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Simple, accurate and low-cost diagnostic predictors of enteric fever among returned travellers: classical relative bradycardia and eosinopenia

Takashi Matono*¹, Satoshi Kutsuna², Yasuyuki Kato¹, Yuichi Katanami¹, Kei Yamamoto¹, Nozomi Takeshita¹, Kayoko Hayakawa¹, Shuzo Kanagawa¹, Norio Ohmagari¹

¹*National Center for Global Health and Medicine, Disease Control and Prevention Center, Tokyo, Japan*

²*National Centre for Global Health and Medicine (Ncgm), Disease Control and Prevention Center, Tokyo, Japan*

Background: Among returned travellers, a differential diagnosis of enteric fever (EF) and other tropical acute febrile illnesses based on the clinical features is often difficult. Moreover, the rapid tests and Widal test are available as diagnostic tools for EF in the clinical setting; however, they lack accuracy and reliability. The aim of the present study was to evaluate the effectiveness of relative bradycardia (RB) and eosinopenia (EP) as diagnostic predictors of enteric fever.

Material/methods: This retrospective case-control study was conducted at a referral centre in Tokyo, Japan, between January 2006 and October 2015. EF was defined as isolation of *Salmonella* Typhi and *S. Paratyphi* A from the blood and/or stool of patients with fever. The controls (3:1), consisting of patients with non-enteric fever (NEF) matched for age (± 3 years) and sex, were randomly selected from those with fever among the returned travellers from tropical regions in the same year. We used Cunha's criteria for RB. Absolute eosinopenia (AE) was defined as eosinophilic counts of 0/ μ L and EP as that of $\leq 1\%$. The groups were compared by Chi-square (χ^2) test for nominal variables and Mann-Whitney test for continuous variables. A logistic regression analysis was performed to evaluate correlation of the variables with EF.

Results: During this study, EF was diagnosed in 40 patients and 120 patients with NEF were included as controls. Among the 40 patients with EF, the median age was 31 (range 4–56) years, 70% were men, and 90% were Japanese. The differences for age, sex and ethnicity were not significant between two groups. Among the 120 controls, 27% were diagnosed with a diarrhoeal disease, 23% with acute respiratory syndrome, 13% with malaria, and 11% with dengue fever. The logistic regression analysis revealed the diagnosis of EF was significantly related to return from South Asia (RSA) (Odds ratio [OR], 9.25; 95% confidence interval [CI], 4.12–20.7), RB (OR, 7.00; 95% CI, 2.57–19.1), and EP (OR, 5.00; 95% CI, 1.13–22.2). The OR was extremely high in the combination of these three variables; i.e. RSA+RB+EP (OR, 24.2; 95% CI, 8.99–65.3). The negative predictive values of RSA, RB, and EP were 88.3%, 92.3%, and 92.6%, respectively. The positive predictive values of RSA+RB, RSA+RB+EP, and RSA+RB+AE were 75%, 77.4%, and 77.8%, respectively.

Conclusions: Each variable, including RSA, RB, and EP, is effective for ruling out EF when considered independently. Furthermore, the combination of these variables including RSA+RB and RSA+RB+EP or AE can lead to a diagnosis of EF. We recommend wisely using these classical diagnostic predictors of EF, which have the combined benefits of simplicity and low-cost, in returned travellers.