# Clinical Experience of Dengue Fever in A Regional Teaching Hospital in Southern Taiwan

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## Abstract

Thirty-seven serologically confirmed cases of dengue fever were studied during the 2006 in Kaohsiung Armed Forces General Hospital in southern Taiwan. Sixty-two percent of the cases occurred among September and October. The mean age of these patients were 45.4 ± 17.7 years. The mean hospital stay was 6.2 days. Classic signs and symptoms were fever (31/37, 84%), gastrointestinal symptoms (17/37, 46%), headache (13/37, 35%), skin rash (13/37, 35%), myalgia and arthralgia as well as bone pain (13/37, 35%) . Only two patients manifested hemorrhagic sign. Positive results for reverse transcriptase-polymerase chain reaction (RT-PCR) developed in 20 patients (20/37, 54%). The average duration of fever from symptom onset was 6 days, with fever peak to normal body temperature of 3.8 days. Prolongation of partial thromboplastin time (PTT) was observed in 18 patients (18/37, 49%). Elevation of aspartate aminotransferase was found in 25 of 37 patients (25/37, 68%). Thrombocytopenia occurred in 27 of 37 patients (27/37, 73%) and 12 of them had severe thrombocytopenia (less than 50,000/mm$^3$), while 30 patients (30/37, 81%) were leucopenia and most of them (16/37, 43%) had severe leucopenia (white blood cells ranged from 1,000 to 2,000/mm$^3$). The average duration of leucopenia and thrombocytopenia to normal range required 4.7 days and 2.1 days. In addition, the findings of gall bladder wall thickening were demonstrated in 10 of 22(10/22, 45%) abdominal sonographic examinations. All patients recovered with favorable outcome. ( J Intern Med Taiwan 2009; 20: 248-254 )

Key Words：Dengue fever, Taiwan

## Introduction

The first definite clinical report of dengue is attributed to Benjamin Rush in 1780, but the viral etiology and its mode of transmission via mosquitoes were not established until the early 20th century. Dengue viruses are small, spherical, single-stranded enveloped RNA viruses of the family Flaviviridae, genus Flavivirus. Dengue infection is caused by 1 of 4 related, but antigenically distinct, viral serotypes: dengue virus 1 (DENV-1), dengue virus 2 (DENV-2), dengue virus 3 (DENV-3), and dengue virus 4 (DENV-4). Dengue fever is a severe, flu-like illness that affects infants, young children and adults, but seldom causes death. Dengue is transmitted by Aedes aegypti (worldwide) and the Aedes albopictus ( United States, Asia, Latin

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America and Caribbean ) mosquitoes[1]. Aedes aegypti, is a mosquito that can host the dengue fever, Chikungunya and yellow fever viruses[2]. Over the decades air travel has geographically deteriorated dengue virus infection in non-endemic countries and now it is estimated that at least 100 million dengue cases occur annually around the world [3,4].

With the rapid growth of worldwide dengue epidemic, several outbreaks, most of which are found to be dengue virus 1(DENV-1), have also been reported since 1981 in southern Taiwan as well as in Kaohsiung region in 1987, 1988, and 1991[5]. Later on, the majority of dengue viral serotype has transformed to dengue virus 2 (DENV-2) and dengue virus 3 (DENV-3), which mainly attack local citizens in southern Taiwan although some cases were also found in northern Taiwan in 1994, 1998, and 2001[5]. In 2002, the dengue outbreak has stretched its arms to neighbor islands such as Pescadores, where the cause of the epidemic was mainly recognized as DENV-1 and DENV-2. During this year a total of 242 DHF cases including 21 mortality cases were reported[5].

Due to being endemic area for dengue fever in Taiwan, especially there were several outbreaks reported since 1981 in Southern Taiwan[6], our clinical study was conducted to elucidate the character of this febrile disease.

## Materials and Methods

Ninety-one patients with clinically suspected dengue fever were admitted in Kaohsiung Armed Forces General Hospital since August 2006 through December 2006. Clinically suspected dengue fever was defined as the presence of fever and any 2 of the following symptoms: headache, retro-orbital pain, myalgia, polyarthralgia, skin rash, nausea and vomiting, and hemorrhagic manifestation. Dengue fever was confirmed by Centers for Disease Control (CDC) of the Department of Health in Taiwan. A confirmed dengue case was required to be positive by either reverse transcription-polymerase reaction, or demonstrate seroconversion by dengue-specific immunoglobulin IgM and seronegativity for Japanese encephalitis virus (JEV)-specific IgM by IgM-enzyme-linked immunosorbent assay (IgM-ELISA). Dengue viruses were isolated in C6/36 cell culture and were identified to serotype with monoclonal antibodies[7]. A serological result was considered to be positive if the immunoglobulin M ( IgM) was ≧ 1:40. When IgM was negative, a dengue infection was diagnosed if there was a 4-fold rise in acute phase in comparison to convalescent phase anti-dengue IgG titer. Blood cultures were collected in all febrile patients and negative findings were noted. Patients' profiles including age, gender, mean hospital stay, and duration between onset of symptom and admission. Clinical basic data and laboratory results were obtained from medical records when available.

## Results

Ninety-one cases of clinically suspected dengue fever treated at the hospital during the study period and 37 cases were confirmed as having dengue fever by laboratory data. Table 1 summarizes the demographic and clinical features of the 37 dengue fever patients. The age of these patients at the time of laboratory diagnosis ranged from 16 to 82 years, and a mean of 45 years. The mean age of male and female patients were 47.3 years and 44.4 years. The median age of male and female patient were 40 years and 47 years. The peak incidence was in the 20-40 years in males and 40-50 years in females (Fig. 1).

Monthly distribution of dengue fever showed the peak incidence occurred among September and October (23/37, 62%) (Fig. 2). The mean hospital stay was 6.2 days. Clinical signs and symptoms of these patients (Table 1) were fever (31/37, 84%), skin rash (13/37, 35%), headache (13/27, 35%),

Table1. Demographic and clinical features of 37 dengue fever patients during study period

| Demographic characteristics | No. of patients | % |
|---|---|---|
| **Age (years)** | | |
| Mean±SD | 45.4±17.7 | |
| **Hospital stay (days)** | | |
| Mean±SD | 6.2±1.9 | |
| **Clinical symptoms/signs** | | |
| Fever>38℃ | 31 | 84% |
| GI symptoms | 17 | 46% |
| Nausea | 9 | 24% |
| Anorexia | 8 | 22% |
| Diarrhea | 7 | 19% |
| Vomiting | 6 | 16% |
| Epigastragia | 1 | 3% |
| RUQ tenderness | 1 | 3% |
| Headache | 13 | 35% |
| Myalgia, arthralgia, bone pain | 13 | 35% |
| Rash | 13 | 35% |
| Eye ball pain/discomfort | 1 | 3% |
| Bleeding signs | 2 | 5% |
| **Laboratory findings** | | |
| Leucopenia ( WBC<4,000/mm$^3$) | 30 | 81% |
| Neutropenia(Neutrophils <500/ mm$^3$) | 3 | 8% |
| Liver dysfunction (AST>30/U/L) | 25 | 68% |
| AST>5 x normal range (150U/L)* | 10 | 27% |
| ALT>5 x normal range (160U/L)** | 4 | 11% |
| Thrombocytopenia ( <100,000/mm$^3$) | 27 | 73% |
| PTT prolong ( >32.7 seconds ) | 18 | 49% |
| Elevation of ALP *** | 4 | 11% |

Normal range *AST:10-30 U/L**ALT:2-32U/L *** ALP-:35-105U/L
AST: aspartate aminotransferase, ALT: alanine aminotransaminase, ALP: alkaline phosphatase
SD: standard variation, WBC: white blood cell, RUQ: right upper quadrant, PTT: partial thromboplastin time

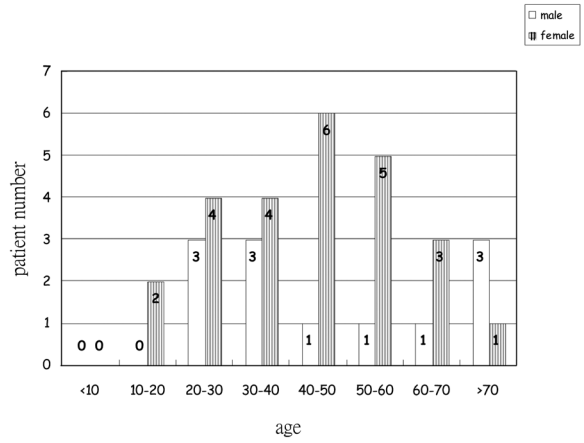


Fig.1. Age distribution of dengue fever patients during study period.

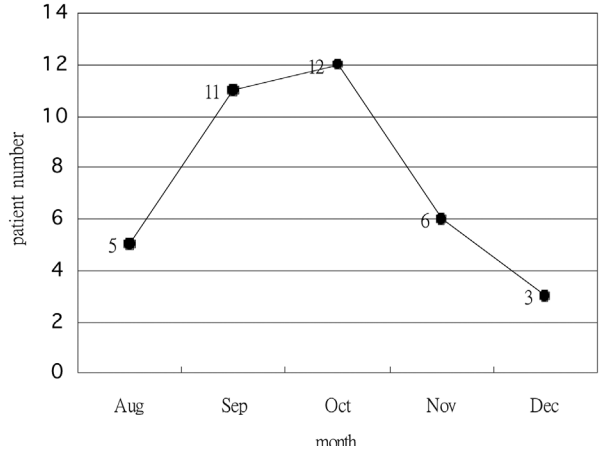


Fig.2. Monthly distribution of dengue fever patients in 2006.

myalgia, arthralgia and bone pain(13/27, 35%) , nausea (9/37, 24%) , anorexia (8/37, 21%) , diarrhea (7/37, 19% ), vomiting (6/37, 16%), epigastragia (1/37, 3%), and right upper quadrant abdominal tenderness (1/37, 3%) . Apart from the above data, there are six afebrile patients (6/37, 16%) with the average maximal body temperature of 36.7℃. Two of six afebrile patients are over the age of sixty; One of these two persons has had diabetes and the other had cirrhosis. Only two patients show hemorrhagic signs (gum bleeding and upper gastrointestinal bleeding). One of them undertook an undifferentiated-serotype PCR test while the other did not receive PCR test. They received blood transfusions with platelet concentrates because of severe thrombocytopenia (platelet count ＜10,000 /mm$^3$) and active upper gastrointestinal bleeding. Positive results for RT-PCR occurred in 20 of 37 patients (20/37, 54%) and dengue virus serotype 3 was identified from 16 patients (16/37, 43%) and undifferentiated type was identified from the others (4/37, 8%). The average duration of peak body temperature to normal (body temperature ＜37℃) required 3.8 days. The average duration from leucopenia to normal (white blood cell count ＞4,000/mm$^3$) required 4.7 days. The

average duration from thrombocytopenia to platelet count ＞100,000/mm$^3$ required 2.1 days. Prolongation of PTT was observed in 18 patients (18/37, 49%). Elevation of aspartate aminotransferase was found in 25 of 37 patients (25/37, 68%), 10 of whom elevate five-fold higher than the normal value. Elevation of alkaline phosphatase was found in 4 of 37 patients (4/37, 11%). Thrombocytopenia (platelet ＜100,000/mm$^3$) occurred in 27 of 37 patients (27/37, 73%) and 12 of them were severe thrombocytopenia (less than 50,000/mm$^3$), while 30 of 37 patients (30/37, 81%) were leucopenia and about half of them (16/37, 43%) had severe leucopenia (white blood cells ranged from 1,000 to 2,000/mm$^3$) , and three of whom (3/37, 8%) suffered from neutropenia (neutrophils ＜500/mm$^3$). In our study, 14 of 37 (38%) patients showed relative bradycardia which refers to the absence of an expected relationship between heart rate and temperature. In addition, the finding of gall bladder wall thickening was demonstrated in 10 of 22 (10/22, 45%) abdominal sonographic examinations.

## Discussion

Dengue has been called the most important mosquito-transmitted viral disease in terms of morbidity and mortality. Dengue fever is a benign acute febrile syndrome occurring in tropical regions. A small proportion of cases, the virus causes increased vascular permeability that leads to a bleeding diathesis or disseminated intravascular coagulation (DIC) known as dengue hemorrhagic fever (DHF). The mean fatality rate of DHF is 3% to 5% with treatment; 50% without treatment[8]. Secondary infection by a different dengue virus serotype has been confirmed as an important risk factor for the development of DHF. In 20-30% of DHF cases, the patient develops shock, known as the dengue shock syndrome (DSS). In Taiwan, DHF and DSS have also been reported in the past[9]. Though not common in the United States, 100 to 200 cases are reported annually from southwest Texas and portions of the southeast[10], too. The clinical features of dengue fever vary according to the age of the patient. Infants and young children may have a non-specific febrile illness with rash[11]. In our study, no patient was younger than 10 years old and the youngest patient was 16 years old. Older children and adults may have either a mild febrile syndrome or the classical incapacitating disease with abrupt onset and high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash[11].

In 2006, a total of 1045 patients were diagnosed having dengue fever in Taiwan who mainly show the following serotypes: DENV-1: 22 patients (22/1045, 2.2%), DENV-2: 56 patients (56/1045, 5.4 % ), DENV-3: 393 patients (393/1045, 37.6%), and undifferentiated type: 570 patients (570/1045, 54.5%)[1]. Dengue virus serotype 3 was isolated from 16 patients (16/37, 43%) in our study which is comparable to the data of CDC in Taiwan that the total numbers of the patients with DENV 3 were 393 patients (393/1045, 37.6%) during 2006[12]. A peak incidence of dengue fever developed during September and October in this study. Dengue fever is characterized by biphasic fever, headache, eye pain, myalgia, arthralgia, prostration, rash, lymphadenopathy, and leucopenia[13]. Persons infected with DENV are generally mild or asymptomatic, but may also present with undifferentiated fever, classic DF, and even DHF and DSS[14]. In this study, the majority of dengue fever patients presented classic symptoms, signs and laboratory finding. According to the result of our study, symptoms that begin more than 2 weeks after traveller depart from an endemic area and fever that lasts longer than 10 days are probably not due to dengue[15]. Relative bradycardia was noted in our study and it may occur in certain infectious diseases including dengue fever, typhoid fever, Legionnaire's disease, pneumonia due to Chlamydia species, and

sandfly fever[16].

Once inoculated into a human host, dengue has an incubation period of 3-14 days (average 4-7 days)[17]. Following incubation, a 5- to 7-day acute febrile illness ensues. Recovery is usually complete by 7-10 days. DHF or DSS usually develops around the third to seventh day of illness, approximately at the time of defervescence[17]. DHF developed in small proportion of patients (2/37, 5.4%) in this study which was similar to previously reported in Taiwan[18]. DSS is a severe form of DHF. Clinical indicators of impending DSS include severe abdominal pain, change from fever to hypothermia, restlessness, sweating, prostration and tender hepatomegaly[19].

According to our observation, the average duration of peak body temperature of hospitalization to normal (body temperature ＜37℃ ) required 3.8 days. Fever is often preceded by chills, erythematous mottling of the skin, and facial flushing (a sensitive and specific indicator of DF )[20]. In this study, leucopenia developed in 30 of 37 patients (81%) and thrombocytopenia (platelet ＜100,000/mm$^3$) occurred in 27 of 37 patients (73%). Elevation of aspartate aminotransferase was found in 25 of 37 patients (68%). However, many of the laboratory and clinical findings about dengue fever are nonspecific and can be attributed to other infection, such as malaria, typhoid fever, leptospirosis, and cytomegalovirus infection[11]. The laboratory diagnosis is made by immunoglobulin (Ig)M ELISA or paired serology during recovery or RT-PCR or by isolating from blood in the acute phase if mosquito inoculation or mosquito cell culture is used. Primary dengue infection is relatively easy to diagnose. IgM is detectable in large amounts after 4-5 days of infection, peak at about 2 weeks. Low levels of IgG are produced just after the IgM[17]. However, false positive of laboratory examination can occur in patients with rheumatoid factor[15]. RT-PCR is more sensitive and faster than viral culture techniques, and can be used as an epidemiologic tool to rapidly detect infecting serotypes[17]. In 2006, confirmed cases of dengue fever happen mostly in southern Taiwan, especially in Kaohsiung city with the major serotype of DENV-3 which differentiate from serotype DENV-1 and DENV-2 in the last outbreak in 2002. For the sake of variant serotype between two outbreaks in 2002 and 2006 respectively, we should pay more attention to patients with bleeding tendency and risk for progression to DHF.

Gall bladder wall thickening could be found in some dengue fever patients[21]. In our observation, the findings of gall bladder wall thickening were demonstrated in 10 of 22(45.4%) abdominal sonographic examinations. Splenomegaly (6/22, 27.2%) and pleural effusion (1/22, 4.5%) were noted too. The studies were performed at the first two days after admission. The ultrasound finding in early mild from of DF include gallbladder wall thickening, pericholecystic fluid, minimal ascites, pleural effusion and hepatosplenomegaly[22]. There is a significant association between gallbladder wall thickening (especially ≧5mm) and severity, as well as progression of DHF and is useful as a criterion for identifying DHF patients as high risk of developing hypovolemic shock[23]. Dengue fever may present clinical manifestation mimicking acute cholecystitis. Dengue fever with acute acalculous cholecystitis is rarely reported and closely monitoring vital signs to avoid shock and correct thrombocytopenia to avoid bleeding is suited for most patients. Surgical treatment may be needed for dengue fever patient with complication of diffuse peritonitis[24].Therefore, in endemic area of dengue, like Taiwan, ultrasound features of thickened gall bladder wall, pleural effusion and ascites should strongly factor the diagnosis of dengue fever[22]. Unnecessary operation should be avoided to prevent hemorrhagic complication.

Treatment of dengue fever, DHF, and DSS is supportive. There is no specific therapy available.

Acetaminophen is favorable if an antipyretic is acquired. However, careful management of fluid and electrolyte by experienced physicians and nurses is crucial and patients must be monitored for development of complications such as hemorrhagic shock. With appropriate intensive supportive therapy, mortality may be reduced to less than 1%. In conclusion, dengue virus infection is a public health concern and it is important to educate patients in endemic area, especially in Southern Taiwan about the prevention of mosquito bite by the control of the vector population, such as repellants, mosquito screen, and elimination of water-holding contains.

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# 南台灣某區域教學醫院登革熱的臨床經驗

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## 摘 要

2006年國軍高雄總醫院共有37 例經血清學診斷爲登革熱確定病例。大部分病人發生於九月及十月 (23/37，62%)。病人的平均年齡爲45.4 ± 17.7歲。病人平均住院天數爲6.2天。典型症狀有發燒 (31/37，84%)，腸胃道症狀 (17/37，46%)，頭痛 (13/37，35%)，皮疹 (13/37，35%)，肌肉疼痛，關節疼痛以及骨頭痛 (13/37，35%)等。只有2個病人有出血徵候。經RT-PCR檢驗結果呈現陽性者有20人。病人平均發燒天數爲6天，從最高體溫降低到正常體溫平均約需要3.8天。白血球減少及血小板降低回復至白血球及血小板正常範圍各需要4.7天及2.1天。在這37個病人中30個病人(81%)有白血球減少的現象，其中又有16個病人的白血球減少較爲嚴重 (白血球數目介於 1,000 至 2,000/$mm^3$ )。27 個病人(73%)有血小板過低，其中又有12個病人爲嚴重血小板過低 (血小板＜50,000/$mm^3$ )的情形。18個病人有PTT 延長現象 (18/37，49%)。25個病人(68%)有天門冬安酸胺基轉化酶 (aspartate aminotransferase，AST) 上升的情形。此外，有22個病人施行腹部超音波檢查，其中有10位病患有膽囊壁增厚的現象。這37個病患經治療後預後良好。