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Dengue, Dengue Haemorrhagic Fever and Dengue Shock Syndrome in the Context of the Integrated Management of Childhood Illness

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List of abbreviations

AFR	WHO African Region
AMR	WHO/PAHO Americas Region
DF	dengue fever
DHF	dengue haemorrhagic fever
DSS	dengue shock syndrome
IMCI	Integrated Management of Childhood Illness
ORS	Oral Rehydration Solution
PAHO	Pan-American Health Organization
SEAR	WHO South-East Asian Region
TT	Tourniquet test
WHO	World Health Organization
WPR	WHO Western Pacific Region

Executive summary

Dengue is not included in the generic Integrated Management of Childhood Illness (IMCI) algorithm but it is an important differential diagnosis of fever in children presenting to first-level health facilities in tropical Asia and Latin America. There has been no previous summary of existing dengue guidelines to explore their usefulness in the context of IMCI and to identify questions for research.

This review summarises the virology, transmission and pathogenesis of dengue, its significance by region, and its epidemiologic, demographic, and clinical features; assesses existing diagnostic guidelines; evaluates the evidence-base for current treatment guidelines; examines IMCI adaptations of dengue algorithms; and discusses experience with home management of dengue and recognition of specific clinical signs and symptoms by caretakers. The studies included in this review were identified by a search on PubMed of the scientific literature published in English from 1966 to the present.

Based on this review, further development of dengue algorithms is suggested, followed by recommendations for necessary research and for country-specific adaptations.

Introduction

Dengue is an important differential diagnosis of fever in children presenting to first-level health facilities in tropical Asia and Latin America. Dengue is not included in the generic Integrated Management of Childhood Illness (IMCI) algorithm, but due to its importance, it was incorporated in several Asian and Latin American IMCI adaptations. Most of these adaptations have not been tested for their performance.

Prior to and in parallel with IMCI, there have been guidelines developed on the management of dengue. The "Guidelines for Treatment of Dengue Fever/Dengue Hemorrhagic Fever in Small Hospitals" developed by the WHO Regional Office is widely used (1).There has been no previous summary of existing dengue guidelines to explore their usefulness in the context of IMCI and to identify questions for research. The objectives of this review are:

- to summarise the virology, transmission and pathogenesis of dengue, its significance by region, and its epidemiologic, demographic, and clinical features;
- to assess existing diagnostic guidelines;
- to evaluate the evidence-base for current treatment guidelines;
- to examine IMCI adaptations of dengue algorithms;
- to search the literature for experience with home management of dengue and recognition of specific clinical signs and symptoms by caretakers; and
- to make suggestions for how to proceed in terms of further development of dengue algorithms, research, and country-specific adaptations.

The studies included in this review were identified by a search on PubMed of the relevant scientific literature published in English from 1966 to the present. Dengue was linked with the following key words: virology, antibody, transmission, pathogenesis, incidence, prevalence, distribution, burden, epidemiology, diagnosis, haemorrhage, shock, treatment, algorithms, home care, treatment seeking, and IMCI. Other material was obtained from various sources (e.g. WHO website and unpublished reports).

Background

VIROLOGY, TRANSMISSION, AND PATHOGENESIS

Dengue is caused by infection with one of four dengue virus serotypes, i.e. dengue 1-4. Infection with one serotype provides life-long immunity against reinfection by that same serotype, but not against the other serotypes. The vast majority of dengue infections are asymptomatic but a proportion manifest as a non-specific febrile illness or progress to severe disease.

Aedes aegypti is the principal mosquito vector of dengue. Adult mosquitoes shelter indoors and bite during the daytime. They are adapted to breed around human dwellings, in water containers, vases, cans, old tyres and other discarded objects (2). The secondary vector for dengue virus is *Ae albopictus*, which contributes significantly to transmission in Asia and whose presence is spreading in Latin American countries. Dengue outbreaks have also been attributed to *Ae polynesiensis* and *Ae scutellaris*, but to a lesser extent.

Uninfected mosquitoes acquire the virus when they feed on a viraemic individual. The virus develops in the mosquito for 1 to 2 weeks and once it reaches the salivary glands, it can be transmitted to humans during feeding attempts, which may occur several times a day over the rest of the mosquito's lifetime of 1 to 4 weeks (total). The virus can have a significant transmission potential (Ro) in certain areas (3). After an infectious mosquito bite, the virus replicates in local lymph nodes and within 2 to 3 days disseminates via the blood to various tissues. The virus circulates in the blood typically for 4 to 5 days during the febrile phase and is cleared within a day of defervescence (4).

The pathogenesis of severe dengue is not well understood. It has been observed that the risk of severe disease is increased at least 15-fold during repeat (secondary) compared to primary dengue infections (5). Various mechanisms have been suggested, including antibody-dependent enhancement or ADE (6, 7), complement activation by virus-antibody complexes (8, 9) and T-cell mediated immunopathology (10). Differences in virulence of viral genotypes have also been suggested to explain the pathogenesis of severe dengue (11-13).

The dominant hypothesis, ADE, postulates that during secondary infection, pre-existing non-neutralising antibodies opsonise the virus and enhance its uptake and replication in macrophages. Secondary infections have been shown to lead to higher viral loads and the manifestations of severe dengue are believed to be due to virus replication which induces infected monocytes to release vasoactive mediators (14-16). ADE may not completely