Factor V Leiden and venous thromboembolism

Vandenbroucke, J.P.; Rosendaal, F.R.

COMMENTS AND RESPONSES

Future Research on Disclosure of Medical Errors

TO THE EDITOR: When we consider the fine study by Mazor and colleagues on disclosure of medical errors (1) and the thoughtful accompanying editorial by Frenkel and Liebman (2), it is important to keep in mind what we do not know. Not unlike much of the research in this area, Mazor and colleagues' empirical study is hypothetical: Participants are asked to imagine how they would respond to receiving or not receiving an apology in hypothetical cases of injury. The results of such research showing, inter alia, limited effects of full disclosure on a patient's decision to seek legal advice are no doubt important. However, just as results of in vitro and in vivo studies can differ, we should keep in mind the possibility that the effects of actual apologies may differ from those of hypothesized apologies. In significant part, apologies function at an emotional level through anger reduction. It is quite possible that how patients say they would respond to an apology in a cognitive, pencil-and-paper exercise and how they would respond in real life may differ.

In my view, the next important step in apology research concerning medical errors will come with empirical studies of the effects of actual apologies. As Frankel and Liebman discuss (2), several states have recently enacted laws requiring disclosure to patients of medical errors that result in serious adverse events. Furthermore, last spring Colorado became the first state to enact a law prohibiting the introduction of a physician's or hospital's apology into evidence in a medical malpractice action (3, 4). Such new laws make it increasingly likely that, over the next decade, we will witness some medical providers switching from a posture of silence to a posture of open disclosure and apology following adverse medical errors, much as occurred in the famed example of the Veterans Affairs Medical Center in Lexington, Kentucky (5). As this happens, we may then obtain the data needed to more accurately assess the empirical effects of disclosure and apology on lawsuit and settlement patterns.

Jonathan R. Cohen, JD, PhD
University of Florida
Gainesville, FL 32611-7625

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D-Dimer and Venous Thromboembolism

TO THE EDITOR: Stein and colleagues' systematic review (1) provides clinicians with a thorough compilation of the data published to date for application of D-dimer in the setting of suspected deep venous thrombosis (DVT) and pulmonary embolism. Unfortunately, I worry that the authors' conclusions may only continue to muddy the waters regarding the utility of the D-dimer assay in this particular setting.

The authors imply in their conclusion that radiographic evaluation of patients for suspected pulmonary embolism is not indicated after a negative result on quantitative rapid enzyme-linked immunosorbent assay (ELISA). This is based on the assumption that negative likelihood ratios less than 0.1 "result in large and often conclusive changes from pre- to post-test probability" (1). Of the 7 types of D-dimer assays evaluated in this review, the only negative likelihood ratio found to be less than 0.1 for the evaluation of pulmonary embolism was obtained by using the quantitative rapid ELISA. The authors failed to address the fact that the upper bound of the 95% confidence limit was 4.15. This is a negative likelihood ratio that would seemingly increase the likelihood of disease.

Even at the stated negative likelihood ratio of 0.05, a negative result on quantitative rapid ELISA would not exclude pulmonary embolism in all patients, regardless of pretest probability. Patients with high pretest probabilities account for 10% to 13% of those evaluated for pulmonary embolism (2–4), and the incidence of pulmonary embolism in this population can range from 39% to 87% (2–5). Applying a D-dimer assay with a negative likelihood ratio of 0.05 to these pretest probabilities would yield post-test probabilities of 9% to 25%, a number clearly too high to abort the work-up of disease.

Stephen J. Wolf, MD
Denver Health Medical Center
Denver, CO 80204

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TO THE EDITOR: In the excellent review by Stein and colleagues (1), the sensitivity of D-dimer testing for the diagnosis of DVT appears to be lower than previously reported, even for ELISAs. In fact, plasma concentration of D-dimer is at least partly related to the volume of the thrombus (2). Hence, D-dimer level may not be increased in patients with isolated distal DVT. Indeed, some of the studies included in Stein and colleagues' meta-analysis included distal as well as proximal thromboses. For example, in the study by Leroyer and associates (3), in which a qualitative rapid ELISA was used, sensitivity reached 97.9% for diagnosis of proximal DVT but only 76.3%

for diagnosis of distal DVT. This limited sensitivity of D-dimer for distal thromboses may account for the relatively low overall sensitivity reported by Stein and colleagues. Is this truly an issue? As the Editor stated in the commentary accompanying Stein and colleagues' article, physicians are confused by the myriad tests for DVT. Few of these tests have received appropriate clinical validation and can safely be used in clinical practice. In management studies including patients with suspected DVT, where the diagnosis was ruled out and patients left untreated because of negative ELISA results (4) or negative results on whole-blood agglutination assay in those with low clinical probability (5), the 3-month thromboembolic risk was about 2%, similar to that observed after negative results on venography. Thus, even if D-dimer testing is not accurate enough to detect distal DVT, patients with a negative result on a D-dimer test may be left untreated without further investigation. Even though sensitivity of D-dimer testing for diagnosing DVT may not be optimal, the test can identify patients in whom anticoagulant therapy is not necessary, which is the true clinically relevant issue.

Grégoire Le Gal, MD
Marc Righini, MD
Henri Bounameaux, MD
Geneva University Hospital
1211 Geneva 14, Switzerland

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TO THE EDITOR: Although Stein and colleagues' conclusion, "a negative quantitative rapid ELISA result is as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding," is technically correct (1), the issues surrounding this use of D-dimer are more complex. For a test used to rule out disease, high sensitivity is not the only important characteristic. Specificity also plays a key role and limits the use of D-dimer for venous thromboembolism (VTE) in at least 2 ways.

First, the likelihood ratio for a negative test result, calculated as (1 − sensitivity)/specificity, is inversely proportional to specificity. Few tests have invariable sensitivity and specificity. Instead, these indexes vary with the clinical characteristics of patient samples. This is particularly true for the specificity of D-dimer. Many conditions besides thromboembolism cause "elevated" D-dimer levels. When large numbers of patients with these conditions, such as cancer, trauma, surgery, and advanced age, are included in a study, specificity will be very low, the likelihood ratio for a negative test result will not be as small as reported by Stein and colleagues (1), and D-dimer levels of those with VTE will sometimes be indistinguishable from levels in those without (2). Thus, unless the clinician orders D-dimer testing only in patients without conditions known to cause elevated levels, results will not be diagnostically useful for VTE.

Second, low specificity leads to many false-positive test results. We performed calculations using Stein and colleagues' values for sensitivity and specificity for DVT (1), assuming a disease prevalence of 20%. For the quantitative rapid ELISA, Stein and colleagues' favored D-dimer assay (sensitivity, 0.91; specificity, 0.43), 46% of all patients tested would have false-positive results. However, for the whole-blood assay (sensitivity, 0.82; specificity, 0.70), only 24% would have false-positive results. Although the high sensitivity of the quantitative ELISA gives it an apparent advantage in ruling out disease, its corresponding low specificity leads to false-positive results in almost half of tested patients. The availability of a simple blood test to rule out VTE may lead physicians to order the test more often, and a positive result would probably mean additional tests to rule out thromboembolism. In an inpatient setting, Goldstein and associates (3) found that lung scans, computed tomography, and pulmonary angiography were ordered more frequently when D-dimer testing was used as the initial diagnostic strategy than when it was not.

We believe D-dimer has a place in the management of patients with suspected VTE, for example, in selected emergency department settings (4). However, its role will always be limited because of its low specificity. In choosing to use the test, clinicians should consider whether patients have conditions likely to cause false-positive results and, if so, should go straight to imaging studies. In addition, clinicians must respect the pitfalls of low specificity and refrain from ordering D-dimer on increasingly wider ranges of patients just because the test is cheap and easy to perform.

John T. Philbrick, MD
Steven Heim, MD, MSPH
Joel M. Schectman, MD, MPH
University of Virginia
Charlottesville, VA 22908

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TO THE EDITOR: In the Discussion section of Stein and colleagues' article (1), the authors pointed out that the clinical utility of D-dimer assays may vary among patients with different diseases. In particular, a higher value can be expected when the probability of having DVT or pulmonary embolism is lower, such as in outpatient setting. We

agree but believe that another important point should be emphasized.

Deep venous thrombosis and pulmonary embolism are common complications in patients with cancer, and in these patients a D-dimer test is probably of limited diagnostic usefulness. In fact, malignant conditions are often associated with elevated D-dimer levels because of tumor-induced activation of intravascular coagulation (2). Accordingly, different studies evaluating the role of D-dimer in patients with cancer and suspected DVT or pulmonary embolism found that the test had lower specificity and negative predictive value than in patients without cancer (3–5). Clinicians should be cautious about applying the results of Stein and colleagues' systematic review to patients with high probability of elevated D-dimer levels (that is, those in whom the test will have low specificity for DVT or pulmonary embolism), such as patients with cancer.

Fabio Puglisi, MD, PhD
Edda Federico, MD
University of Udine
1-33100 Udine, Italy

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IN RESPONSE: Dr. Wolf has identified the upper 95% confidence limit for the quantitative rapid ELISA's negative likelihood ratio from the sensitivity analysis. The lower 95% confidence limit was 0.00, which is statistically as likely as the value for the upper 95% limit. Both of these extreme values are unlikely to occur clinically. The sensitivity analysis provided a central estimate of 0.05, which is consistent with the primary analyses. It should be noted that the value for sensitivity in the sensitivity analysis was 0.98, with a 95% confidence limit of 0.88 to 1.00, a much narrower range of values than was seen for the negative likelihood ratio. The primary analyses in our Table 1 show similar findings with narrower confidence limits. The key fact from the sensitivity analysis is that there was no shift in the observed values for sensitivity and negative likelihood ratio, although the confidence limit was broader for the latter. A recent rigorous clinical outcome study in a large number of patients supports our findings (1): Perrier and colleagues reported that the quantitative rapid ELISA was effective and safe as the first-line test for ruling out pulmonary embolism in outpatients. We agree that using the clinical probabilities adds further value to the diagnostic process and stated this in our Discussion. We also concluded from our data that a negative quantitative rapid ELISA result is as diagnostically useful as a normal or near-normal lung scan or negative duplex ultrasonography finding. As we indicated, "combining a negative rapid ELISA result with a low or moderate clinical probability for DVT or PE [pulmonary embolism] rules out these diagnoses." We agree that a high-probability clinical assessment in combination with negative results on quantitative rapid ELISA indicates the need for further testing.

We agree with the conclusion of Drs. Le Gal, Righini, and Bounameaux that "the [D-dimer] test can identify patients in whom anticoagulant therapy is not necessary, which is the true clinically relevant issue." In a commentary that accompanied our article, the Editor showed how the D-dimer test (quantitative rapid ELISA) best fits in the diagnostic process.

Regarding the comments of Drs. Philbrick, Heim, and Schectman, we stated in our Discussion that "the values for specificity and positive likelihood ratio differed among the assays, but all were within a range considered to be of little clinical value in altering probability of disease." We also said that "the clinical utility of the D-dimer assays is limited by the nonspecificity of a positive result" and that it "differs among patient samples and may be higher in outpatients."

It is unclear whether the presence of cancer interferes with the more sensitive D-dimer ELISAs. Drs. Puglisi and Federico cited non-ELISA D-dimer assays, which have a lower overall sensitivity.

Russell D. Hull, MBBS, MSc
William A. Ghali, MD
Rollin F. Brant, PhD, MPH
University of Calgary
Calgary, Alberta T2N 2T9, Canada

Paul D. Stein, MD
Saint Joseph Mercy Oakland
Pontiac, MI 48341

Reference

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Factor V Leiden and Venous Thromboembolism

TO THE EDITOR: The paper by Juul and colleagues (1), which estimated the increased risks for venous thromboembolism (VTE) in the adult Danish population according to the factor V Leiden genotype, is clearly of great interest. What appears to be of at least equal interest are the authors' findings that risk for VTE is higher in factor V Leiden heterozygotes and homozygotes who smoke. Over the years, studies have suggested that incidence of VTE is lower in smokers than in nonsmokers (2), although results of such case–control studies may well have been biased by factors such as age and exclusion of persons at high risk. More recently, a prospective cohort study of older men that did not exclude high-risk persons showed a relative risk of 2.8 for deep venous thrombosis in smokers compared with nonsmokers (3). Despite this, major reviews of VTE do not usually include smoking in their lists of risk factors.

It would be helpful if Juul and colleagues could shed further light on the role of smoking as a risk factor for VTE in their study sample. For example, was smoking a predominant risk factor for VTE in the 7.8% of their patients who were heterozygous or homozygous for factor V Leiden, as appears to be the case in their Figure 2? In addition, what was the relationship among smoking, estrogen-containing preparations, and factor V Leiden genotype in women with VTE? Smoking increases risk for VTE in women who take oral contraceptives (4), and the risk is 50 times higher in women who are heterozygous for the factor V Leiden genotype and are taking third-generation combined oral contraceptives than it is in nonusers who are not factor V Leiden carriers (5). Further data from Juul and colleagues' study might help to determine whether factor V Leiden genotyping would be a useful predictive test for VTE risk in smokers planning to use estrogen-containing preparations.

Philip T. Murphy, MD
Beaumont Hospital
Dublin 9, Ireland

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TO THE EDITOR: Juul and colleagues (1) reported the results of the Copenhagen City Heart Study, a Danish cohort study that followed 9253 individuals beginning in 1976. They found that risk for VTE was increased 3-fold among carriers of factor V Leiden (216 events and 43 carriers) (1). This relative risk was substantially lower than the 7-fold risk that we reported in a case–control study of 474 patients with thrombosis and 474 controls (92 and 14 carriers, respectively) (2). Juul and colleagues ascribe this difference to "ascertainment bias" and a preponderance of risk factors among patients with venous thrombosis.

This is a misapprehension of case–control studies. Persons who develop disease always have more risk factors, in whatever study design (3). As an example, Juul and colleagues noted that 66% of young women with venous thrombosis in our study used oral contraceptives and none of the patients in their study did so. This does not mean that something is wrong with case ascertainment in a case–control study and certainly does not mean that oral contraceptives play no role in venous thrombosis in Danish adults. Rather, this is a consequence of the Danish study sample, which consisted of an aging cohort of mainly middle-aged and older persons. The one-time addition of 500 younger persons is of little help, given the low incidence of VTE. In contrast, we included patients with venous thrombosis who were 15 years of age and older as cases occurred in the general population. Thus, a difference in relative risk associated with factor V Leiden between our study and that of Juul and colleagues may reflect an age difference in the study samples. Moreover, Juul and colleagues' inclusion of persons with previous VTE, persons with cancer, and persons with a primary diagnosis of pulmonary embolism tends to lower the relative risk because these conditions are less associated with factor V Leiden.

Estimates from both studies might be correct: ours for first episode of deep venous thrombosis of the legs in the general cancer-free population and Juul and colleagues' for all VTE cases in a cohort of middle-aged and elderly persons. However, Juul and colleagues' figures may suffer from diagnostic misclassification. Their study was initially prospective, but cases were detected by searching routine administrative registries. Cases were verified afterward and had occurred over 23 years in many different hospitals and medical practices. Since Juul and colleagues' case ascertainment amounts to a retrospective chart review spanning 2 decades, a large degree of diagnostic uncertainty is likely. In contrast, in our case–control study, case-patients were enrolled concurrently over a short period and were included only when a diagnosis was made by using appropriate and recent methods.

Jan P. Vandenbroucke, MD, PhD
Frits R. Rosendaal, MD, PhD
Leiden University Medical Center
2300 RC Leiden, the Netherlands

References

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IN RESPONSE: As Dr. Murphy points out, the role of smoking in VTE is controversial. In our study, smoking overall was a risk factor for VTE (hazard ratio, 1.7 [95% CI, 1.2 to 2.2]) after adjustment for sex, factor V Leiden, body mass index, myocardial infarction, physical activity, estrogen-containing preparations, menopause, and year of study entry. Because smoking did not interact with factor V Leiden genotype or estrogen-containing preparations to affect risk for VTE, our data can suggest only additive effects of these 3 factors on VTE risk. However, because of limited statistical power, we are unable to provide accurate risk estimates for smoking as a risk factor for VTE within small subgroups such as factor V Leiden heterozygotes and homozygotes, and certainly not when these groups are further stratified for sex and use of estrogen-containing preparations. We agree with Drs. Vandenbroucke and Rosendaal that this does not mean that oral contraceptives do not play a role in VTE, since this association has been convincingly demonstrated in several previous studies.

We also agree with Drs. Vandenbroucke and Rosendaal that

most previous case–control studies have used more stringent diagnostic criteria for VTE than we were able to do. However, end point misclassification in the Copenhagen City Heart Study is unlikely to explain the difference in risk estimates: Assuming a diagnostic false-positive rate of 5 events per 10 000 person-years (that is, incorrectly diagnosed VTE) and a sensitivity of 0.6 (that is, only 60% of VTE cases diagnosed), the true hazard ratio for VTE in factor V Leiden heterozygotes versus noncarriers would be only 4.3.

There are many other examples in which genetic risk estimates are higher in case–control studies than in prospective studies of the general population. In a study of hospital case-patients with hereditary hemochromatosis, 83% were homozygous for Cys282Tyr of the *HFE* gene (1). However, when we screened patients in the Copenhagen City Heart Study and identified 23 Cys282Tyr homozygotes, all had biochemical signs of iron overload but none had hereditary hemochromatosis (2). The most likely explanation for such discrepancies is ascertainment bias, that is, the fact that hospital case-patients have a more severe phenotype than the average case-patient in the general population and often are selected particularly to identify genetic risk. Therefore, case–control studies will often overestimate disease risk due to genetic factors in the general population. Consequently, advice on genetic risk factors intended for the lay public should be based on results from prospective studies of the general population.

Klaus Juul, MD
Børge G. Nordestgaard, MD, DMSc
Herlev University Hospital
DK-2730 Herlev, Denmark

Anne Tybjærg-Hansen, MD, DMSc
Copenhagen University Hospital
DK-2100 Copenhagen, Denmark

References

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Excess Body Weight in Critically Ill Patients

TO THE EDITOR: In a secondary analysis of a randomized trial of ventilator management in patients with acute lung injury, O'Brien and colleagues (1) demonstrated that excess body weight was not independently associated with clinical outcomes. Lack of interaction between body mass index (BMI) and ventilator protocol assignment may indicate that the benefit of lower tidal volumes was similar for all patients. However, we have some doubts about whether BMI was calculated adequately. From the manuscript, it is unclear how weight was calculated or measured, although it mentions that there were adjustments for fluid balances. In our experience, it is extremely difficult to predict the body weight of critically ill patients. Most often, body weight is unknown and just a "good guess." Thus, we are not sure whether the BMI groups were adequately formed.

More important, though, is the question of whether treatment goals (6 mL/kg or 12 mL/kg of predicted body weight) were reached evenly in all patient groups. From one of the original publications by O'Brien and colleagues' group, we learned that tidal volumes varied (6.2 ± 0.9 mL/kg and 11.8 ± 0.8 mL/kg) (2). It would be interesting to see whether overweight or obese patients received different tidal volumes than patients with normal BMI when assigned to the conventional or lower tidal volume strategy.

Marcus J. Schultz, MD, PhD
Esther K. Wolthuis, MD
Academic Medical Center, University of Amsterdam
1105 AZ Amsterdam, the Netherlands

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IN RESPONSE: Drs. Schultz and Wolthuis raise questions about the technique for weight and BMI determination in our study. At study enrollment, study personnel recorded patient weights according to medical records. We presume that weight was most commonly recorded as a part of daily clinical care and that it was determined by using bed scales in the participating centers. Study personnel measured patient height to calculate predicted body weight and, subsequently, tidal volume. Although we acknowledge that the weight assessment was not subject to a rigorous protocol, we contend that any systematic measurement errors are unlikely. There is no reason to believe that such inaccuracies were associated with any particular BMI category. In addition, use of BMI as a continuous variable (and lack of an effect in this analysis) reduces the likelihood of unappreciated misclassification of BMI. We cannot account for the patients' weights and BMIs before whatever insult led to acute lung injury. Therefore, we cannot make statements about "healthy" obese persons and their prognoses should they succumb to such injury. Instead, we can only comment on the BMI at the time of study enrollment, which was within 48 hours of the onset of acute lung injury.

Drs. Schultz and Wolthuis also ask if study tidal volumes differed among the BMI categories. We appreciate the opportunity to clarify this point. We examined the mean tidal volume over study days 1 to 3, stratified for treatment assignment. Among those assigned to the lower tidal volume strategy, no significant difference in tidal volume was seen among the BMI categories (6.16 ± 0.71 mL/kg of predicted body weight in the normal BMI group, 6.19 ± 0.78 mL/kg in the overweight BMI group, and 6.18 ± 0.85 mL/kg in the obese BMI group; $P > 0.2$). Similarly, there was no significant difference among the BMI groups assigned to the conventional strategy (11.85 ± 0.72 mL/kg in the normal BMI group, 11.84 ± 0.73 mL/kg in the overweight BMI group, and 11.86 ± 0.66 mL/kg in the obese BMI group; $P > 0.2$). However, as mentioned in our article, tidal volume per predicted body weight was higher in obese patients than in patients with normal body weight before study enrollment. This suggests that clinicians were providing larger tidal volumes on the basis of actual weight rather than predicted weight. Such process disparities could explain recent

findings of an increased mortality risk among mechanically ventilated obese patients (1).

James M. O'Brien Jr., MD
Ohio State University
Columbus, OH 43210

Carolyn H. Welsh, MD
Denver Veterans Affairs Medical Center
Denver, CO 80220

Reference

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Update in Perioperative Medicine

TO THE EDITOR: In the 2004 Update in perioperative medicine (1), Smetana and colleagues reviewed the latest revision of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for perioperative cardiovascular evaluation before noncardiac surgery, which essentially confirm the earlier version. The ACC/AHA guidelines recommend using functional capacity based on the Duke Activity Status Index. These guidelines are at odds with those issued in an American College of Physicians (ACP) position paper, which stated that functional assessment "has not been shown to add to clinical risk index evaluation in the operative setting" (2). The ACP did not include functional assessment in its algorithm because the "Duke Activity Status Index has not been specifically tested in the perioperative setting, and it is not known whether formal evaluation of functional status adds risk information to that obtained from a clinical risk index" (3). These conflicting guidelines present a dilemma for the consulting internist, since functional assessment may involve additional recommendations regarding stress testing. Would the authors of the Update comment on these 2 sets of guidelines and indicate which one they recommend?

Paul Casner, MD, PhD
Texas Tech University Health Sciences Center
El Paso, TX 79905

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TO THE EDITOR: Smetana and colleagues (1) stated that extended-duration thromboprophylaxis should be used for patients undergoing high-risk orthopedic surgery and abdominal cancer surgery. Because of cost, our local transitional care facility will not accept a patient receiving low-molecular-weight heparin (usually enoxaparin). Given some evidence that low-molecular-weight heparin is superior to warfarin (2–5), how would the authors handle this situation? I'm not aware of any study comparing extended-duration warfarin with extended-duration low-molecular-weight heparin. I'm also not aware of any study that examines initial therapy with low-molecular-weight heparin followed by extended-duration warfarin therapy outside of the hospital setting.

Stephen A. Hilty, MD
San Luis Obispo, CA 93405

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IN RESPONSE: We thank Drs. Casner and Hilty for their thoughtful letters. Dr. Casner inquires about the value of functional assessment before surgery and the conflicting recommendations of 2 national guidelines. The ACP guideline was published in 1997. At that time, no studies correlated exercise capacity with perioperative outcomes. In 1999, Reilly and colleagues (1) tested the hypothesis that self-reported exercise capacity would predict postoperative complications. The authors defined good exercise capacity as the self-reported ability to walk 4 blocks and climb 2 flights of stairs. Among 600 consecutive patients undergoing major noncardiac surgery, cardiovascular complications (relative risk, 0.54; $P = 0.04$) and total serious complications (relative risk, 0.51; $P = 0.001$) were both significantly less common in patients with good exercise tolerance. There was a nonsignificant trend toward fewer pulmonary complications (relative risk, 0.70; $P > 0.2$).

In our recent Update, we cited a study by Girish and colleagues (2), which demonstrated that directly observed stair climbing was the strongest predictor of major cardiopulmonary complications after high-risk surgery and outperformed clinical variables (2). However, this test had modest sensitivity and specificity (71% and 77%, respectively) when good exercise capacity was defined as the ability to climb 4 flights of stairs. We believe that the literature now supports the use of functional capacity (either self-reported or directly observed) as an important component of preoperative risk stratification. It complements, but does not replace, existing cardiovascular risk indexes.

Regarding the question of extended-duration thromboprophylaxis posed by Dr. Hilty: while short-duration warfarin and enoxaparin are equally effective by 3 months after hospital discharge (3), few studies have evaluated the efficacy of extended-duration oral anticoagulants. Prandoni and colleagues (4) studied 360 patients undergo-

ing total hip arthroplasty and demonstrated superiority of extended-duration warfarin therapy (4 weeks after hospital discharge) compared with short-term prophylaxis (4). Venous thromboembolism rates were 5.1% and 0.5%, respectively (absolute difference, 4.57 percentage points [95% CI, 1.15 to 7.99 percentage points]). Samama and colleagues (5) compared extended prophylaxis using fixed-dose reviparin (a low-molecular-weight heparin) with adjusted-dose acenocoumarol in 1279 patients undergoing total hip replacement (5). The failure rate (the combination of symptomatic thromboembolism, major hemorrhage, or death) was 3.7% with low-molecular-weight heparin prophylaxis and 8.3% with oral anticoagulants ($P = 0.001$). Most of this difference was due to a higher bleeding rate among acenocoumarol-treated patients. On the basis of these limited data, extended-duration prophylaxis with warfarin may be inferior to low-molecular-weight heparin. Individual institutions must create policies on the cost-effectiveness of extended prophylaxis by examining actual local costs associated with medications and excess hospitalizations due to bleeding complications.

Gerald W. Smetana, MD
Beth Israel Deaconess Medical Center
Boston, MA 02215

Steven L. Cohn, MD
State University of New York Downstate
Brooklyn, NY 11203

Valerie A. Lawrence, MD
University of Texas
Health Sciences Center
San Antonio, TX 78229

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Occupational Exposure to Bloodborne Pathogens

TO THE EDITOR: The letter by Drs. Behrman and Allan (1) made many valuable suggestions for the efficient and effective evaluation of patients with occupational bloodborne pathogen exposure. We appreciate their suggestions on ways to minimize health care worker anxiety. One additional measure that we have found to be particularly useful is HIV rapid testing of source patients.

In our institutions, like most U.S. health care settings, most incidents of bloodborne pathogen exposure involve a source patient with unknown HIV status. This uncertainty leads to several psychological reactions, including anxiety, difficulty sleeping, guilt, pessimism about the future, and the desire to quit one's job (2), as well as unnecessary administration of postexposure prophylaxis antiretroviral medications in many instances. Rapid HIV testing allows health care workers to make timely and rational decisions regarding postexposure prophylaxis, yielding lower rates of unnecessary use (3) and lower overall cost of the bloodborne pathogen exposure program (4). It also offers some measure of psychological relief to the exposed health care worker (5). Three currently available U.S. Food and Drug Administration–approved rapid HIV tests are well suited for the postexposure setting: the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Inc., Bethlehem, Pennsylvania), the Reveal Rapid HIV-1 Antibody Test (MedMira Laboratories, Halifax, Nova Scotia, Canada), and Uni-Gold Recombigen HIV (Trinity Biotech, Bray, Ireland). Since we introduced HIV rapid testing of source patients using the OraQuick device, our exposed health care workers have benefited as expected: They receive unnecessary postexposure prophylaxis less frequently and report significantly less anxiety than they did before the rapid tests were in use.

Michael L. Landrum, MD
Robert J. O'Connell, MD
Wilford Hall Medical Center
Lackland Air Force Base, TX 78236

Gregory A. Deye, MD
Landstuhl Regional Medical Center
66849 Landstuhl/Kirchberg, Germany

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"Wait-and-See": An Alternative Approach to Managing Acute Hepatitis C with High-Dose Interferon-α Monotherapy

TO THE EDITOR: *Background:* The treatment of acute hepatitis C (that is, infection within 6 months of exposure) remains an open question. (Management of Hepatitis C: 2002, 10–12 June 2002, NIH Consensus 2 developmental meeting on hepatitis C). In a clinical trial by Jaeckel and colleagues (1), all acutely infected patients ($n = 45$) were treated empirically with interferon-α2b monotherapy for 6 months; 43 (98%) achieved a sustained virologic response. This is becoming the standard of care. Some treated patients (10% to 67%) would have achieved spontaneous virologic recovery (particularly if they were icteric [2–4]) and would not have needed interferon, which is costly and has adverse effects (5).

Objective: We tested a novel strategy for treating acute hepatitis C that would achieve a high virologic cure rate yet permit spontaneous responders to remain untreated.

Methods and Findings: From 1993 to 1997, we recruited 10 patients with acute hepatitis C. Each of the 10 patients had an index infection (**Table**). At the time of exposure, all patients tested negative for HCV RNA and were negative by a multiantigen enzyme immunoassay for anti–hepatitis C virus antibodies (6). All had baseline normal serum aminotransferase levels. None of the 10 patients had other causes for hepatitis. The risk factors for HCV infection in the 10 patients were needle stick ($n = 5$), 1-time intravenous drug use ($n = 1$), exposure to Gammagard (Baxter Healthcare Corp., Glendale, California) ($n = 2$), prisoner assault ($n = 1$), and nosocomial exposure ($n = 1$). The latter patient donated his own HCV-negative blood for surgery and developed postsurgery acute hepatitis C. No patients were excluded from this study, and all gave written informed consent. The University of California, Davis, Institutional Review Board approved this study.

Patients were monitored by anti–HCV antibody testing and by 2 tests for serum HCV RNA (week 6 and week 12 after exposure) using a reverse transcriptase polymerase chain reaction assay with a detection limit of 100 copies/mL. Seven patients had genotype 1 infection and 3 had genotype 2 or 3 infection. Four of the 6 symptomatic patients were icteric. Seroconversion developed at an average of 7 weeks, except for 1 patient who nevertheless had documented new-onset viremia at 6 weeks after needlestick. Three patients, 2 with genotype 1 infection, achieved spontaneous virologic eradication before the 12-week viral count. The sustained virologic response persisted over 2 years of follow-up.

In the remaining 7 patients, viremia persisted 12 weeks after exposure (**Table**). Six were treated with interferon-α2b 14 weeks after exposure. The patient with postsurgical nosocomial infection started treatment at week 20. Interferon-α2b therapy was commenced at 5 MU per day for an induction period of 12 weeks, followed by 3 MU three times per week for another 40 weeks. All patients receiving therapy became HCV RNA negative within 6 weeks and achieved 100% sustained virologic response at 6, 12, and 24 months after completion of therapy (**Table**).

Conclusion: Our findings support a wait-and-see approach to identify patients with spontaneous remission. This research letter provides a strategy to avoid treating those with an ability for self-cure yet retain a high level of success for those who are treated. However, treatment should not be delayed because the patient's immune response is heightened by the transient activation of HCV-specific $CD4^+$ and $CD8^+$ lymphocytes during the peak of acute hepatitis (7). Early treatment may minimize the diversity of quasispecies. Daily induction prevents between-dose viral rebound that may translate into higher sustained virologic response (8, 9). Future clinical trials for acute hepatitis C may involve the use of pegylated interferon monotherapy (10) or combination therapy with ribavirin. Six months of therapy may be sufficient.

Neville R. Pimstone, MD, PhD
Daniel Pimstone, BSc
Theparat Saicheur, DVM, PhD
Jerry Powell, MD
University of California, Davis, Medical Center
Sacramento, CA 95817

Table. **Characteristics and Outcomes of Patients with Acute Hepatitis C***

Patients	Sex	Age, *y*	Risk Factors	HCV RNA Level at 6 wk, *copies/ML*	HCV RNA Level at 12 wk, *copies/mL*	Clinical Findings	Outcome
1	Male	32	Prisoner assault	753 000	<100	Symptomatic/icteric; peak ALT level, 3000 IU/L	Spontaneous resolution
2	Female	58	Needlestick	370 000	280 000†	Symptomatic/icteric; peak ALT level, 1200 IU/L	SVR at 2 y
3	Male	41	Needlestick	700 000	604 000†	Asymptomatic/anicteric; peak ALT level, 66 IU/L	SVR at 2 y
4	Female	42	Needlestick	320 000	975 000†	Symptomatic/icteric; peak ALT level, 2100 IU/L	SVR at 2 y
5	Male	40	Needlestick	1 200 000	<100	Symptomatic/icteric; peak ALT level, 172 IU/L	Spontaneous resolution
6	Female	48	Needlestick	440 000	<100	Symptomatic/icteric; peak ALT level, 800 IU/L	Spontaneous resolution
7	Female	32	Gammagard exposure	550 000	996 000†	Asymptomatic/anicteric; peak ALT level, 175 IU/L	SVR at 2 y
8	Female	42	Gammagard exposure	540 000	476 000†	Asymptomatic/anicteric; peak ALT level, 73 IU/L	SVR at 2 y
9	Male	40	Nosocomial exposure	760 000	555 000†	Symptomatic/icteric; peak ALT level, 640 IU/L	SVR at 2 y
10	Female	31	Intravenous drug use	376 000	719 000†	Asymptomatic/anicteric; peak ALT level, 545 IU/L	SVR at 2 y

* ALT = alanine aminotransferase; HCV = hepatitis C virus; SVR = sustained virologic response.
† These patients received interferon-α2b therapy for 1 year as per protocol.

Andy S. Yu, MD
Stanford University Medical Center
Stanford, CA 94305

Note: This study was presented in part at the Digestive Disease Week 2000 meeting, San Diego, California, 20–24 May 2000, and at the International Association for the Study of the Liver—Asian Pacific Association for the Study of the Liver joint meeting, Fukuoka, Japan, 2–7 June 2000.

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