

# The Natural History of Dengue Illness Based on a Study of Hospitalised Patients in Singapore

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## ABSTRACT

**Aim of Study:** To study the clinical features of dengue illness in hospitalised patients in Singapore.

**Methods:** One-hundred and thirty hospitalised patients with serologically confirmed dengue illness, from 1 April 1992 to 31 October 1992, were analysed retrospectively.

**Results:** Teenagers and young adults between 15 to 30 years of age were most commonly affected. The male to female ratio was 1.3:1. The mean duration of fever and rash prior to admission were  $5.2 \pm 1.5$  (mean  $\pm$  SD) days and  $1.7 \pm 1.7$  days respectively. Petechiae were present in 52.3% of the patients. Three-quarters of the patients with petechiae had platelet counts (PCs) of  $100 \times 10^3 \text{ ul}^{-1}$  or less. Thrombocytopenia (PCs of  $100 \times 10^3 \text{ ul}^{-1}$  or less) was first documented  $5.8 \pm 1.4$  days after the onset of illness. The nadir of thrombocytopenia occurred on the  $6.4 \pm 1.6$  day of illness. The mean duration of thrombocytopenia was  $3.6 \pm 1.6$  days. Nineteen patients (14.6%) had non life-threatening clinical bleeding or coagulopathy, namely bleeding gums (9 patients), epistaxis (5), vaginal spotting/menorrhagia (4) and prolonged PTT (3). Six patients (4.6%) required platelet transfusion because of severe thrombocytopenia (PCs less than  $30 \times 10^3 \text{ ul}^{-1}$ ) and clinical bleeding. There was no secondary fall in the PCs over 2 or more consecutive days when the PCs were in the recovery phase. It took 1 more day to reach PCs of  $100 \times 10^3 \text{ ul}^{-1}$ , the "safe" level commonly used in Singapore to decide discharge of patients, as compared to  $80 \times 10^3 \text{ ul}^{-1}$ . At PCs of  $80 \times 10^3 \text{ ul}^{-1}$  or more, 2 patients had bleeding gums, 1 each had epistaxis and vaginal spotting. No transfusion was required for these 4 patients. The mean hospital stay was  $4.2 \pm 1.5$  days. There was no mortality in this study.

**Conclusion:** Dengue illness is a relatively benign self-limiting illness. When the PCs are on the rising trend and in the absence of clinical bleeding, it is reasonably safe to discharge patients when the PCs reach  $80 \times 10^3 \text{ ul}^{-1}$ , instead of  $100 \times 10^3 \text{ ul}^{-1}$ . This will shorten each patient's stay by 1 day, resulting in cost saving and more efficient use of hospital beds.

**Keywords:** dengue fever, thrombocytopenia, bleeding

## INTRODUCTION

In Singapore, dengue haemorrhagic fever (DHF) first appeared in 1960 when 70 hospitalised cases with 1 death were reported<sup>(1)</sup>. Since then, the disease has reached epidemic proportions at intervals of 1 to 5 years, with outbreaks in 1963 – 1964, 1966 – 1968, 1973 and 1978<sup>(2)</sup>. In recent years, epidemics have become more frequent and progressively bigger with outbreaks in 1986 (354 cases with 1 death), 1987 (436 cases with 2 deaths), 1989 (944 cases with 2 deaths), 1990 (1,733 cases with 3 deaths) and 1991 (2,179 cases with 6 deaths)<sup>(3)</sup>. A record of 2,878 cases of dengue fever (DF)/DHF with 4 deaths was recorded in 1992<sup>(4)</sup>.

There are not many local clinical studies on DF/DHF despite its endemicity. This retrospective hospital based study described the clinical features of DF/DHF during the 1992 epidemic in Singapore.

## MATERIALS AND METHODS

This retrospective study was performed with data obtained from the hospital case records of patients admitted to Tan Tock Seng Hospital, the second largest acute general hospital sited in the north-eastern sector of Singapore. The hospital has a large patient catchment area of residential houses, flats and factories.

For the 7-month study period (1 April 1992 to 31 October 1992), the computer in the Information and Service Section of the hospital was programmed to generate a list of hospitalised patients with a diagnosis of DF, DHF or dengue shock syndrome (DSS) according to the World Health Organisation's recommended classification of dengue illness<sup>(5)</sup>. Eight hundred names were generated, of which 400 case records were randomly selected for review. Patients who satisfied the following criteria were enrolled into the study: i) compatible clinical picture; ii) positive dengue serological test, and iii) absence of concurrent infection or disease causing thrombocytopenia.

A positive serological test was confirmed by the presence of dengue-specific IgM antibody by enzyme immunoassay and dengue-specific IgG antibody by dengue blot test<sup>(6)</sup>. If one or both tests were negative, the haemagglutination-inhibition (HI) test was done on the acute and convalescent specimens. A four-fold rise of HI titre or a titre of 1,280 or more confirmed

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acute dengue infection. Out of these 400 patients, 268 did not have a positive serological test, one had concurrent urinary tract infection and another had systemic lupus erythematosus. Thus 130 patients finally entered the study.

## RESULTS

### Demographic characteristics

The mean age was  $28.0 \pm 13.3$  years, with a range of 3 to 81 years. Seventy-five percent of the patients were 35.5 years or less. Sixty percent of the patients were between 15 to 30 years. The male ( $n = 74$ ) to female (56) ratio was 1.3:1. The racial distribution was as follows: Chinese 80.8%, Malays 4.6%, Indians 10.0% and Others 4.6%.

### Clinical features

The most common clinical type was DF 84.6% (110 patients), followed by DHF 14.6% (19) and DSS 0.8% (1).

Fever and rash were the 2 main symptoms which brought the patients to the hospital. The mean duration of fever prior to admission was  $5.2 \pm 1.5$  days. About half of the patients had fever for 5 days prior to admission and by the sixth day, 75% of the patients would have sought treatment at the hospital.

On the other hand, the mean duration of the rash prior to admission was  $1.7 \pm 1.7$  days. Half of the patients were admitted after having the rash for 1 day and by the second day, three-quarters of the patients were admitted.

Ninety-five patients (73.1%) had their first documented thrombocytopenia, defined as PCs of  $100 \times 10^3 \text{ ul}^{-1}$  or less<sup>(7)</sup>, before the fever settled, 28 (21.5%) on the same day as the defervescence of fever and only 7 (5.4%), after the fever settled. Eighty-seven patients (66.9%) had their first documented thrombocytopenia within the period of 3 days before to the day of defervescence of the fever.

The mean hospital stay was  $4.2 \pm 1.5$  days (range: 2 to 10 days). A large proportion (73%) stayed between 3 to 5 days and 83% was hospitalised for 5 days or less. All the patients made a complete recovery in this study.

### Platelet counts

The mean PC on admission was  $85.3 \pm 41.2 \times 10^3 \text{ ul}^{-1}$ . About 50% had thrombocytopenia of  $80 \times 10^3 \text{ ul}^{-1}$  or less, and 25% had PCs of  $55 \times 10^3 \text{ ul}^{-1}$  or less on admission.

The mean duration between onset of illness and nadir of PCs was  $6.4 \pm 1.6$  days. A large majority (81.7%) hit the nadir between days 5 to 8 of illness. The mean lowest PC was  $60.0 \pm 30.6 \times 10^3 \text{ ul}^{-1}$ . Three patients had PCs of  $5 \times 10^3 \text{ ul}^{-1}$ . About a quarter had a nadir of  $40 \times 10^3 \text{ ul}^{-1}$  or less. In another 25%, the PCs never dropped below  $70 \times 10^3 \text{ ul}^{-1}$ .

The mean duration of thrombocytopenia was  $3.6 \pm 1.6$  days. In 76.3% of the patients, thrombocytopenia lasted between 2 to 5 days. On average, it took 9 days from the onset of illness for

thrombocytopenia to reach a PC of  $100 \times 10^3 \text{ ul}^{-1}$ , compared to 8 days to reach a count of  $80 \times 10^3 \text{ ul}^{-1}$ .

Secondary fall is defined in this paper as fall in PCs on at least 2 consecutive days during the rising trend of the PCs. By this definition, there was no secondary fall in PCs in this study. There were 7 cases of a single fall during the recovery phase of the PCs but by the following day, the PCs were on the rising trend again.

### Bleeding manifestations

Sixty-eight out of 130 patients in this study (52.3%) had petechiae. Three-quarters of those patients with petechiae had PCs of  $100 \times 10^3 \text{ ul}^{-1}$  or less. On the other hand, in those patients without petechiae ( $n = 62$ ), 79.4% had PCs of  $100 \times 10^3 \text{ ul}^{-1}$  or less, and 27.6% had PCs of  $40 \times 10^3 \text{ ul}^{-1}$  or less.

Nineteen patients had non-cutaneous bleeding or coagulopathy as shown in Table I. Six patients required platelet transfusion because of severe thrombocytopenia (PCs of  $30 \times 10^3 \text{ ul}^{-1}$  or less) and clinical bleeding. Clinical bleeding is defined as any of the following: purpura, ecchymosis, epistaxis, bleeding gums, haemetemesis, malaena, haematuria spotting per vagina or menorrhagia, and bleeding into other internal sites eg. brain. None required red blood cell transfusion.

One-hundred and eleven out of 130 cases (85.4%) did not have any clinical bleeding. The mean nadir PCs of this subgroup of patients was  $63.3 \pm 30.6 \times 10^3 \text{ ul}^{-1}$ . About 80.1% in this subgroup had PCs of  $80 \times 10^3 \text{ ul}^{-1}$  or less, with 22.5% having PCs of  $40 \times 10^3 \text{ ul}^{-1}$  or less.

During the recovery phase, at PCs of  $100 \times 10^3 \text{ ul}^{-1}$  or less, 91.9% of the patients did not manifest any clinical bleeding. At PCs of at least  $80 \times 10^3 \text{ ul}^{-1}$ , 4 patients had non life-threatening bleeding, namely bleeding gums (2 cases), epistaxis (1), and menorrhagia (1), all of which resolved spontaneously.

## DISCUSSION

### Epidemiological aspect

Dengue illness tends to affect adolescents and young adults<sup>(4)</sup> as this subgroup has probably not been previously exposed to the dengue viruses which occur as 4 distinct serotypes. A previous study done in Singapore revealed that more than three-quarters of the patients were below 24 years of age<sup>(8)</sup>. A retrospective epidemiological study of DF/DHF in Malaysia for the years 1975 – 1987 showed that the incidence rates were highest in 2 age groups, namely 10- to 19-year and 20- to 29-year age groups<sup>(9)</sup>. A recent prospective study of an outpatient management for dengue infection in Malaysia showed that the mean age of the patients was 27.3 years<sup>(10)</sup>. In a study of 583 hospital patients in China<sup>(11)</sup>, 81.3% were aged 21 to 50 years, with a male to female ratio of 1.2:1.

In Singapore, more females were affected in 1960 and 1963/1964, in the ratio of 1.67:1 and 1.3:1 respectively<sup>(12)</sup>. In subsequent years, more males than

**Table I – Clinical bleeding and platelet counts**

Platelet counts (x 10 <sup>3</sup> u <sup>-1</sup> )	Gum bleeding	Epistaxis	Spotting per vagina or menorrhagia	Prolonged PTT
10 -	2			
20 -			1	
30 -	1		1	2
40 -	2	2	1	
50 -	1	2		
60 -	1			
70 -				1
80 -	1		1	
90 -		1		
100 -				
110 -	1			
Total number of patients	9	5	4	3

NB. The total number of patients was more than 19 as a few patients had more than 1 sources of bleeding.

females were affected in the ratios of 1.46:1 in 1973, and 1.34:1 in the period 1974 – 1976<sup>(8,12)</sup>. In a nationwide surveillance of DF/DHF in 1992, a slight male predominance in the ratio of 1.3:1 was noted which was consistent with our findings<sup>(4)</sup>. In a 1973 DHF outbreak in Singapore, Chan et al<sup>(8)</sup> reported the racial distribution in their study, which was rather similar to our study, which is as follows: Chinese (86.6%), Malays (5.2%), Indians (5.0%) and Others (3.0%).

#### Clinical features

The frequency of the clinical types of dengue illness in Singapore was similar to that in a recent study in urban Malaysia<sup>(10)</sup> where DF constituted the largest proportion (82.7%), followed by DHF (13.0%) and DSS (4.3%). A study of 517 hospitalised patients in Philippines reported 78.3% DF, 21.3% DHF and 0.3% DSS<sup>(13)</sup>.

#### Fever and rash

As in other studies, fever was present in 100% of the cases<sup>(1,10,14-19)</sup>. In a prospective study of outpatient management of dengue infection in Malaysia<sup>(10)</sup>, the patients presented at an average of 4.7 days after the onset of fever, that was similar to our findings. The reported duration of fever ranged from 1 to 12 days<sup>(1,14,17,19-21)</sup>, with the majority lasting between 4 to 6 days<sup>(17,21)</sup>. The height of the fever did not correlate with the severity of the illness<sup>(18)</sup>. Often, the temperatures returned almost to normal usually on about the fifth day of illness, during the period of the more critical symptoms and coinciding with a shock-like syndrome<sup>(14)</sup>.

In this study, 79.2% of cases presented with rash. The appearance of rash was more alarming than fever and patients would seek medical attention almost immediately. The rash would also have alerted the attending doctors to the diagnosis and hence they would refer the patients to hospital. Therefore, 50% of the patients were admitted after having the rash for 1 day and 75% by the second day.

Lim et al<sup>(22)</sup> reported that morbilliform rashes characteristic of DF developed in about half of the patients during the course of fever in a study in Singapore. Another local study showed that rash was present in 78.4% of the cases, and that presence or absence of a rash was not predictive of shock<sup>(23)</sup>. In a study in Malaysia in 1973<sup>(17)</sup>, 51.2% and 42.1% of patients with DF and DHF respectively had rash. Another Malaysian study reported that no rash could be detected in 65% of the cases<sup>(21)</sup>.

The frequency of petechiae in our study sample (52.3%) was similar to that of Paramaesar<sup>(18)</sup> and Rudnick et al<sup>(14)</sup> where petechiae were present in slightly less than half the cases. Petechiae seemed to appear around the third to fifth day of illness<sup>(18,20)</sup>.

The recovery of thrombocytopenia often lagged behind the subsidence of fever. This is a problem often encountered in the wards when the patients were already asymptomatic and they were not discharged because of thrombocytopenia. This lag in the recovery of the PCs probably represents the time taken for the generation of the platelets to replace those destroyed by immune mechanism<sup>(24)</sup>.

#### Platelet counts and bleeding

Severe thrombocytopenia may herald the development of massive bleeding and shock, which are the most important complications that may cause fatality in DHF/DSS<sup>(10,15,19,23)</sup>. The most critical period of the illness, when the PCs were the lowest<sup>(20)</sup>, was between the fifth and eighth day of illness in our study. This is consistent with the observations that haemorrhagic manifestations occurred between the third and sixth day of illness<sup>(18,20)</sup>. A Malaysian study reported that the critical period of illness was the fifth to sixth day when circulatory failure associated with a high mortality occurred<sup>(18)</sup>.

Interestingly, Ruangjirachuporn et al<sup>(25)</sup> detected the maximal amount of circulating immune complexes in patients with DHF on the fourth or fifth day of illness. Thrombocytopenia is largely a result of increased platelet destruction via immunologic mechanism<sup>(24,26,27)</sup> and decreased production<sup>(27)</sup>. Low complement levels and circulating immune complexes were demonstrated in DHF/DSS<sup>(25,28)</sup>. There was also evidence for platelet dysfunction in DHF<sup>(26)</sup>. Many complex mechanisms are involved in the haemostatic defects. Vasculopathy and coagulopathy are the other 2 factors involved with bleeding diathesis in DHF/DSS<sup>(29)</sup>.

A study conducted during the 1973 epidemic in Malaysia showed that 92.6% of DHF patients and 68.4% of DF patients had PCs of less than 100 x 10<sup>3</sup> ul<sup>-1</sup>. Two earlier studies in Malaysia in the early 1960s showed similar findings<sup>(14,18)</sup>. Paramaesar<sup>(18)</sup> reported that 85% of the cases had PCs of less than 120 x 10<sup>3</sup> ul<sup>-1</sup>, and about half had PCs of less than 20 x 10<sup>3</sup> ul<sup>-1</sup>. Rudnick<sup>(14)</sup> showed that 69% of the cases had PCs of less than 100 x 10<sup>3</sup> ul<sup>-1</sup>, 47% had less than 50 x 10<sup>3</sup> ul<sup>-1</sup> and 16% had PCs between 100 to 150 x 10<sup>3</sup> ul<sup>-1</sup>. Two local studies<sup>(22,23)</sup> reported that 63% to 82.7% of the patients had PCs of less than 100 x 10<sup>3</sup> ul<sup>-1</sup>.

Lin et al<sup>(27)</sup> reported thrombocytopenia (PCs < 100 x 10<sup>3</sup> ul<sup>-1</sup>) in 54% of the patients, and reached nadir (20 to 50 x 10<sup>3</sup> ul<sup>-1</sup>) on the fifth to seventh day after the onset of fever, which was similar to our findings. Halstead<sup>(7)</sup> reported that a PC of less than 100 x 10<sup>3</sup> ul<sup>-1</sup> was usually seen between the third and eighth day. In an earlier study by Paramasvaran<sup>(18)</sup>, the PC began to fall on the third day of illness, hit its lowest level between the fourth and sixth day of illness, and then started to rise on the seventh day of illness. Rudnick et al<sup>(14)</sup> also reported that the majority of thrombocytopenia occurred on the fourth to sixth days of illness and a sharp rebound in the PC during convalescence was seen in most cases. Thrombocytopenia and haemostatic derangements began to normalise on the fifth to eighth day of illness<sup>(30)</sup>.

PC has been proven to be a reliable predictor of bleeding<sup>(31)</sup>. It has been demonstrated that the severity of thrombocytopenia correlated with gastrointestinal bleeding<sup>(32,33)</sup>. The detection rate of upper gastrointestinal bleeding was 48.6% in patients with platelets less than 50 x 10<sup>3</sup> ul<sup>-1</sup>, compared to 29.7% in patients with platelets more than 50 x 10<sup>3</sup> ul<sup>-1</sup><sup>(33)</sup>.

Severe bleeding was not common and usually non life-threatening, despite the very low levels of PCs encountered in dengue illness<sup>(15)</sup>. In the outpatient study by Chin et al<sup>(10)</sup> in Malaysia, the frequency of bleeding was 7.1%. The bleeding sites included gums (3%), nose (2%) and per vagina (2%). In other studies of hospitalised patients, haemorrhagic manifestations were observed in 62% to 68.8%<sup>(17,20)</sup>. Four recent studies from Taiwan revealed that the incidence of gastrointestinal bleeding varied from 11.1% to 58.5%<sup>(32-35)</sup>. Kuberski et al found 4.5% of 199 household cases of dengue gave a history of haemetemesis, melaena or haematuria<sup>(36)</sup>. A larger percentage had epistaxis or gingival bleeding. In the pre-virological literature, it was generally recognised that dengue was a cause of menometrorrhagia in the menstruating female<sup>(37)</sup>.

There is no uniform criterion in Singapore for discharge of patients hospitalised for dengue illness. Thrombocytopenia is a major factor in this decision making. In a prospective study of dengue illness in young adults in urban Malaysia with daily reviews in the outpatient clinic until they recovered, 72.8% of the patients would have been admitted if a PC of less than 100 x 10<sup>3</sup> ul<sup>-1</sup> was used as an admitting criterion. However, only 43.8% needed admission if the threshold of PC was 50 x 10<sup>3</sup> ul<sup>-1</sup> or less<sup>(10)</sup>. In that study, a high compliance rate of 86.4% by the doctors, a low patient default rate of 16.4%, and no deaths among the 162 patients showed that the protocol was practical.

In Singapore, patients are usually discharged if the PCs reached 100 x 10<sup>3</sup> ul<sup>-1</sup> and in the absence of clinical bleeding. We observed that it took about 9 days from the onset of illness for the thrombocytopenia to recover to at least 100 x 10<sup>3</sup> ul<sup>-1</sup>. On average, it took 1 day more for the PCs to reach this level or more, compared to a count of at least 80 x 10<sup>3</sup> ul<sup>-1</sup>. There was no case of secondary fall in PCs

during the recovery phase. Hence, it would be safe to discharge patients in the absence of clinical bleeding when the PCs are on the rising trend and reached at least 80 x 10<sup>3</sup> ul<sup>-1</sup>. This would shorten the hospital stay by 1 day. However in the presence of clinical bleeding, it would be more prudent to observe till the bleeding ceases.

In most cases, dengue infection is a benign self-limiting viral illness with low mortality. There was no mortality in this study. In Singapore, the reported mortality rate was low; it was between 0 for the years 1960, 1961, 1972 and 1976, and 1.24 per 100,000 for the years 1966 and 1973<sup>(12,22)</sup>. In Malaysia, the case fatality ratio ranged from 0% to 8.2%<sup>(10,16,17, 20)</sup>. A few recent studies from China<sup>(11)</sup>, Taiwan<sup>(34,35)</sup>, Philippines<sup>(13)</sup> and India<sup>(38)</sup> reported no fatalities. In Thailand, the overall mortality rate has declined from over 10% in 1985 to below 2% in 1986 and reached a low of 0.6% in 1987<sup>(39)</sup>. This improved mortality trend was attributed to better public awareness, early diagnosis and improvement in medical care.

## CONCLUSION

Dengue illness, though relatively benign, has a high morbidity and places a great burden on the hospital beds, especially in countries where dengue infection is endemic. About 93% to 95% of the reported cases were hospitalised during the period 1990 to 1992<sup>(3,4,40)</sup>. It is useful to understand the natural history of DF/DHF so that the patients can be managed with greater confidence and the hospital beds can be utilised more efficiently.

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