

TO THE EDITOR: The study by McMahon and colleagues (1) showed the association between previous use of macrolide antibiotics and resistance of Helicobacter pylori to clarithromycin and metronidazole. Besides past antibiotic use, clinicians should also consider other risk factors, such as geographic location, age, ethnicity, and ulcer status. In the Surveillance of H. pylori Antimicrobial Resistance Partnership (SHARP) study (2), many risk factors were found to be associated with resistance to individual agents. Clarithromycin resistance was significantly associated with older age, female sex, and geographic region, and the highest resistance rates, 13.9% and 13.0%, occurred in the mid-Atlantic and northern regions of the United States, respectively. In the multivariable model, metronidazole resistance was significantly associated with Asian ethnicity and female sex. Metronidazole resistance rates were 50% in women younger than 40 years of age, compared with 47% in women at least 40 years of age, 32.4% in men younger than 40 years of age, and 30.7% in men at least 40 years of age. Dual resistance to clarithromycin and metronidazole was significantly associated with female sex, older age, and ethnicity; Asians had the highest rate of dual resistance (8%).

Lifestyle may also influence the extent of H. pylori infection and subsequent treatment. A study conducted in Germany (3) suggested that alcohol consumption protected against active H. pylori infection. Prevalence of infection decreased significantly among people who drank more than 75 g of ethanol per week compared with nondrinkers. Alcoholic beverages stimulate acid secretions and gastric release and thus may affect lining conditions of H. pylori in the stomach. Wine also has strong antibacterial activity. However, the German study found that infection was considerably higher (20%) among persons who drank 3 or more cups of coffee per day. In addition, infection rates were slightly higher among former smokers (25%) and current smokers (22%) than among those who had never smoked (18%).

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References

IN RESPONSE: We agree that the SHARP study (1) was useful for establishing the prevalence of antimicrobial resistance among H. pylori in the United States. However, the SHARP analysis did not include the most important determinant of antimicrobial resistance: an individual’s antimicrobial use. Therefore, we believe the factors associated with antimicrobial-resistant H. pylori in the SHARP study are useful for hypothesis generation, but their value for clinical decision making is highly suspect. The factors cited by Drs. Seow and Chew are likely to be markers for patients with higher antimicrobial use. For example, the higher frequency of metronidazole-resistant H. pylori infection among women is explained in our study by higher rates of metronidazole use. In addition, it is unclear how to apply Drs. Seow and Chew’s recommendation of using multiple risk factors to assess the risk for antimicrobial-resistant infection when those risk factors are contradictory, as would be the case for a person of low-risk ethnicity living in a high-risk geographic region. We believe that until antimicrobial susceptibility testing becomes more readily available for clinical use, past antimicrobial use will remain the simplest and most reliable means of assessing the risk for metronidazole- or clarithromycin-resistant H. pylori.

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Reference

Use of Angiotensin-Converting Enzyme Inhibitors in Heart Failure and Renal Insufficiency

TO THE EDITOR: We agree with Shlipak (1) that it is difficult to determine the efficacy of angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure and renal insufficiency on the basis of subgroup analysis of data from randomized, controlled trials of ACE inhibitors in heart failure. However, data from retrospective follow-up studies suggest that ACE inhibitors are equally or more beneficial in patients with heart failure and renal insufficiency (2–4). Our group has demonstrated that use of ACE inhibitors was associated with lower 1-year mortality rates in patients with heart failure and perceived contraindications to ACE inhibitors (adjusted hazard ratio, 0.34 [95% CI, 0.14 to 0.81]). Renal insufficiency (serum creatinine concentration ≥221 μmol/L [≥2.5 mg/dL]) was the most common condition perceived as a contraindication (56%). In patients with acute myocardial infarction and left ventricular systolic dysfunction who also had renal insufficiency (serum creatinine concentration ≥265 μmol/L [≥3 mg/dL]), use of ACE inhibitors was associated with lower 1-year mortality rates (adjusted hazard ratio, 0.63 [CI, 0.48 to 0.84]) (3). In another study, in patients with heart failure who were treated with ACE inhibitors, the odds for 6-month mortality were similar for those with normal renal function (adjusted odds ratio, 0.75 [CI, 0.50 to 1.13]) and those with renal insufficiency (serum creatinine concentration ≥177 μmol/L [≥2 mg/dL]) (adjusted odds ratio, 0.90 [CI, 0.43 to 1.82]) (4). These data are consistent with Shlipak’s conclusion (1) and with the American Col-

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College of Cardiology/American Heart Association guidelines regarding the use of ACE inhibitors in patients with heart failure and renal insufficiency (5).

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Grant Support: Dr. Ahmed is supported by a National Institute of Health Mentored Patient-Oriented Research Career Development Award (1-K23-AG19211-01).

References

IN RESPONSE: I appreciate Dr. Ahmed’s comments, and I agree that ACE inhibitors are likely to be beneficial in patients with systolic heart failure and renal insufficiency. The observational studies that demonstrate ACE inhibitor effectiveness in this setting are reassuring (1–3). However, subgroup analyses from randomized clinical trials of ACE inhibitors would add valuable and more definitive evidence to support the use of these agents in these patients.

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References

Patient Safety and Medical Malpractice

TO THE EDITOR: Brennan and Mello (1) presented a malpractice case that is all too typical of those occurring today. They were concerned that the need to prove negligence has been blurred and that juries are determining awards on the basis of injury severity rather than the presence of negligence.

A short section titled “A New Paradigm” mentioned a “no-fault” patient compensation program that would eliminate the prosecution of physicians and hospitals if a patient is injured while interfacing with the health care industry.

An entire issue should have been devoted to this subject. Most physicians are practicing defensive medicine and feel as if they live in a polarized world. This increases the cost of care and may subject patients to even more risk as practitioners perform more tests to be sure of their diagnoses.

The “new paradigm” described by Brennan and Mello would be evolutionary. It would create a mutual relationship among patients, hospitals, and physicians. We would no longer feel besieged by a system that seeks to prosecute us when no actual crime has been committed. We would have shown only that we cannot practice zero-defect medicine.

We want to partner with our patients again, and the current highly charged polarized environment would no longer exist.

I feel that this type of change will occur only through a ballot initiative, with the physicians leading the charge. Our state and federal legislatures are top-heavy with attorneys who are easily influenced by the attorneys’ lobby, which wishes to protect the “sacred cow” of torts. Our law was developed in the Middle Ages. It has stopped serving us.

The American College of Physicians should develop an implementation plan that most states would accept and that would replace the current system. We should be leading the way. We know better than most how important such a plan would be for improved patient relationships and cost containment.

A superfund should be developed that would pay injured parties or their families immediately through a fixed and nonmodifiable multi-tiered structure. This fund could be administered through for-profit corporations. All parties who receive profits from the system, including medical insurance companies and patients, would pay into it. Drug companies would also have to pay a share for adverse drug reactions.

We would certainly need a central databank that would allow us to assign responsibility to various parties. Also, data on individual physicians and institutions would have to be published, as would information on adverse outcomes, along with their causes, and remedies. Patients would still be able to confront their physician or institutional representative in a public forum.

Independent boards would be maintained in all counties. Board members would be called upon to advocated for patients. They would be appointed or elected and could include attorneys.

Again, all providers and institutions would be exempt from prosecution if a patient outcome should be associated with injury.

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Reference
IN RESPONSE: Dr. Gale’s proposal for an injured patient superfund is an interesting concept and one that deserves further exploration.

The College is aggressively pushing for changes to the U.S. medical tort system. We are examining options such as a no-fault system, alternative dispute resolution, and enterprise liability.

Currently, we are primarily concerned with reforming the tort system by capping noneconomic damage awards (that is, awards for pain and suffering) at $250,000. Such a cap has already been successfully tested in California. A recent study by economist Kenneth Thorpe titled “The Medical Malpractice ‘Crisis’: Recent Trends and the Impact of State Tort Reforms,” which was published in Health Affairs (1), clearly demonstrated this fact. Mr. Thorpe’s sweeping examination of past state tort reform efforts showed that the $250,000 cap is the most effective way to reduce rates of professional liability insurance premiums.

Given the multitude of financial pressures faced by physicians, and the need for immediate relief from high professional liability insurance premiums, we believe pursuing the $250,000 cap offers the best path to follow for the College.

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Reference

Practice Guidelines for Chronic Kidney Disease

TO THE EDITOR: Screening for microalbuminuria is clearly recommended, especially for diabetes, by the American Diabetes Association, the new guidelines from the Seventh Joint National Commission on Health Care, and the European Society of Hypertension (1). Levey and colleagues (2) reported the National Kidney Foundation guidelines for chronic kidney disease. The problem with these guidelines regarding microalbuminuria is the initial step where an albumin–creatinine ratio can indicate that an intervention has been effective (4, 5).

Follow-up and confirmation are clearly important because there may be other reasons for increased albumin–creatinine ratio, especially urinary tract infection and other infections. Heavy physical exercise and vaginal discharge can also increase albumin–creatinine ratio, but such cases are rather rare. Patients should be informed about renal disease in diabetes. Better glycemic control is certainly indicated and may reverse microalbuminuria, as shown in recent studies (3).

I also propose, besides better metabolic control, that the renin–angiotensin system should be blocked with appropriate doses (not too low) of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. For example, it has been shown that 1.25 mg of ramipril is not effective (type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril [DIABHYCAR] Study) contrast in range to 10 mg (Heart Outcomes Prevention Evaluation [HOPE] Study) (3).

Clinical proteinuria (detected by using a dipstick test) is usually indicated by an albumin–creatinine (A–C) ratio of >300 mg/g. For microalbuminuria, A–C ratio is 30–300 mg/g; for normoalbuminuria, A–C ratio is <30 mg/g; RAS = renin–angiotensin system. * Patients who have negative results on Albustix reagent strips (Bayer Diagnostics, Tarrytown, New York) or similar tests should always be screened for microalbuminuria.

Figure. Search strategy to detect patients with early renal disease, especially early diabetic nephropathy.

Clinical proteinuria (detected by using a dipstick test) is usually indicated by an albumin–creatinine (A–C) ratio of >300 mg/g. For microalbuminuria, A–C ratio is 30–300 mg/g; for normoalbuminuria, A–C ratio is <30 mg/g; RAS = renin–angiotensin system. * Patients who have negative results on Albustix reagent strips (Bayer Diagnostics, Tarrytown, New York) or similar tests should always be screened for microalbuminuria.

4. Yuyun MF, Dinneen SF, Edwards OM, Wood E, Wareham NJ. Absolute level and rate of change of albuminuria over 1 year independently predict mortality and cardio-
Many studies, including one appearing in the same issue of Annals Renal Disease Study, indicate that nitrogen clearances appear to equal the Modification of Diet in Renal Disease (MDRD) formula sound clinical practice. This is misleading. TO THE EDITOR: The clinical guidelines published by the Kidney Disease Outcomes Quality Initiative (KDQI) Work Group on Chronic Kidney Disease (1) allow physicians to assess their patients’ risk for chronic kidney disease. In particular, prediction equations for glomerular filtration rate (GFR) are easy to use and extremely helpful for disease stratification. Beyond these equations, however, the Work Group recommends the use of 24-hour urine collections for the estimation of GFR only under special clinical circumstances. That and the A rating given in Table 1 to avoiding 24-hour creatinine clearances to estimate GFR seem to imply that the routine use of timed urine collections does not constitute sound clinical practice. This is misleading.

For example, the average of 24-hour urinary creatinine and urea nitrogen clearances appears to equal the Modification of Diet in Renal Disease Study’s equation in accuracy (2). It has been used in many studies, including one appearing in the same issue of Annals as the National Kidney Foundation guidelines (3). Obtaining a 24-hour urine sample does not only allow secondary confirmation of GFR; urea nitrogen clearances also provide important additional information regarding daily dietary protein intake, given that malnutrition frequently accompanies chronic kidney disease.

Supplementary to GFR prediction equations, 24-hour urine creatinine and urea nitrogen collections give the practitioner added tools in the evaluation and management of chronic kidney disease.

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References

IN RESPONSE: Many of the points raised by Drs. Mogensen and Korosi are discussed in the full version of the guidelines (1). Page numbers cited below refer to pages in that publication.

Dr. Mogensen agrees with the recommendation to test patients at increased risk for chronic kidney disease for "microalbuminuria" in a spot urine sample. However, he suggests measuring the albumin-to-creatinine ratio rather than an albumin-specific dipstick, as depicted in Figure 2 of our article in Annals. We agree that that testing could begin with measurement of albumin-to-creatinine ratio (page S215), as discussed in a more recent consensus conference sponsored by the National Kidney Foundation and the National Institute of Diabetes and Digestive and Kidney Diseases (2). The gold standard method for detection of microalbuminuria is based on immunoassay in a timed urine collection. Sensitivity of detection of microalbuminuria using an albumin-specific dipstick or an albumin-to-creatinine ratio in spot urine samples is 80% to 90% (pages S97–S98). The guidelines also recommend periodic reevaluation of patients with negative test results using either method.

Currently available methods are sensitive enough to detect urine albumin concentrations just above the normal range (Table 3). Ultimately, many factors, including cost, influence the decision about whether testing should begin with a dipstick in the physician’s office or with a laboratory test. Clinicians must also be attentive to common causes of false-positive and false-negative results (page S99). A recent report demonstrated limited sensitivity of an immunoassay compared with high-performance liquid chromatography (4). More studies are needed to determine the appropriate reference range and clinical importance of albuminuria detected by high-performance liquid chromatography.

Dr. Korosi agrees with the recommendation to estimate GFR.

Table. Methods for the Detection of Microalbuminuria

<table>
<thead>
<tr>
<th>Method (Manufacturer)</th>
<th>Type of Analysis</th>
<th>Detection Limit, mg/L</th>
<th>Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multistix PRO test strips (Bayer Corp.)</td>
<td>Semi-quantitative; reagent strip test</td>
<td>80–150</td>
<td>Dye binding; at a constant pH, albumin causes a sulphophenalein dye impregnated in the pad to change color</td>
</tr>
<tr>
<td>CLINITEST microalbumin test strips (Bayer Corp.)</td>
<td>Semi-quantitative; reagent strip test; requires CLINITEST instrument</td>
<td>20–40</td>
<td>Same principle as Multistix PRO Test Strips; however, detection limit differs</td>
</tr>
<tr>
<td>Micral test strips (Roche Diagnostics)</td>
<td>Semi-quantitative; reagent strip test</td>
<td>15–20</td>
<td>Immunochemical; albumin binds with gold-labeled monoclonal antibody; albumin–antibody complexes migrate to dye-impregnated detection pad; intensity of color increases with albumin concentration</td>
</tr>
<tr>
<td>ImmunoDip (Diagnostic Chemicals Ltd.)</td>
<td>Semi-quantitative; modified reagent strip</td>
<td>12–18</td>
<td>Immunochemical; comparison of 2 blue-colored bands; albumin complexed with antibody (albumin–antibody) migrates to top band; intensity of top band increases with albumin concentration</td>
</tr>
<tr>
<td>Immunoturbidimetry</td>
<td>Quantitative</td>
<td>5–8</td>
<td>Immunochemical; albumin–antibody complexes decrease light transmission through sample</td>
</tr>
<tr>
<td>Nepleomter</td>
<td>Quantitative</td>
<td>0.5–1.0</td>
<td>Immunochemical; albumin–antibody complexes scatter light</td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>Quantitative</td>
<td>0.1–0.3</td>
<td>Immunochemical; radionabeled albumin competes with sample albumin for a limited amount of antibody</td>
</tr>
<tr>
<td>Radial immunodiffusion</td>
<td>Quantitative</td>
<td>~6</td>
<td>Immunochemical; antibody present in the middle forms precipitin rings with albumin from the sample; diameter of ring is proportional to the albumin concentration</td>
</tr>
</tbody>
</table>
from serum creatinine measurements using prediction equations but also advocates collection of 24-hour urine samples for confirmation of GFR and estimation of dietary protein intake. Estimating GFR from the mean of the 24-hour urea and creatinine clearance has been validated only in individuals with GFRs less than approximately 15 mL/min per 1.73 m² (5). Studies in patients with higher GFRs show that 24-hour creatinine clearance does not provide a more accurate estimate of GFR than the Modification of Diet in Renal Disease Study prediction equation. Thus, the guidelines do not recommend routine collection of a 24-hour urine sample to confirm the estimate of GFR in routine practice. In subspecialty practice, a 24-hour urine sample can be useful to confirm GFR estimates lower than 15 mL/min per 1.73 m² and to estimate dietary protein intake (pages S89–S90). Other indications for clearance measurements to estimate GFR (S90) and recommended filtration markers (S77) are discussed in the guidelines.

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References

**Table. Success Rate and Mean Discomfort for Blood Collection with the Butterfly Device and the Conventional Needle**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Venipunctures, n</th>
<th>Success Rate (% CI), %*</th>
<th>P Value†</th>
<th>Mean Score for Discomfort on the Visual Analogue Scale (95% CI)‡</th>
<th>P Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood collection device</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butterfly</td>
<td>539</td>
<td>98.3 (96.7–99.2)</td>
<td>0.01</td>
<td>1.3 (1.2–1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Needle</td>
<td>564</td>
<td>96.8 (94.2–98.3)</td>
<td></td>
<td>1.9 (1.7–2.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Location of venipuncture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial wrist</td>
<td>18</td>
<td>94.6 (81.1–98.6)</td>
<td>&gt;0.2</td>
<td>2.5 (1.9–3.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Forearm</td>
<td>100</td>
<td>98.4 (95.8–99.4)</td>
<td></td>
<td>1.7 (1.4–2.0)</td>
<td></td>
</tr>
<tr>
<td>Back of the hand</td>
<td>99</td>
<td>98.3 (95.8–99.3)</td>
<td></td>
<td>2.0 (1.7–2.3)</td>
<td></td>
</tr>
<tr>
<td>Antecubital fossa</td>
<td>886</td>
<td>98.2 (96.8–99.0)</td>
<td></td>
<td>1.5 (1.4–1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Subjective evaluation of veins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>396</td>
<td>99.5 (98.7–99.8)</td>
<td>&lt;0.001</td>
<td>1.3 (1.2–1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>466</td>
<td>97.1 (95.0–98.3)</td>
<td></td>
<td>1.6 (1.5–1.7)</td>
<td></td>
</tr>
<tr>
<td>Bad</td>
<td>241</td>
<td>84.8 (76.7–90.5)</td>
<td></td>
<td>2.0 (1.8–2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood tubes collected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 tube</td>
<td>447</td>
<td>97.8 (95.4–98.9)</td>
<td>&gt;0.2</td>
<td>1.5 (1.4–1.7)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>&gt;1 tube</td>
<td>656</td>
<td>97.7 (95.7–98.8)</td>
<td></td>
<td>1.6 (1.5–1.8)</td>
<td></td>
</tr>
</tbody>
</table>

* Estimated probabilities from logistic regression model with terms for blood collection device, location of venipuncture, subjective evaluation, number of blood tubes collected, and phlebotomist.
† From logistic regression.
‡ Least-squares means from a general linear mixed model with terms for blood collection device, location of venipuncture, subjective evaluation, number of blood tubes collected, and phlebotomist.
§ From a general linear mixed model.
TO THE EDITOR:

Pulmonary embolism is one of the leading causes of morbidity and death in the United States, with a purported 500,000 to 600,000 cases and an estimated 50,000 to 100,000 deaths occurring per year (1). The currently accepted diagnostic algorithm is integrated and includes a methodical history and physical examination supplemented by selective laboratory and radiologic testing with chest radiography; ventilation–perfusion scanning; helical computer tomography (CT); and the current gold stan-

Editor’s Note: The lead author of the following Clinical Observation was one of a dozen Associates of the American College of Physicians selected to present a clinical vignette at the 2002 Annual Session in Philadelphia. We are proud to present this case report through a special arrangement with the Council of Associates of the College.

A Novel Diagnostic Method for Acute Pulmonary Embolism: Technetium-99m Apocitide Scintigraphy

TO THE EDITOR: Background: Pulmonary embolism is one of the leading causes of morbidity and death in the United States, with a purported 500,000 to 600,000 cases and an estimated 50,000 to 200,000 deaths occurring per year (1). The currently accepted diagnostic algorithm is integrated and includes a methodical history and physical examination supplemented by selective laboratory and radiologic testing with chest radiography; ventilation–perfusion scanning; helical computer tomography (CT); and the current gold stan-
Figure 1. Transaxial, sagittal, and coronal perfusion images on single-photon emission computed tomography of lungs showing a marked perfusion defect within the superior segment and lateral basal segment of the left lower lobe.
scintigraphy. This confirmed that the patient probably formed acute thrombus within regions of chronic thrombus.

Historically, angiography and ventilation–perfusion scintigraphy were the 2 primary radiologic tests available to accurately detect pulmonary embolism, although the diagnostic value of ventilation–perfusion scanning was controversial. In 1990, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) solidified the scan’s utility as a valid and reliable method for diagnostic imaging (6). Soon thereafter, helical CT was added to the diagnostic algorithm. Recent literature has confirmed its accuracy and suggests that it excludes clinically significant pulmonary embolism, although it may miss small, isolated, subsegmental clots (7). Of importance, helical CT also often provides an alternative diagnosis when venous thromboembolism is not seen (7). Although helical CT is less invasive than angiography, the potential risk from contrast allergy still limits its use in certain populations. Also, it is an anatomically based imaging protocol and therefore may not be able to distinguish acute thrombus from chronic thrombus.

Apcitide is a synthetic peptide, chemically labeled to technetium-99m, that binds to glycoprotein IIb/IIIa receptors on activated platelets. Glycoprotein receptors are all cross-linked by platelets in thromboembolism and are unavailable for binding; therefore, technetium-99m apcitide will not highlight chronic emboli. This method was originally designed to target and detect DVT in the lower extremities. One major multicenter clinical trial, enrolling 280 patients, directly compared technetium-99m apcitide scintigraphy with contrast venography. In a subset analysis of 63 patients who presented within 3 days of onset of signs and symptoms of acute DVT, technetium-99m apcitide had a sensitivity of 90.6%, a specificity of 83.9%, a positive likelihood ratio of 5.63, and a negative likelihood ratio of 0.112 (1). The authors concluded that this technology is best suited for patients presenting with acute signs and symptoms of DVT. Another study involving the same lead author had previously compared technetium-99m apcitide with contrast venography in 39 patients and found that when technetium-99m apcitide scintigraphic images captured at 10, 60, and 120 minutes after injection were analyzed, the test had a sensitivity of 86.4%, a specificity of 88.3%, a positive likelihood ratio of 7.38, and a negative likelihood ratio of 0.154. The researchers concluded that combining early (approximately 10 to 20 minutes) and delayed (3 hours) imaging provided the best results (8).

Although technetium-99m apcitide has been shown to be a relatively accurate imaging method for DVT, no studies have examined its use for diagnosis of pulmonary embolism. In fact, to our knowledge, this is the first case in which it assisted in the evaluation of suspected pulmonary embolism. This new technology has 2 principal advantages. First, it highlights only acute emboli, and second, it does not have the nephrotoxic or allergic risks of intravenous contrast dye. It would probably fit into the diagnostic algorithm for pulmonary embolism in the following clinical situations. First, in patients with recurrent pulmonary embolism, it would enable clinicians to distinguish acute emboli from chronic emboli. Second, it would offer an alternative method of rapid diagnosis in patients with acute renal failure or contrast allergies who have intermediate to high pretest probabilities of pulmonary embolism and abnormal results on chest radiography. In this context, we believe that technetium-99m apcitide deserves further prospective evaluation.

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References
7. van Strijen MJ, de Monye W, Schareck J, Kieft GJ, Prins MH, Huisman MV, et al. Single-detector helical computed tomography as the primary diagnostic test in sus-


**Correction**

**Correction: Update in Infectious Diseases**

The Update in Infectious Diseases by Sande and Ronald (1) stated that “95% of SARS [severe acute respiratory syndrome] cases in Taiwan occurred among health care workers.” According to the summary published on the World Health Organization Web site (2), the correct figure is 20%.

**References**


Successful Treatment of Sarcoidosis

TO THE EDITOR: Ocular inflammation is a prominent manifestation of several autoimmune diseases. Although anti–tumor necrosis factor (TNF) therapy has been successfully used to treat uveitis associated with the HLA-B27 gene, the Behçet syndrome (1), and refractory idiopathic uveitis (2), its effect in sarcoid uveitis is unknown. We describe successful treatment using intravenous infliximab, a human–murine chimeric monoclonal antibody directed against TNF in a patient with sarcoid-related uveitis.

The patient presented with anterior uveitis, Bell palsy, and low-grade fever. Sarcoidosis was diagnosed on the basis of stage 1 bilateral hilar lymphadenopathy and an elevated angiotensin-converting enzyme level. Ocular examination revealed 2+ cells, 3+ flare with keratic precipitates and early posterior synechiae. His vision declined from normal to 20/50. Vision loss persisted despite weekly treatment with methotrexate and prednisone for 3 months. Because of the intolerable side effects of corticosteroids, the patient was given infliximab, 5 mg/kg of body weight, as a steroid-sparing agent. Within 2 weeks, the patient’s vision had improved dramatically to 20/25, and ocular inflammatory infiltrate had resolved. The patient continues to receive infliximab every 2 months and remains symptom-free with 20/20 vision at 6 months. His oral methotrexate dose has been reduced to 15 mg weekly, and his treatment with oral corticosteroids has been discontinued.

Infliximab was an attractive therapeutic option for several reasons. First, intravenous infusion provides high levels of bioavailable drug in the context of vision loss. Second, it has been successfully used in other granulomatous diseases, such as Crohn colitis. Third, previous beneficial use in patients with systemic sarcoidosis (3) has been documented. Nevertheless, the therapeutic benefit of inhibiting TNF may not be a class effect. A recent study (4) demonstrated excessive treatment failures in patients with stage 2 or 3 pulmonary sarcoid who were given soluble TNF receptor antagonist (etanercept). Experimental autoimmune uveitis models in animals have suggested a role for TNF-α in the pathogenesis of uveitis. Neutralization of this molecule has been shown to suppress the induction of experimental autoimmune uveitis, possibly by inhibiting antigen priming (5). Our patient’s remarkable response to this drug also suggests that TNF may be important in the pathogenesis of ocular sarcoidosis.

We believe that the successful treatment of sarcoid-related uveitis with infliximab is an important observation. This drug should be considered in patients who do not respond to traditional anti-inflammatory medications.

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References

Clinical Implications of Genetic Polymorphism of CYP2D6 in Mexican Americans

TO THE EDITOR: Background: Mexican Americans make up 66% of U.S. Hispanics, the country’s largest ethnic minority group (1). Few studies report antidepressant treatment in this population, and they have conflicting results (Table).

Objective: To perform an 8-week, prospective, double-blind trial investigating the pharmacogenetics of antidepressant response to desipramine or fluoxetine.

Results: We describe 2 Mexican-American women homozygous for CYP2D6*4 with resultant toxic levels of desipramine and severe adverse drug reactions at minimal doses.

Case Reports: JR and IA are Mexican-American women age 59 and 31 years who received a diagnosis of recurrent major depression. IA had a history of severe adverse drug reactions after paroxetine treatment. They began blinded treatment with desipramine, 50 mg/d. Both patients had orthostatic hypotension, which is a transient and common adverse drug reaction to desipramine. The dose was increased to 100 mg/d after 1 week, according to protocol.

IA returned the following week with worsened anxiety and physical symptoms including palpitations, hyperventilation, and myalgias. Electrocardiogram confirmed sinus tachycardia. Her desipramine level was 544.33 nmol/L (therapeutic range, 375.4 to 938.5 nmol/L). Medication frequency was decreased to every other day. One week later, she had a desipramine level of 1358.9 nmol/L and persistent tachycardia requiring discontinuation of therapy with the medication. She reported improved sleep and decreased somatic symptoms. The following week, she continued to have tachycardia (desipramine level, 345.37 nmol/L).

JR’s depression improved after initial treatment, but adverse drug reactions (including blurry vision) continued to worsen. Drug level after 2-week treatment (100 mg/d) was 2545.14 nmol/L. Therapy with the medication was discontinued, and cardiac function normalized. After a week without the drug, desipramine levels were undetectable. Severity and frequency of somatic and depressive symptoms increased, and desipramine was restarted at 10 mg/d. The dosage was titrated to 25 mg/d over 1 month to result in a serum level of 397.91 nmol/L. JR’s mood and adverse drug reactions greatly improved.

Discussion: CYP2D6 metabolizes 50% of the 100 best-selling drugs, including antidepressants such as fluoxetine and desipramine. The CYP2D6 gene has been shown to have at least 70 alleles, with more than 20 of these changing the metabolism of its substrates (http://medicine.iupui.edu/flockhart/). This is reflected in divergent rates of drug metabolism among individuals and ethnic groups.

References
1. Lichtenstein CA, Marder SR, Takahashi M, Nelson BR, Johnson JA, Wu HS. Genetic polymorphisms of CYP2D6 and risperidone metabolism: a pharmacogenetic study in more than 20 of these changing the metabolism of its substrates (http://medicine.iupui.edu/flockhart/). This is reflected in divergent rates of drug metabolism among individuals and ethnic groups.

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Five percent to 10% of white persons and 1% of Asians are poor CYP2D6 (5) metabolizers. Mendoza and colleagues (6) found that 4 of 349 Mexican-American persons (1%) were homozygous for the CYP2D6*4 allele responsible for poor drug metabolism.

An estimated 30,000 to 100,000 patients have died in hospitals from adverse reactions to properly administered, U.S. Food and Drug Administration–approved medications (7). Medical care of persons with atypical CYP2D6 metabolism is thought to cost an average of $5000 more per year compared to normal CYP2D6 metabolizers, presumably because of increased rates of adverse drug reactions (8). Our patients had been receiving small doses of the medication for 2 weeks in the context of a highly structured clinical research program when they developed severe adverse drug reactions. This allowed us to stop treatment immediately and rapidly individualize it, interventions that would have been unlikely to have happened in a general outpatient clinic where patients are seldom seen weekly. A key point to consider is the importance of carefully assessing patients for adverse drug reactions. In Hispanic women, depressive symptoms frequently present as somatic symptoms (9). These symptoms may include fatigue, headaches, backaches, insomnia, and loss of appetite. Therefore, a detailed history and physical examination and close follow-up visits, especially when therapy with a new medication is started, are essential.

**Conclusions:** Adverse drug reactions in Hispanics may be misattributed to cultural factors, when they may be due to genetic background. CYP2D6 genotyping can be done rapidly and reliably and is of considerable public health relevance because it can reduce the rate and severity of adverse drug reactions. Such genotyping should be performed routinely because genotyping costs offset medical costs related to atypical gene variants that affect pharmacokinetic pathways.

**Table. Studies on U.S. Hispanics with Antidepressants Metabolized by CYP2D6**

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Hispanic Subtype</th>
<th>Participants, n</th>
<th>Medication Used</th>
<th>Method of Study</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcos and Cancro, 1982 (2)</td>
<td>MDD Puerto Rican Female</td>
<td>41</td>
<td>Tricyclics</td>
<td>Retrospective review of medical records; no drug levels</td>
<td>Puerto Rican women require half the tricyclic dose compared to white persons for full recovery</td>
</tr>
<tr>
<td>Gaviria et al., 1986 (3)</td>
<td>Nondepressed Mexican American Male</td>
<td>10</td>
<td>Nortriptyline</td>
<td>Single dose of medication; drug levels and pharmacokinetic data collected</td>
<td>No major differences in pharmacokinetics of Hispanics vs. white persons</td>
</tr>
<tr>
<td>Alonso et al., 1997 (4) [Letter]</td>
<td>MDD Mexican American Female</td>
<td>13</td>
<td>Paroxetine or fluoxetine</td>
<td>Prospective, open-label treatment; no drug levels</td>
<td>No difference in treatment response or side effects between Hispanics and white persons</td>
</tr>
</tbody>
</table>

* MDD = major depressive disorder.

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**References**