"needle-to-balloon time" (defined as the difference between the time at which thrombolysis would be administered and the time of the first balloon inflation) exceeds 60 minutes, the survival benefit provided by PCI, as compared with thrombolysis, might be lost.[1] However, other studies have suggested a continuous benefit of PCI, even when substantial delays due to transport time or other factors are expected and, in particular, in patients with the longest time from the onset of symptoms to treatment.[2-4] Thus, in view of these conflicting data, the relative benefit of "early" thrombolysis, as compared with "delayed" PCI, continues to be the topic of vivid debate. The significance and magnitude of the controversy surrounding this issue, which would deserve a full editorial by itself, and the fact that the article by Bradley et al. was about process rather than treatment are among the reasons why we elected not to address this issue in our editorial.

Mauro Moscucci, M.D.
Kim A. Eagle, M.D.
University of Michigan Cardiovascular Center
Ann Arbor, MI 48109

1. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? Am J Cardiol 2003;92:824-6.
2. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003;349:733-42.
3. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J 2006;27:779-88.
4. Widimsky P, Budesinsky T, Vorac D, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial — PRAGUE-2. Eur Heart J 2003;24:94-104.

Whipple's Disease

TO THE EDITOR: In their Medical Progress article on Whipple's disease, Fenollar and colleagues (Jan. 4 issue)[1] raise important issues regarding culture-negative endocarditis. We report on a 38-year-old-man with a 6-month history of polyarthralgia. He had clubbing of the fingers as well as aortic and mitral regurgitant murmurs. Transesophageal echocardiography showed vegetations on both the mitral and aortic (bicuspid) valves. Multiple blood cultures and routine serologic tests were negative. A species-specific polymerase-chain-reaction (PCR) assay for *Tropheryma whipplei* and broad-range PCR for 16S ribosomal DNA[2] on whole blood were negative.

After replacement of the aortic and mitral valves, tissue samples from both valves were found to be positive for *T. whipplei* on broad-range PCR assay[2] (with sequence analysis) and species-specific PCR assay. Macrophages with positive inclusions on periodic acid–Schiff (PAS) staining were confirmed as the organisms seen on electron microscopy (Fig. 1).

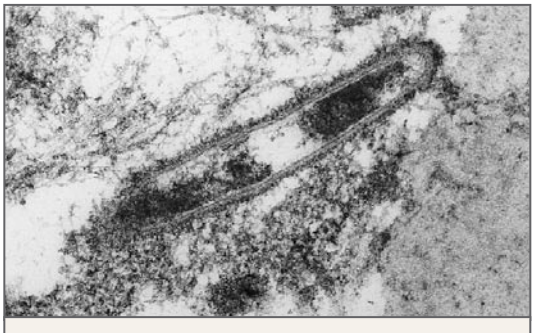

Figure 1. Electron Micrograph of Valvular Tissue Showing Rodlike Organisms with the Characteristic Trilamellar Cell Wall of *Tropheryma whipplei*.

The modified Duke criteria[3] are often unreliable in detecting culture-negative endocarditis; our patient was clinically categorized as having possible endocarditis (one major and one minor sign). We suggest that other clinical signs (including clubbing[4]) and serologic[5] and molecularly based tests should be included as part of the initial diagnostic workup for patients with suspected infective endocarditis and that valvular tissue removed during surgery should be investigated with the use of molecular techniques.

Owen M. Williams, Ph.D.
Health Protection Agency South West Regional Laboratory
Bristol BS2 8HW, United Kingdom
martinx.williams@ubht.nhs.uk

Angus K. Nightingale, M.D.
Bristol Heart Institute
Bristol BS2 8HW, United Kingdom

John Hartley, M.R.C.Path.
Great Ormond Street Hospital
London WC1N 3JH, United Kingdom

1. Fenollar F, Puéchal X, Raoult D. Whipple's disease. N Engl J Med 2007;356:55-66.

2. Harris KA, Hartley JC. Development of broad range 16s rDNA PCR for use in the routine diagnostic clinical microbiology service. J Med Microbiol 2003;52:685-91.
3. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.
4. Lamas CC, Eykyn SJ. Suggested modifications to the Duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. Clin Infect Dis 1997;25:713-9.
5. Raoult D, Casalta JP, Richet H, et al. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005;43:5238-42.

TO THE EDITOR: Fenollar and colleagues propose treatment with doxycycline plus hydroxychloroquine for Whipple's disease without neurologic involvement. In our view, it is difficult to exclude the central nervous system as a sanctuary for *T. whipplei*. Neither histopathological examination nor PCR on cerebrospinal fluid is sufficiently sensitive for technical reasons (low number of cells in cerebrospinal fluid for PAS staining, and inhibition of the PCR reaction).[1] Given a relapse rate of 32% after tetracycline treatment (as shown in Table 4 of the article) and the high mortality among patients with cerebral relapse, we suggest that it is prudent to use antibiotics with therapeutic cerebrospinal fluid concentrations (e.g., cotrimoxazole) as standard practice for all patients with Whipple's disease.[2]

T. whipplei resides in subgingival dental plaque in up to one third of the white population in Central Europe.[3] This suggests that *T. whipplei* is common in the environment. Therefore, reinfection is a real concern for patients with treated Whipple's disease, considering that they may have an immune defect.[4] We recommend lifelong follow-up of patients who have been treated for Whipple's disease and consideration of antibiotic prophylaxis.

Matthias Bramkamp, M.D.
Fabio Ruggieri, M.D.
Markus Schneemann, M.D.
University Hospital of Zurich
8091 Zurich, Switzerland

Dr. Schneemann reports receiving lecture fees and travel grants from Merck Sharp & Dohme, Pfizer, and Bristol-Myers Squibb.

1. Wilson IG. Inhibition and facilitation of nucleic acid amplification. Appl Environ Microbiol 1997;63:3741-51.
2. Gerard A, Sarrot-Reynauld F, Liozon E, et al. Neurologic presentation of Whipple disease: report of 12 cases and review of the literature. Medicine (Baltimore) 2002;81:443-57.
3. Zinkernagel AS, Gmur R, Fenner L, Schaffner A, Schoedon G, Schneemann M. Marginal and subgingival plaque — a natural habitat of Tropheryma whipplei? Infection 2003;31:86-91.
4. Desnues B, Ihrig M, Raoult D, Mege JL. Whipple's disease: a macrophage disease. Clin Vaccine Immunol 2006;13:170-8.

THE AUTHORS REPLY: Williams and colleagues report a case of blood culture–negative endocarditis caused by *T. whipplei*. We agree that the Duke criteria perform poorly for patients with endocarditis associated with Whipple's disease, as previously reported.[1] The Duke criteria are the absence of fever (major criterion), previous valve lesion (minor criterion), and available microbiologic tests — blood culture (major criterion) and serologic findings (minor criterion). Thus, additional criteria are welcome. Among them, arthralgias, as reported in their patient, are important. The prevalence of long-lasting arthralgias in the history is very high and should trigger a suspicion of Whipple's disease. Valve examination remains the key to the diagnosis, since duodenal biopsies and blood tests may be negative on PCR assay. Thus, PCR assay cannot be proposed as a reliable diagnostic test; a reliable blood test is urgently needed.

Bramkamp and colleagues suggest that cotrimoxazole should be added to the treatment of all patients with Whipple's disease and that such patients may benefit from long-term follow-up. We agree that patients should have lifelong follow-up to detect late relapses. However, with respect to cotrimoxazole, one should remember that only sulfamides are active against *T. whipplei*, whereas trimethoprim is not.[2] We have documented treatment failures associated with specific mutations in the genome of *T. whipplei* (unpublished data), and relapses have been documented. Therefore, in our view, alternatives to cotrimoxazole would be useful, because the treatment conundrum remains unsolved. We suggest avoiding cotrimoxazole in the absence of neurologic symptoms plus a negative result of a PCR assay performed on cerebrospinal fluid. As we stated in our article, preliminary results with a regimen of doxycycline and hydroxychloroquine appear to be encouraging. One hopes that further studies will clarify the best strategies for curing this difficult disease.

Didier Raoult, M.D., Ph.D.
Florence Fenollar, M.D., Ph.D.
Université de la Méditerranée
13385 Marseille, France
didier.raoult@medecine.univ-mrs.fr

Xavier Puéchal, M.D., Ph.D.
Le Mans General Hospital
72037 Le Mans, France

1. Raoult D. Afebrile blood culture-negative endocarditis. Ann Intern Med 1999;131:144-6.
2. Boulos A, Rolain JM, Mallet MN, Raoult D. Molecular evaluation of antibiotic susceptibility of *Tropheryma whipplei* in axenic medium. J Antimicrob Chemother 2005;55:178-81.

Retraction: Hussain HM, Hotopf M, Oyebode F. Atypical Antipsychotic Drugs and Alzheimer's Disease. N Engl J Med 2007;356:416.

TO THE EDITOR: A letter that I submitted to the *Journal* was published in the January 25 issue.[1] Because there has been concern about the provenance and authorship of that letter, I request that it be retracted.

Hadi Meeran Hussain, M.B., B.S.

Military Hospital
Rawalpindi 46000, Pakistan

1. Hussain HM, Hotopf M, Oyebode F. Atypical antipsychotic drugs and Alzheimer's disease. N Engl J Med 2007;356:416.

Multiple-Triazole–Resistant Aspergillosis

TO THE EDITOR: The use of voriconazole has become common for the management of invasive aspergillosis. However, therapy with voriconazole still sometimes fails, more often because of unresponsive underlying disease than because of resistance of the fungus. Since the first description of itraconazole resistance in *Aspergillus fumigatus*,[1] three amino acid substitutions in the 14α-sterol demethylase *cyp51A* gene, which is the target site for azole drugs, have been described.[2]

Our laboratory receives fungal isolates for identification and susceptibility testing from throughout the Netherlands. Since 2002, using Clinical and Laboratory Standards Institute methodology, we have observed an increase in the number of *A. fumigatus* isolates with elevated minimum inhibitory concentrations of voriconazole (2 to >16 mg per liter), itraconazole (>16 mg per liter), the investigational azole ravuconazole (4 to >16 mg per liter), and posaconazole (0.5 to 1.0 mg per liter). Thirteen isolates were cultured from nine patients from six hospitals in the Netherlands (Table 1). Primary aspergillosis was diagnosed in four patients, and five patients presented with breakthrough invasive aspergillosis.

A new mechanism of resistance, consisting of a Cyp51A amino acid substitution at codon 98 (L98H) together with a tandem repeat in the gene promoter, was found to be responsible for the azole-resistant phenotype. This resistance mechanism was present in 12 of the 13 isolates. Genotyping of the isolates showed no evidence for clonal spread of a single *A. fumigatus* genotype.

The prevalence of multiple-triazole resistance was compared with a previously conducted nationwide survey of 170 *A. fumigatus* isolates collected from 114 patients from 21 Dutch hospitals between 1945 and 1998.[4] In this period, no patients with multiple-triazole–resistant isolates were found as compared with 10 of 81 patients in the period since 2002 ($P<0.001$).

Although the emergence of this new resistance mechanism coincides with the approval of voriconazole, the factors that may explain this phenomenon remain unclear. Four patients became infected with a multiple-triazole–resistant strain during long-term prophylaxis with itraconazole, a drug that has been widely available for clinical use since 1991. The recovery of multiple-triazole–resistant strains in patients who had not been previously treated with azoles suggests that alternative sources of azoles, such as the use of azole compounds in agricultural environments, might play a role.[5]

Our observation underscores the need to make an etiologic diagnosis of invasive mold infection