

# Do young adults with uncomplicated dengue fever need hospitalisation? A retrospective analysis of clinical and laboratory features

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## ABSTRACT

**Introduction:** Approximately 80 percent of all notified cases of dengue infections in Singapore were hospitalised from 2000 to 2005. We aimed to determine if hospitalised dengue patients had significant morbidity and mortality, and if admissions were in accordance with previously-published admission criteria.

**Methods:** The medical records of the first 20 patients with laboratory-confirmed dengue from two consecutive months in three time periods were retrospectively reviewed. Demographical, clinical and laboratory data on admission, during hospitalisation and on discharge, were compared.

**Results:** There were 120 patients with a mean age of 35 years. Males comprised 77 percent and foreign workers 51 percent. Of the published admission criteria, 33 percent had vomiting, 22 percent diarrhoea, 13 percent abdominal pain, 18 percent bleeding and one patient had hypotension. 30 percent were above the minimum platelet threshold of 80,000/uL, but 50 percent had safe levels of platelets between 50,000 and 80,000/uL. Dengue haemorrhagic fever occurred in 4 percent with no death. After admission, platelet nadir was below 20,000/uL in only 9 percent and below 10,000/uL in only 2 percent of cases. Bleeding did not correlate with platelet count. Medical referral to the hospital was significantly associated with thrombocytopenia, while self-referral was significantly associated with vomiting.

**Conclusion:** Severe adverse outcome among young adults with uncomplicated dengue fever is rare. Instead of hospitalisation, daily outpatient monitoring with symptomatic treatment and medical leave may be a safe and feasible alternative.

**Keywords:** dengue fever, dengue haemorrhagic fever, dengue infection, platelet count,

## thrombocytopenia, uncomplicated dengue fever

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## INTRODUCTION

Acute dengue infections range from asymptomatic infections,<sup>(1)</sup> undifferentiated fever, dengue fever (DF) syndrome, dengue haemorrhagic fever (DHF) potentially leading to dengue shock syndrome (DSS),<sup>(2)</sup> and atypical dengue manifestations such as encephalitis.<sup>(3)</sup> Case fatality from DHF is higher in young children and the elderly than young adults<sup>(4)</sup> which correlated with physiological evidence of increased capillary permeability in the extremes of age.<sup>(5)</sup> In Singapore, dengue infections mainly occur in young adults.<sup>(6)</sup> However, about 80% of notified cases of dengue infections from 2000 to 2005 were hospitalised<sup>(6-11)</sup> despite low rates (1.8%–2.8%) of DHF.<sup>(6,7)</sup> The necessity of hospitalisation of uncomplicated DF patients has been questioned.<sup>(12,13)</sup>

In September 2005, we proposed new admission and discharge criteria for DF patients after conducting a literature review.<sup>(14)</sup> We recommended admission for all patients who are diagnosed with DHF according to the World Health Organisation (WHO) criteria at hospital presentation, as well as for DF patients who fulfilled certain objective and subjective criteria (Table I). We performed a retrospective review of 120 patients to assess concordance with our published admission criteria over three time periods (prior to the proposed criteria, during the peak of the dengue epidemic and after the proposed guidelines, and after the dengue epidemic had abated), and to describe any morbidity and mortality associated with acute dengue infections in Singapore in the entire patient cohort.

## METHODS

We reviewed the medical records of the first 20 patients who were admitted to the Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore, and who had a discharge diagnosis of laboratory-confirmed dengue in June and July 2005 (prior to the proposed criteria), September and October 2005 (during the peak of the dengue epidemic and after the proposed guidelines), and in January and February 2006 (after the dengue epidemic and the proposed criteria). This study received ethical

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**Table I. Admission criteria for patients with dengue fever (excludes dengue haemorrhagic fever) and concordance in the study cohort.**

Objective criteria		Subjective criteria	
Description of criteria	Percentage fulfilling criteria	Description of criteria	Percentage fulfilling criteria
Significant bleeding	Any bleeding 18%	Severe vomiting or diarrhoea requiring intravenous fluid	Vomiting 33% Diarrhoea 22%
Blood pressure < 90/60 mmHg and/or pulse rate > 100/minute	Hypotension 0.8%	Severe abdominal pain	Abdominal pain 13%
Dehydration with electrolyte abnormality and/or postural hypotension	Not available	Elderly patients with medical comorbidities and who are unwell	> 65 years old 1.7%
Haematocrit > 50%	3%		
Platelet count < 80,000 /uL	70% (but 20% if < 50,000/uL)		

approval from the Institutional Review Board, National Healthcare Group. We recorded age, gender, presence of medical comorbidity, nationality, source of referral to hospital, source of admission to hospital, clinical features and laboratory data on admission, laboratory diagnosis of dengue, clinical and laboratory data after admission, and laboratory data on discharge. We used the WHO criteria to reclassify all cases into DF and DHF.<sup>(2)</sup>

For the sample size calculation in this descriptive study, to assess concordance with the admission criteria over three time periods, we assumed a proportion with a positive response of 0.5 to obtain the largest possible sample size. Based on a margin of error of 0.1, the calculated sample size was 96. Analysis was performed to compare the clinical and laboratory variables. Categorical variables were compared with the chi-square and Fisher's exact test. *t*-tests and the nonparametric Mann-Whitney test were used to compare means and medians for continuous outcomes, respectively. Tests were performed with Stata Release 9.0 (Stata Corporation, College Station, TX, USA), with the level of significance set at  $p < 0.05$ .

## RESULTS

There were 120 patients with a mean age of 35 (range 15–73) years, and 77% were male. Foreign workers accounted for 51%. Among Singaporeans, 39 of 59 (66%) patients were male, compared with 53 of 61 (87%) among foreign workers ( $p = 0.009$ ). Only 1.7% of patients were older than 65 years. Only 10% of patients reported medical comorbidity. General practitioners referred 35% of patients, government polyclinics 30% and the remainder self-presented to the emergency department (ED). 83% of cases were admitted from ED.

At presentation, the mean duration of fever was 5 (range 3–9) days. Among all cases, vomiting occurred in 33%, diarrhoea 22%, and abdominal pain 13%. Bleeding

was noted in 18%. Importantly, 58% were not febrile and only one patient had hypotension. Only 3% of all cases had haematocrit > 50% suggestive of DHF, and 80% had a safe level of platelet count exceeding 50,000/uL although only 30% exceeded the platelet threshold of 80,000/uL in the proposed criteria. While 85% of patients had elevated aspartate transaminase, only 29% exceeded 150 IU/L and 4% exceeded 500 IU/L.

Dengue was diagnosed with polymerase chain reaction in 65% of 46 patients, compared with serology in 90% of 88 patients. Secondary dengue infection was diagnosed in 31% with positive immunoglobulin G with Dengue Duo IgM and IgG Rapid Strip (Panbio Diagnostics, Queensland, Australia). DHF, according to the WHO criteria, was present in 4% of cases throughout hospitalisation, but there were no deaths among all the patients. After admission, fever lasted a mean of one day (range 0–4 days). Hypotension occurred in 4% while bleeding was reported in 18%. Prophylactic platelet transfusion (i.e. patients with no bleeding but had low platelet counts) was given in 8% for some cases with platelets below 20,000/uL, depending on the managing clinician's decision.

Mean time of platelet increase from platelet nadir to more than 50,000/uL was one day (range 0–4 days). Importantly, the individual platelet nadir was below 20,000/uL in only 9% and below 10,000/uL in 2% of cases. The individual platelet nadir was between 20,000 and 50,000/uL in 39%, and between 50,000 and 100,000/uL in 46% of patients. Haematocrit rose above 50% in only 5% of patients after admission. The mean length of stay was 3 (range 1–7) days. At discharge, 48% of patients had platelet counts above 100,000/uL, 30% were between 80,000 and 100,000/uL, and 20% were between 50,000 and 80,000/uL. No readmission within 14 days of discharge was noted.

**Table II. Number of patients meeting the admission criteria for each time period.**

Criteria	Time periods			p-value
	June–July 2005	September–October 2005	January–February 2006	
Bleeding	8	9	5	0.49
Hypotension	0	1	0	1
Tachycardia	0	2	0	0.33
Haematocrit > 50%	0	3	1	0.32
Platelet count < 80,000/uL	30	34	27	0.19
Vomiting	15	15	9	0.26
Diarrhoea	9	7	10	0.71
Abdominal pain	4	5	7	0.60
Elderly (> 65 years)	2	0	0	0.33

Concordance with published admission criteria is shown in Table I. We were unable to assess the severity of bleeding, vomiting, diarrhoea and abdominal pain. Thus, the numbers were an overestimation because some patients may have responded to symptomatic treatment. If the artificial platelet threshold of 80,000/uL were reduced to 50,000/uL,<sup>(12)</sup> that could potentially reduce admission from 70% to 20% in a patient cohort with uncomplicated dengue infection. There was no statistically significant difference between concordance with admission criteria in the three time periods assessed (Table II).

Of those with bleeding at presentation, 73% had gum bleeding, 23% had menorrhagia and 5% had epistaxis. Bleeding persisted in 64% after admission. Of those with no bleeding at presentation, 7% developed gum and nose bleeding after admission. Bleeding occurred in 14% of those with platelet count above 100,000/uL, 23% between 8,000 and 100,000/uL, 18% between 50,000 and 80,000/uL, and 18% between 20,000 and 50,000/uL ( $p > 0.05$ ). No bleeding occurred in two patients with platelet count below 20,000/uL. No patient suffered gastrointestinal bleeding.

Patients without fever at presentation to ED were more likely to have platelet counts below 50,000/uL ( $p < 0.01$ ), compared with those with fever at presentation. There was no significant difference in vomiting, abdominal pain, bleeding, hypotension, haematocrit above 50%, and aspartate transaminase above 500 IU/L between patients with and without fever at presentation. Similarly, those with platelet count below 50,000/uL were more likely to be febrile at presentation to ED ( $p < 0.01$ ), while there was no significant difference in the same morbidity data between patients with platelet count above and below 50,000/uL. We did not detect any statistically significant difference between patients with primary and secondary dengue in age, gender, nationality, duration of fever from onset of illness, vomiting, diarrhoea, abdominal pain, bleeding, presence of fever, hypotension, haematocrit above 50%, platelet count below 50,000/uL, and aspartate transaminase above 500 IU/L at presentation to ED.

## DISCUSSION

This is a small retrospective study which allows us to study in detail the clinical and laboratory features of uncomplicated dengue infections in young adults in Singapore. Only 4% of patients had DHF, and there were no cases of gastrointestinal bleeding and no deaths. Patients self-presenting to the hospital accounted for only 35% of cases. We hypothesise that a majority of referred patients from general practice and government polyclinics may be for platelet count rather than symptomatic illness. Indeed, 47% of self-presented patients had vomiting compared with 27% of those referred by general practice or government polyclinics ( $p = 0.04$ ), while 26% of patients referred from general practice and government polyclinics had platelet count below 50,000/uL compared with 8% of those who self-presented ( $p = 0.03$ ). Because the majority of our patients were admitted from ED, any admission criteria had to be endorsed by, and promoted in ED. In fact, based on concordance with admission criteria, the commonest reason patients were hospitalised was for thrombocytopenia even though in the majority of cases platelet count did not drop below 20000/uL and there was no evident correlation between platelet count and bleeding.

However, despite admission to hospital, there was very little morbidity and no mortality in the majority of patients. We could find no difference in morbidity between patients with platelet counts above or below 50,000/uL, and with or without fever. More importantly, clinical course in the hospital was also low in morbidity, with only 9% of cases having platelet count below 20,000/uL and 5% with haematocrit above 50%. Mucosal bleeding was not uncommon and this was often confused with DHF, whose pathogenesis depends on increased capillary permeability leading to intravascular volume depletion and narrowing pulse pressure. If uncorrected by aggressive fluid resuscitation (e.g. 5–10 ml/kg of intravenous fluid for several hours) and intensive clinical and laboratory monitoring at the onset of DSS (defined by the presence of DHF and pulse pressure  $\leq 20$  mmHg), intractable shock

ensues, with disseminated intravascular coagulopathy and severe gastrointestinal bleeding.<sup>(2)</sup> This study failed to demonstrate any association between bleeding and platelet counts; this is consistent with another retrospective paediatric study involving mainly DSS, where platelet count was not a predictor of severe bleeding,<sup>(15)</sup> although we acknowledge our numbers were small.

Our findings were compatible with a previous retrospective local study which reported on 130 patients with 14.6% DHF and no deaths,<sup>(16)</sup> and another prospective Malaysian study with 162 patients with 13% DHF and no deaths.<sup>(12)</sup> The latter study showed that it was safe to monitor patients daily in an outpatient setting unless platelet count was below 50,000/uL, blood pressure below 90 mmHg, haematocrit above 50% or bleeding occurred. Both studies involved young adults and emphasised that dengue infections in young adults are associated with low case fatality rate,<sup>(4)</sup> compared with young children and the elderly.

Our study emphasised the benign nature of uncomplicated dengue infections in young adults. We acknowledge that currently, there are no simple clinical and laboratory markers to identify patients with acute dengue infections that are likely to develop DHF subsequently. To this end, we have embarked on the EDEN study<sup>(17)</sup> and completed a retrospective review of 1,973 hospitalised patients with acute dengue infections in 2004 to identify useful clinical and laboratory predictors of DHF.<sup>(18)</sup> If the majority of hospitalised patients can be safely monitored as outpatients,<sup>(12)</sup> this will increase the ability of doctors to look after DHF<sup>(19)</sup> patients who require intensive monitoring and aggressive fluid resuscitation; this is the time-tested way of treating DHF and DSS.<sup>(19)</sup> It is imperative for doctors to reduce the relatively high case fatality (6.4% or 25 of 393 cases in 2005) of DHF in Singapore.<sup>(6)</sup>

Limitations of this study include the small sample size, which may have resulted in a lack of power. This will be addressed by other studies mentioned above.<sup>(17,18)</sup> In addition, the lack of association between bleeding and platelet count was only on admission; this may not include subsequent clinical development. Conclusive studies on the association between platelet count and bleeding, and the impact of transfusion, should utilise randomised control trials, if possible, and include the entire duration of admission. In conclusion, in a predominantly young adult population with uncomplicated dengue infections, morbidity was low and hospitalisation may be unnecessary. Daily outpatient monitoring either at government polyclinics, general practitioners or dedicated dengue clinics at public hospitals during dengue outbreaks, with symptomatic treatment and medical leave, may be a safe and feasible alternative.

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