Approach to Fever in the Returning Traveler

TO THE EDITOR: The review article by Thwaites and Day (Feb. 9 issue)[1] provides comprehensive and concise information regarding the countless causes of fever in the returning traveler. For clinicians who are less familiar with travel-related pathology, however, it is important to highlight that approximately 90% of the febrile tropical illnesses are due to a rather limited set of infections, including malaria, dengue, rickettsial infection, enteric fever, and recently chikungunya fever and Zika virus infection.[2,3] In addition to the incubation period and specific exposure, some features (symptoms and signs) at presentation may help the clinician to work through the complex diagnostic approach. The presence of any malaria predictor, such as an enlarged spleen, thrombocytopenia, or indirect hyperbilirubinemia,[4] contributes to the identification of the subgroup of febrile travelers in whom malaria testing really needs to be repeated if the initial result is negative. Once malaria is ruled out, several initial findings (rash, leukopenia, or thrombocytopenia for dengue; rash or eschar for rickettsial infection; and enlarged spleen or elevated aminotransferase levels for enteric fever) help the clinician to prioritize the relevant investigations.[5] The identification of diagnostic predictors of less frequent diseases in travelers ought to become a collaborative research priority.

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TO THE EDITOR: In their review article, Thwaites and Day suggest ribavirin for Lassa fever but not for Crimean–Congo hemorrhagic fever. A beneficial effect of ribavirin was shown in a study that included 281 patients with laboratory-confirmed Crimean–Congo hemorrhagic fever.[1] In a multivariate analysis that was adjusted for a severity scoring index, ribavirin was shown to be significantly effective in reducing the case fatality rate.[1] The early use of ribavirin was evaluated in another study that included 342 patients with a confirmed case of Crimean–Congo hemorrhagic fever, and the case fatality rate was reported to be 2.9%.[2] In a multivariate analysis, severe disease was less likely to develop in patients who received oral ribavirin than in those who did not.[2] The authors of recent case series of Crimean–Congo hemorrhagic fever virus infection among health care workers supported the use of ribavirin as postexposure prophylaxis.[3,4] Thus, in patients with Crimean–Congo hemorrhagic fever virus infection, ribavirin was found to be effective in treatment[1] and in postexposure prophylaxis,[3] and earlier administration was associated with better outcomes.[1-3]

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THE AUTHORS REPLY: We agree with Bottieau regarding the emphasis on a small number of common infections causing fever in the returning traveler. The discrimination of rarer causes is difficult and worthy of study. The GeoSentinel network is well placed to conduct such research.

We believe that the role of ribavirin in postexposure prophylaxis and the treatment of Crimean–Congo hemorrhagic fever is uncertain. There are few data to support a strong recommendation for ribavirin as postexposure prophylaxis for Crimean–Congo hemorrhagic fever. The studies cited by Ergönül and Keske are both observational, without controls, and they report data on seven health care workers with exposure to Crimean–Congo hemorrhagic fever who were given ribavirin as postexposure prophylaxis (the disease developed in none of these health care workers)[1] and data from nine health care workers who were exposed to and infected with Crimean–Congo hemorrhagic fever virus, with asymptomatic infection in the two health care workers who were given ribavirin as postexposure prophylaxis.[2] Stronger evidence for the benefit of ribavirin as postexposure prophylaxis comes from a recent retrospective report of health care–related exposure to Crimean–Congo hemorrhagic fever by means of needlestick injury, in which infection was confirmed in 18 of 25 persons (72%) who did not receive ribavirin as postexposure prophylaxis and in 0 of 19 who received ribavirin as prophylaxis.[3] However, mortality among the source patients was substantially lower in the group of health care workers who received ribavirin than in the group who did not, which suggests that the disease severity and possibly infectivity was lower in these patients, which may have confounded the effect of ribavirin.

Only one randomized, controlled trial of ribavirin for the treatment of Crimean–Congo hemorrhagic fever has been published. This trial compared ribavirin with supportive treatment in 136 Turkish adults with Crimean–Congo hemorrhagic fever and showed no significant effect of ribavirin on survival or any outcome measure.[4] This finding was supported by a subsequent meta-analysis that did not show that ribavirin prolonged survival among patients with Crimean–Congo hemorrhagic fever, as compared with those who did not receive ribavirin (relative risk for death, 1.06; 95% confidence interval, 0.97 to 1.16).[5]

Ergönül and Keske assert that ribavirin prolongs survival among patients with Crimean–Congo hemorrhagic fever by pointing to data from two observational studies that used multivariate logistic regression to adjust for potential confounders. The limitations of such an approach are well known, and the findings are supportive but not definitive, especially when they contradict the results of a randomized, controlled trial. We suggest that data from additional randomized, controlled trials are needed before strong recommendations can be made concerning the use of ribavirin in the prevention and treatment of Crimean–Congo hemorrhagic fever.

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