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The Diagnostic and Prognostic Value of Dengue Non-Structural 1 Antigen Detection in a Hyper-Endemic Region in Indonesia

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Abstract

As dengue fever is undifferentiated from other febrile illnesses in the tropics and the clinical course is unpredictable, early diagnosis is important. Several commercial assays to detect dengue NS1 antigen have been developed; however, their performances vary and data is lacking from hyper-endemic areas where all four serotypes of dengue are equally represented. To assess the sensitivity of the Bio-Rad platelia Dengue NS1 antigen assay according to virus serotype, immune status, gender, and parameters of severe disease, acute sera from 220 individuals with confirmed dengue and 55 individuals with a non-dengue febrile illness were tested using the Bio-Rad platelia Dengue NS1 antigen assay. The overall sensitivity of the NS1 ELISA was 46.8% and the specificity was 100%. The sensitivity in primary infections was significantly higher than in secondary infections (100% vs. 35.7%). In secondary infections, the sensitivity of NS1 detection was highest in DENV-3 (47.1%), followed by DENV-1 (40.9%), DENV-2 (30%) and DENV-4 (27%) infections. NS1 was less frequently detected in sera with high titers of HI antibodies or in acute samples from patients whose pre-illness sera showed neutralizing antibodies to more than one serotype. The detection of NS1 was higher in females, severe cases, and individuals with lower platelet counts (<100,000/mm^3). While the overall sensitivity of this NS1 ELISA is poor, our data suggest that in secondary infections, detection may be predictive of a more severe illness.

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Introduction

Dengue fever (DF) is a major public health problem with 50 million annual cases worldwide. It has been reported in more than 100 countries and continues to spread to previously unaffected regions[1]. DF is caused by dengue viruses (DENV), which consist of four serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. Infection with any serotype usually results in asymptomatic infection or mild non-specific febrile illness, but in a subset of patients, severe disease develops, characterized by a transient capillary leakage syndrome (dengue hemorrhagic fever/ DHF)[2]. This unpredictable disease course and the need to differentiate DF from other causes of fever make an early and sensitive diagnosis of acute dengue virus infection important.

Non-structural 1 protein (NS1) is encoded by the virus and secreted in a soluble form[3]. Several commercial assays to detect dengue NS1 have been developed recently[4]. Advantages of NS1 tests are: NS1 is detected early in disease, several days prior to the appearance of anti-dengue IgM antibodies[5], and the test is inexpensive, easy, and fast. Moreover, NS1 levels early in dengue disease have been correlated with disease severity [6], suggesting that NS1 tests may also have prognostic value.

Previous studies evaluating the diagnostic value of NS1 antigen assays have had varying results [4,7] (Table S1). Several factors may account for this: proportion of primary vs. secondary infections [4,8-11], timing of sample collection[4,7,8,12,13], infecting serotype[4,7,8,13,14], viremia levels [6,13,15,16] and severity of illness[6,7,15]. A low