Safety and cost savings of reducing adult dengue hospitalization in a tertiary care hospital in Singapore

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Background: Previously, most dengue cases in Singapore were hospitalized despite low incidence of dengue hemorrhagic fever (DHF) or death. To minimize hospitalization, the Communicable Disease Centre at Tan Tock Seng Hospital (TTSH) in Singapore implemented new admission criteria which included clinical, laboratory, and DHF predictive parameters in 2007.

Method: All laboratory-confirmed dengue patients seen at TTSH during 2006–2008 were retrospectively reviewed for clinical data. Disease outcome and clinical parameters were compared over the 3 years.

Results: There was a 33.0% mean decrease in inpatients after the new criteria were implemented compared with the period before (p < 0.001). The proportion of inpatients with DHF increased significantly from 31.7% in 2006 to 34.4% in 2008 (p = 0.008); 68 DHF cases were managed safely on an outpatient basis after compared with none before implementation. DHF inpatients had more serious signs such as clinical fluid accumulation (15.5% vs 2.9% of outpatients), while most DHF outpatients had hypoproteinemia (92.7% vs 81.3% of inpatients). The eight intensive care unit admissions and five deaths during this time period all occurred among inpatients. The new criteria resulted in a median cost saving of US$1.4 million to patients in 2008.

Conclusion: The new dengue admission criteria were effective in sustainably reducing length of hospitalization, yielding considerable cost savings. A minority of DHF patients with mild symptoms recovered uneventfully through outpatient management.

Keywords: Dengue hemorrhagic fever, Arbovirus, Triage, Admission criteria, Singapore

Introduction

Dengue is a mosquitoborne disease endemic to most tropical and subtropical countries. It encompasses a wide range of symptoms, ranging from dengue fever (DF) to the more serious forms of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) using WHO 1997 criteria.[1] In 2009, the WHO proposed classifying dengue as with or without warning signs and severe dengue.[2]

In Singapore, the annual incidence of reported dengue cases has increased despite a decrease in the mosquito premises index because of several postulated factors, including waning herd immunity and disease transmission outside the home.[3] Although reported DHF cases are few (1.8–2.8%),[4–8] 78–83% of cases from 2000 to 2004 were hospitalized.[4,9–11]

Hospitalization for i.v. fluid when dehydration is equivalent to more than 10% body weight was recommended by WHO in 1997.[1] The new admission criteria proposed by WHO in 2009 included warning signs of hypotension, bleeding, organ impairment, rising hematocrit or pleural effusion or ascites or gallbladder thickening, comorbidities and social circumstances.[2]

There are few studies that evaluate dengue admission criteria. In Malaysia, young adult dengue patients without a history of bleeding, blood pressure >90/60 mmHg, platelet count >50 000/mm^3, or hematocrit <50% were safely managed as outpatients.[12] In Singapore, adult dengue patients were safely treated as outpatients if the following criteria were met: age <60 years, non-immunocompromised status, no significant comorbidities, good social support, ability to tolerate oral fluids, ability to attend the clinic daily, platelet count >50 000/mm^3,

hematocrit <49% (male) or <43% (female), and absence of confusion, severe abdominal pain, bleeding or shock.[13]

We aimed to evaluate new admission criteria implemented at the Communicable Disease Centre, Tan Tock Seng Hospital (TTSH), Singapore, in March 2007 to determine their efficacy in reducing hospitalization. We compared inpatient and outpatient populations before, during and after the criteria were implemented to establish whether hospitalized and ambulatory cases were triaged appropriately without adverse consequence. The cost savings due to reduced dengue hospitalizations were determined.

Methods

Study population

Our study cohort comprised all laboratory-diagnosed dengue patients identified from the hospital microbiology laboratory who were treated using a standardized dengue clinical care path in the Communicable Disease Centre, TTSH, from January 2006 to December 2008. TTSH is the major center for infectious disease referral in Singapore and treated about 37% of dengue public hospital patients in 2005.[14]

The patients' medical records were retrospectively reviewed for demographic, serial clinical, laboratory, radiological, treatment and outcome data. These cases were either positive by real-time PCR[15] or positive by acute phase dengue IgM/IgG serology[16] with clinical presentation fulfilling WHO 1997[1] or 2009[2] guidelines for probable dengue.

Although the new admission criteria were introduced in March 2007, they did not immediately take full effect. Therefore, in comparisons of patient characteristics, we compared 2006, 2007 and 2008 patients with each other, representing the time periods before, during and after the criteria were used, respectively. However, when quantifying the change in inpatients, we compared the time periods January 2006–February 2007 vs April 2007–December 2008.

Dengue classifications

Cases were categorized using serial clinical and laboratory data from the entire clinical course as DF, DHF or DSS using WHO 1997 classifications.[1] In addition, all cases were also categorized as dengue without warning signs, dengue with warning signs or severe dengue using WHO 2009 classifications.[2]

Admission criteria

Our admission criteria implemented in March 2007 included the following: platelet count $\leq$50 000/mm^3, serum hematocrit $\geq$50%, blood pressure $\leq$90/60 mmHg, postural drop in blood pressure >20 mmHg, pulse $\geq$100/min, clinical bleeding (except petechiae), clinically unwell patients (in particular, severe abdominal pain, persistent vomiting), elderly patients with comorbidities (such as diabetes, hypertension, heart failure, cancer, stroke), and whether patients fulfilled our DHF predictive model.[17,18] These criteria differed from WHO 1997 and 2009 guidelines[1,2] and the two published studies[12,13] because they incorporated our DHF predictive model, which included a computerized predictive equation

using clinical bleeding, lymphocyte proportion, serum urea and protein levels to generate an output of high vs low risk for DHF (see Supplementary Appendix A),[17] and a decision tree with three decision nodes of clinical bleeding, urea >4 mmol/l and protein $\leq$67 g/l.[18] Fulfillment of any one of the eight criteria was deemed appropriate for admission.

Statistical analysis

We modeled monthly dengue inpatients seen at TTSH from 2006 to 2008, removing the March 2007 implementation period, using the autoregressive moving average (ARMA) time series model to examine the mean change in the percentage of inpatients after the new criteria were implemented. The ARMA model correctly accounts for any autocorrelation in the data, as compared with simple models such as the linear regression model. It uses two parameters to describe changes in time: AR (autoregressive) and MA (moving average).

The Box–Jenkins method, which consists of the following steps, was used to determine the final model.[19] The correlogram and partial correlogram were used to generate preliminary estimates of the MA and AR coefficients of the model, respectively. Several models were considered, and the Akaike Information Criterion was used to select the most optimal model. The residuals of the final model were checked to make sure that they corresponded to white noise and were not autocorrelated.

In order to compare patient characteristics during the study period, the Kruskal–Wallis test was used to assess significance of continuous variables and χ^2 or Fisher's exact test for categorical variables. The level of significance was set at 5%. All statistical analyses were performed using Stata 12 (Stata Corp., College Station, TX, USA).

Results

From 2006 to 2008, 3558 patients were treated, of which 1292 (36.3%) were outpatients. The median age of the entire cohort was 34 years (IQR 26–42 years) and 2418 (68.0%) patients were male. Dengue diagnosis was confirmed by PCR in 829 (23.3%) patients, while probable dengue was diagnosed in 2545 (71.5%) patients using WHO 1997 dengue criteria and 2994 (84.1%) patients using WHO 2009 dengue criteria. In terms of dengue severity, DHF occurred in 754 (21.2%) patients, DSS in 131 (3.7%) patients and severe dengue in 523 (14.7%) patients. Dengue with warning signs was noted in 2032 (57.1%) patients. Intensive care unit admission was needed for eight patients and death occurred in five patients, all of whom were inpatients.

Interrupted time series analysis of monthly dengue hospitalizations

Figure 1 shows the monthly percentage of dengue patients admitted to TTSH from January 2006 to December 2008. In 2006, 468 of 509 (91.9%) patients were admitted; this decreased to 1005 of 1579 (63.6%) in 2007, and to 793 of 1470 (53.9%) in 2008. The final ARMA time series model with a coefficient of AR(1) showed that there was a 33.0% decrease in dengue inpatients in the April 2007 to December 2008 time period compared with those during January 2006

to February 2007 (p < 0.001). These periods are directly after and before the new criteria were implemented, respectively.

Characteristics of dengue inpatients

The demographic and clinical characteristics of dengue inpatients during the 3 years are summarized in Table 1. There was a significant increase of DHF/DSS inpatients (from 31.7% in 2006 to 34.4%

in 2008; p = 0.008) without a significant increase in inpatients with severe dengue (21.4% in 2006 vs 18.2% in 2008; p = 0.294), as our predictive model was for DHF and not severe dengue. Notably, there was a significant increase in dengue with warning signs (60.3% in 2006 to 64.6% in 2008; p = 0.006). Importantly, there were notable decreases in i.v. fluid use (p = 0.038), platelet transfusion (p = 0.091) and length of hospitalization (p < 0.001), without a significant change in the number of deaths (p = 0.189).

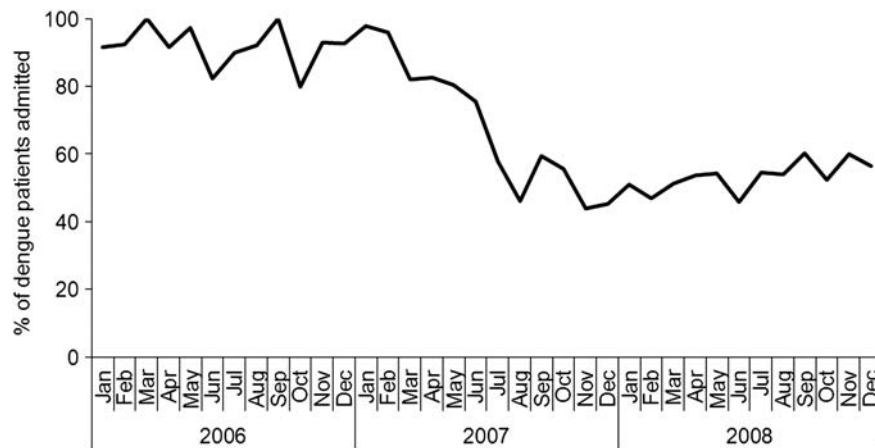**Figure 1.** Monthly proportion of dengue patients admitted to Tan Tock Seng Hospital, Singapore, January 2006–December 2008.

Table 1. Demographic and clinical characteristics of dengue inpatients at Tan Tock Seng Hospital, Singapore, 2006–2008

	2006 (n = 468)	2007 (n = 1005)	2008 (n = 793)	p-value
Demographics				
Age (years) [median (IQR)]	34 (27–42)	35 (27–45)	35 (26–45)	0.045
Male gender	327 (69.9)	657 (65.4)	536 (67.6)	NS
Charlson score ≥3	8 (1.7)	13 (1.3)	4 (0.5)	NS
WHO 1997 classification				
Dengue fever	292 (62.4)	578 (57.5)	498 (62.8)	0.045
Dengue hemorrhagic fever	122 (26.1)	332 (33.0)	239 (30.1)	0.025
Dengue shock syndrome	26 (5.6)	64 (6.4)	34 (4.3)	NS
WHO 2009 classification				
Dengue without warning signs	80 (17.1)	214 (21.3)	130 (16.4)	0.018
Dengue with warning signs	282 (60.3)	574 (57.1)	512 (64.6)	0.006
Severe dengue	100 (21.4)	207 (20.6)	144 (18.2)	NS
Treatment				
Intravenous fluids ever given	432 (92.3)	902 (89.8)	696 (87.8)	0.038
Blood ever given	5 (1.1)	8 (0.8)	3 (0.4)	NS
Platelet ever given	53 (11.3)	85 (8.5)	62 (7.8)	NS
Outcome				
Length of stay, days[a] (IQR)	4.2 (3–5)	3.8 (3–5)	3.8 (3–5)	<0.001
Intensive care unit admission	2 (0.4)	6 (0.6)	0	0.051
Death	2 (0.4)	3 (0.3)	0	NS

Data are number (%), unless otherwise indicated.
NS: not significant.
[a]Geometric mean.

Characteristics of dengue outpatients

Comparisons among outpatients during the same time periods are summarized in Table 2. There were 37 DHF and 5 DSS outpatients in 2008 vs none in 2006, and 29 severe dengue cases in 2008 vs 2 in 2006, although both differences were not statistically significant. Notably, outpatient dengue with warning signs increased from 48.8% in 2006 to 55.7% in 2008 (p = 0.005).

Trend in outpatient and inpatient DHF and severe dengue

Table 3 shows clinical signs for inpatients with DHF and for those with severe dengue. The proportion of DHF inpatients with clinical fluid accumulation[2] increased from 8.1% in 2006 to 18.7% in 2008 (p = 0.015), while the proportion of inpatients with hypoproteinemia[1] decreased from 84.5% in 2006 to 76.2% in 2008 (p = 0.030). Among inpatients with severe dengue, the proportion of those with severe bleeding[2] increased significantly from 41.0% in 2006 to 49.3% in 2008 (p = 0.004), while severe organ impairment[2] fluctuated during the 3-year period from 23.0% in 2006 to 8.7% in 2007 to 13.2% in 2008 (p = 0.003).

There were no DHF outpatients in 2006. Overall, there were no significant differences in DHF outpatients over the 2007–2008 period. In 2007, of 26 DHF outpatients, there was 1 with hematocrit change ≥20%, 1 with clinical fluid accumulation and 24 with hypoproteinemia. In 2008, of 43 DHF outpatients, there were 3 with hematocrit change ≥20%, 1 with clinical fluid accumulation and 39 with hypoproteinemia.

Table 2. Demographic and clinical characteristics of dengue outpatients at Tan Tock Seng Hospital, Singapore, 2006–2008

	2006 (n = 41)	2007 (n = 574)	2008 (n = 677)	p-value
Demographics				
Age (years) [median (IQR)]	34 (29–41)	32 (26–39)	32 (25–39)	NS
Male gender	28 (68.3)	403 (70.2)	467 (69.0)	NS
WHO 1997 classification				
Dengue fever	35 (85.4)	529 (92.2)	613 (90.6)	NS
Dengue hemorrhagic fever	0	24 (4.2)	37 (5.5)	NS
Dengue shock syndrome	0	2 (0.4)	5 (0.7)	NS
WHO 2009 classification				
Dengue without warning signs	18 (43.9)	257 (44.8)	263 (38.9)	NS
Dengue with warning signs	20 (48.8)	267 (46.5)	377 (55.7)	0.005
Severe dengue	2 (4.9)	41 (7.1)	29 (4.3)	NS

Data are number (%), unless otherwise indicated.
NS: not significant.

Table 3. Clinical characteristics of inpatients with dengue hemorrhagic fever and inpatients with severe dengue at Tan Tock Seng Hospital, Singapore, 2006–2008

	2006	2007	2008	p-value
Types of plasma leakage for DHF/DSS patients				
Hematocrit ≥20%	54 (36.5)	116 (29.3)	86 (31.5)	NS
Clinical fluid accumulation	12 (8.1)	64 (16.2)	51 (18.7)	0.015
Hypoproteinemia	125 (84.5)	331 (83.6)	208 (76.2)	0.030
Types of severe dengue				
Severe plasma leakage	58 (58.0)	115 (55.6)	82 (56.9)	NS
Severe bleeding	41 (41.0)	125 (60.4)	71 (49.3)	0.004
Severe organ impairment	23 (23.0)	18 (8.7)	19 (13.2)	0.003

Data are number (%), unless otherwise indicated.
DHF: dengue hemorrhagic fever; DSS: dengue shock syndrome; NS: not significant.

Cost savings from new admission criteria

The decreased patient admissions resulted in a median bill size saving of US$1.4 million in 2008 (90th percentile US$2.7 million; 2010 US$) to patients (see Supplementary Appendix B for calculation).

Discussion

Our new dengue admission criteria implemented in March 2007 resulted in considerable cost savings and decreased demand on hospital beds without adverse patient outcomes, as all outpatients recovered without complications. This is particularly invaluable if an outbreak were to occur, as happened in 2005[5] and 2007[7]

We observed a significant increase in DHF inpatients, possibly because our new admission criteria incorporated our DHF predictive models.[17,18] These models were based on our 2004 cohort during a predominantly dengue serotype 1 outbreak[6] and were recently validated in our 2007 predominantly dengue serotype 2 cohort.[20] Of note, we hospitalized more DHF patients with clinical fluid accumulation and severe dengue patients with bleeding after the new criteria were implemented, while allowing patients with milder signs such as hypoproteinemia to be managed on an outpatient basis. Additionally, our new admission criteria were associated with an increase of dengue inpatients with warning signs, which may be due to our admission criteria of severe abdominal pain and persistent vomiting.

Our study has several limitations. We were unable to obtain national data to allow comparison of dengue admission rates across all public hospitals, but our cost savings calculation was estimated based on publicly available information.[21] We did not make a direct before and after comparison as our new admission criteria did not result in an immediate reduction in hospitalization after March 2007 (Figure 1). Therefore we made a 3-year comparison rather than choose an arbitrary cutoff for time comparison. Before and after comparisons using January 2006–February 2007 vs March 2007–December 2008 and January 2006–May 2007 vs June 2007–December 2008 similarly showed a significant increase in DHF inpatients but not inpatients with warning signs. Thus the chosen arbitrary cutoff may affect the validity of the significance of the subanalysis, which may need to be confirmed by prospective studies.

Additionally, we did not have dengue serotype data for our patients. The new criteria were introduced during the 2007 outbreak when there was a switch from dengue serotype 1 to serotype 2,[22] but the proportion of nationally notified DHF cases did not increase concurrently,[6–8] nor was there a significant increase in severe dengue in our cohort. We also did not know which of our patients had secondary dengue infection, which has been cited as a risk factor for DHF/DSS,[23] since we did not have paired sera. In a 2005 study, 49 of 164 Singapore adults aged 18–30 years were positive for at least one dengue serotype by plaque reduction neutralization assay. Of the 49, 37 (75.5%) were positive for two or more dengue serotypes.[24]

Overall, our dengue admission criteria effectively and sustainably reduced adult dengue hospitalization at TTSH without adverse patient outcome but with significant associated cost savings and reduced demand for hospital beds. A small minority of mild DHF patients were managed without complications as outpatients. Our admission criteria were applied to adult dengue in Singapore and await validation in other countries and where pediatric dengue is prevalent.

Supplementary data

Supplementary data are available at *Transactions* Online (http://trstmh.oxfordjournals.org/).

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