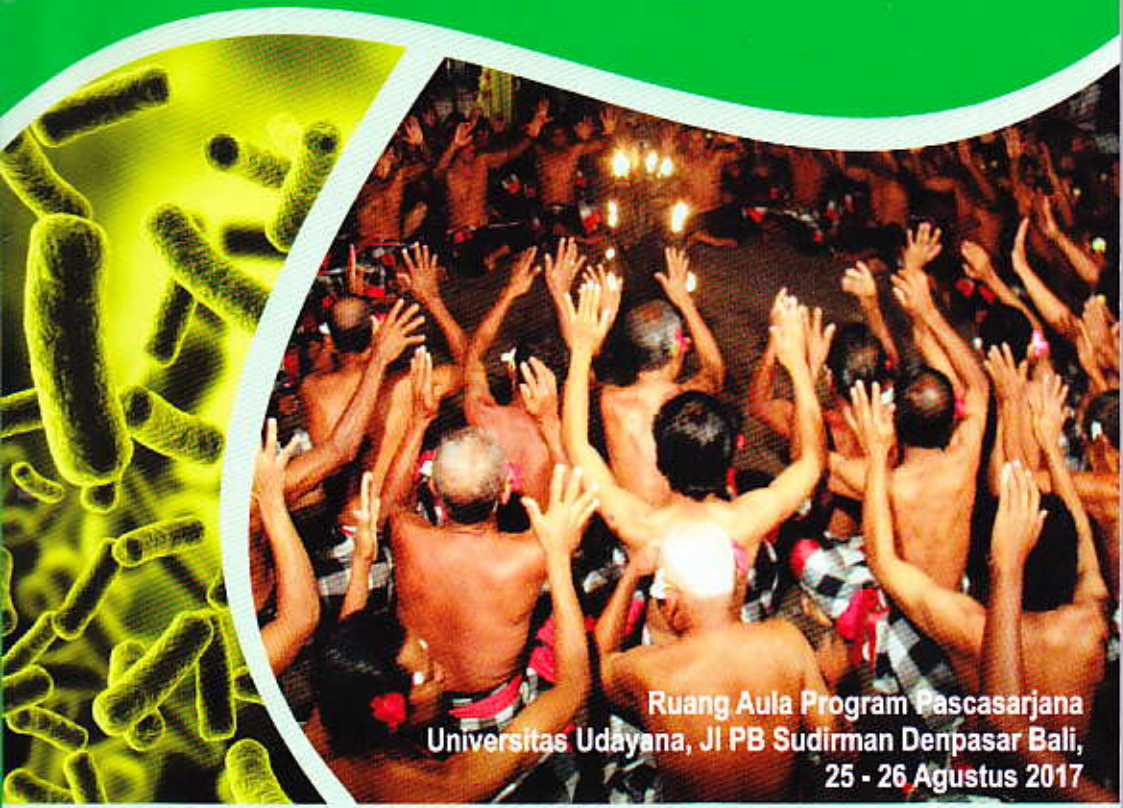
PROCEEDING BOOK

BIDs 9 & BAMHOI 4

Bali Infectious Disease Symposium (BIDs)-9
Bali Annual Scientific Meeting for HIV & Opportunistic Infection (BAMHOI-4)

Reappraisal of Infectious Diseases and HIV Infection : Focus on Current Management Approach



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ABSTRACT

CURRENT ADVANCE IN DENGUE INFECTION

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Dengue virus (DENV), a flavivirus, can cause a mosquito-borne infection to human. Dengue is now established as one of among the important arboviral infection worldwide due to its major impact as an emerging infectious disease with significant public health burden. Dengue is endemic in over 100 countries with exceeding 40% world population reside in those endemic area. These leave about 3.6 billion people at risk for infection: each year around 400 million people are infected with DENV; 100 million become ill and among those 21,000 deaths attributed to Dengue infection.

The DENV, descend from family Flaviviridae and genus Flavivirus, is a single strand RNA positive virus. Within the genus Flavivirus, also includes the Zika virus, Japanese encephalitis virus, Yellow Fever virus, Thick Borne encephalitis virus, West Nile Virus and some other viruses which can causing encephalitis as clinical manifestation.[1] The clinical manifestations of DENV infection in human is vary from asymptomatic, self limiting infection to severe, life-threatening syndrome, and some cases the manifestation can be obscure as the expanded dengue syndrome.[2] One report in year 2013 mentioned on the discovery of the fifth serotype of DENV, but most of academic publication only mentioned the four antigen's different serotypes of the

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virus, namely DENV-1, DENV-2, DENV-3, and DENV-4.[3,4] Humans are the primary host of DENV transmitted by peridomestic mosquito species of *Aedes aegypti* and *A. albopictus*

The **Dengue Virus**

Differs from other members in Flaviviridae family which were mostly monotypic species, DENV has multiple (I – 4) serotypes characterized by virus plaque reduction neutralization assays. The difference in serotypes could be responsible for different severity manifestation of infection.[5] Recently, a phylogenetically distant serotype, the fifth serotype, has been mooted. The confirmation of the fifth serotype to be considered as DENV-5 was under studies, if confirmed, it will impact the strategy in combating dengue fever: the currently available vaccine will be deemed intrinsically suboptimal and the refinement of current guidelines for diagnosis, treatment and control will face major update.

The **Pathogenesis**

Dengue pathogenesis is linked to host immune system, triggered by DENV infection. After incubation period of 3 – 14 days with average 7 days (Figure 1), the infection usually mild in primary infection; however, secondary infection with different serotypes or multiple infection with different serotype may cause severe infection range from Dengue Hemorrhagic Fever (DHF) to dengue shock syndrome (DSS).[6]

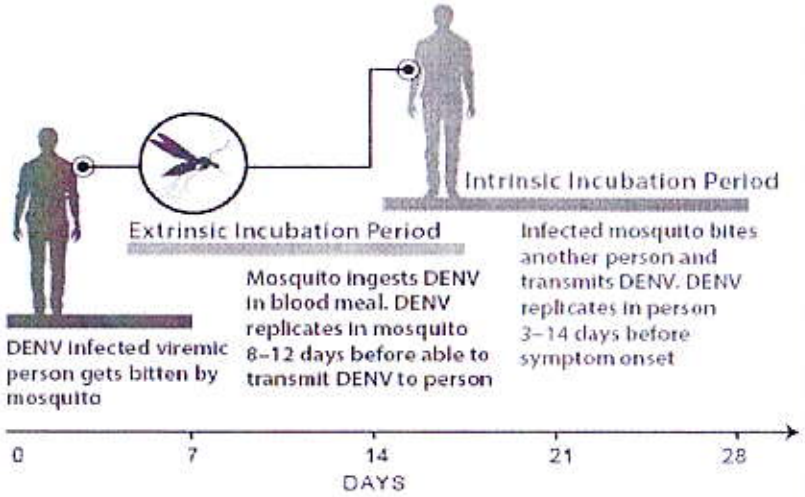

Figure 1. The time line of mosquito borne infection

After infection of DENV, an individual can develop lifelong serotype specific antibody and short term cross-immunity against other serotypes lasting for about two months. Previous primary infection elicits non-neutralizing, cross-reactive antibodies thus further involved in antibody-dependent enhancement (ADE) and causing heavy viral burden. The major replication sites for DENV are cells of monocyte-macrophage lineage; other tissues in the body can also be infected such as the liver, brain, pancreas and heart.[6,7]

Antigen presenting dendritic cells and both humoral and cell-mediated immune response are responsible for dengue clinical manifestations. T-cell memory proliferation and pro-inflammatory cytokines production leads to dysfunction of endothelial cells dysfunction in vasculature resulting plasma leakage.[7,8] The leakage is

hallmark of DHF and DSS, and can cause Hemoconcentration, hypoalbuminemia and third space fluid accumulation (e.g. ascites and pleural effusion). Hemorrhage usually related to coagulation disorders and thrombocytopenia.[8]

Cases with severe infection, loss of intravascular fluid lead to tissue hypoperfusion, lactic acidosis, hypoglycemia, hypocalcemia and multiple organ dysfunctions. The dysfunction of organ such as myocarditis, encephalopathy and liver cells necrosis can be as a direct effect of viral damage on tissue and subsequent tissue inflammation. Severe dengue infection in infant during primary infection could manifest as severe dengue due to trans-placental transfer of maternal antibody that enhancing infant immune response to primary DENV infection.[9,10]

Classification, diagnosis and management

The traditional classification of Dengue infection based on WHO 1997 divide as Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) (Figure 2).[11,12] The 1997 dengue case definition was limited in terms of complexity and applicability in clinical setting. The new WHO classification was made based on study in seven countries in Asia and Latin America, classified dengue into Dengue without warning sign, Dengue with warning sign and Severe Dengue (Figure 3).

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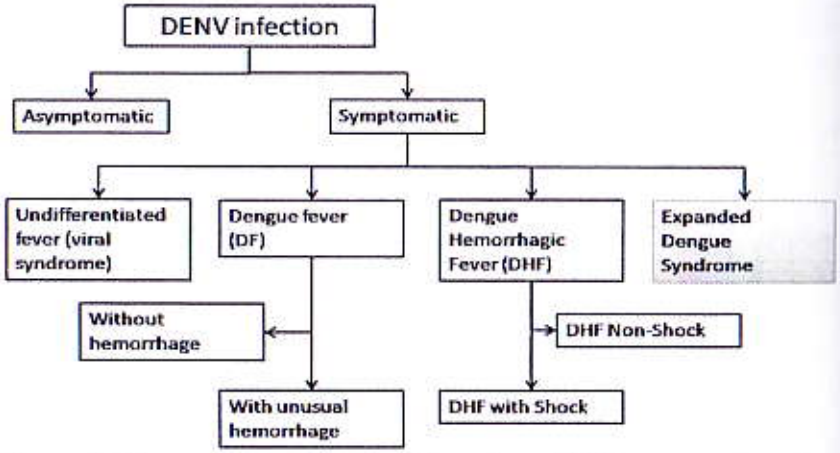


Figure 5. Dengue classification based on WHO comprehensive guideline 2012

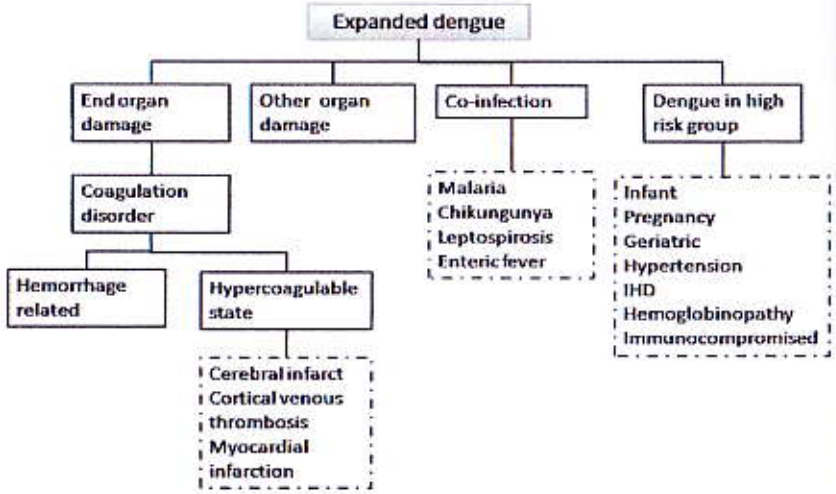
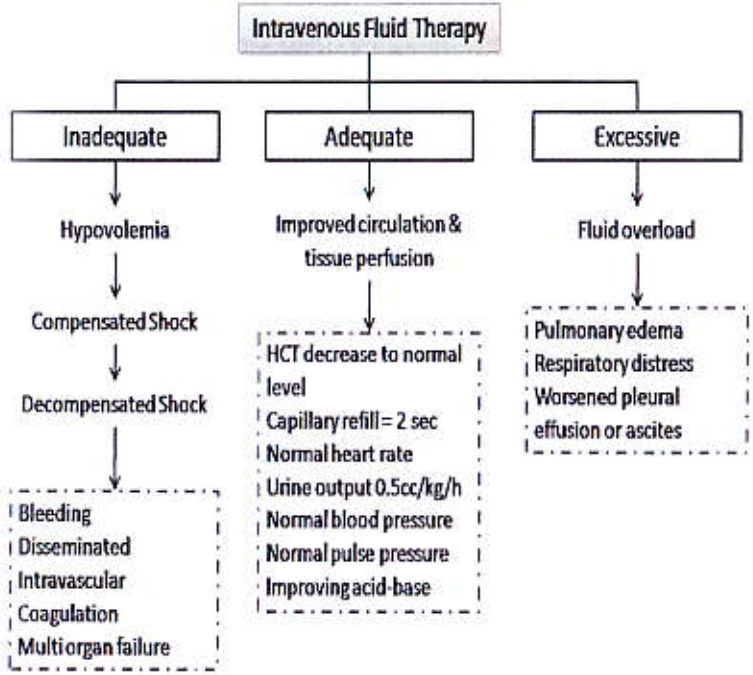


Figure 6. Expanded dengue syndrome manifestations

The management of Dengue mainly concerned for symptomatic relief with appropriate hydration as the major important aspect.[14] It is important to retain balanced fluid, for inadequate or excessive fluids may lead to disastrous state (Figure 7).



Patients can be discharged from the hospital when: without fever for 24 – 48 hours, improvement of clinical status (general well being, appetite, hemodynamic, urine output, without respiratory distress), increasing trend of platelet, and stable HCT with adequate oral fluid intake without IVF.[13,14]

Preventing Dengue Infection

Insect bite prevention and vaccination play role in preventing dengue infection. One dengue vaccine has been licensed, Dengvaxia® (CYD-TDV, Sanofi Pasteur). Approximately five additional dengue vaccine candidates are in clinical development, with two candidates (developed by Butantan and Takeda) expected to begin Phase III in 2016. The Dengvaxia, recombinant tetravalent vaccine, licensed for individual age 9 – 45 years of age living in endemic area. Pooled efficacy was 79.1% varied by serostatus, serotype of virus and age when vaccinated: higher in prior exposure to DENV, serotype 3 and 4, and age over 9 years.[15]

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