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.

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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.[1]

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.

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Since publication of their article, the authors report no further potential conflict of interest.

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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)[1] 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.[2-4] 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

Table 1. Outcomes and Prices of Common Immunochemotherapeutic Regimens for Waldenström's Macroglobulinemia.*

Variable	Cyclophosphamide plus Rituximab–Dexamethasone	Bortezomib plus Rituximab–Dexamethasone	Bendamustine–Rituximab	Ibrutinib–Rituximab
Reference	Kastritis et al.[2]	Gavriatopoulou et al.[3]	Rummel et al.[4]	Dimopoulos et al.[1]
No. of patients	72	59	22	75
Duration of therapy	18 wk	23 wk	24 wk	52 wk
Median progression-free survival	35 mo	42 mo	69 mo	NR
Drug price for 1 yr of therapy†	$56,000	$107,869	$123,280	$247,206

* NR denotes not reached.
† Drug prices were calculated for a patient with a body-surface area of 2.0 m^2, according to dosing and regimens in the referenced articles, with the use of average wholesale prices obtained from the Lexicomp Online database (Lexicomp), accessed on June 2, 2018.

hemorrhage), clinicians should consider the potential risk–benefit ratio of first-line tyrosine kinase inhibitor–based treatment as compared with immunochemotherapy; the former is used for a shorter duration, is less expensive, and yet is still highly effective.

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TO THE EDITOR: Dimopoulos and coworkers report higher rates of progression-free survival with the use of ibrutinib–rituximab than with placebo–rituximab among patients with Waldenström's macroglobulinemia who had not received previous treatment and among those with disease relapse. Why was the moderately effective rituximab[1] chosen as a comparator in a trial that used progression-free survival as the primary end point and assessed continuous treatment versus a fixed duration of treatment? In a previous trial, bendamustine–rituximab was associated with a median progression-free survival of 69.5 months among patients who had not previously received treatment,[2] and in the trial conducted by Dimopoulos et al., the rate of progression-free survival at 30 months among patients who received ibrutinib–rituximab was 80 to 85%.

In the iNNOVATE trial, the incidence of atrial fibrillation of grade 3 or higher among patients receiving ibrutinib–rituximab was 12%, and other adverse events were also more frequent among patients receiving ibrutinib–rituximab than among those receiving placebo–rituximab. Was quality of life — an important goal in patients with Waldenström's macroglobulinemia[3] — assessed?

Finally, the causes of 10 deaths were not reported. This is not trivial, considering that ventricular arrhythmias in patients receiving ibrutinib were described and investigators had previously recommended the reporting of such arrhythmias and sudden deaths in trials.[4]

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Dr. Rigolin reports receiving lecture fees from Janssen, Gilead, and AbbVie, and Dr. Cuneo, receiving honoraria from Janssen. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Olszewski and Castillo and Cavazzini et al. discuss our choice of comparator in the iNNOVATE trial. We agree that immunochemotherapy is a valid treatment option in patients with Waldenström's macroglobulinemia; however, the association with occasionally severe toxic effects[1,2] justifies the development of targeted, chemotherapy-free treatment. When the iNNOVATE trial was designed, the goal was to compare the efficacy of two chemotherapy-free options, ibrutinib–rituximab versus rituximab, since single-agent rituximab was recommended in guidelines for the treatment of Waldenström's macroglobulinemia because of its efficacy and low toxicity.[3] In addition, retrospective analyses indicated that rituximab is frequently used to treat Waldenström's macroglobulinemia in the United States and the European Union.[3-5] Therefore, a comparison with rituximab alone is not inappropriate, especially considering the lack of a well-defined standard of care for patients with Waldenström's macroglobulinemia. Olszewski and Castillo also discuss the cost of ibrutinib–rituximab as compared with immunochemotherapy. Although we agree that additional studies are needed to analyze the long-term outcomes, quality of life, and resource use associated with various regimens, this was beyond the scope of our trial.

Cavazzini et al. question atrial fibrillation, deaths, and quality of life in the iNNOVATE trial. With a longer median duration of treatment, the safety data collection period was longer for ibrutinib–rituximab than for placebo–rituximab, which may explain the higher frequency of some adverse events. Among patients in whom atrial fibrillation developed, events led to discontinuation in three patients who were receiving ibrutinib–rituximab. Of four deaths in the ibrutinib–rituximab group, none occurred during the trial treatment (126 to 585 days from the last dose), and causes of death that occurred more than 30 days after the last dose were not collected, unless they were deemed by the investigators to be related to treatment. In the placebo–rituximab group, three deaths were due to intracranial hemorrhage, nervous system disorder, and not specified, and three occurred outside the collection period. Patient-centric care is important. We reported clinically meaningful improvement in hemoglobin levels and in patient-reported outcomes related to anemia (with the use of Functional Assessment of Cancer Therapy–Anemia scores) for ibrutinib–rituximab. Further analyses of patient-reported outcomes are under way. Also, from the patient's perspective, a reduction in the incidence of rituximab-related toxic effects such as IgM flare and infusion reactions is a meaningful outcome. Ibrutinib, as a single agent or in combination, is an active treatment for Waldenström's macroglobulinemia, and the results of our trial show the clinically significant antitumor efficacy of a chemotherapy-free approach to treatment.

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fees from Pfizer, and lecture and consulting fees from Gilead. Updated disclosure forms have been posted with the full text of this article at NEJM.org. No further potential conflict of interest relevant to this letter was reported.

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Clinical Course and Management of Hypertrophic Cardiomyopathy

TO THE EDITOR: In his review article, Maron (Aug. 16 issue)[1] does not mention the potential of physical examination in patients with hypertrophic cardiomyopathy (HCM). In addition to history taking, physical examination is still a cornerstone in clinical medicine, and cardiac auscultation, in particular, is considered to be synonymous with clinical cardiology,[2] although collective skills in auscultation have reportedly declined.[3] The physical signs of HCM may depend to some extent on the presence of a systolic pressure gradient within the left ventricle, which is detected in 70% of patients with this condition.[1]

Far beyond a sophisticated description of physical findings, a pulsus bisferiens and a late systolic murmur at the left sternal border and the apex, and to a lesser extent in the aortic area, as well as the postextrasystolic potentiation known as the Brockenbrough phenomenon[4] should arouse suspicion of HCM. This suspicion should lead health care providers to evaluate patients for this disease and to perform tests with high specificity, such as echocardiography and, in some patients, high-resolution tomographic magnetic resonance imaging, as stated by Maron.[1]

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

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TO THE EDITOR: In line with guidelines, Maron advocates the exclusion of patients with HCM from most competitive sports. An alternative management strategy is the consideration of placement of an implantable cardioverter–defibrillator (ICD). The theoretical risks and benefits of these contrasting strategies are well understood; however, data are lacking on their relative effectiveness and acceptability to patients.

One study[1] followed 65 patients with HCM who participated in organized sports after placement of an ICD. No deaths were recorded, and only 1 patient received a shock. These findings contrast with those of a study[2] in the United Kingdom that examined the outcomes of would-be professional soccer players participating in a screening program. Five participants with HCM were identified and were advised to stop competing, 3 of whom accepted medical advice, and 2 of whom chose to continue playing; both of the latter patients died while playing soccer. The medical community and patients may benefit from studies of the efficacy of making participation in competitive sports an indication for ICD placement in patients with HCM.

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