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Short Commutation

Triage for Severe Dengue Using Early Severe Dengue Identifier

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Dengue is a mosquito transmitted viral infection. It is the leading arthropod-borne viral disease in the world. Since 1950 the number of people infected has risen steadily and it has become a health threat with an estimated 3.6 billion persons at risk [1]. In distribution also it has become a global problem. While Southeast Asia and India were well known areas of endemicity now South and Central America have also become endemic. Even developed countries like USA where it was considered under control, is also facing the threat of dengue [2]. Dengue which was once considered a pediatric illness is now increasingly being reported in adults as well. This geographic and demographic expansion warrants more studies on dengue infections.

Dengue viruses (DENV) are members of the family *Flaviviridae*, genus *Flavivirus*. They are small, enveloped viruses having a single positive strand of ribonucleic acid (RNA) [3]. There are four serotypes of dengue based on neutralization tests, DENV-1, DENV-2, DENV-3, and DENV-4. Though the serotypes show extensive cross-reactivity, they are distinguishable with the highly specific plaque reduction neutralization test (PRNT) [4]. Human and several sub-human primates are vertebrate hosts of the virus. Virus is transmitted to them by Aedes group of mosquitoes like *A. aegypti, A. albopictus and A. polynesiensis.*

Infection with DENV results in a wide spectrum of clinical presentations. In majority of the infection outcome is asymptomatic. In symptomatic patients, majority recover following a self-limiting illness and only a small portion of patients develop severe disease. Who will progress from non-severe to severe is difficult to define but it is very important concern since an appropriate treatment starting early may decrease the chances of mortality.

In symptomatic patients, natural pattern of disease has three phases: febrile, critical and recovery. Febrile phase usually last 2 - 7 days. Here patient suddenly develops high grade fever. These patients may manifest wide variety of symptoms like nausea, anorexia, vomiting, sore throat, conjunctival injection, facial flushing and frontal headache with retro orbital pain [5]. Severe muscle and bone pain and arthralgia are characteristic and usually more pronounced in the back, justifying it being termed 'break bone fever'.

On days 3 - 7 of illness, defervescence occurs and an increase in capillary

Permeability in parallel with increasing haematocrit levels may occur [6,7]. These changes mark the starting of the critical phase. Patients not having increase in capillary permeability will improve while those showing increase may worsen. Ascites and pleural effusion may be detectable. When a critical volume of plasma is lost, shock occurs. Non-severe dengue is that where patient improves after effervescence.

A general wellbeing ensues if patient survives critical phase. Phase of recovery happens over next 48 - 72 hours and gradual reabsorption of extravascular compartment fluid takes place.

World Health Organization (WHO) in 1997 suggested the dengue classification where symptomatic patients were grouped into three categories as undifferentiated fever, dengue fever (DF) and dengue haemorrhagic fever (DHF). Grades III and IV of DHF were called as dengue shock syndrome (DSS) [8]. This classification of DF/DHF/DSS was widely used but had certain practical difficulties.

In 2009 World Health Organization revised the dengue case definition. The 2009 WHO criteria classify dengue according to lev-

els of severity: non-severe dengue and severe dengue. Non-severe dengue was organized into two subgroups, dengue with warning signs or dengue without warning signs [9].

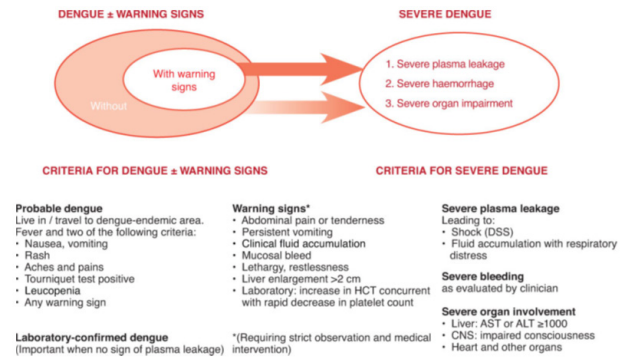

Figure 1: Suggested dengue case classification and levels of severity [9].

How severe dengue develops is not clear but immune enhancement has been suggested as cause of it. In immune enhancement infection by one serotype of dengue virus expands the population of cells that can be infected by a second serotype [10]. Patient with warning signs are more prone to develop severe dengue [11]. These signs include severe abdominal pain, persistent vomiting, lethargy, mucosal bleeding, difficulty in breathing, and on laboratory level a rapid decline in platelet count with an increase in haematocrit.

Increased capillary permeability is hallmark of severe dengue. Increased capillary permeability may lead to hemorrhagic manifestations like petechiae, epistaxis, gastrointestinal bleeding (hematemesis or melena), menorrhagia, and a positive tourniquet test. This continuous capillary-leak syndrome cause fluid loss into tissue spaces and with haemoconcentration and hypotension it can result in shock. DSS manifests in critical phase between fourth and sixth day.

There are no specific anti dengue drugs. Treatment remains supportive, with fluid replacement either orally or by intravenous route. Continuous monitoring of temperature pattern, fluid loss, vital signs and appearance of warning signs is of utmost importance. Such monitoring can be provided in intensive care units and dengue case fatality rate has declined over the last few years because of it. Importance of proper therapy and monitoring is evident in many settings where hospitalized cases show < 1% of case fatality rate9. This rate can exceed 20% if treatment or monitoring is inadequate [12].

Severe complications occur between the fourth and sixth day of illness thus first few days of illness provide an opportunity. If an early definitive diagnosis could be made and patients at increased risk could be identified then their management can also be improved.

Many attempts have been made in the past to identify these clinical signs and symptoms, but with limited success. Inability to differentiate between non-severe and severe dengue leads to over hospitalization and drains the available health resources.

To identify such prognostic indicating factors a large prospective study was conducted in Vietnam from 2010-2013 [11]. Dengue is endemic in Vietnam [13]. This study enrolled 7563 pediatric cases presenting to outpatient clinics in 6 different hospitals with history of fever onset of 3 days or less. To develop a prognostic model a detailed history was taken and certain variables were chosen. They identified four variables as independent correlates of severe dengue. Out of these four variables, three were laboratory based: positive non-structural protein 1 (NS1) rapid test, low platelet count and elevated aspartate aminotransferase (AST). Fourth variable was a symptom, persistent vomiting, which is also a warning sign in WHO classification [9]. If we look closely at these four variables their utility in developing a prognostic model becomes obvious. A rapid test to detect NS1 antigen is widely available. It is not costly and can be performed in any laboratory. Simultaneously NS1 antigen becomes positive in 1 - 2 days of illness making it useful as early prognosis indicator. Platelet count is also cheap and universally available test. Continuous platelet monitoring is useful in early management as well and a continuously reducing platelet count, which is also a warning sign, alarms the clinician at proper time. Reticuloendothelial (RE) system involvement is evident by hepatomegaly and increased AST levels prove involvement of RE system.

They used the history of vomiting, platelet count, AST level, and NS1 rapid test result to make a nomogram (Figure 2). This nomogram converts these histories into numerical score and this collective score is used to predict the risk of severe dengue. Authors called this prognostic model Early Severe Dengue Identifier (ESDI).

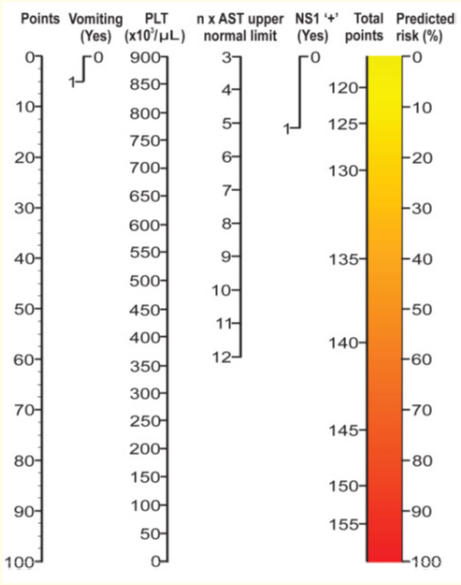

Figure 2: Nomogram of the prognostic model to predict the risk of severe dengue. A vertical line from a predictor value to the "points" axis assigns points to the 4 required variables: vomiting, platelet count (PLT), nonstructural protein 1 (NS1) rapid test status, and aspartate aminotransferase (AST) level. The sum of these points (total points) can then be translated to the corresponding predicted risk of severe dengue [11].

ESDI showed sensitivity of 87% (95% confidence interval [CI], 80% – 92%), and specificity 88% (95% CI, 87%–89%). Positive and negative predictive values were and respectively. The low positive predictive value, 10% (95% CI, 9% – 12%), was due to low prevalence of severe dengue results. The drawback of low positive predictive value is that it will lead to overestimated number of true severe dengue cases. A high negative predictive value, 99.8% (95% CI, 99.6% – 99.9%), ensured that ESDI accurately predicts non-severe dengue. It helps in ruling out hospitalization for low ESDI score patients.

The ESDI could be helpful as an evidence-based tool to improve triage and management. It will help to resolve the dilemma of the physicians sitting in emergency departments who see a patient with 3 days of fever and suspected dengue and question themselves, whether to send the patient home or admit for observation. A low ESDI score will boost the confidence of the physician that he is taking right decision by sending the patient home.

Parameters used in calculating ESDI were well known but to use them collectively to generate a predictive score is appreciable. ESDI could be of much value in countries where dengue is endemic. More studies in such setups will throw light on complexity of dengue progression.

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