When fever is not malaria

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In the past few years, major efforts in malaria control, alongside a renewed emphasis on malaria elimination and eradication, have led to declines in disease incidence.[1,2] Nowadays, malaria is just one of many causes of fever in most endemic contexts, and often a fairly rare one.[3,4] Investigation of non-malarial causes of fever is therefore a priority, as was underlined at WHO's informal consultation meeting on fever management in January, 2013.[5] In *The Lancet Global Health,* Mayfong Mayxay and colleagues[6] discuss this crucial subject. The investigators provide invaluable information about causes of non-malarial febrile illness in the malaria-endemic country Laos and suggest some indications for evidence-based management of non-malarial and non-dengue fevers. Rapid diagnostic tests might be available for these illnesses at the primary level of care, whereas laboratory facilities are often scarce for other causes.

Mayxay and colleagues had previously done a systematic review of the causes of non-malarial febrile illness in southeast Asia,[7] in which they noted a substantial heterogeneity of study designs, diagnostic methods, and causes of fever. Moreover, previous studies in Laos were concentrated in the capital Vientiane. In their present study of 1938 patients, despite logistical constraints, the investigators did their study at two rural hospitals in northern and southern Laos to account for possible geographical heterogeneity of fever causes. The prospective study design and the high standard of the microbiological methods used are major strengths of this study. Although only a diagnosis that relied on almost 100% specific methods was considered confirmed (conservative approach), the proportion of patients with a confirmed diagnosis (799 [43%]) was not negligible. With exclusion of influenza, two of the most frequently diagnosed, treatable causes of fever were scrub typhus (caused by *Orientia tsutsugamushi*) in 7% of patients, and leptospirosis in 6%.

The investigators suggest use of doxycycline, which is effective for both diseases, as a possible empirical treatment at the primary level of care. Because the consequences of an untreated true case of rickettsiosis or leptospirosis are much greater than are those of unnecessary treatment, Mayxay and colleagues suggest that treatment of many false positives is a reasonable method to minimise the number of true cases remaining untreated. Note that in real (ie, hospital) practice, when fully trained study physicians were in charge of clinical management, almost half the study patients with bacteraemia (not known at the moment of the clinical decision) were left with no effective antibiotic treatment, and so were most of those who were subsequently diagnosed with typhus or leptospirosis. Unfortunately, because of the difficulties in organisation of a proper follow-up, the outcome of a quarter of patients was unknown, and therefore the consequences of the missed treatment could not be assessed. Interestingly, in a similar study in Indonesia,[8] no patient with leptospirosis or rickettsial fever was treated with doxycycline because of a low index of suspicion.

Systematic treatment with doxycycline alone would eliminate some diseases while leaving other severe infections untreated, such as typhoid fever and other bacteraemias for which this antibiotic is ineffective. Although in Mayxay and colleagues' study, typhoid fever and other bacteraemias were identified less frequently than other infections, this finding could be partly due to the logistical constraints (eg, sample transport to reference laboratory) acknowledged by the investigators, which could have affected the sensitivity of blood culture for *Salmonella typhi* and other bacteria. Use or no use of a combined therapeutic approach (doxycycline plus another antibiotic) would be dependent on both an accurate cost-effectiveness analysis and the level of care, with additional consideration that other bacterial infections, such as pneumonia, that are less likely to yield a microbiological isolation in blood, are also difficult for rural health workers to diagnose clinically (cough was common in some of the confirmed causes). Other possible bacterial causes, such as urinary infections, were not specifically targeted.

Studies of causes of non-malarial febrile illness with rigorous microbiological methods and clinical assessment are urgently needed in different epidemiological contexts to provide the best available evidence to inform a clinical management that remains largely empirical. Equally, research in diagnostics should focus on accurate, point-of-care techniques, not only for malaria, but also for non-malarial febrile illness, according to local epidemiology.[8] In addition

to diagnostics, which could ideally combine the most common local causes in the same device,[9] another line of investigation concerns possible generic biomarkers of bacterial infection or clinical severity.[10,11] Mayxay and colleagues noted, for example, that C-reactive protein (CRP) concentrations of 5 mg/L or more had some predictive potential for a bacterial infection, although CRP was higher than this cutoff in 71% of the identified viral causes and therefore might not contribute much to more focused treatment.

Despite some weaknesses regarding clinical issues and the exclusion of children younger than 5 years—a particularly vulnerable group—this study is an excellent example of a local study with global implications, which clearly shows the need for a sound knowledge base for algorithms in development of clinical guidelines.

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