

~ CHAPTER 2 ~

LITERATURE REVIEW

2.1 Scope of Review

The following review of the past work done in the area of dengue disease is divided into two parts. The first part covers the past profile and management of dengue patients in the Malaysian milieu. The second part delves into the symptomatology of dengue infection, in particular the clinical and laboratory features that define and distinguish the three types of dengue infection – dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

2.2 Profile and Management of Dengue Patients

For the period of 1988 to 1992, Poovaneswari (1993) found that majority of the reported DF/DHF cases came from the 5 to 29 years age group. The age specific morbidity rate for DHF was the highest for the 20 to 29 age group, followed by the 10 to 19 years and 30 to 39 years age group. Singh (2001) reported high incidence rate for the school-going and the middle age group from 1991 to 1998. He contended that the high incidence rate in school appeared to correspond to the relatively high *Aedes* Index (percentage of site positive of *Aedes* out of total premises inspected) in schools. Those aged below 4 and above 55 years old were seldom affected because they were usually at home where the *Aedes* Index was low during that period.

There was an unequal distribution of male and female for the majority of the outbreaks in the country as observed by Singh (2001) for the period of 1992 to 1998.

Slightly more male than female were reported with male to female ratio of 11:10 to 13:10 for the said period.

According to Singh (2001), from 1995 to 1998 the percentage of Malay dengue cases ranged from 39.8% to 55.9%, followed closely by Chinese which ranged from 31.0% to 42.4% while Indians from 7.9% to 8.2%.

Tham (2001) noted the relatively low *Aedes* Index (AI) of only 0.6% in houses and shops. In comparison, areas such as construction sites, schools, factories, cemeteries, rubbish dumpsites, vacant land and children playgrounds recorded high AI. The fact of high AI even though only a small number of these areas were examined leads Tham to advocate for more inspection in the said areas.

Poovaneswari (1993) acknowledged that the serology examination was not done for all reported cases. According to Singh (2001), from 1995 to 1999, the proportion of serologically confirmed DF/DHF cases over reported cases based on clinical diagnosis ranged from 40.9% to 50.2%.

Poovaneswari (1993) noted the delay in the notification in 34.5% of the dengue cases from a sample analysis of cases reported in 1992. An analysis of a sample of laboratory results revealed that out of 1,026 serologically confirmed dengue cases, only 26% was duly notified as dengue.

2.3 Clinical and Laboratory Findings on Dengue Infection

According to a comprehensive guide on dengue infection published by WHO (1997a), common clinical features of DF range from mild febrile syndrome to sudden high fever, severe headache, pain behind the eyes (retro-orbital), muscle and bone or joint pains (myalgia/arthralgia), nausea and vomiting, and rash depending on the age of the patient in many situations. Unusual haemorrhages (bleeding) may be observed. Bleeding complications such as epistaxis, gingival bleeding, gastrointestinal bleeding, haematuria and menorrhagia are common in some epidemics. Leukopenia (low white blood cell count) usually occurs in patients with DF. The number of platelets in the blood may also reduce, a syndrome known as thrombocytopenia.

DHF is differentiated from DF in that there is a leakage of plasma shown by the elevated haematocrit which reflects haemoconcentration (increased red blood cell mass due to reduced plasma volume). Concurrently, thrombocytopenia, which is a distinctive clinical laboratory finding of DHF, can also be observed. These two symptoms provide the basis for the clinical diagnosis of DHF. Other major clinical presentations of DHF include high fever, haemorrhagic tendencies and sometimes, enlarged liver (hepatomegaly) and circulatory failure. Epigastric discomfort and generalized abdominal pain are common in children with DHF.

Uncorrected plasma loss during the course of DHF can lead to DSS with signs of circulatory failure evidenced by rapid and weak pulse with narrowing pulse pressure or hypotension (systolic pressure <90mmHg for those aged 5 years or older) with cold,

clammy skin and restlessness. The excerpt below taken from the WHO guideline best describes patients with DSS.

“There are the typical signs of circulatory failure: the skin becomes cool, blotchy, and congested; circumoral cyanosis is frequently observed; the pulse becomes rapid. Patients may initially be lethargic, then become restless and rapidly enter a critical stage of shock. Acute abdominal pain is a frequent complaint shortly before the onset of shock.”

In classifying dengue infection, it should be noted that DSS is essentially the severe form of DHF. According to WHO, DHF can be categorized into four grades of severity, namely DHF Grade I, II, III and IV. DHF cases with grading of I and II are termed the normal DHF while III and IV are analogous to DSS. All four dengue virus serotypes (DEN-1 to DEN-4) have been linked to the different severity grading of DHF.

In providing the criteria for provisional diagnosis of DHF/DSS, WHO states that the clinical observation of high fever of acute onset and haemorrhagic manifestation (at least a positive tourniquet test) coupled with one of the laboratory findings of either thrombocytopenia (100,000 cells per mm³ or less) or haemoconcentration (hematocrit elevated at least 20% above average for age, sex and population) are sufficient to establish a provisional diagnosis of DHF. If shock is present in patients with provisional diagnosis of DHF, the diagnosis of DSS is supported.

WHO emphasized the need for laboratory confirmation of dengue infection. The variability and often over-lapping clinical symptoms associated with dengue infection render it inappropriate to adopt a detailed and clear-cut clinical definition of such disease.

Given the overwhelming multitude of clinical and laboratory manifestations of dengue infection, it is necessary to identify and summarize these symptoms based on the WHO case definition for each category of dengue infection – DF, DHF and DSS. Table 2.1 encapsulates the key symptoms cited in the preceding literature review. The presentation is according to the WHO proposed definition.

Table 2.1: World Health Organization case definition for Dengue Fever, Dengue Haemorrhagic Fever and Dengue Shock Syndrome

Case	Definition
DF	<p>Fever with two or more of the following:</p> <ul style="list-style-type: none"> ○ Headache ○ Retro-orbital pain ○ Myalgia ○ Arthralgia ○ Rash ○ Haemorrhagic manifestations ○ Leukopenia
DHF <i>(can be further classified as DHF Grade I or II)</i>	<p>The following four criteria must be present:</p> <ol style="list-style-type: none"> 1. Fever, or history of acute fever 2. Haemorrhagic tendencies, evidences by: <ul style="list-style-type: none"> ○ Positive tourniquet test ○ Petechiae, ecchymoses or purpura ○ Bleeding from mucosa, gastrointestinal tract, injection sites or other locations ○ Haematemesis or melaena 3. Thrombocytopenia (100,000 cells per mm³ or less) 4. Plasma leakage evidenced by: <ul style="list-style-type: none"> ○ Hematocrit changes ≥ 20% ○ Signs such as pleural effusion, ascites and hypoproteinaemia.
DSS <i>(also known as DHF Grade III or IV)</i>	<p>All the above signs for DHF must be present, plus circulatory failure manifested by:</p> <ul style="list-style-type: none"> ○ Rapid and weak pulse ○ Narrowing pulse pressure (< 20 mmHg (2.7 kPa)) <p>or manifested by:</p> <ul style="list-style-type: none"> ○ Hypotension ○ Cold, clammy skin and restlessness.

Source: World Health Organization, (1997a).

Note: The grading severity of DHF is further defined in the WHO 1997 guidelines from which the above information is cited.

In an article on the outpatient management of dengue infection at the University Hospital, Kuala Lumpur (now known as University Malaya Medical Centre or UMMC), Chin (1993) quoted that patients with the following features were referred for admission, according to the admission protocol for adult dengue cases at the said hospital.

- Evidence of bleeding other than cutaneous petechiae;
- Blood pressure of less than 90/60 mmHg;
- Platelet count of less than $50,000/\text{mm}^3$; and
- Hematocrit of more than 50% increase.

In a two-month study on 162 clinically diagnosed dengue patients at the University Hospital in 1991, Chin (1993) noted the admission rate was 43.8%. Most of the cases were categorized as dengue fever (82.7%), while 13% was DHF and 4.3% DSS. No fatality occurred during the period. The primary reason for admission was severe thrombocytopenia (less than $50,000$ per mm^3), which accounted for 58.6% of total admission. This was followed by raised haematocrit (19.2%), hypotension (7.1%) and bleeding (7.1%). Chin claimed that if all patients with thrombocytopenia¹ of less than $100,000$ per mm^3 were to be admitted, the admission rate would have been 72.8%. Nevertheless, with the current low admission rate and high compliance by doctors and patients, no adversity was recorded suggesting the current protocol was practical for the hospital.

¹ The number is a direct count using a phase-contrast microscope. The normal level is 200,000-500,000 mm^3 . For count less than $100,000$ mm^3 , it is considered low and is recognized as one of the criteria for provisional diagnosis of DHF/DSS (WHO, 1997a).

Taib et al. (1983) noted that the clinical and laboratory manifestations of 46 adults admitted to the University Hospital during the 1982 outbreak in Malaysia were quite comparable to those in the 1973 to 1974 outbreak (Table 2.2). However, they found a lower incidence of positive tourniquet test but higher percentage of haemoconcentration in the DHF cases of the 1982 outbreak. In addition, hepatomegaly and lymphadenopathy were observed more frequently. All DHF patients in both outbreaks suffered thrombocytopenia.

Table 2.2: Clinical and laboratory manifestations of adult DF/DHF cases in the 1973-74 and 1982 outbreaks in Malaysia.

	Findings in % Cases			
	1982 ^a		1973 – 74	
	DF	DHF	DF	DHF
Fever	90	87	100	100
Positive tourniquet test	19	20	4.2	82.6
Petechiae / ecchymosis	48	60	12.5	65.2
Hepatomegaly	3	67	37.5	47.8
Lymphadenopathy	10	47	12.5	26.1
Leukopenia	55	67	54.2	60.9
Thrombocytopenia	87	100	58.3	100
Haemoconcentration	0	40	8.3	13.0
Gastrointestinal bleeding	0	13	0	4.3
Epistaxis (Nose-bleed)	6	7	0	8.6

^a Observed from 46 adults admitted to University Hospital, Kuala Lumpur. Two-thirds had the classical dengue fever, while the rest had DHF.

Source: Modified from Taib et al., (1983).

In the same study, Taib et al. (1983) also explained that the clinical and laboratory findings in children with DHF correlate well with the WHO diagnostic criteria derived from the values in the Thai children, except there was slightly higher percentage of lymphadenopathy and leukopenia in the 1982 outbreak. The study also documented high

incidence of hepatomegaly in this dengue episode. For comparison purpose, the observed frequency of clinical and laboratory findings in Thai children diagnosed as DHF were presented in Table 2.3.

Table 2.3: Comparison of DHF manifestations in 34 children admitted to University Hospital, Kuala Lumpur in the 1982 outbreak with the findings in Thai children diagnosed as DHF

	Percentage of DHF Cases (%)	
	University Hospital	Thai
Fever	89	76 – 100
Positive tourniquet test	84	76 – 100
Petechiae / ecchymosis	53	26 – 50
Confluent petechial rash	-	1 – 25
Maculopapular rash	-	1 – 25
Myalgia / arthralgia	-	1 – 25
Hepatomegaly	95	76 – 100
Lymphadenopathy	63	26 – 50
Leukopenia	63	26 – 50
Thrombocytopenia	95	76 – 100
Haemoconcentration	32	-
Gastrointestinal bleeding	5	1 – 25
Epistaxis	26	-
Shock	-	26 – 50
Pre-shock symptoms	5	-

Source: Modified from Taib et al., (1983) and World Health Organization, (1997a).

In an attempt to distinguish the clinical features of DF and DHF, Rudnick (1986) compared the clinical pictures of the first DHF outbreak in Penang (1962-64) to the subsequent DF outbreak (1967-68) and found that the incidence of haemorrhagic signs, circulatory collapse (shock) and hepatomegaly was relatively higher in the 1962 DHF episode (Table 2.4). The frequency of fever, abdominal pain, lymphdenopathy, headache and vomiting were fairly similar for both outbreaks. Comparatively, the 1967 DF

outbreak recorded higher incidence of myalgia / arthralgia, conjunctival injection and pharyngeal / tonsillar inflammation. Rudnick also explained that the haemorrhagic signs reported for the 1967 DF cases were mild and transitory.

Table 2.4: Clinical features compared in 61 DHF cases (1962-64) and 102 DF cases (1967-68) in Penang, Malaysia.

	Findings in % cases	
	DF (1967 – 68)	DHF (1962 – 64)
Fever	100	100
Abdominal pain	43	45
Lymphadenopathy	30	33
Headache	33	26
Vomiting	47	76
Haemorrhagic signs	7	62
Shock	3	45
Hepatomegaly	3	43
Myalgia / arthralgia	43	9
Conjunctival injection	20	7
Pharyngeal / tonsillar injection	70	7

Source: Modified from Rudnick et al., (1986).

In a similar attempt to classify dengue infection, George (1993) wrote that the most important feature to look for was the evidence of plasma leakage. She explained that the presence of serous effusion and a rising hematocrit confirmed the evidence of plasma leakage, which is the most important criterion that differentiates DF from DHF.

2.4 Summary

By and large, DF is marked by the sudden onset of high fever, usually biphasic (two peaks), severe headache, nausea, pain behind the eyes, muscles and joints. At times, unusual bleeding complications can accompany DF. According to WHO, such case should not be confused with DHF.

DHF (Grade I and II) is more severe with evidence of haemorrhages such as epistaxis, petechiae, gum bleeding, gastrointestinal bleeding and bruising at the site of injection in addition to the symptoms observed in DF. Thrombocytopenia and the concurrent rising hematocrit are the two significant laboratory findings that hallmark DHF. Hepatomegaly may also be observed.

DSS, also known as DHF Grade III and IV, is characterized by circulatory failure with presentation of rapid, weak pulse and narrowing of blood pressure or hypotension with cold, clammy skin and restlessness.

Children with DHF are often presented with enlarged pharynx and/or tonsils. Conjunctival injection and generalized abdominal pain may also be observed.

While the frequency of certain dengue symptoms may differ between the adults and children, the age of patients as well as their gender and ethnicity are not recognized as the criteria in establishing dengue infection.