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# Mortality in Serologically Unconfirmed Mediterranean Spotted Fever [with Reply]

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iterranean spotted fever (MSF), however, is milder than that of RMSF, especially in children, and the fatality rate is considered to be <5% [2]. In 1993, Wolach and I [3] reported fatal MSF in 3 Israeli children who had presented with a febrile disease lasting 5–7 days, septic shock, mental changes, hyponatremia, and bleeding tendency. A rash, macular or purpuric, was present in 2 children and absent in the third. A presumptive diagnosis of meningococcemia or sepsis of unknown origin was entertained. The 3 children were empirically treated with β-lactam antibiotics and aggressive supportive therapy but died within 24 h of admission. The diagnosis of MSF was confirmed in 2 patients by cell culture and by animal inoculation in the third. Antibodies to spotted fever–group rickettsiae, as determined by microimmunofluorescence, were negative in 2 children, whereas a borderline titer of 1 : 80 was found in 1.

Early administration of specific therapy with tetracyclines or chloramphenicol significantly decreases mortality due to rickettsial infections [4]. Institution of such therapy, however, requires that the rickettsial etiology of the illness be suspected on clinical and/or epidemiologic grounds, because these antimicrobial drugs are not usually given empirically to febrile patients. In addition, pediatricians frequently hesitate to start therapy with tetracycline in febrile young children without a definitive proof of a rickettsial diagnosis, because of the potential risk of teeth staining. Usually the diagnosis of rickettsioses relies on serologic tests, whereas culture of the organism and polymerase chain reaction methods are not routinely used or universally available. The series of patients reported by Paddock et al. [1] and our 3 patients clearly show that serologic tests may be unreliable for diagnosing or excluding rickettsial infections, especially in persons presenting with fulminant disease. Had specific isolation techniques for rickettsiae not been attempted, the diagnosis would have been missed in our 3 patients, and their deaths would have been attributed to infections caused by unidentified pathogens. Thus, it appears that, when alternative methods for confirming the disease are not used, the diagnosis of MSF may be missed by serology, resulting in underestimation of the true case/fatality rate of the infection. Because MSF may follow an unpredictable, rapid fatal course similar to that of RMSF, it seems prudent to advise prompt administration of empirical tetracycline therapy whenever the diagnosis is suspected.

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## Mortality in Serologically Unconfirmed Mediterranean Spotted Fever

**To the Editor**—I read with interest the article by Paddock et al. [1], who described the detection of occult mortality due to Rocky Mountain spotted fever (RMSF) by demonstrating *Rickettsia rickettsii* antigens or DNA in blood and tissues [1]. In Mediterranean countries, including Israel, spotted fever is caused by members of the *R. conorii* complex, which are antigenically related to *R. rickettsii.* The clinical course of Med-

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## Reply

**To the Editor**—We appreciate the comments by Yagupsky [1], which underscore several of the salient features of spotted fever–group rickettsial infections that we emphasized in our report [2]. For patients, diagnosticians, and clinicians faced with the potentially tragic consequences of Rocky Mountain spotted fever or severe Mediterranean spotted fever (MSF), these points merit repeating. First, the nonspecific signs and symptoms early in the course of rickettsial infections mimic many other infectious and noninfectious syndromes. Second, the diagnostic challenges posed by these diseases are compounded by the lack of rapid and widely available confirmatory tests early in the course of the illnesses. Finally, spotted fevers have the potential to kill otherwise healthy persons in <1 week after onset of symptoms, emphasizing the need for early administration of appropriate therapy.

The immunohistochemical (IHC) test described in our report uses an antibody that reacts with multiple spotted fever–group rickettsiae, including members of the *Rickettsia conorii* complex that causes MSF. In this context, we have used this assay to diagnose previously unexplained fatal illnesses caused by spotted fever–group rickettsiae other than *R. rickettsii.* Our experience reinforces the comments of Yagupsky [1] and includes confirmation of fatal spotted fever infections in 2 adult Israeli patients for whom serologic evidence of MSF was lacking. The first patient was a 31-year-old woman who died 6 days after onset of an illness characterized by fever, myalgias, headache, and respiratory insufficiency. The second patient was a 38-year-old man who died 7 days after being hospitalized for fever and vomiting. Both patients developed thrombocytopenia and petechial or purpuric rashes over the course of their illnesses. Similar to 2 of the pediatric patients described in the earlier report by Yagupsky and Wolach [3], neither of these 2 patients demonstrated diagnostic levels of antibody reactive with spotted fever–group rickettsiae when serum samples were tested by use of an indirect immunofluorescence assay. However, tissues from both patients obtained at autopsy demonstrated microscopic lesions consistent with histopathologic findings of fatal MSF [4], and IHC staining for spotted fever–group rickettsiae revealed abundant rickettsial antigens and intact rickettsiae in and around blood vessels and within reticuloendothelial cells (figure 1).

We agree with Yagupsky's recommendation to administer tetracycline antimicrobials (preferably doxycycline) to children of any age when spotted fever–group rickettsioses are considered in the differential diagnosis. The recognized propensity of tetracyclines to bind to dental enamel should not dissuade physicians from using the most effective drug for the treatment of these potentially life-threatening infections. The decision to use doxycycline in young children is never made casually, and the rationale for this choice of therapy should be discussed with the child's parents [5]. However, it should be recognized that a single short course (i.e., 5–7 days) of doxycycline should not result in cosmetically significant staining of teeth [6, 7]. For patients with Rocky Mountain spotted fever or severe MSF, there is a relatively narrow window of time during which effective antibiotic therapy dramatically reduces the risk of death [8]. Since laboratory tests available to most physicians do not assist in early diagnosis, initiation of therapy should be based on clinical, and especially epidemiologic, findings (e.g., unexplained febrile illness associated with known tick bite or tick exposure or unexplained fever with thrombocytopenia, rash, or headache occurring during spring or summer months in an area where the disease is endemic).

Isolation of *R. conorii* from patients' blood and tissues confirmed the diagnosis of spotted fever for each of the 3 pediatric patients described by Yagupsky and Wolach [3] and reflects the clinical acumen of these investigators. Although isolation is the reference standard for diagnosis, culture is seldom attempted during the acute phase of illness, even when a rickettsial infection is suspected, and cannot be performed retrospectively on autopsy specimens unless samples were appropriately collected and stored (e.g., frozen at −70°C). Biosafety level 3 practices and facilities are recommended if culture of spotted fever–group rickettsiae is attempted [9]. In contrast, IHC testing provides a method for retrospective confirmatory diagnosis on archived samples months or even years after the illness. In this context, IHC is a versatile technique that can help resolve problematic issues relating to the diagnosis of otherwise unexplained illnesses and provide new insights into the clinical course and epidemiologic features of these diseases [10].

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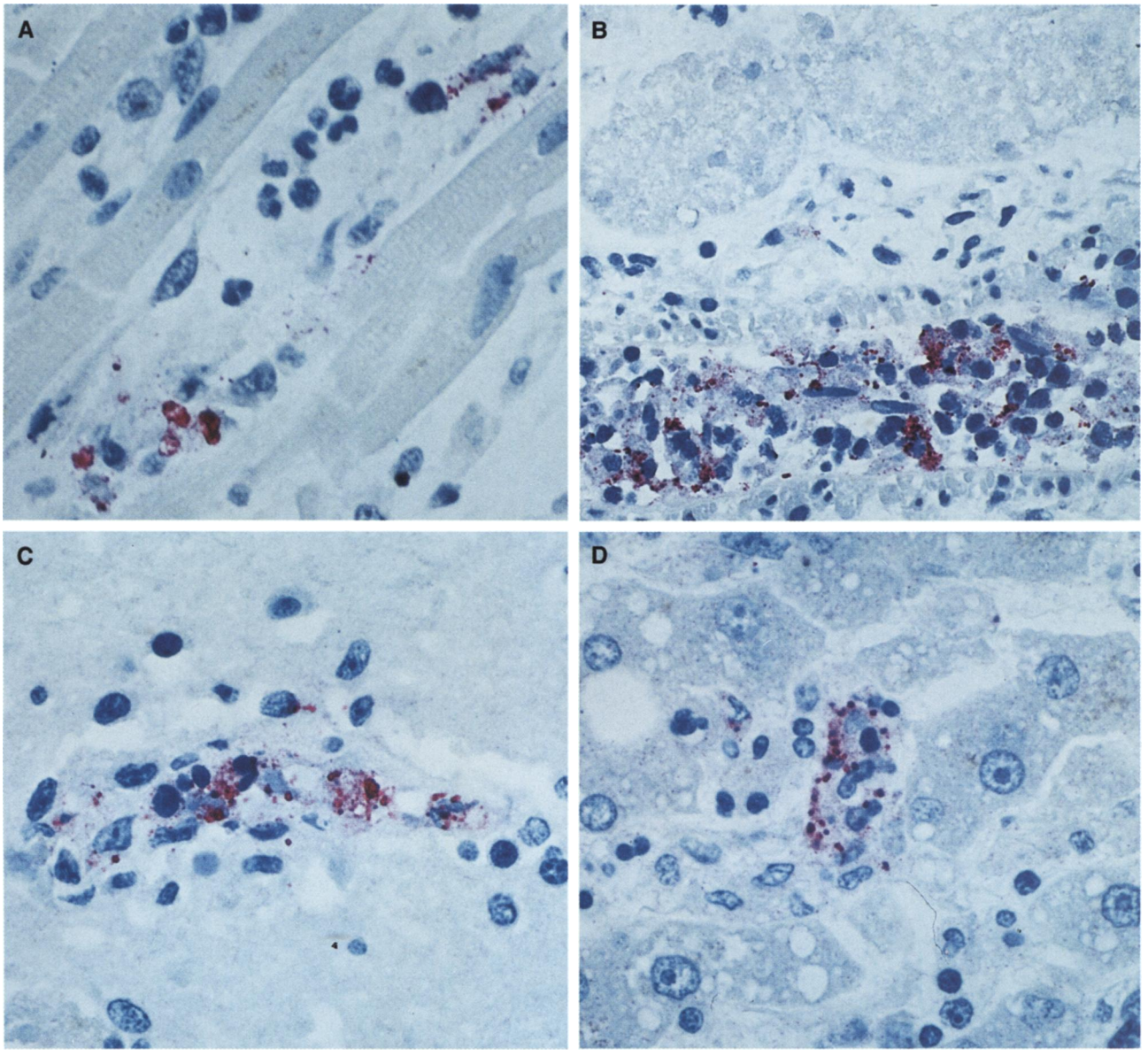


**Figure 1.** Immunohistochemical localization of spotted fever–group rickettsial antigens in tissues of patients with fatal spotted fever, by immunoalkaline phosphatase stain with naphthol phosphate–fast red substrate and hematoxylin counterstain. *A,* Rickettsiae and rickettsial antigens associated with damaged endothelium in myocardial interstitium (patient 1); original magnification, ×158. *B,* Abundant rickettsial antigens within denuded intravascular endothelial cells in small vessel in kidney (patient 1); original magnification, ×100. *C,* Rickettsial nodule in cerebral cortex (patient 1); original magnification, ×158. *D,* Spotted fever–group rickettsiae and rickettsial antigens in cytoplasms of Kupffer cells in liver (patient 2); original magnification, ×158.

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