Cost-Effectiveness of Cyclooxygenase-2 Inhibitors in Chronic Arthritis

TO THE EDITOR: Spiegel and colleagues (1) examined the cost-effectiveness of cyclooxygenase-2 inhibitors compared with generic naproxen among patients with chronic arthritis. The authors critiqued our health economic analysis comparing rofecoxib with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and in doing so misstated both our methods and conclusions (2). We would like to address these errors.

Spiegel and colleagues reported the conclusions of our analyses as follows: "Rofecoxib is likely to be both more effective and cost-saving when compared with nonselective NSAIDs." In fact, we reported that the daily drug cost differences between rofecoxib and nonselective NSAIDs were partially offset by expected savings due to gastrointestinal (GI) problems averted and GI co-medications avoided. However, our base-case analysis explicitly did not report rofecoxib to be dominant, that is, more efficacious and cost-saving, versus nonselective NSAIDs. In sensitivity analyses, we did illustrate situations where rofecoxib was dominant relative to nonselective NSAIDs.

Spiegel and colleagues attempted to illustrate how we may have concluded that rofecoxib was dominant in the model’s base case. Their calculations assumed that our analyses assigned omeprazole to all recipients of prophylactic GI co-medications. However, we did not do so. This would have made the initial cost of prescribing a nonselective NSAID more expensive than the cost of rofecoxib, even before factoring in the additional savings in GI-related costs for rofecoxib users. Spiegel and colleagues then compounded their mistake by stating that the rofecoxib analyses “did not allow for the decreased rate of GI complications afforded by PPIs [proton-pump inhibitors],” thus “economically penalizing the nonselective NSAID arm without rewarding additional effectiveness.” This result is directly at odds with the base-case conclusions of costs offset that we drew in our published analyses.

Our paper was designed to investigate the potential economic impact of rofecoxib therapy versus therapy with nonselective NSAIDs in patients with osteoarthritis from the perspective of the third-party payer. To simulate real-world conditions, our NSAID cost data were derived from the weighted market share of the nonselective NSAIDs available. This approach incorporated both brand-name and generic NSAIDs. We obtained co-prescription rates of gastroprotective agents from the literature (3), and patients receiving co-medications were assigned a PPI, an H$_2$-receptor antagonist, or misoprostol on the basis of the weighted market share of these medications at the time of the analyses. GPA drug costs were assigned on the basis of the average wholesale price and were presented in tabular form in the paper. The resulting weighted daily cost of co-medications was markedly lower than the daily cost of using PPIs for every patient, as in the calculations by Spiegel and colleagues. Furthermore, the efficacy of PPIs and misoprostol in the reduction of GI events was fully assigned as described in the literature. Forty percent reductions in major GI events were assigned to PPIs and misoprostol on the basis of published work (4–6), while no reduction in major GI events was assigned for H$_2$ antagonists. These approaches and the resulting values were all detailed in the Methods section of our paper.

The utility of health economic analyses for decision making depends greatly on clarity of methods and explicitness in stating the assumptions used in the models. Therefore, it is important for the presentation of analyses based on such models to be both comprehensive and transparent and for the potential implications of any assumptions to be discussed. We feel our previously published model was both transparent in its presentation and comprehensive in its analyses.

In addition, it is important to recognize that many more nonselective NSAIDs, both brand-name and generic, are available and in use for treatment of arthritis in the United States. The article by Spiegel and colleagues compared generic naproxen with rofecoxib and celecoxib (coxibs). However, the conclusions of the paper were not limited to this comparison but instead were generalized to all nonselective NSAIDs. The results of these analyses are quite sensitive to the cost of the nonselective NSAID comparator, and the range of potential nonselective NSAID drug costs extends well beyond the $0.04 to $0.50 range described by Spiegel and colleagues, as used in a probabilistic sensitivity analysis. Comparison of coxibs with a single, generic NSAID without regard to other nonselective NSAID alternatives is useful, but limited.

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References

IN RESPONSE: We thank Pellissier and colleagues for their interest in our study. Whereas we estimated that it costs more than $275 000 per quality-adjusted life-year gained to prescribe a coxib in lieu of naproxen in average-risk patients with arthritis, Pellissier and colleagues came to very different conclusions. Specifically, the authors estimated that it costs only $4738 more per ulcer complication avoided to use a coxib instead of a nonselective NSAID when clinical data are incorporated, and further concluded that coxibs dominate
when endoscopic data are considered (1). Our statement that Pellissier and colleagues found that rofecoxib was “more effective and cost-saving when compared with nonselective NSAIDs” is precisely in line with their latter conclusion and in fact is the very definition of dominance. We did not specify whether the conclusion arose from their base-case analysis or their sensitivity analysis.

When we compared our analyses, several potential biases were apparent in the work by Pellissier and colleagues. First, although the paper was published in 2001, the authors relied on the 1998 Red Book to adopt their cost estimates. In doing so, they determined that the average wholesale price of a coxib was $2.42 per pill, whereas the current cost is closer to $2.70 (2). Similarly, using an undisclosed recipe of weighted averages (by market share) of NSAIDs, the authors estimated that nonselective NSAIDs cost $1.47 per pill, compared with average wholesale prices of $0.18 for naproxen and $0.10 for ibuprofen (2). Moreover, by failing to report sensitivity analyses on either of these key estimates, the authors failed to demonstrate the degree to which they affected the model results. The net effect of these cost assumptions is to improve the relative cost-effectiveness of coxibs versus nonselective NSAIDs.

Second, rather than compare the head-to-head cost-effectiveness of coxibs and nonselective NSAIDs, the authors instead assumed that a proportion in each arm received co-prescribed GI prophylaxis. On the basis of the “input of an expert panel,” the authors estimated that the co-prescription of prophylactic agents was “75% less than with nonselective NSAIDs.” They further assumed that 25.5% of the nonselective NSAID group received co-prescriptions. Where we reported that all 25.5% received omeprazole, Pellissier and colleagues noted that their analysis allowed for a combination of gastroprotective agents, including misoprostol and H$_2$-receptor antagonists. However, the authors did not report the relative proportion of PPI use (that is, did PPIs account for all, half, or none of the 25.5%)?

Moreover, because misoprostol is rarely used for GI prophylaxis because of side effects and H$_2$-receptor blockers are proven ineffective for this indication, there is little doubt that PPIs are the drug class of choice for NSAID gastropathy. The more important issue is whether co-prescribed therapy should be modeled in the choice for NSAID gastropathy. The more important issue is whether coxibs alone are cost-effective versus nonselective NSAIDs.

Diagnosis and Management of Adults with Pharyngitis

TO THE EDITOR: I take exception with the conclusions of Neuner and colleagues in their article on the diagnosis and management of adults with pharyngitis (1). I am not an academic, but the late Dr. Louis Weinstein was. He related the following tale on more than one occasion while I was a student at Haynes Memorial Hospital in Boston, Massachusetts, some years ago. Dr. Weinstein became concerned about the validity of throat cultures when he was able to obtain only a 70% positive return on known group A $\beta$-hemolytic streptococcal infections, using as his gold standard a personally documented increase in the antistreptolysin-O (ASLO) titer (blood was drawn twice, once on seeing the individual for the first time and the second time 2 weeks later). Dr. Weinstein made his own blood agar plates, personally performed the throat culture, and did the serologic work himself. He repeated the study and got identical results. He then spoke with another pioneer in the field, Dr. Charles H. Ramelkamp Jr. in Cincinnati, Ohio, who stated that he, too, obtained the identical result, namely only a 70% positive throat culture return when compared with the ASLO titer increase that proved that any given individual had had the infection in question.

Granted, we are now in another era when immunoassays are in vogue, but the gold standard should still be the ASLO titer, not the throat culture and not the optical (or any other) immunoassay.

Incidentally, I asked Dr. Weinstein what he did clinically. He replied that if he found that he was getting positive throat cultures with any regularity, he would treat all suspicious pharyngeal infections with penicillin or erythromycin.

In any event, in the absence of ASLO titer confirmation, the results quoted in Neuner and colleagues’ article remain suspect, at least to me.

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Reference
TO THE EDITOR: Neuner and colleagues’ cost-effectiveness analysis on the diagnosis and management of adults with pharyngitis (1) concluded that observation, culture, and rapid antigen test strategies for possible group A β-hemolytic streptococcal pharyngitis have similar effectiveness. They also concluded that empirical treatment was not the best strategy, regardless of prevalence.

This result assumes that the adverse consequences of antibiotic therapy exceed the derived treatment benefit. The rationale for treating group A β-hemolytic streptococcal pharyngitis includes the prevention of suppurative complications (peritonsillar abscess) and non-suppurative complications (acute rheumatic fever) as well decreasing contagion and relieving symptoms. Neuner and colleagues appropriately considered peritonsillar abscess and acute rheumatic fever but did not address contagion and underestimated the suffering (disutility) of patients with severe pharyngitis. Given that peritonsillar abscess and acute rheumatic fever are rare (2.3% and 0.05%, respectively), accurate utility assessment of pharyngitis becomes paramount. Neuner and colleagues estimated a utility for sore throat of 0.95 by using published patient survey data (2, 3) that compared pharyngitis with other common symptoms, such as diarrhea and dyspepsia. They then used the patient-assigned utility score of 0.95 for diarrhea and dyspepsia (4) as a proxy for pharyngitis. The analysis does not consider that patients who present with severe pharyngitis (at least 3 or 4 clinical findings) would have greater disutility than those with less severe pharyngitis.

To achieve accurate utilities for adult pharyngitis, Rousculp (5) recently administered a utility survey using a modified time-tradeoff method. In his survey, the mean utility for mild pharyngitis was 0.945; however, the utility score dropped to 0.861 for severe pharyngitis. If Neuner and colleagues had applied pharyngitis utilities that took symptom severity into account, we suspect that in patients with severe pharyngitis. Given that peritonsillar abscess and acute rheumatic fever are rare (2.3% and 0.05%, respectively), accurate utility assessment of pharyngitis becomes paramount. Neuner and colleagues estimated a utility for sore throat of 0.95 by using published patient survey data (2, 3) that compared pharyngitis with other common symptoms, such as diarrhea and dyspepsia. They then used the patient-assigned utility score of 0.95 for diarrhea and dyspepsia (4) as a proxy for pharyngitis. The analysis does not consider that patients who present with severe pharyngitis (at least 3 or 4 clinical findings) would have greater disutility than those with less severe pharyngitis.

To achieve accurate utilities for adult pharyngitis, Rousculp (5) recently administered a utility survey using a modified time-tradeoff method. In his survey, the mean utility for mild pharyngitis was 0.945; however, the utility score dropped to 0.861 for severe pharyngitis. If Neuner and colleagues had applied pharyngitis utilities that took symptom severity into account, we suspect that in patients with severe sore throat, empirical therapy may have been the most effective and least expensive, that is, dominant.

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References

IN RESPONSE: Dr. Corwin is concerned about the possible poor sensitivity of pharyngeal culture compared with the ASLO titre. The test characteristics of pharyngeal culture when compared with a variety of other tests have varied in the literature, as we reviewed in our article and its appendix. Probably because ASLO assessment takes at least a week and thus cannot be used for treatment decisions in the clinical setting, there is unfortunately little information regarding ASLO titers in a group of patients “suspicious” for streptococcal pharyngitis or in patients receiving rapid immunoassay testing. This lack of data made it difficult for us to use ASLO as our gold standard. Furthermore, some of the issues regarding sensitivity may be reduced with careful attention to culture technique (1), and recent studies using polymerase chain reaction to assess both immunoassays and pharyngeal culture suggest that test performance of culture is much better than the 70% sensitivity cited by Dr. Corwin (2). For these reasons, although we agree that it is less than ideal, we and authors of similar studies have chosen to use pharyngeal culture as a gold standard.

Drs. Cohen and Centor report some interesting unpublished data (3) on the patient utility for sore throat and are concerned that our analysis of patients with severe pharyngitis (that is, those who had positive results on 3 to 4 Centor criteria) did not take into account the possibility of a different utility for these patients. Although our estimates for the sequelae of sore throat were taken from a patient survey that compared them with sore throat (4), our utility estimate for pharyngitis was certainly limited by the lack of information in the literature on patients’ utilities for sore throat. We note that our utility estimate for our base-case scenario was identical to that reported by Drs. Cohen and Centor for “mild” pharyngitis. We agree with Drs. Centor and Cohen that patient utilities vary for many disease states and are likely to be higher on average in patients with more severe symptoms and signs of pharyngitis. In pharyngitis, a disease in which sequelae are rare, individual patient utilities should be carefully considered and may indeed drive decision making. The typical patient encountered in primary care has a less severe sore throat, so the incorporation of Rousculp’s findings would not change our main, baseline findings. Empirical therapy without testing was neither the most effective nor least expensive strategy at any prevalence of group A β-hemolytic streptococcal infection typically seen in adult populations.

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References
Mammography and Palpable Breast Abnormalities

TO THE EDITOR: In their article on evaluation of abnormal mammography results and palpable breast abnormalities, Kerlikowske and colleagues (1) calculated likelihood ratios correctly but incorrectly defined the term in their footnotes to Tables 2, 3, and 5. They defined a likelihood ratio as “the ratio of diseased to nondiseased persons for a given test result.” A hypothetical example illustrates why this is incorrect. If among patients with a positive test result 90 had a given disease and 1 did not, and if among patients with a negative test result 10 had the disease and 9 did not, the ratio of diseased to nondiseased persons for a positive test result would be 90 to 1. However, the likelihood ratio for a positive test result would be 90%/10%, or 9. Very different.

One of several correct definitions of a likelihood ratio is “the ratio of the relative frequency of a given test result in diseased and nondiseased persons (where relative frequency is a proportion)” (2).

Errors in defining likelihood ratios are common. An early edition of a classic text on clinical epidemiology contains errors (3), describing a likelihood ratio as an odds or a ratio of odds (rather than a ratio of probabilities). The current edition of a popular text on diagnostic tests contains a similar error (4). Some texts commit more serious errors—incorrectly calculating likelihood ratios in addition to incorrectly defining them (5, 6)—actually applying the erroneous definition used by Kerlikowske and colleagues.

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References

IN RESPONSE: We appreciate Dr. Evans’s correspondence and the opportunity to clarify the use of the term likelihood ratios in our paper. Likelihood ratios are being used more frequently by clinicians in clinical practice but are still not as familiar as the sensitivity and specificity of a diagnostic test. Sensitivity is calculated among diseased persons and specificity is calculated among nondiseased persons, whereas likelihood ratios are calculated using a given test result among diseased and nondiseased persons, as noted in the footnotes of our Tables 2, 3, and 5. As stated by Dr. Evans, the likelihood ratios reported in our article are calculated correctly for screening and diagnostic mammography and fine-needle aspiration biopsy, and a clear description of how to apply likelihood ratios for these tests in clinical practice is provided. We reference the source data (1) used to calculate likelihood ratios reported in our paper as well as the formulas, which are as follows.

Positive likelihood ratio = sensitivity/1 − specificity
Negative likelihood ratio = 1 − sensitivity/specificity

These formulas show that likelihood ratios are calculated as the probability that persons with the disease have a particular test result divided by the probability that persons without the disease have the same test result. Additional information on how to calculate likelihood ratios for a given test result can be found in a classic epidemiology text (2).

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References

The Discrepancy between Observational Studies and Randomized Trials of Menopausal Hormone Therapy

TO THE EDITOR: In their article on the discrepancy between observational studies and randomized trials of menopausal hormone therapy, Col and Pauker (1) correctly recognized that differences in socioeconomic status or other risk factors (“healthy user effect”) between postmenopausal hormone users and nonusers are unlikely to substantially explain differences in the coronary heart disease (CHD) findings from the Nurses’ Health Study (NHS) (2) and the Women’s Health Initiative (WHI) trial (3). They noted, as we have (4), that any such effects would also alter findings for other diseases, especially stroke. The nearly identical results from the NHS and WHI for stroke suggest that the explanation for the difference in CHD lies elsewhere. Col and Pauker speculated that misclassification of CHD in the NHS and other observational studies biased the findings. They suggested that if women taking hormones thought they were protected from heart attack, they would be less likely to present with its symptoms. However, one could as easily speculate that the health-conscious women taking hormones would be more likely to seek medical attention for symptoms than nonusers. Also, in the NHS, we do not include silent infarctions (because we cannot perform periodic electrocardiography in this large cohort), Col and Pauker speculated that this omission biased the findings, claiming that one third of infarcts are silent. This ignores the WHI finding that 3% (9 of 265) of nonfatal myocardial infarctions were silent (3) and that results were identical whether silent infarctions were included or excluded. Even extreme bias in this small group would have negligible impact.

Col and Pauker also suggested systematic misclassification of CHD death in the NHS. They implied that investigators’ coding of cause of death could alter the diagnosis on the basis of medication use. We apply uniform and strict criteria for CHD, similar to the WHI. Fatal CHD is based on previous evidence of CHD, diagnostic tests, clinical findings, autopsy reports, and the death certificate. Previous medication use is not reviewed and is included in less than
20% of CHD death files. Most fatal CHD codes are based on previously diagnosed CHD and the death certificate. Moreover, the NHS results for nonfatal MI and fatal CHD were nearly identical, and authors accept our adjudication process for nonfatal MI. Finally, widespread belief that hormones were protective for CHD developed only over the past 15 to 20 years. Thus, if expectations of physicians or investigators led to an association because of misclassification of CHD, one would expect an increasing apparent benefit of hormones over time. In fact, the NHS observation of a lower risk among hormone users was present in data from 1976 to 1980 (5), and the magnitude of the association has not increased since then.

A more plausible explanation of differences between NHS and WHI is based on biology and differences in the populations. In the NHS, and most observational studies, most hormone use began at menopause. In contrast, 67% of WHI participants were 60 years of age or older. The WHI found a trend toward lower risk with decreasing time since menopause; among women who went through menopause less than 10 years previously (n = 65), the relative risk for CHD with estrogen plus progestin compared with placebo was 0.89 (95% CI, 0.55 to 1.46). For women for whom 10 to 19 years had passed since menopause, the relative risk was 1.22, and for those who had menopause 20 or more years previously, it was 1.71 (3). Such findings are consistent with studies showing that estrogen benefits were reversed in the presence of endothelial dysfunction in rabbits (6). Likewise, monkeys that began receiving hormone therapy at ovarioectomy had reduced atherosclerosis, but those who started therapy years after ovarioectomy had no benefit (7). In women, atherosclerosis abrogates the estrogen effect on vasodilatation (8). In a randomized trial among younger postmenopausal women, estrogen significantly reduced carotid atherosclerosis progression compared with placebo (9). Thus, a likely explanation for the different results from WHI and NHS is the difference in age at starting hormone use.

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References

IN RESPONSE: Despite mounting evidence concerning the risks of hormone therapy, the WHI authors still believe that it is cardioprotective if initiated in newly menopausal women without atherosclerosis. However, NHS data show that the cardioprotective effect was the same among women in their 50s and 60s (relative risk, 0.71 vs. 0.66) and among women with and without CHD risk factors (1). Grodstein and colleagues’ argument hinges on one statistically insignificant subgroup analysis of WHI women within 10 years of menopause (relative risk, 0.89; 65 CHD cases). Of note, subgroup analysis of WHI women 50 to 59 years of age yielded conflicting results: a relative risk of 1.27. Because of the complexities of dating menopause, the subgroup defined by age is probably the more robust estimate of the effect of hormone therapy among newly menopausal women.

The NHS authors have not recognized the importance of unblinded assessment of outcomes. The bias introduced by the lack of concealment of treatment allocation is substantial and has been empirically demonstrated among randomized, controlled trials. Unblinded trials substantially overestimate (41%) treatment effects compared with blinded trials (2). The impact of unblinding within observational studies could potentially be larger given the other potential sources of bias within nonrandomized studies.

The NHS authors dispute the potential impact of excluding silent events, stating that the rate of silent events in their study should mirror the 3% reported in the WHI rather than the 34% range reported in the Framingham Study and many other population-based studies (3). Because risk factors for silent myocardial infarction were similar in the NHS and the Framingham Study, their rates should also be similar. In contrast, silent event rates in population-based studies should not mirror those in randomized, controlled trials, whose protocols were designed to recognize adverse events that might otherwise have gone unnoticed.

Literature on the purported cardioprotective effect of hormones long predates the NHS observation period. In the 1960s, 2 trials were published (4, 5) and a third nationwide collaborative study began, all hoping to extend cardioprotection from women to men (6). In 1985, one explanation offered for discrepant results between the first NHS and the Framingham Study was predicated on the widespread belief that hormone therapy was cardioprotective: “Could the [Framingham Study] data . . . be seriously biased by one or several physicians who were unusually alert to possible estrogen effects?” (7).

Is it plausible to believe that hormone therapy prevents CHD in newly menopausal women but induces it in all others? While this issue is not completely resolvable with the data at hand, the argument for such a window rests on one statistically insignificant, discordant subgroup analysis from the WHI and 3 small studies of...
unopposed estrogen. Unopposed estrogen is markedly different from combined estrogen and progesterone in its effects on the heart. One of these studies (8), involving only 83 women, found an inconsequential 0.0053-mm change in arterial walls; the other studies were in animals (9, 10).

Should the treatment of all women be driven by these data despite the experience of 16 608 women in a well-designed randomized, controlled trial? We believe not and think that clinicians should continue to advise only substantially symptomatic women to take hormone therapy.

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References

CLINICAL OBSERVATION

Helicobacter pylori and Idiopathic Thrombocytopenic Purpura

TO THE EDITOR: Background: Idiopathic thrombocytopenic purpura (ITP) is a hematologic disorder characterized by sensitization of platelets by autoantibodies leading to platelet destruction (1–4). Although its cause remains unclear, ITP is associated with several diseases, including infections (5–8).

Figure. Cross-reactivity between anti–cytotoxin-associated gene A (anti-CagA) antibodies and human platelet antigens.

Monoclonal anti-CagA antibodies recognized 2 platelet antigens (50 and 55 kDa) in patients with previous idiopathic thrombocytopenic purpura (ITP) (patients A, B, G, and H) or active ITP (patients C, D, I, and L (patients C and D were Helicobacter pylori-positive)), but only 1 antigen (50 kDa) in 3 of 4 normal controls (patients E, F, and M) (P < 0.01 by chi-square analysis). Among the normal controls, only patient N showed the additional 55-kDa band.

Helicobacter pylori, a gram-negative bacterium, is a frequent cause of upper gastrointestinal tract infection (9). Of interest, the presence of the cytotoxin-associated gene A (CagA), an important determinant of pathogenicity, is associated with greater gastric mucosal immune responses (9).

Objective: In a previous study, we described increasing platelet counts in patients with ITP 4 months after eradication of CagA-positive H. pylori infection (10). Therefore, we tested the hypothesis that cross-reactivity between H. pylori and platelet antigens may affect platelet survival.

Methods and Findings: Eleven patients (9 women and 2 men; mean age ±SD, 43 ± 14 years) with ITP and H. pylori infection underwent eradication therapy with amoxicillin, 1000 mg twice daily; clarithromycin, 250 mg 3 times per day; and pantoprazole, 40 mg twice daily, for 7 days (10). Seven uninfected patients with ITP (4 women and 3 men; mean age ±SD, 49 ± 12 years) served as controls. No patient received treatment for ITP. Helicobacter pylori status was determined by using the 13C-urea breath test, and anti–CagA antibodies were evaluated by enzyme-linked immunosorbent assay (Radim, Pomezia, Italy). Platelet counts were assessed in all patients.

Platelets were isolated from 6 patients with active and untreated ITP (3 were H. pylori–positive and were not treated for the infection, while 3 were H. pylori–negative); 6 patients whose antiplatelet antibodies disappeared and whose platelet counts significantly improved after H. pylori eradication, as previously reported (10); and 6 normal controls.

Washed platelets were lysed in sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) sample buffer, separated by SDS-PAGE, and transferred to polyvinylidene difluoride membranes. Membranes were then blotted with monoclonal anti–CagA antibodies (Austral Biologicals, San Ramon, California). Reactive bands were visualized by chemiluminescence. Lysates from both colonic smooth muscle (2 patients) and normal arteries (3 patients)
were used as controls. This study was conducted in compliance with local institutional review board regulations and the revised Helsinki protocol.

Both the \(^{13}\)C-urea breath test and anti-CagA antibodies became negative in 8 of 11 patients with \(H.\) pylori infection who completed the eradicating therapy but remained positive in the 3 patients who did not complete the treatment. Before therapy, 5 of these 11 patients had anti–glycoprotein (GP) IIb/IIIa antibodies; no changes in antibody levels were observed in the 3 patients who were positive for anti-GP IIb/IIIa antibodies but had successful eradication therapy or in the 2 patients in whom therapy failed. Mean platelet counts (±SD) increased significantly only in patients with successful \(H.\) pylori eradication (86 ± 25 vs. 168 ± 68 × 10\(^9\) cells/L; \(P < 0.001\)). No significant changes were observed in unsuccessfully treated patients (88 ± 23 vs. 100 ± 28 × 10\(^9\) cells/L; \(P > 0.2\)) or in untreated \(H.\) pylori–negative patients with ITP (103 ± 27 vs. 84 ± 25 × 10\(^9\) cells/L; \(P > 0.05\)). Mean platelet counts (±SD) increased in 3 anti-GP IIb/IIIa–positive patients (83 ± 24 to 118 ± 48 × 10\(^9\) cells/L; \(P < 0.04\)) and in 5 anti-GP IIb/IIIa–negative patients (from 89 ± 26 to 218 ± 88 × 10\(^9\) cells/L; \(P < 0.001\)).

Anti-CagA antibodies reacted with all platelet samples. However, a single 50-kDa band was detected in 5 of 6 samples from normal controls, and 2 bands (50 kDa and 55 kDa) were detected in all samples from patients with active ITP and resolved ITP (Figure 2). The immunoreaction of anti-CagA antibodies with the 55-kDa platelet antigen was significantly associated with resolved or active ITP (\(P < 0.01\)). In neither smooth-muscle nor normal artery lysates did anti-CagA antibodies react with the 50-kDa or the 55-kDa bands.

Conclusions: Our hematologic and serologic data support a temporal association between the disappearance of anti-CagA antibodies in the serum and improvement of ITP. Moreover, anti-CagA antibodies recognized 2 platelet antigens in ITP patients but only 1 in normal controls. We hypothesize that anti-CagA antibodies could lead to reduced platelet survival only in patients displaying the 55-kDa platelet antigen. Additional studies are necessary to identify the cross-reacting platelet antigens and their population prevalence.

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References

CORRECTIONS

Corrction: Responsiveness of Thrombotic Thrombocytopenic Purpura to Rituximab and Cyclophosphamide

In a letter on responsiveness of thrombotic thrombocytopenic purpura to rituximab and cyclophosphamide (1), some of the symbols in the Figure were incorrect and did not match the legend. The white diamonds (◇) should have been daggers (†), and the pound signs (#) should have been section marks ($§$).

Reference

Correction: Beyond Semmelweis: Moving Infection Control into the Community

In an editorial on antibacterial products (1), the second sentence in the seventh paragraph should read as follows:

Among the risks associated with antibacterial-containing products is the possible link between resistance to their antibacterial ingredients and the development of resistance to drugs used to treat infections.

Reference
Delayed Drug Hypersensitivity Reactions

TO THE EDITOR: The article by Dr. Pichler (1) explored the underlying mechanisms that operate in delayed drug reactions. However, no information was provided on whether drug dosage or duration of use affects these mechanisms. Furthermore, is there any indication from these mechanisms that when patients report a “reaction” to their medication, one could safely eliminate a delayed hypersensitivity reaction as having occurred on the basis of how long the patient has been using the medication?

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Reference

IN RESPONSE: Drug dosage is important in generating an immune response, but there are no data available that would suggest that a high dosage may cause, for example, bullous skin diseases while a small dose causes urticaria. It seems that an individual’s predisposition and the type of drug are more important to the type of reaction than the drug dosage. In already sensitized persons, drug dose is also important for eliciting symptoms. However, small doses can often cause symptoms, which obscures the role of dosage.

It is controversial, and probably depends on the drug, whether continued treatment and thus higher dosage may aggravate a mild exanthematous reaction and lead to more bullous or systematic disease (a so-called drug hypersensitivity syndrome). In many instances, continuous treatment may not aggravate the mild exanthema, but with certain drugs (such as antiepileptic agents, allopurinol, nevirapine, and abacavir), a “mild” exanthema might be a precursor of a more severe reaction and immediate withdrawal of the drug is advisable.

Most delayed hypersensitivity reactions develop in the first 2 weeks after treatment is started. Severe drug hypersensitivity syndromes with eosinophilia and internal involvement often appear later (2 to 8 weeks after the start of treatment) (1). In this case, dosage is clearly important because patients who have been receiving long-lasting treatment with antiepileptic agents may suddenly develop a severe drug hypersensitivity reaction if the dose is increased.

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Reference