Differentiating dengue from other febrile illnesses: a dilemma faced by clinicians in dengue endemic countries

See Articles page e361

Many countries experienced large dengue outbreaks in 2022 and it is predicted that the incidence of dengue will further increase and spread to many geographical regions in the future due to climate change.[1] Although most individuals infected with the dengue virus develop an asymptomatic or mild illness, some individuals develop fluid leakage leading to dengue haemorrhagic fever, severe bleeding, shock, and organ dysfunction.[2] As there is no specific treatment for dengue, all patients who have suspected dengue are closely monitored to identify the development of complications so that timely supportive interventions can be carried out. Early detection of fluid leakage and complications have markedly reduced the case fatality rates from dengue to less than 0·5% in most countries, whereas many countries reported case fatality rates of more than 5–10% when they first had dengue outbreaks.[3]

Patients with dengue present with a sudden onset of fever accompanied by headache, myalgia, arthralgia, loss of appetite, and sometimes vomiting—as seen in many other infections.[2] As a result, health-care facilities that have been overwhelmed during dengue outbreaks have the added challenge of differentiating dengue from COVID-19, influenza, and other febrile illnesses, which are currently causing outbreaks in several regions in the world. Although specific point-of-care diagnostics (eg, the dengue NS1 antigen test) are available for detecting patients with acute dengue, the sensitivity of this test is less than 70% after 72 h of illness, especially in patients with a secondary dengue infection.[4,5] Furthermore, many countries endemic for dengue do not have adequate resources to carry out such tests in all febrile patients presenting to their out-patient departments for treatment. Therefore, there is an urgent need to identify clinical diagnostic indicators that can differentiate dengue from other febrile illnesses during early illness.

To address this important question, Kerstin D Rosenberger and colleagues[6] have carried out an extensive longitudinal study in eight countries in Latin America and southeast Asia over a period of 6 years. This study recruited patients with a febrile illness during the first 84 h of the onset of illness, to identify clinical and laboratory parameters that could be incorporated into predictive models to differentiate dengue from other febrile illnesses. The authors show that the presence of cough and rhinitis was more likely to indicate other febrile illnesses, whereas the presence of anorexia, mucosal bleeding, and flushing was strongly associated with dengue. However, 17–25% of patients who had dengue presented with cough during the first 2–5 days of illness. This observation that some patients with dengue do indeed have respiratory symptoms is as important finding, which supports findings in other studies, that the presence of respiratory symptoms does not exclude dengue infection.[7] Flushing and mucosal bleeding were found to be positively associated with the clinical diagnosis of dengue over the course of illness. Although flushing is an important clinical feature, this might be a less reliable sign in some patients in south Asia and Africa, where flushing can be more difficult to observe on dark skin tones. Although thrombocytopenia and leukopenia are seen in many other viral infections, such as chikungunya, SARS-CoV-2, Zika virus, viral haemorrhagic fevers, and influenza, the thrombocytopenia is usually not as marked as in dengue infections and usually occurs later.[8] Therefore, as shown by Rosenberger and colleagues, compared with many other febrile illnesses in different regions in the world, thrombocytopenia and leukopenia during day 2–5 of illness was strongly associated with dengue.

Rosenberger and colleagues have also evaluated the usefulness of the WHO 2009 dengue warning signs[9] in identifying patients with dengue. However, as clinical features such as persistent vomiting, liver enlargement, clinical fluid accumulation, lethargy, and restlessness was present in a lower frequency, they could not include these clinical features in the analysis. Abdominal pain, which was one of the warning signs included, was not shown to be specific for dengue. In a different study,[10] which included adults and children, the dengue warning signs were shown to have an overall sensitivity of 77·3% and specificity of 39·7% to predict the progression to severe dengue. However, in adults the sensitivity was lower than in children, with a sensitivity of 66·7% and a specificity of 45·2%. Although the sensitivity and specificity of the less common WHO warning signs in

differentiating dengue from other febrile illnesses was not evaluated by Rosenberger and colleagues, their presence could still have positive predictive value for a dengue diagnosis in the subset of people who develop them. However, the WHO dengue warning signs do appear to have a low sensitivity and specificity in identifying people who are likely to progress to severe disease.

In conclusion, in this important, large, longitudinal, and comprehensive study, Rosenberger and colleagues have identified clinical and laboratory predictors that can be used in early illness to support differentiation of dengue infection from other febrile illnesses, highlighting the importance of an improved availability of facilities for blood counts in countries endemic for dengue. The authors will follow up with a separate analysis of the predictors of severe dengue disease. The usefulness of these clinical and laboratory parameters can be further strengthened by the availability of cheaper point-of-care diagnostics with higher sensitivity and specificity than the diagnostics currently available.

We declare no competing interests.

*Gathsaurie Neelika Malavige, Ananda Wijewickrama, Graham S Ogg
gathsaurie.malavige@ndm.ox.ac.uk

Allergy, Immunology and Cell Biology Unit, Department of Immunology and Molecular Medicine, Faculty of Medical Sciences, University of Sri Jayawardenapura, Nugegoda 10250, Sri Lanka (GNM, GSO); National Institute of Infectious Diseases, Angoda, Sri Lanka (AW); MRC Human Immunology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK (GNM, GSO)

1 Colón-González FJ, Sewe MO, Tompkins AM, et al. Projecting the risk of mosquito-borne diseases in a warmer and more populated world: a multi-model, multi-scenario intercomparison modelling study. *Lancet Planet Health* 2021; **5:** e404–14.
2 WHO. Comprehensive guidelines for prevention and control of dengue fever and dengue haemorrhagic fever. New Delhi: World Health Organization, 2011.
3 Malavige GN, Jeewandara C, Ghouse A, Somathilake G, Tissera H. Changing epidemiology of dengue in Sri Lanka—challenges for the future. *PLoS Negl Trop Dis* 2021; **15:** e0009624.
4 Santoso MS, Yohan B, Denis D, et al. Diagnostic accuracy of 5 different brands of dengue virus non-structural protein 1 (NS1) antigen rapid diagnostic tests (RDT) in Indonesia. *Diagn Microbiol Infect Dis* 2020; **98:** 115116.
5 Paranavitane SA, Gomes L, Kamaladasa A, et al. Dengue NS1 antigen as a marker of severe clinical disease. *BMC Infect Dis* 2014; **14:** 570.
6 Rosenberger KD, Phung Khanh L, Tobian F, et al. Early diagnostic indicators of dengue versus other febrile illnesses in Asia and Latin America (IDAMS study): a multicentre, prospective, observational study. *Lancet Glob Health* 2023; **11:** e361–72.
7 Bodinayake CK, Tillekeratne LG, Nagahawatte A, et al. Evaluation of the WHO 2009 classification for diagnosis of acute dengue in a large cohort of adults and children in Sri Lanka during a dengue-1 epidemic. *PLoS Negl Trop Dis* 2018; **12:** e0006258.
8 Raadsen M, Du Toit J, Langerak T, van Bussel B, van Gorp E, Goeijenbier M. Thrombocytopenia in Virus Infections. *J Clin Med* 2021; **10:** 877.
9 WHO. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization, 2009.
10 Liu YE, Saul S, Rao AM, et al. An 8-gene machine learning model improves clinical prediction of severe dengue progression. *Genome Med* 2022; **14:** 33.