PIDSP Journ, 1999; 3

Volume 3 No 1

PREDICTORS OF BLEEDING (OTHER THAN PETECHIAE) IN CHILDREN WITH SEROLOGICALLY CONFIRMED DENGUE HEMORRHAGIC FEVER

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Introduction:

Dengue infection, caused by one of four closely related virus serotypes of genus *Flavivirus*, ranks highly among newly emerging infectious diseases in public health significance and is considered to be the most important arthropod-borne viral disease.[1] According to the Centers for Disease Control and Prevention, this is the most important tropical infectious disease after malaria, with an estimated 2.5 billion people living in areas at risk for epidemic transmission.[2] Currently, dengue is endemic in all continents except Europe. Epidemic dengue hemorrhagic fever (DHF) occurs in Asia, the Americas, and some Pacific islands. In Southeast Asia, epidemic DHF first appeared in the 1950's. In the Philippines, the first outbreak was described in 1954, and since then, there have been reports of epidemics on an almost yearly basis.[3] According to the National Epidemic Sentinel Surveillance System of the Department of Health, 35,602 dengue fever (DF) cases have been reported from all regions of the country during the 1998 outbreak. The incidence of dengue infections locally was shown to have dramatically peaked over the second half of the year, particularly in the months of August, September, and October.[4]

Several previous studies done abroad have shown that important risk factors for DHF include the strain and serotype of the virus involved, as well as the age, immune status, and genetic predisposition of the patient.[5] Infants less than one year of age were reported to be at greater risk of developing hemorrhagic manifestations, besides the presence of secondary or sequential infection, white racial phenotype, presence of chronic illness, or a combination of these factors.[6] Biochemical and hemostatic abnormalities have been reportedly more marked in children with Dengue shock syndrome.[7]

In the Philippines, a few studies have been undetaken to demonstrate risk factors for DHF. A retrospective study by Bernardo et. al, in 1988 presented a preliminary proposal for a dengue scoring index wherein a score of seven or higher and significant Hemaggutination-Inhibition (HI) titer signalled a "stormier" course of disease.[8] In 1995, another retrospective study by Fajardo et. al, showed that past history of dengue infection, nutritional state and economic status were significantly related to morbidity and mortality.[9] A prospective study by Chua et. al, in 1993 demonstrated a greater tendency to bleed among patients with prolonged partial thromboplastin time and prothrombin time in a study population of children clinically diagnosed with DHF based on the world Health Organization (WHO) criteria.[10] In this study, serologic confirmation was not done. It must be noted, at this point, that in a study by Reyes in 1993 on the reliability of doctors in diagnosing DF based on the WHO criteria alone, 82% of patients diagnosed with Dengue infection were confirmed by HI test.[11] However, only 2% satisfied all four requirements of the criteria. Hence, so as to guide the physician in the evaluation and management of DHF, this prospective study was undertaken to determine the clinical and laboratory predictors for the occurrence of bleeding (other than petechiae) among children diagnosed with Dengue Hemorrhagic Fever based on the Subjects and Methods:

Study Population:

All patients below 18 years of age admitted between September to November 1998 at the Philippine General Hospital and suspected to have Dengue infection were selected for possible inclusion. Among these, patients who met the World Health Organization (WHO) criteria for Dengue Hemorrhagic Fever (Table 1) and were confirmed by Hemmaggutination-Inhibition titers were included in this study.

Table 1. WHO Criteria for Dengue Hemorrhagic Fever

The following must all be present:

- Fever, or history of acute fever, lasting 2-7 days, occassionally bishapic
-Hemorrhagic tendencies, evidenced by at least one of the following:

Keywords: dengue hemorrhagic fever, dengue fever
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> a positive tourniquet test
> petechiae, ecchymoses or purpura
> bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
> hematemesis or melena

- Thrombocytopenia (100,000 cells per mm3 or less)
- Evidence of plasma leakage due to increased vascular permeability,
manifested by at least one of the following:
> a rise in the hematocrit equal to or greater than 20% above average for age, sex, and population;
> a drop in the hematocrit following volume-replacement treatment equal to or greater than 20% of baseline;
>sign of plasma leakage such as pleural effusion, ascites and hypoproteinmia.

Table 2: Variable analyzed as predictors of bleeding other than petechiae in DHF patients:

Basic characteristics
- sex
- age
- dengue grading

History
- duration of illness at the time of admission
- duration of at the time of onset of bleeding
- past history of dengue infection
- presence of concomitant/chronic illness
- chief complaint
- abdominal pain on admission

Physical Examination
- tourniquet test
- hypotension on admission
- narrowed pulse pressure on admission
- presence of rash/flushing on admission
- bleeding (including site of bleed)
- tachycardia/bradycardia on admission
- hepatomegaly
- serosal involvement (pleural effusion/ascites)

Laboratory Examination
- platelet count on admission
- lowest platelet count during stay
- hemoconcentration
- WBC count on admission
- lowest WBC count during stay
- Prothrombin time/Partial thromboplastin time
- Liver function test derangements
- hypoalbuminemia
- Chest roentgenoram abnormalities
- Electrocardiogram abnormalitites
- Blood type
- Primary or secondary Dengue infection (serology)

Methods:

A. Dengue Form

Upon admission, complete clinical histories and physical examinations were taken from all patients included in this study and the severity of each patient's illness was graded based on the spectrum by Nimmanitya and Halstead as cited by the WHO . A Dengue Form for each patient was filled out and updated daily and included the following demographic data (age, sex, anthropometric measurements, address, case number), initial and daily monitoring of clinical signs and symptoms (reflecting daily changes in temperature, malaise, headache, gastrointestinal symptoms, bleeding, etc.), and laboratory examination results. Appropriate treatment accordingly to the recommended WHO protocol for DHF was administered.

Grading Severity of Dengue Hemmorrhagic Fever

Grade 1: Fever accompanied by non-specific constitutional symptoms: the only Hemorrhagic manifestations is a positive tourniquet test and/or easy bruising.

Grade 2: Spontaneous bleeding in addition to the manifestations of Grade 1 patients, Usually in the form of skin or other hemorrhages

Grade 3: Circulatory failure manifested by a rapid, weak pulse and narrow or hypotension, with the presence of cold, clammy skin and restlessness.

Grade 4: Profound shock with undetectable blood pressure or pulse.

B. Laboratory Investigations

Upon admission, the following laboratory work-up were requested: complete blood count, differential count, platelet count, blood typing, albumin, blood urea nitrogen, creatinine, liver finctions tests, prothrombin time, partial thromboplastin time, urinalysis, and 12-lead electrocardiogram. Hematocrit and platelet counts were monitored every eight hours until values returned to normal. All other laboratory examinations and chest roentgenograms were done as deemed necessary by the resident physician in charge. Because of occassional missing values, e.g. failure to collect a blood specimen or unavailability of certain tests, denominators vary a little for different comparisons.

C. Serologic Confirmation

Serum was drawn for the acute phase of Dengue HI titers upon admission. A convalescent sample was taken at least seven days after the initial titer or upon discharge of the patient, whichever was longer. The paired acute and convalescent sera were sent to the Research Institute of Tropical Medicine following proper specimen collection and transport for testing using a single assay. Interpretation of the results was based on specific criteria as defined by the WHO.

Appendix B. Interpretation of Dengue Hemagglutination-Inhibition Antibody Response

Antibody response	S1-S2 interval	Convalescent titer	Interpretation
≥ 4-fold rise	≥ 7 days	≤ 1:1280	Acute flavivirus infection, primary
≥ 4-fold rise	Any specimen	≥ 1:2560	Acute flavivirus infection, secondary
≥ 4-fold rise	< 7 days	≤ 1:1280	Acute flavivirus infection, either primary or secondary
No change	Any specimen	> 1:2560	Recent flavivirus infection, Secondary
No change	≥ 7 days	≤ 1:1280	Not dengue
No change	< 7 days	≤ 1:1280	Uninterpretable
Unknown	Single Specimen	≤ 1:1280	Uninterpretable

Statistical Analysis:

The variables analyzed as possible predictors for presence of hemorrhagic manifestations other than petechiae are listed in table 2. Data were analyzed using the Statistical Analysis System (SAS) and Epi-Info pack

Results:

Subjects:

A total of 241 patients were initially in the study but only 40 patients fulfilled the WHO criteria and returned for convalescent HI titers. Of these, 36 patients were confirmed serologically as Dengue infections and thus they comprised the final study population. Two were primary responders while 34 had secondary type of antibody response (Table 3). The remaining 4 were interpreted as "not Dengue" and of these, 3 still had a final clinical diagnosis of DHF grade II while one was discharged with a diagnosis of urinary tract infection.

Table 3. Results of Dengue HI Antibody Determination based on 40 paired sera

HI Interpretation	Number of Patients	Percentage
(+) Dengue infection	36	90%
Definite primary	2	5%
Definite secondary	13	32.5%
Presumptive secondary	21	52.5%
(-) Dengue infection	4	10%
TOTAL	40	100%

Of the 36 serologically confirmed patients with Dengue infection, there were 15 males and 21 females with a ratio of 1:1.4. Their ages ranged from 3 to 17 years old with a mean of 10 years. Most patients were admitted in the month of September (21), (grade I to 2) whereas 3 had severe DHF (grade 3). Their mean duration of illness before seeking consult was 4 days. The most frequent clinical findings among them were fever, a positive tourniquet test, abdominal pain, headache, and tachycardia.

Bleeding:

Hemorrhagic manifestations other than petechiae were observed in 40% of patients manifested as gastrointestinal bleeding (8 patients), epistaxis (4 patients), and/or gum bleeding (5 patients). Two patients had 2 or more bleeding manifestations. In all bleeding patients, the mean duration of illness prior to onset of hemorrhagic manifestations was 4.7 days (range of 3 to 6 days). Some 30.8 % were febrile during the onset of bleeding.

Predictors of Bleeding:

The relation of demographic variables analyzed as predictors to presence of bleeding other than petechiae are as shown in Table 4. As seen in this table, the tendency to bleed was greater among the female sex and slightly older children (mean age of 11.2+/- 3.8), however there was no significant difference statistically (by Chi-square test and unpaired t-test respectively). All patients with Dengue grade I had no hemorrhagic manifestations, whereas all 3 patients with severe Dengue (grade III) experienced bleeding other than petechiae. Majority of patients with hemorrhagic signs had a grading of II.

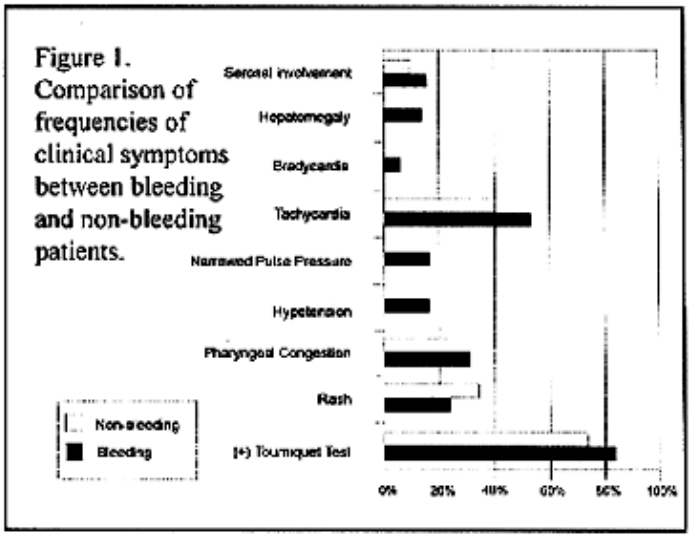

Figure 1. Comparison of frequencies of clinical symptoms between bleeding and non-bleeding patients.

Figure 1 shows the symptoms found in the bleeding and non-bleeding groups. Their presenting symptoms were generally comparable. None of the clinical parameters observed such as the mean duration of illness, past history of Dengue, and presence of a concomitant or chronic illness, had a significant positive or negative predictive value for bleeding. There was a lesser tendency for bleeding among those manifesting with headache (p=0.17), but by Chi-square testing, this was also insignificant. Upper respiratory tract involvement was slightly more common in the group of patients with bleeding manifestations as compared to those without.

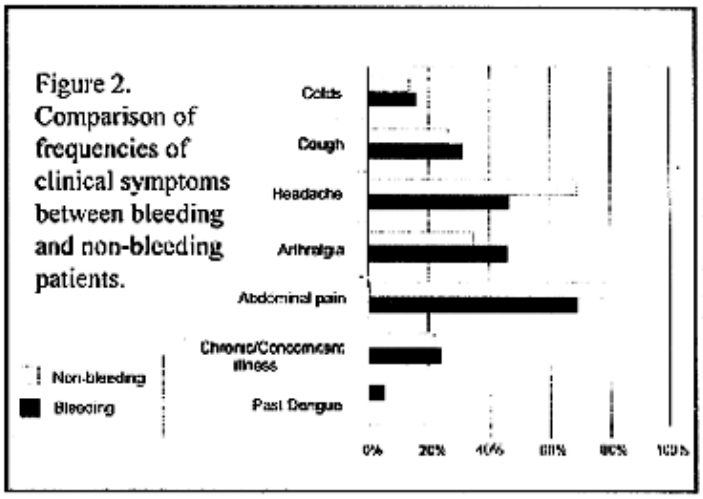

Figure 2. Comparison of frequencies of clinical symptoms between bleeding and non-bleeding patients.

Clinical signs were also comparable between the two groups of patients, as shown in Figure 2. The presence of a positive tourniquet test, rashes, tonsillopharyngeal congestion, heart rate abnormalitites, hepatomegaly, and /or serosal involvement in the patients upon admission had no significant effect on the rate of hemorrhagic manifestations. Only 2 patients presented with hypotension and narrowed pulse pressure, both in the hemorrhagic group, and these were not enough to be statistically conclusive Tachycardia also tended to be more common in this group.

Laboratory parameters observed included blood counts and typing, bleeding parameters, liver function tests, and dengue serology. The results of the aforementioned examinations are seen in Table 5. The mean hematocrits between the two groups were

similar. The mean white cell count (WBC) upon admission was lower in the bleeding group (3.8 x 10^9 /L) as compared with the non-bleeding group (5.1 and 5.1X 10^9 /L). This also holds true for the lowest WBC obtained in each group (3.3 and 4.3 X 10^9 /L respectively), although these differences in WBC were not significant by unpaired testing. The mean platelet counts on admission and lowest platelet counts for both groups were also comparable. The prothrombin time and partial thromboplastin time could not be compared because only 14PT and 3 PTT tests were performed. The liver function test results tended to be slightly increased among the group with hemorrhagic manifestations, although results were still comparable. The Alanine aminotransferases were normal in both groups, but Aspartate aminotransferases and Alkaline phosphatases were twice elevated for both. The mean Blood urea nitrogen and Creatinine were within normal values for both groups. Only a total of 9 roentgenograms and 11 electrocardiograms were taken and thus were too few to be compared between both groups.

Table 4. Laboratories variables analyzed as predictors for bleeding other tha

Variable		(+) Bleeding	(-) Bleed
Mean Hematocrit		44.3 +/- 6.7	43.7 +/-3
Mean WBC on admission		3.8 +/- 1.4	5.1 +/- 2
Lowest WBC		3.5 +/- 1.1	4.2 +/-1
Mean Platelet count on admission		128.1 +/- 94.7	128.3 +/
Lowest platelet count		59.0 +/- 45.5	65.4 +/-
Mean AST (u/L)		150.2 +/- 128.5	107.3 +/
Mean ALT (u/L)		54.8 +/- 65.7	49.2 +/-
Mean alkaline phosphatase		254.7 +/- 93.1	225.6 +/
Mean albumin (g/L)		38.4 +/- 6.0	41.2 +/-
Mean Blood Urea Nitrogen (mmol/L)		496.6 +/-264.0	402.1 +/
Mean Creatinine (umol/L)		78.5 +/- 61.3	65.6 +/-
Blood Type	A	3 (25%)	7 (38.9%
	AB	1 (8.3%)	0 (0%)
	B	7 (50%)	2 (11.1%
	O	2 (16.7%)	9 (50%)
Type of Dengue Infection (HI)			
	Primary	1 (7.7%)	1 (4.3%)
	Secondary	12 (92.3%)	22 (95.6

The Hemagglutination-inhibition titers showed one patient for each group among the patients with primary Dengue infection. Among the patients with secondary infection, 35% manifested with bleeding and 65% had no bleeding other than petechiae. The patient's blood type was significantly correlated with hemorrhagic manifestations by Chi-square testing. Some 50% of bleeding patients were of blood type B whereas 50% of non-bleeding patients were type O. Blood types A and AB were not significantly correlated with bleeding.

Discussion and Conclusion:

The emergence of Dengue Hemorrhagic Fever as a major health problem in the Philippines has once again been dramatized in the 1998 outbreak. Some 35,602 cases were reported nationwide with 514 deaths.[4] The present study has shown that the most number of admissions coincided with the reported peak of the outbreak by the DOH, i.e. during the month of September. The number of patients included in the study became less during the subsequent months following the nationwide pattern. Also, there were slightly more female patients included in this study (M:F ratio of 1:1.4),in congruence with early local and foreign literature which report that DHF is more likely in girls.[8,12] In contrast, the DOH surveillance report for the same year this study was carried out showed an almost equal ratio (M:F ratio of 1.07:1) while previous local studies showed more involvement in males (1.2:1 in 1997 by Capeding et.al and 2.6:1 in 1995 by Fajardo et. al).[4,9,13] The mean age of the study population was 10 years, and this was comparable with a few previous local and foreign reports.[12,13] Other local studies, however, were more consistent with the 1998 nationwide data that reported a peak in a younger age group (age 1 to 9 years).[3,4,9,11] The WHO also reported a modal age at hospitalization of 4-6 years.[1] The older population of the subjects of this study may account for the finding that most of the subjects had a secondary antibody response to infection. The study of Reyes et. al. in 1992 found that primary antibody response was frequent in the 6-10 age group while secondary response was seen more often in those 11-13 years of age.[11]

There were 241 potential subjects in this study, however, only 16% (40) patients were diagnosed to have DHF strictly following the WHO criteria. This was also the difficulty encountered in a previous study by Reyes in 1992 wherein only 2% satisfied all the criteria set by the WHO. Strict adherence to the set criteria had allowed some missed cases of DHF, thus Reyes had suggested revision because not all the criteria were usually fulfilled.[3,13] On the other hand, the present study has shown that some 4 (10%) of the DHF cases defined by the same criteria were serologically proven to be"not Dengue" infections. Hence, overdiagnosis may also be encountered using the WHO criteria, although the admitting physicians in this study may have been biased because dengue was leading cause for fever and hospital admission during the study period.

Though most of the patients in this study experienced a secondary type of infection, their clincal course was generally mild. This is in contrast with the results of a study by Bernardo et. al. in 1988 wherein the HI antibody titer was found to be correlated with severity of the disease. Abroad, several reports showed that secondary infection is important in the development of DHF and Dengue Shock Syndrome.[14,15] Nevertheless, Capeding at al. in 1997 confirmed studies done a decade earlier which found that, unlike abroad, most often it did not progress into profound circulatory compromise[13] Reyes, in 1992, had shown that while most of their patients had secondary response to infection, only 8% had severe manifestations (grade III to IV). [11] Furthermore, an inherent limitation of this study is the requirement for a convalescent titer after 7 days or upon discharge of the patient. This has skewed the study population to those who were alive and capable of following up a week after admission. Thus, some 89% of the patients had mild Dengue, only 4 manifested with circulatory failure, and no mortality was reported. Notwithstanding, comparatively during the same period of observation, a review of records showed that there were only 4 mortalities out of the 241 patients admitted and clinically diagnosed to have Dengue infection (1.6% case fatality rate). The DOH also reported a similar 1% fatality rate for the year 1998.[4]

The classic description of the end of the febrile phase as the critical period for circulatory disturbance was observed in some subjects. However, a significant 30.8% manifested with hemorrhagic signs whilst febrile. A similar finding was reported earlier by Bernardo et. al., who in addition, showed that onset of bleeding during the febrile phase prolonged the duration of hemorrhagic manifestations.[8] The duration of bleeding was not reported in the present study, however it was noted that bleeding

manifested within 3 to 6 days of illness, consistent with the usual time span described by the WHO. Gastrointestinal bleeding was found to be the most common hemorrhagic manifestations other than petechiae in this study, similar to that reported by Aggarwal et. al. in the 1996 DHF epidemic in India. [16] In the studies of Reyes and Capeding et. al., epistaxis was found to be the most common manifestation of bleeding besides petechiae.[11,13]

Clinical findings were similar to previous local reports on DHF. Fever, a positive tourniquet test, abdominal pain, and headache were the most common clinical findings in those with and those without hemorrhagic manifestations. In 1992, Reyes reported flushing, a positive tourniquet test, rash, and abdominal pain as the most frequent manifestations in her study, while Capeding in 1997 reported abdominal pain, headache, flushing, and vomiting as most common.[11,13] In 1998, Chua reported that in the Philippine Pediatric Society registry of diseases, fever, a positive tourniquet test, and abdominal pain were the most common findings.[3] The clinical findings upon admission of the subjects in this study were comparable between both bleeding and non-bleeding groups. Not a single clinical symptom nor sign was significantly predictive of subsequent bleeding other than petechiae, although this study is limited by its sample size. Notwithstanding, Bernardo et.al. attempted to provide a scoring index for DHF in 1988, where the presence of rash, abdominal pain, a positive tourniquet test, bleeding during the febrile phase, narrow pulse pressure, tachycardia, and serosal involvement were given a higher score.[8] The study cited that a score of 7 gave a higher probability of a "stormier" course of illness, however this score only had a sensitivity of 54.5%, and thus was also not highly predictive of complications. On the other hand, Fajardo's 10 year study (1981 to 1991) showed that hemorrhagic manifestations were significantly related to a past history of dengue infection, hypotension or narrowed pulse pressure on admission, a negative tourniquet test, and absence of rash.[9] It must be pointed out, though, that the subjects of Fajardo's restrospective study were included based on WHO criteria alone. Capeding has since pointed out that because the clinical signs and symptoms of dengue are protean, laboratory confirmation is important.[13]

Most of the laboratory findings in this study also failed to identify a predictor for bleeding. The platelet counts of patients in the bleeding and non-bleeding groups upon and during admission were comparable. Capeding et al. found thrombocytopenia in only 37% of cases (but this was not correlated with bleeding).[13] In contrast, Fajardo et. al. ,earlier found that a platelet count of 50,000/L and below was significantly related to hemorrhagic manifestations, and Bernardo's scoring index assigned a higher score for the presence of thrombocytopenia and marked leukopenia, although as aforementioned, the predictive value of this scoring index was limited.[8,9] The aminotransferases in this study were only occasionally deranged in both groups, a finding different from that reported by Ray et al. which cited that AST and ALT were deranged in 79% and 50% of DHF cases respectively.[7]

The ABO blood typing of the subjects was significantly correlated with the presence of hemorrhagic manifestations other than petechiae. Blood type B seemed to predispose patients to bleeding whereas blood type O seemed protective against bleeding. Whether this finding was made significant because of the limited sample (and is thus a red herring) or this truly predictive warrants a confirmatory study. The relationship between blood type and DHF has never been described in published literature. Several studies have shown that T lymphocyte activation and increased cytokine levels, i.e., immune activation contributes to the pathogenesis of DHF, but ABO blood grouping has not yet been correlated with DHF nor with the propensity for bleeding or dessiminated intravascular coagulation in other diseases.[17] A genetic risk factor for DHF was suggested by one study finding a possible relationship between histocompatibility antigens and DHF.[18] Seeking a relationship between blood groups and bleeding, the authors have only found one study which cited a higher frquency of bleeding during pregnancy among Rh(+) women.[19] Nevertheless, there have been reports correlating blood groups with other illness such as hypertension and diabetes mellitus (blood types A and B).[20]

In conclusion, the present study has demonstrated that except for ABO blood group typing, the clinical and laboratory findings upon admission were not predictive of hemorrhagic manifestations besides petechiae. Therefore, utmost vigilance for hemorrhagic complications is still very important for all cases of DHF. Whether a specific blood type is truly protective of or predisposes to bleeding warrants further confirmatory investigation. A review of the WHO criteria for DHF may also be needed because of the changing clinical pattern of the disease. The limitation of this study include its sample size, its requirement for a convalescent titer, and the unavailability of some laboratory tests.

References:

1. World Health Organization. Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention, and Control. (2nd edition)Geneva, 1997.
2. Gubler DJ and Hayes EB: Dengue and Dengue Hemorrhagic Fever. Dengue Branch and the Division of Vector Borne Infectious Diseases, Center for Disease Control, CID, Fort Collins, CO., 1992.
3. Chua MN and Galsim-Hernandez F: Dengue Hemorrhagic Fever: The Philippine Report. Phil J Pediatr. Vol. 47 no.3; 172-176, 1998.
4. National Epidemic Sentinel Surveillance System. Field Epidemiology and Training Program, Department of Health, 1998.
5. Dietz V Gubler DJ, Ortz S, et al.: The 1986 Dengue and Dengue Hemorrhagic Fever Epidemic in Puerto Rico: Epidemiologic and Clinical Observations. P R Health Sci J. Vol. 15 no. 3; 201-210, 1996.
6. Bravo JR, Guzman MG, Kouri GP: Why Dengue Hemorrhagic fever in Cuba? Individual Risk Factors for Dengue Hemorrhagic Fever/Dengue Shock syndrome (DHF/DSS). Trans R Soc Trop Med Hyg. Vol. 81 no.5; 816-820, 1987.
7. Ray G, Kumar V, Kapoor AK, et al.: Status of Antioxidants and Other Biochemical Abnormalities in Children with Dengue Fever. J Trop Pediatr. Vol 45. No 1; 4-7, 1999
8. Bernardo ML, Fernando BA, Flores MA, et al.: A Preliminary Report on the Validity of a Dengue Scoring Index in Dengue Fever/Dengue Hemorrhagic Fever. Sto Tomas J

Med. Vol. 37 no.1; 11-15, 1988.
9. Fajardo MT, Santos JA: Factors Associated with Morbidity and Mortality in Dengue Hemorrhagic Fever/Dengue Shock syndrome. Phil J Pediatr. Vol. 44 no. 1; 8-15, 1995.
10. Chua MN, Molanida R, de Guzman M et al.: partial Thromboplastin Time as a Predictor of Bleeding in Patients with Dengue Hemorrhagic Fever. Phil J Pediatr. Vol. 42 no.3; 248-251, 1993.
11. Reyes MC: Can Doctors Reliably Diagnose Dengue fever Based on clinical Manifestations? Phil J Pediatr. Vol. 42 no.1; 23-31, 1993.
12. Kautner I, Robinson MJ, Kuhnle U: Dengue Virus Infection: Epidemmiology, Pathogenesis, Clinical Presentations, Diagnosis, and Prevention. J Pediatr. Vol 131 no. 4; 516-524, 1997.
13. Capeding MR, Paladin FJ, et al.: Dengue Surveillance in Metro Manila. Southeast Asian J Trop Med Public Health. Vol. 28 no.3; 530-534, 1997.
14. Hayes EB, Gubler DJ: Dengue and Dengue Hemorrhagic Fever. Pediatr Infect Dis J. Vol. 11 no. 4; 311-317, 1992.
15. Lange WR, Beall B, Denny SC: Dengue Fever: A Resurgent Risk for the International Traveler. AmFam Physician. Vol. 45 no.3; 1161-1168, 1992.
16. Aggarwal A, Chandra J, Aneja S, et al.: An Epidemic of Dengue Hemorrhagic Fever and Dengue Shock Syndrome in Children in Delhi. Indian Pediatr. Vol. 35 no.8; 727-732, 1998.
17. Green S, Vaughn DW, Kalayanarooj S, et al.: Early Immune Activation in Acute Dengue Illness is Related to Development of Plasma leakage and Disease Severity. J Infect Dis. Vol. 179 no.4; 755-762, 1999.
18. Chiewslip P, Scott RM, Bhamarapravati N, et al.: Histocompatibility Antigens and Dengue Hemorrhagic Fever. Am J Trop Med Hyg. Vol. 30; 1100-1105, 1981.
19. Cifuentes LO: Adverse Outcomes of pregnancy and Blood Groups: A Relationship with No Importance? Hum Hered. Vol 44 no. 6; 350-352, 1994.
20. Sidhu LS, Malhotra P, Singh SP: ABO and Rh Blood Groups and Diabetes Mellitus. Anthropol Anz. Vol. 46 no.3; 269-275, 1988.