential conflict of interest relevant to this letter was reported.


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THE AUTHORS REPLY: Pulia et al. correctly note that implementation of a procalcitonin guideline in our trial had minimal effect on antibiotic prescription in cases of community-acquired pneumonia, but in patients with acute bronchitis, antibiotic prescription in the ED dropped by 50%. However, the finding for acute bronchitis, while robust to correction for multiple comparisons, is a secondary outcome of a subgroup.

We agree with Bremmer et al. that combining two tools — a new diagnostic test and an antimicrobial stewardship program — could be effective and can be tested. We did not design that trial, seeking rather to assess the effect of a procalcitonin guideline alone, implemented in accordance with quality-improvement principles. ASPs require considerable resources.

Spellberg and Gaffin posit that in settings with higher baseline antibiotic use than observed in our trial, a procalcitonin guideline might have a different effect. The potential for variable effects applies to all interventions, with the extent of the effects varying in accordance with the surrounding environment. For example, the effects of educating clinicians on national antibiotic guidelines might differ depending on their current baseline use. We disagree with the suggestion that training in the use of procalcitonin was inadequate. As reported, we provided extensive education, real-time prompts, and feedback, modeling a best-case scenario for the deployment of a new intervention.

David T. Huang, M.D., M.P.H.
Donald M. Yealy, M.D.
Derek C. Angus, M.D., M.P.H.
University of Pittsburgh
Pittsburgh, PA
huangdt@upmc.edu
for the ProACT Investigators

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Ibrutinib and Rituximab in Waldenström’s Macroglobulinemia

TO THE EDITOR: The results of the iNNOVATE trial reported by Dimopoulos et al. (June 21 issue) showed the improved efficacy of ibrutinib when added to rituximab monotherapy for Waldenström’s macroglobulinemia. This practice-changing, phase 3 trial involved patients with a rare form of lymphoma.

The authors used rituximab monotherapy as the comparator. However, other first-line immunochemotherapeutic regimens evaluated in phase 2 trials have provided response rates of greater than 80% and a median progression-free survival that exceeded 3 years. These combinations offer a limited duration of treatment (5 to 6 months) rather than open-ended therapy with ibrutinib. Another important aspect is the cost of the drugs. Although data from formal cost-effectiveness analyses are lacking, the price of ibrutinib–rituximab is twice that of bendamustine–rituximab during the first year of therapy (Table 1). Additional studies comparing these regimens with respect to overall survival, quality of life, and use of health care services are needed to allow full assessment of value. Because ibrutinib has nontrivial long-term adverse effects (including an increased risk of atrial fibrillation and