Thompson, CN; Blacksell, SD; Paris, DH; Arjyal, A; Karkey, A; Dongol, S; Giri, A; Dolecek, C; Day, N; Baker, S; Thwaites, G; Farrar, J; Basnyat, B (2015) Undifferentiated Febrile Illness in Kathmandu, Nepal. The American journal of tropical medicine and hygiene, 92 (4). pp. 875-8. ISSN 0002-9637 DOI: https://doi.org/10.4269/ajtmh.14-0709

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DOI: 10.4269/ajtmh.14-0709

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Undifferentiated Febrile Illness in Kathmandu, Nepal


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Abstract. Undifferentiated febrile illnesses (UFIs) are common in low- and middle-income countries. We prospectively investigated the causes of UFIs in 627 patients presenting to a tertiary referral hospital in Kathmandu, Nepal. Patients with microbiologically confirmed enteric fever (218 of 627; 34.8%) randomized to gatifloxacin or ofloxacin treatment were previously reported. We randomly selected 125 of 627 (20%) of these UFI patients, consisting of 96 of 409 (23%) cases with sterile blood cultures and 29 of 218 (13%) cases with enteric fever, for additional diagnostic investigations. We found serological evidence of acute murine typhus in 21 of 125 (17%) patients, with 12 of 21 (57%) patients polymerase chain reaction (PCR)-positive for *Rickettsia typhi*. Three UFI cases were quantitative PCR-positive for *Rickettsia* spp., two UFI cases were seropositive for Hantavirus, and one UFI case was seropositive for Q fever. Fever clearance time (FCT) for rickettsial infection was 44.5 hours (interquartile range = 26–66 hours), and there was no difference in FCT between ofloxacin or gatifloxacin. Murine typhus represents an important cause of predominantly urban UFIs in Nepal, and fluoroquinolones seem to be an effective empirical treatment.
Additionally, two cases were serologically positive for Hantavirus, and one case was serologically positive for Q fever.

Although the study design allowed for limited comparison, the clinical presentations and basic laboratory values, such as complete blood count, liver function test, and creatinine, of 21 rickettsial patients and 29 enteric fever patients were, in general, similar. However, the FCT was significantly prolonged in the enteric fever patients, with a median of 88 hours compared with the FCT in those with rickettsial infections, with a median of 44.5 hours (IQR = 26–66; hazard ratio = 3.71; P < 0.001).

Our study has a number of limitations. First, we were unable to test the whole study population for alternative causes of UFI, and the 20% proportion of patients selected may not have been truly representative of the whole population. Second, serological testing for *Rickettsia* may lack specificity, although fluoroquinolones are known to be an effective alternative for the treatment of SFG rickettsioses. Without control groups of untreated or doxycycline-treated patients, only tentative conclusions can be drawn, despite previous reports of poor responses to ciprofloxacin in murine typhus and our findings suggest that gatifloxacin and ofloxacin may be effective empirical treatment choices in Nepalese patients with UFIs.

The recommended therapy for murine typhus is doxycycline, although fluoroquinolones are known to be an effective alternative for the treatment of SFG rickettsioses. Without control groups of untreated or doxycycline-treated patients, only tentative conclusions can be drawn, despite previous reports of poor responses to ciprofloxacin in murine typhus and our findings suggest that gatifloxacin and ofloxacin may be effective empirical treatment choices in Nepalese patients with UFIs.

Received November 9, 2014. Accepted for publication December 16, 2014.

Published online February 9, 2015.

Acknowledgments: We are grateful to the Patan Hospital patients and their families for their assistance, Thanks to Krishna Prajapat and Bijaya Karanjit from Patan Hospital for laboratory support. We also thank Ampai Tanganuchitcharnchai and Suthatip Jintawon from Mahidol Oxford Tropical Medicine Research Unit for performing the serological studies.
Figure 1. Flowchart of patients from the RCT and the substudy of UFIs. In total, 627 patients were enrolled into the clinical trial comparing gatifloxacin with ofloxacin in the treatment of enteric fever. In total, 316 patients were randomized to receive gatifloxacin, and 311 patients were randomized to receive ofloxacin. One patient was not randomized. There were 109 culture-confirmed enteric fever cases in each arm, leaving 207 and 202 culture-negative patients in the gatifloxacin and ofloxacin arms, respectively. In total, 125 patients were selected for the UFI diagnostic substudy; 29 of these 125 patients were selected from culture-positive enteric fever group, and an additional 96 patients from the culture-negative groups.

Financial support: This work was funded by the Wellcome Trust of Great Britain.

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REFERENCES


