# Management dilemmas in the treatment of dengue fever*

***Kolitha H Sellahewa#***

*National Hospital of Sri Lanka, Regent's Street, Colombo 8, Sri Lanka*

**Abstract**

This paper is aimed at highlighting some of the dilemmas faced by clinicians in the management of adult patients with dengue and my views in resolving these issues.

Even though early diagnosis and prompt fluid therapy are central to reduce morbidity and mortality in dengue, achieving these goals are contentious issues and are often hampered by the limited access to expensive laboratory data in most developing countries which would enable a rapid and accurate diagnosis. My viewpoint on overcoming these dilemmas is to make an early diagnosis on the clinical features, and apply clinical predictors of disease severity in selecting patients for interventions. In this regard, diffuse blanching erythema in a patient with features of a viral fever during dengue epidemics would suffice to diagnose and treat the patient as a dengue case. Laboratory confirmatory data are expensive, not readily available and could delay treatment. Fluid therapy and intervention modalities for thrombocytopaenia should be judged clinically on an individual basis rather than the blind, strict adherence to theoretical fluid regimens with the potential risk of fluid overloading. Capillary refill time, pulse pressure, cervical lymphadenopathy, and changes in the sensorium are useful clinical parameters for selection of patients for intervention as well as subtle adjustments and termination of fluid therapy. A practically feasible step-wise approach to dengue management is described in this paper.

**Keywords**: Dengue; management; disease severity predictors.

## Introduction

The management dilemmas faced by busy clinicians in developing countries where dengue has reached epidemic proportions are centred on:

- Early diagnosis of dengue;
- Prediction of disease severity;
- Selection of patients for aggressive interventions;
- Implementation of the concept of judicious fluid therapy on an individual basis to prevent fluid overloading and its attendant complications;

* The conclusions and recommendations in this paper are based on the personal experiences of the author while treating adult patients with dengue. The views expressed here are entirely of the author and are subject to technical analysis or confirmation by other experts. These do no necessarily reflect the opinions or decisions of WHO. – Editor

#*E-mail: kolithah@gmail.com*

- Concerns on thrombocytopaenia and decisions on when to intervene, and how to intervene.

It has been widely recognized that early diagnosis and prompt appropriate treatment of dengue prevents both morbidity and mortality[1]. The vast majority of adult patients with dengue recover completely without specific aggressive interventions (personal experience). It is thus necessary to select the minority of patients early in the disease for close monitoring and appropriately timed fluid therapy to prevent progression to dengue shock syndrome (DSS). Achieving this objective, which is a fundamental requirement for proper management, requires dengue to be diagnosed early and then be able to predict disease severity. Dengue-specific IgM is positive in only 55% of patients in 4$^{th}$ to 7$^{th}$ days while 94% positivity is evident after the 7$^{th}$ day. No IgM is detected in 1 to 3 days after infection[2]. PCR amplification for dengue RNA provides a fast diagnosis but is expensive and false positive reports are seen. In numerous acute dengue fever patients an early diagnosis will be obtained only by combining IgM antibody detection with detection of virus or virus RNA using RT-PCR[2,3].

These facilities are also not available to most clinicians at the point of delivery of care. Consequently, they need to rely on clinical skills to arrive at an early diagnosis. The diagnostic dilemma, however, is that the classic clinical features of dengue such as saddle-back fever and break-bone pain are not seen in all the patients, and varying degrees of headache, myalgia, arthralgia and vomiting are common to most non-specific viral fevers often encountered in the community and among inpatients in a medical unit. However, what is encountered very often in dengue patients is diffuse blanching erythema (personal experience)[4,5,6]. Any patient with features of a viral fever having diffuse blanching erythema should be treated as dengue fever during epidemics.

The management dilemma is compounded by the current WHO classification of grading dengue haemorrhagic fever (DHF) from I to IV, as there is an overlap of DHF grades III and IV with dengue shock syndrome (DSS). Also, the case definition of DHF requires there to be evidence of plasma leakage[7]. However, there are many patients with haemorrhage, particularly skin haemorrhages, who do not have evidence of plasma leakage and therefore cannot be classified as DHF despite the presence of haemorrhages. This can confuse the inexperienced clinician and lead to unnecessary and inappropriate overzealous fluid therapy.

A more practical classification based on the clinical findings would be more appropriate and simpler to determine. Dengue patients without any haemorrhages or shock are classified as dengue fever. Patients who have diffuse blanching erythema or blanching papular erythema would also fall into this category. Blanching papular erythema should not be mistaken for petechiae. Petechiae will not blanch on pressure and implies skin haemorrhages. Dengue patients with haemorrhages, irrespective of its magnitude or site, are classified as DHF. Dengue patients in shock are classified as DSS. Intervention decisions at all levels of care could then be based on accurate and easily determined clinical parameters such as capillary refill time and pulse pressure.

Accurate prediction of disease severity requires the analysis of specific data related to pathogenesis and plasma leakage such as viral serotype, serum levels of non-structural protein 1 (NS1), immunoglobulin G (IgG) subclass, dengue-specific and total immunoglobulin E (IgE), serum concentration of antiplatelet antibodies, and levels of cytokines such as TNF $\alpha$, IFN $\alpha$ and IL-10[8,9,10,11,12]. Non-availability of such information to clinicians at the point of delivery of care leaves no option but to rely on clinical parameters to predict disease severity.

Thrombocytopaenia is a common problem in dengue, which causes a lot of concern not only to the patient but also to the relations as well as the attending physician. No clear guidelines exist for its management. The natural tendency is to transfuse platelets. Thrombocytopaenia in dengue is primarily immune-mediated. It can therefore be surmised that platelet transfusions by presenting a strong antigenic stimulus can aggravate the thrombocytopaenia by an exalted immune response. Besides, the short life span of transfused platelets would result only in a transient non-sustained elevation of the platelet count. Additionally, platelet transfusions can evoke hypersensitivity reactions and fluid overloading with attendant complications of pleural effusions, such as ascites, and pulmonary oedema.

Clearly, prophylactic platelet transfusions for dengue are baseless and appear to be an irrational and inappropriate intervention. However, transfer of patients from peripheral hospitals to tertiary care hospitals primarily for platelet transfusions reflect the dilemmas confronting clinicians in managing thrombocytopaenia in patients with dengue.

## Management

From a practical point of view, reduction in morbidity and mortality of dengue rests firstly in the early diagnosis of dengue and then on the ability to identify the minority of patients with a propensity to develop severe disease early in the disease course. Individually-tailored parameters designed to detect potential complications should be monitored in such patients. Critically-timed appropriate interventions based on changes in the monitoring parameters could thereby thwart disease progression and an adverse outcome.

Diffuse blanching erythema is a very useful sign in the early clinical diagnosis of dengue in adults during epidemics[1,13]. This is recognized as a generalized flushed appearance in the skin, particularly in the posterior aspect of the chest when observed in a good light (Figure 1). The erythematous areas have no clear boundaries and blanch on light pressure applied with the fingers. Some patients have blanching papular erythema, particularly in the limbs (Figure 2). These appear as minute erythematous papules which blanch when light pressure is applied with the finger tip. It should not be mistaken for petichiae which do not blanch on pressure. Serological confirmation is not required for management and should be requested only if

***Figure 1:*** Diffuse blanching erythema

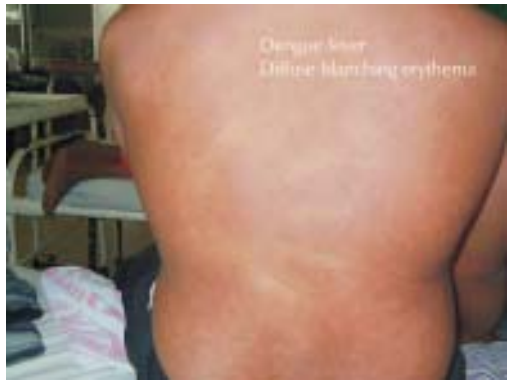
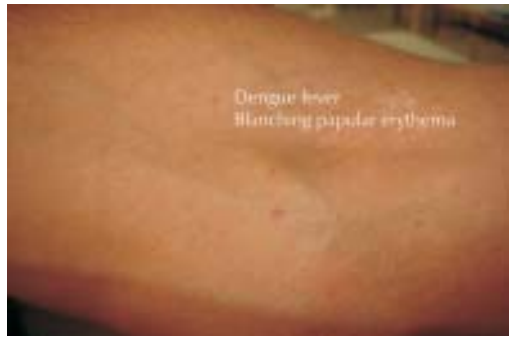



***Figure 2:*** Blanching papular erythema



there is a doubt in the diagnosis, specially to differentiate from other febrile illnesses with myalgia and thrombocytopaenia like leptospirosis.

Patients with a normal sensorium, good peripheral circulation with warm extremities, bounding pulse, capillary refilling time <2 seconds, posterior cervical lymphadenopathy and platelet counts over 50 000/µL are bound to make an uneventful recovery. Patients with a pulse pressure of <20 mmHg and poor capillary refilling will require aggressive fluid therapy to prevent progression to DSS. Interventions in such patients should be early, decisive and aggressive. The quantum and quality of the fluid infused should be dictated by clinical judgement and changes in the monitoring parameters, particularly pulse pressure, haematocrit and platelet count.

Peripheral pulse, capillary refill time, and pulse pressure are the most consistent and important parameters to base decisions on interventions at all levels of care. However, in difficult and ambiguous situations, seeking additional information on predictors of disease severity and capillary leakage facilitates decision-making. These include cervical lympadenopathy, acute right hypochondrial pain and tenderness, retro-orbital pain, altered sensorium, pleural effusions, ascites, oedematous gall bladder on ultrasonography, positive tourniquet test, platelet count, and aspartate amino transferase (AST) levels. It should be noted that in this context the presence of cervical lymphadenopathy[4] and normal levels of AST[13] are strong negative predictors of dengue fever progressing to DHF or DSS. Such patients very often will not require aggressive fluid therapy. On the contrary, the presence of any one or more of the other predictors of disease severity mentioned above should alert the clinician to the potential probability of an adverse outcome and the need for close monitoring of pulse pressure, capillary refill time and haemotocrit and to be more liberal on fluid therapy. Less than optimal care, both with regard to monitoring and fluid therapy early in the disease course in such patients, could result in DSS[14].

Clinicians are cautioned against aggressive and overzealous fluid therapy in the face of stable haemodynamics even in patients with extensive blotchy erythema and the above-mentioned predictors of disease severity, which imply incipient increase in vascular permeability, and increased vulnerability to fluid overloading and attendant mortality. A dynamic approach to management and subtle adjustments in fluid therapy, based on astute clinical judgement, requires one to strike the correct balance between augmentation of fluid therapy to offset a drop in the pulse pressure and capillary filling on the one hand and decrementation of fluids without compromising the haemodynamics on the other, when increased capillary permeability has shifted the balance towards aggravation of pleural effusions and pulmonary oedema. The entire quantum of intravenous fluid as calculated per guidelines need not necessarily be given to patients with pleural effusions provided haemodynamic parameters are satisfactorily maintained, usually with 1 to 1.5 litres of isotonic saline infused over 24 hours. Any deterioration in the haemodynamics should prompt the immediate administration of an intravenous saline bolus (10 ml/kg). Satisfactory circulation is reflected by a pulse pressure of over 20 mmHg, capillary refill time <2 seconds, and hourly urine output of >0.5 ml/kg body weight. These are the parameters to be monitored and utilized to optimize fluid therapy.

Platelet transfusions are hardly ever required even with counts as low as 10 000/µL because the circulating platelets are haematologically active and sufficient to prevent bleeding by thrombocytopaenia per se.

Besides, the survival of transfused platelets is very short in cases with DSS[15]. In general, platelet transfusions are given only when there are serious haemorrhagic manifestations. Transfusion requirements correlate with the occurrence of bleeding in the gastrointestinal tract but not with the platelet count[16]. There is no place for prophylactic platelet transfusions[17].

Fresh frozen plasma is an useful and safer therapeutic option than platelet transfusions for patients with severe thrombocytopaenia. Its use, however, should be reserved only for highly selected patients with severe thrombocytopaenia early in the disease[18].

In summary, the management dilemmas can be resolved by applying the following steps when treating a febrile patient with suspected dengue in an adult medical ward.

## Step I: Early diagnosis of dengue

It should be a clinical diagnosis based on the presence of diffuse blanching erythema in a patient with features of a viral fever.

## Step II: Classify the clinical type as DF, DHF or DSS

## Step III: Risk stratification and selection of patients for specific interventions

(1) **Minor disease:** Patients with a normal sensorium who do not look too ill, have a good appetite, warm extremities, pulse pressure of 20 mmHg, bounding peripheral pulse, capillary refill time <2 seconds and enlarged posterior cervical lymphnodes. A majority of patients fall into this category (personal experience). Intravenous fluids are not mandatory and can be managed effectively with oral fluids[7,17]. Intravenous fluids will be required if there are excessive fluid losses due to undue vomiting.

(2) **Severe disease:** Patients with altered sensorium, sustained right hypochondrial pain, absence of cervical lymhpadenopathy, cold extremities, pulse pressure <20 mmHg, capillary refill time >2 seconds or any other predictors of severe disease should be selected for monitoring and judicious fluid therapy.

## Step IV: Monitoring and critical care

Patients with clinical markers of severe disease or predicted to develop severe disease should be shifted to a high dependency area in the ward where close observation and monitoring is feasible with the prioritized utilization of limited facilities in a resource-poor setting. Monitoring charts in these selected patients should be simple and practical. The monitoring parameters should be individualized and should have predictive utility to base interventional decisions. These include the pulse rate, pulse pressure, capillary refill time, respiratory rate, and hourly urine output. Serial estimation of haematocrit and platelet count in the first 24 to 48 hours where facilities are available will provide additional and useful information to base decisions on interventions.

Judicious fluid therapy for this category of patients is aimed at maintaining circulatory stability in the face of continuing plasma leakage and thereby preventing progression to DSS. The approach is less aggressive and is dictated by clinical judgement which takes into consideration the pulse pressure, urine output and haematocrit. This is achieved by infusing

the minimal quantum of intravenous fluid to maintain a pulse pressure of 20 mmHg or more and an hourly urine output of 0.5 ml/kg body weight. This usually amounts to approximately 1000 to 1500 ml of isotonic saline over 24 hours. Necessarily the fluid intake has to be adjusted appropriately for those patients with excessive fluid losses due to undue vomiting. Plasma leakage continues for about 24 to 48 hours and good pulse volume, wide pulse pressure diuresis and stable haemotocrit are indicators to stop fluid therapy[17]. Over-treatment with fluids at this stage will have an adverse outcome and will lead to pleural effusions and pulmonary oedema. Progressive increase in the respiratory rate in the monitoring chart should alert the clinician to the possibility of this complication, prompting a careful evaluation of the lungs clinically, radiologically and measurements of oxygen saturation as well as the need to withhold intravenous fluids provided minimal haemodynamic stability is maintained.

### Step V: Aggressive fluid therapy

Urgent and aggressive fluid therapy is required for those with a pulse pressure <20 mmHg, cold clammy skin, rapid weak pulse and restlessness. Aggressive intervention entails an intravenous bolus of isotonic saline or Hartman's solution at a dose of 10 ml/kg body weight. If the pulse pressure remains less than 20 mmHg the same dose is repeated twice. If there are still no signs of improvement, up to two doses of colloid (plasma or dextran) at a dose of 10 ml/kg body weight should be given[17].

### Step VI: Consider intervention for thrombocytopaenia

Platelet transfusions are hardly ever indicated even with counts as low as 10 000. It should be considered only if there is significant bleeding attributable to thrombocytopaenia[17].

Consider fresh frozen plasma as a therapeutic option for thrombocytopaenia in highly selected patients early in the disease course[18].

## Conclusion

The management of dengue patients, particularly during epidemics, should be based on arriving at a clinical diagnosis early in the disease course. Recognition of clinical predictors of disease severity at the time of presentation, avoiding unnecessary platelet transfusions, and judicious fluid therapy dictated by clinical judgement early in the disease course are of crucial importance. Proper utilization of simple parameters for monitoring such as pulse pressure, capillary refill time and haematocrit play a central role in the selection of patients for interventions as well as determination of end points and optimization of fluid therapy to reduce morbidity and mortality due to dengue.

## Recommendations

(1) Utilize a simple and practical six-step approach to manage adult dengue patients in a ward setting. This approach is particularly applicable to busy overcrowded hospitals with limited resources and little access to intensive care units, as is the case with most rural and district hospitals in developing countries where dengue is common.

(2) Develop clear consensus guidelines on the management of thrombocytopaenia in dengue.

(3) Current classification of the grading of dengue needs to be reviewed.

(4) Aggressive educational programmes targeting care-providers at all levels to avoid unnecessary transfers, irrational platelet transfusions and fluid overloading.

## References


[1] Malavige GN, Fernendo S, Fernando DJ, Seneviratne SL. Dengue viral infections. *Postgrad Med J.* 2004; 80: 588-601.

[2] Schilling S, Ludolfs D, Van An, Schmitz H. Laboratory diagnosis of primary and secondary dengue infection. *J. Clin.Virol*. 2004 Nov; 31(3): 179-84.

[3] Ole Wichmann, Klaus Stark, Pei-Yun Shu, Matthias Niedrig, Christina Frank, Jyh-Hsiung Huang, Tomas Jelinek. Clinical features and pitfalls in the laboratory diagnosis of dengue in travelers. *BMC Infect Dis*. 2006; 6: 120.

[4] Sellahewa KH, Samaraweera DN, Thusita KPGD, Vallipuranathan M. Clinical predictors of disease severity in dengue patients at National hospital of Sri Lanka. *Ceylon Medical Journal*. 2007; 52 (Suppl1): 28.

[5] Salem K, Shaikh I. Skin lesions in hospitalized cases of dengue fever. *J College of Physicians.& Surgeons Pakistan.* 2008 Oct; 18(10): 608-11.

[6] Premaratna R, Pathmeswaran A, Amarasekara ND, Motha MB, Perera KV, de Silva HJ. A clinical guide for early detection of dengue fever and timing of investigations to detect patients likely to develop complications. *Trans R Soc Trop Med Hyg*. 2009 Feb; 103(2): 127-31.

[7] World Health Organization, Regional Office for South-East Asia. *Prevention and control of dengue and dengue haemorrhagic fever: comprehensive guidelines*. WHO regional publication, SEARO, No. 29. New Delhi: WHO SEARO, 1999.

[8] Libraty DH, Young PR, Pickering D, Endy TP, Kalayanarooj S, Green S, Vaughn DW, Nisalak A, Eniss F A, Rothman AL, High circulating levels of the dengue virus non-structural protein NS 1 early in dengue illness correlate with the development of dengue haemorrhagic fever. *J Infect Diseases*. 2002; 186(8): 1165-8

[9] Koraka P, Suharti C, Setiati TE, Mairuhu AT, Van Gorp E, Hack CE, Juffrie M, Sutaryo J, Van Der Meer GM, Groen J, Osterhaus AD. Kinetics of dengue virus specific serum immunoglobulin classes and subclasses correlate with clinical outcome of infection. *J Clinical Microbiol*. 2001; 39: 4332-8.

[10] Thein S, Aaskov J, Myint TT, Shew TN, Saw TT, Zaw A. Changes in levels of anti-dengue virus IgG subclasses in patients with disease of varying severity. *J Med Virol*. 1993; 40: 102-6.

[11] Koraka P, Murgue B, Deparis X, Setiati TE, Suharti C, van Gorp EC, Hack CE, Osterhaus AD, Groen J. Elevated levels of total and dengue virus-specific immunoglobulin E in patients with disease of varying severity. *J Med Virol*. 2003; 70: 91-8.

[12] Mustafa AS, Elbishbishi EA, Agarwal R, Chaturvedi UC. Elevated levels of interleukin-13 and IL-18 in patients with dengue hemorrhagic fever. FEMS *Immunol Med Microbiol*. 2001 Apr; 30(3): 229-33.

[13] Jacobs M. Dengue. *Medicine International*. 2005; 5(3): 46-8.

[14] Sellahewa KH. Dengue fever – predictors of disease severity and their influence on management. *Ceylon Medical Journal*. 2008; 53: 75–78.

[15] Isarangkura P, Tuchinda S. The behavior of transfused platelets in dengue haemorrhagic fever. *Southeast Asian J Trop Med Public Health*. 1993; 24 Suppl 1: 222-4.

[16] Chuansumrit A, Phimolthares V, Tardtong P, Tapaneya-Olarn C, Tapaneya-Olarn W, Kowsathit P, Chantarojsiri T. Transfusion requirements in patients with dengue haemorrhagic fever. *South East Asian J Trop Med Public Health*. 2000; 31: 10-4.

[17] Ministry of Health, Sri Lanka. *Guidelines on clinical management of dengue fever/dengue haemorrhagic fever*. Colombo: Epidemiology Unit, 2005.

[18] Sellahewa KH, Samaraweera N, Thusita KP, Fernando JL. Is fresh frozen plasma effective for thrombocytopaenia in adults with dengue fever? *Ceylon Med J*. 2008 Jun; 53(2): 36-40.