Screening for Abdominal Aortic Aneurysms

TO THE EDITOR: The U.S. Preventive Services Task Force (USPSTF) recommended screening for abdominal aortic aneurysms (AAAs) with ultrasonography only in male smokers 65 to 75 years of age. Other subsets were excluded in part because of “good evidence that screening and early treatment result in important harms, including an increased number of surgeries with associated morbidity and mortality, and psychological harms” (1). I question the evidence regarding harms.

First, the companion review on this topic by Fleming and colleagues (2) concluded that “screening does not appear to be associated with significant physical or psychological harms.” Second, the harm related to morbidity and mortality of “unnecessary” operations requires an unstated assumption that small AAAs identified by screening would be inappropriately repaired before they reached a size of substantial rupture risk. The members of the USPSTF do not provide evidence for this assumption, nor do they indicate the magnitude of this effect on their conclusions. In fact, evidence from randomized trials of AAA screening indicates that more than 90% of subsequent elective AAA repairs were performed at recommended size criteria (3).

The USPSTF made separate recommendations for men on the basis of smoking, even though randomized trials favor screening for all men (2). To do so, the USPSTF relied on separate analyses of AAA prevalence, based on risk factors such as smoking. Clearly, screening is more cost-effective if the screened population has a higher prevalence of AAA, so the impact of smoking is an important consideration. It is unclear, however, why the USPSTF did not evaluate women on the basis of smoking history. Female smokers have the same AAA prevalence as male nonsmokers (1.9% for 3-cm AAAs [4]), yet they were bundled into a grade D recommendation against screening for all women while male smokers received a neutral grade C recommendation. I do not believe that risk factor analysis should be differentially applied on the basis of sex.

Finally, it is disappointing that the USPSTF ignored the importance of a family history of AAA in its overall recommendations. Most studies have found that first-degree relatives of patients with AAA have a much higher prevalence of small AAAs (25% to 43% in brothers, 6% to 16% in sisters [5]) than the 5.9% prevalence in male smokers (4), for whom the USPSTF issued a grade B recommendation for screening.

I believe that the USPSTF recommendations were too conservative in not recommending AAA screening for all men older than age 64 years, for female smokers in this age group, and for men or women in this age group whose sibling or parent had an AAA. The Society for Vascular Surgery and the Society for Vascular Medicine and Biology have recommended more comprehensive screening that reflects these concerns (6).

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: The USPSTF released its recommendations on screening for AAA on 1 February 2005. The USPSTF recommends 1-time screening for men 65 to 75 years of age who have ever smoked. The recommendation is based on the high prevalence of AAA in this population, their high risk for AAA rupture, and the good-quality evidence from large-population-based screening trials showing that screening leads to decreased AAA-specific mortality in men. The USPSTF makes no recommendation for or against screening men 65 to 75 years of age who have never smoked because the balance of harms and benefits is too close to call. Prevalence of AAA is lower in men who have never smoked than in those who have ever smoked and, therefore, the potential for benefit in this population is lower when balanced against important harms. Finally, the USPSTF recommends against routine primary care screening for women on the basis of 3 important pieces of evidence: 1) The prevalence of AAA in women is low compared with its prevalence in men (1.3% vs. 7.6%); 2) the peak prevalence of AAA in women is 10 years later than it is for men and AAAs in women therefore occur at ages when there are important competing causes of mortality; and 3) the available trial evidence shows no benefit from screening and repairing AAAs in women (1, 2).

Contrary to Dr. Cronenwett’s assertion, the USPSTF did not base its concerns about AAA screening on psychological harms or the harms of unnecessary surgeries. The USPSTF considered both the benefits and harms of screening and early intervention associated with AAA screening. The USPSTF carefully assessed the evidence of harms and concluded that the harms of surgery for AAAs greater than 5.5 cm are important ones: 4% to 6% in-hospital mortality rates and 32.4% major complication rates (2). Higher rates of complications are anticipated in older women, that is, at the ages when women develop AAAs. Therefore, it is likely that the net benefit of screening these women for AAA is, at best, zero. It is for these reasons that the USPSTF recommends against screening women for AAA. According to USPSTF methodology (3), the demonstration of no net benefit is sufficient for the USPSTF to recommend against providing a preventive service; no evidence of net harms is needed.

Dr. Cronenwett points out that AAA prevalence in female smokers is about the same as it is in male nonsmokers. He disagrees...
Letters

with the USPSTF for making no recommendation for or against screening men who have never smoked for AAA and for recommending against screening women. The combination of low prevalence, late age of onset, and the negative results from the available screening trial in women explains the reasons for not screening women for AAA (1, 2). The Task Force recognizes, however, that individualization of care is still required. For example, a clinician may choose to discuss screening in the unusual circumstance in which a healthy female smoker in her early 70s has a first-degree family history of AAA that required surgery.

The USPSTF found poor-quality evidence that family history is associated with an increased risk for AAA. Studies by Larcos and Webster and colleagues (4, 5), which involved ultrasonographic examination of relatives of patients with AAA, found the prevalence of AAA to be much lower—0% and 4%, respectively—than that reported by Frydman and associates (6). Small sample sizes in all studies of relatives of patients with AAA translated into large confidence intervals.

In conclusion, the USPSTF used the best available evidence on the risk factors for AAA and the benefits and harms of screening and treatment to recommend in favor of screening men 65 to 75 years of age who have ever smoked. In such cases, there is evidence that AAA screening can save lives.

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References

TO THE EDITOR: Sarnak and colleagues (1) concluded that a low target blood pressure slowed the progression of nondiabetic kidney disease. However, Ruggenenti and associates (2) recently reported that no additional benefit from further blood pressure reduction by felodipine (dihydropyridine calcium-channel blockers) could be shown in patients with nondiabetic proteinuric nephropathies receiving background angiotensin-converting enzyme (ACE) inhibitor therapy. As Sarnak and colleagues pointed out, more participants in the low target blood pressure group received ACE inhibitors in their study (1). Angiotensin-converting enzyme inhibitors are known to slow progression of kidney disease independently of their blood pressure–lowering effect (3). In the African-American Study of Kidney Disease and Hypertension, targeting antihypertensive therapy at a mean blood pressure of 92 mm Hg compared with usual targets of 102 to 107 mm Hg did not slow progression of hypertensive nephrosclerosis (4). In that study, an identical proportion of patients in the usual and lower blood pressure groups were taking ACE inhibitors (4). In the study by Ruggenenti and associates (2), the proportion of participants receiving ramipril in both the conventional (diastolic blood pressure <90 mm Hg) and intensified (target blood pressure 130/80 mm Hg) blood pressure groups was identical in order to measure the pure effect of lowering blood pressure by felodipine on the progression of kidney disease. Therefore, although Sarnak and colleagues’ sensitivity analysis did not affect their results, their conclusion that blood pressure reduction confers an additional renoprotective effect remains questionable.

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Target Blood Pressure and Kidney Disease

TO THE EDITOR: Sarnak and colleagues (1) presented an observational follow-up of the Modification of Diet in Renal Disease (MDRD) Study. They reported that after a total of 10 years, the hazard ratio for time to progression to kidney failure in the low blood pressure group was 0.68 (95% CI, 0.57 to 0.82) compared with the usual blood pressure group. However, in presenting this optimistic report, they seem to ignore the 2-ton gorilla in the living room. A total of 10.1% of patients in the low blood pressure group died compared with 6.3% in the usual blood pressure group, a result that is statistically significant. However, there is no mention of increased deaths and no attempt to explain why this finding occurred. Perhaps death is outweighed by the clinical benefit of a delay in dialysis, although it would be interesting to see how patients would accept that reality in a “shared decision-making” process. In any event, I would ask that the authors provide an additional graph for their Figure 3 detailing the cumulative probability of death over time, along with the appropriate statistical analysis for this outcome.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

www.annals.org
IN RESPONSE: Dr. Good raises the concern that deaths in our study may have been higher in the group with the lower target blood pressure. It is important to note, however, that the deaths to which Dr. Good refers include only those that occurred before development of kidney failure (see the legend to our Figure 2). Consideration of deaths that occurred only before kidney failure may result in an informative censoring bias. That is, those patients who reach kidney failure first may be more likely to die; however, the deaths that occur after kidney failure are not included in the comparison. Our Figure 2 also does not provide data on follow-up time, which limits the comparison. In fact, median follow-up time was longer in the lower blood pressure group because of a delay in reaching kidney failure. A longer follow-up time will of course allow more deaths to occur.

Without censoring for kidney failure, there were 101 and 107 deaths in the low and usual blood pressure groups, respectively. When Cox regression analyses were used, the adjusted hazard ratio of mortality was 0.97 (P > 0.2) for the low target blood pressure group compared with the usual blood pressure group. Thus, there is no evidence to support the contention that the low blood pressure target results in a higher death rate.

Of note, we presented the results of the composite of kidney failure and mortality. This incorporates the competing risk for death into the kidney failure models. The results were consistent with the kidney failure models and demonstrated a benefit of the lower blood pressure target.

We agree with Dr. Kida that we cannot disprove the possibility that ACE inhibitor use may have had an effect on the outcome. As noted, however, we believe this is unlikely for the following reasons. First, adjustment for ACE inhibitor use did not diminish the benefit of the lower blood pressure target. Second, the benefit achieved in the low blood pressure target group (a hazard ratio of 0.68 with only a 19% difference in use of ACE inhibitors) is much greater than would be expected if one compared these results with those of other nondiabetic ACE inhibitor trials that observed a similar hazard ratio with a 100% difference in use of ACE inhibitors (1).

We believe that the MDRD Study differs from the studies mentioned by Dr. Kida because it involves longer follow-up and more kidney failure outcomes. We propose that it may take time for the benefit of a lower blood pressure goal to be appreciated.

References

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Clinical Observations

High-Output Heart Failure Associated with Anagrelide Therapy for Essential Thrombocytosis

TO THE EDITOR: Background: Congestive heart failure (CHF) is usually associated with disorders causing low cardiac output; disorders associated with high cardiac output rarely cause CHF (1, 2). Medications have not previously been thought to cause high-output heart failure. New-onset CHF and cardiovascular death have rarely been associated with therapy with anagrelide (3–5), a novel treatment for essential thrombocytosis. The mechanism of cardiac dysfunction related to anagrelide has not previously been reported.

Objective: To report a case of high-output heart failure associated with anagrelide use in a patient with essential thrombocytosis.

Case Report: A 34-year-old man was referred for evaluation of pulmonary hypertension. He had received a diagnosis of essential thrombocytosis at age 25 years, and his course was marked by recurrent gastrointestinal bleeding and arterial thromboembolic disease. Four years before the evaluation reported here, he began treatment with anagrelide. In the year before the patient’s cardiac evaluation, the dose of anagrelide was titrated upward to 8 mg/d, with a subsequent reduction in platelet count from 1800 × 10^9 cells/L to 400 × 10^9 cells/L. Over the next several months, he noted palpitation, pedal edema, increasing abdominal girth, exertional dyspnea, and muscle wasting. Furosemide was given with a subsequent 20-pound weight loss, but the palpitations, dyspnea, and ascites persisted. Echocardiography performed after onset of symptoms revealed mild left ventricular dilatation (5.9 cm) and moderate left atrial dilatation (5.3 cm) and right atrial dilatation. Left ventricular wall motion and ejection fraction were normal. There was mild tricuspid regurgitation with a peak jet velocity of 3.5 m/s. Cardiac catheterization revealed moderate pulmonary hypertension and prompted referral to a subspecialty pulmonary hypertension clinic.

Physical examination revealed a blood pressure of 120/60 mm Hg, a pulse of 80 beats/min, oxygen saturation of 97% on room air, moderate elevation of jugular venous pressure, no S3 or murmur, a moderately enlarged pulsatile liver, and 2+ pedal edema. Leukocyte count was 18.4 × 10^9 cells/L, hemoglobin level was 11%, hematocrit was 0.34, platelet count was 962 × 10^9 cells/L, brain natriuretic peptide level was 326 ng/L, and thyroid-stimulating hormone level...
was 3.29 mU/L (within normal range). Results of serologic tests for HIV infection were negative. Electrocardiography showed first-degree atrioventricular block. A pulmonary ventilation–perfusion scan showed low probability of pulmonary embolism, and computed tomography of the pulmonary arteries yielded negative results with no evidence of acute or chronic pulmonary embolism. Repeated right-heart catheterization showed evidence of CHF related to high cardiac output (Figure, Table).

After a discussion with the patient’s hematologist, anagrelide therapy was discontinued. Within 1 week, symptoms had improved dramatically and signs of CHF regressed. Diuretics were withdrawn. Repeated right-heart catheterization 6 weeks later revealed resolution of all hemodynamic abnormalities (Figure, Table). Six months later, the patient was asymptomatic and taking hydroxyurea therapy for essential thrombocytosis.

Discussion: High-output heart failure is an uncommon syndrome that has been described in association with anemia, thyrotoxicosis, systemic arteriovenous fistulas, Paget disease, and nutritional deficiencies, such as beriberi heart disease (1, 2). High cardiac output is also known to occur in association with certain types of renal and hepatic disease, pregnancy, and treatment with certain vasodilators (for example, epoprostenol), but the clinical syndrome of CHF is rarely seen under these circumstances.

Anagrelide, a thrombocytopenic agent, is a quinazoline derivative that inhibits cyclic nucleotide phosphodiesterase type IV and is approved for use in essential thrombocytosis and for control of

*Figure. Intracardiac pressure tracings before and after discontinuation of anagrelide.*
thrombocytosis associated with polycythemia vera. In some studies, commonly reported cardiovascular side effects included palpitations, tachycardia, and fluid retention or edema (3). In a study of 577 patients treated with anagrelide, 14 developed CHF; of these, 2 died suddenly (4). In another study of 942 patients taking anagrelide for thrombocytosis, 15 died of cardiac causes (5). None of the heart failure cases in either of these studies was studied in detail.

The present case is remarkable for 2 major features: marked elevation of cardiac output and normal left ventricular ejection fraction in the setting of clinical CHF, and nearly immediate resolution of clinical and hemodynamic abnormalities after withdrawal of anagrelide. The observation of high cardiac output as a part of the pathophysiologic characteristics of this case is not entirely unexpected. Anagrelide is known to have positive inotropic activity in animals (4). As a phosphodiesterase inhibitor, it may have actions in common with such drugs as amrinone, milrinone, and enoximone, phosphodiesterase type 3 inhibitors known for their positive inotropic and for their adverse effect on mortality when used over the long term in patients with heart failure (6).

Cardiac disease is a major cause of death (including sudden death) in patients treated with anagrelide. Since the adverse hemodynamic effects were reversible in our case, clinicians should consider discontinuing anagrelide therapy when even mild cardiac side effects are noted.

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References

Subungual Splinter Hemorrhages: A Clinical Window to Inhibition of Vascular Endothelial Growth Factor Receptors?

TO THE EDITOR: Background: Over the past few years, cancer therapy has been profoundly changed by the development of drugs targeting specific kinases involved in the proliferation of tumor or endothelial cells. Some kinase inhibitors exhibit antiangiogenic activity by targeting vascular endothelial growth factor receptors (VEGFRs).

Objective: We report the results of tests of 2 such inhibitors: SU11248 (Pfizer, New York, New York), which inhibits VEGFR-2, platelet-derived growth factor receptor (PDGFR), KIT, and flt3, and BAY 439006 (Onyx Pharmaceuticals, Emeryville, California, and Bayer, Leverkusen, Germany), which targets VEGFR-2 and VEGFR-3, PDGFR, and RAF gene products.

Methods and Findings: In a phase I study, we treated patients with various types of cancer with escalating doses of SU11248. Patients with renal-cell carcinoma received BAY 439006 in a phase III study. During systematically performed prospective dermatologic examinations, we observed uncommon side effects, such as hair depigmentation in patients treated with SU11248 (1). Unexpectedly, the most common side effect associated with these drugs was multiple, painless distal subungual splinter hemorrhages (Figure), which developed in 2 to 4 weeks in 30% of patients taking SU11248 and in more than 60% of patients taking BAY 439006. The hemorrhages were not associated with thrombotic or embolic clinical events.
Discussion: First described in 1920 in patients with infective endocarditis, subungual splinter hemorrhages are well known to internists (2). They appear as black or red lines that look like wood splinters under the nails. They are formed and confined in the epidermis of the nail bed and consist of a mass of blood in a layer of squamous cells adhering to the undersurface of the nail. Depending on their origin, they may occur in clusters, and their pattern of distribution, color, location (proximal or distal), and painful or painless character vary. They were initially thought to be a typical sign of bacterial endocarditis but were subsequently reported to occur in various conditions, such as the antiphospholipid syndrome, severe rheumatoid arthritis, thromboangiitis obliterans, mitral stenosis, or when arterial catheters are used (2, 3). They can also be seen in healthy patients, in whom trauma seems to be the most common cause (2, 4). Traumatic subungual splinter hemorrhages occur where the nail plate separates from the nail bed; delicate specialized spiraled capillaries beneath the nail bed can easily rupture.

Subungual splinter hemorrhages are not usually drug-related and have not been reported with other kinase inhibitors. SU11248 and BAY 489006 both target receptors with angiogenic activity: VEGFR and PDGFR. However, subungual splinter hemorrhages are seen only rarely with imatinib, a potent PDGFR inhibitor. Thus, if we correlate the action spectrum of the kinase inhibitors with the observed side effect, it seems that subungual splinter hemorrhages could result from elective VEGFR blocking.

Indeed, VEGFR may be constitutively involved in the continuous renewal of the delicate spiral capillaries that sustain frequent microinjuries at the extremities of the fingers. Blocking these receptors might prevent the physiologic repair of traumatized nail bed capillaries and result in subungual splinter hemorrhages. According to this hypothesis, subungual splinter hemorrhages could directly reflect the anti-VEGFR properties of these new agents, and nail beds might offer an interesting clinical monitoring window to the antiangiogenic effects of drugs.

Inhibitors of epidermal growth factor receptor also frequently target the skin, resulting in a diffuse follicular rash. There is now strong evidence that the cutaneous rash is associated with objective response and prolonged survival, supporting the role of cutaneous response as a surrogate marker of activity (5). In our report, if multiple subungual splinter hemorrhages reflect the antiangiogenic effect of the drug, they could also be associated with an antitumor therapeutic benefit.

Conclusions: We remind other investigators to examine their patients’ nails to identify subungual splinter hemorrhages in this clinical setting. Through collaboration, data could be collected from a large number of patients, possibly allowing researchers to determine whether multiple subungual splinter hemorrhages are indeed a signature of anti-VEGFR agents and whether they are associated with a better tumor response.

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References
Disseminated Aspergillosis Mimicking Hepatic Veno-Occlusive Disease

TO THE EDITOR: Background: The incidence of invasive aspergillosis is increasing in parallel with the number of immunosuppressed patients (1). Although Aspergillus is not known as a pathogen with liver tropism, 11% of patients who die of or with invasive aspergillosis have liver involvement (2). The clinical patterns of hepatic aspergillosis vary and depend on the extent of invasion and the anatomic site of the liver involved. To our knowledge, invasion of sinusoids by fungal hyphae resulting in a syndrome mimicking hepatic veno-occlusive disease has not been previously reported.

Case Report: A 53-year-old woman was admitted to our hospital with a 10-day history of productive cough and fever (temperature, \(\leq 38.6 ^\circ C\)). Chest radiograph and computed tomography of the thorax revealed infiltrates in both apices without cavitation. The patient underwent bronchoscopy, and the bronchoalveolar lavage cultures grew Aspergillus fumigatus. Amphotericin B was initiated at a daily dose of 1 mg/kg of body weight. Two weeks after initiation of treatment, the patient had remarkable clinical and radiographic improvement. She was doing well until the twenty-third day of treatment, when her hospital course was complicated with staphylococcal sepsis related to a subclavian vein catheter. The line was removed, amphotericin B was withdrawn, and dicyclaxillin and gentamicin therapy was started. Three days later, the patient became afebrile and her clinical condition stabilized.

One week after withdrawal of amphotericin B, while the patient was receiving antistaphylococcal treatment, she developed abdominal distention, pain in the right upper quadrant of the abdomen, and a temperature of 38 \(^\circ C\). On physical examination, jaundice, tender hepatosplenomegaly, and ascites were present. Laboratory evaluation revealed the following: hemoglobin level, 74 g/L; leukocyte count, 12 \times 10^9 cells/L; platelet count, 60 \times 10^9 cells/L; bilirubin level, 236 \mu mol/L (13.8 mg/dL); alkaline phosphatase level, 87 U/L; alanine aminotransferase level, 44 U/L; total serum protein level, 65 g/L; albumin level, 3.0 g/L; globulin level, 3.5 g/L; prothrombin time, 12 seconds (control, 11 seconds); creatinine concentration, 115 \mu mol/L (1.3 mg/dL); pH, 7.43; Pco2, 24 mm Hg; and PO2, 77 mm Hg. The patient’s condition deteriorated: She was intubated and transferred to the intensive care unit. Computed tomography of the chest showed extensive infiltrates in both lung fields and bilateral pleural effusion; computed tomography of the abdomen revealed hepatomegaly, splenomegaly, and ascites without focal lesions. Doppler ultrasonography of hepatic and portal veins and inferior vena cavaography did not reveal any obstruction. The ascitic fluid was turbid and hemorrhagic and showed a protein level of 40 g/L and 8.0 \times 10^9 leukocytes/L with 80% neutrophils on examination. All cultures were negative for bacteria and fungi. Liver biopsy revealed invasion of hepatic sinusoids, central veins, and the portal tract by fungal hyphae associated with sinusoidal dilatation and atrophy of hepatic cords (Figure).

Results of serologic tests for HIV-1, HIV-2, and human T-cell lymphotrophic virus types 1 and 2 were negative twice. Levels of immunoglobulins, including IgG subclasses and IgE, were within normal limits. Leukocyte chemotaxis, results of the nitroblue tetrazolium test, and complement components C3, C4, and total hemolytic activity CH50 were normal. Bone marrow biopsy was not revealing. The CD4 cell count was 0.196 \times 10^9 cells/L, and the CD4/CD8 ratio was 0.45. The patient began receiving liposomal amphotericin B (AmBisome, Fujisawa Healthcare, Inc., Deerfield, Illinois), 5 mg/kg per day. Two weeks after initiation of treatment, she had remarkable clinical and laboratory improvement. The amphotericin B regimen was continued for 1 month, and the patient was discharged home in good condition while taking itraconazole (400 mg/d). On follow-up visits, the patient had no clinical or laboratory evidence of active infection and her absolute CD4 cell count was 0.212 \times 10^9 cells/L. Itraconazole therapy was discontinued after 1 year.

Discussion: Disseminated aspergillosis occurs in different patient groups (1). Our patient had persistently low CD4 cell counts (< 0.3 \times 10^9 cells/L) without any other recognized immune defect, leading to the diagnosis of idiopathic CD4 lymphopenia (3). Apparently, the profound immune dysfunction of the host, as indicated by the low CD4 cell count, and the inadequate initial antifungal treatment were the main factors that contributed to hematogenous dissemination of Aspergillus from a pulmonary focus to the liver.

Characteristically, Aspergillus forms abscesses in the liver with vascular invasion, thrombosis, and infarction of tissue in the surrounding area (2). When the abscesses are small, patients may have no symptoms and modest liver function abnormalities. However, when the abscesses are large and associated with hepatocellular damage, patients have pronounced symptoms and marked liver function abnormalities (2). It is of interest that invasion of particular anatomic sites by Aspergillus produces several distinct syndromes. As reported previously, invasion of the hepatic veins by fungi may produce the Budd-Chiari syndrome (4). In our patient, obstruction of hepatic venous outflow by masses of fungal hyphae occurred at the level of sinusoids and central hepatic veins, resulting in a syndrome characterized by tender hepatomegaly, splenomegaly, ascites, and jaundice, mimicking hepatic veno-occlusive disease. Hepatic veno-occlusive disease was first described in South Africa and was linked to the ingestion of pyrrolizidine alkaloids contained in Senecio tea. More recently, veno-occlusive disease has been seen in liver and hematopoietic disorders.
Conclusion: This case illustrates a not previously recognized form of hepatic aspergillosis that had all the clinical characteristics of veno-occlusive disease and occurred in a patient with idiopathic CD4 lymphopenia. It also highlights the importance of liver biopsy to establish the diagnosis and distinguish hepatic aspergillosis from other causes of veno-occlusive disease.

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References

CORRECTION

Correction: Recommendations for the Diagnosis and Treatment of the Acute Porphyrias

A review on recommendations for diagnosis and treatment of acute porphyrias (1) contained an error. In the Key Summary Points on page 440, under “Treatment of the Acute Attack,” the unit of hemin in the third paragraph should be 3 to 4 mg/kg daily.

Reference