ORIGINAL ARTICLE

Compliance of WHO Guideline on Dengue Management among Indian Patients: An Interventional Quality Improvement Study

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Abstract

Introduction: Dengue fever management is guided by WHO guideline, the recent one being 2009; however, compliance to the guideline is difficult to assess and in India there is no data on it. The present study, a longitudinal pre-post interventional quality improvement study, was done to determine the compliance to the guideline on dengue patients before and after resident physicians' training during two peak seasons and their impact on survival.

Methods: This study was conducted in a tertiary health care centre in North India over 18 months. Data of hospitalized patients who admitted with dengue fever diagnosis in a peak season was collected in the form of quality indicators as described by the WHO-2009 guideline on dengue. Resident physicians were then given appropriate training about the guideline during the off season. Data of new dengue patients in next peak season after resident training was collected and compared with the baseline by standard statistical tests.

Results: The post-intervention compliances of all components increased (total mean score by giving one point to each of the quality indicators reached 7.9 from 6.4). The compliance to individual indicator also increased: the admission criteria (baseline, 44% to post-intervention, 52%, $p = 0.37$), classification criteria (91.7% to 96%, $p = 0.33$), correct staging/triage (42.9% to 86%, $p < 0.01$), vitals monitoring (85.7% to 92%, $p = 0.28$), correct usage of bolus fluids (34.3% to 69.5%, $p < 0.01$), crystalloid as choice of fluid (100% in both groups), proper fluid titration (26.2% to 56%, $p < 0.01$), hematocrit monitoring (95.2% to 98%, $p = 0.42$), platelet transfusion when indicated (65.5% to 58%, $p = 0.39$), antibiotic use when required (61.5% to 80%, $p = 0.03$), and discharge criteria (100% in both groups). The mortality decreased from 7.1% (baseline) to zero (post-intervention). The median duration of hospital stay also reduced by 1 day.

Conclusions: The study affirms that the compliance to WHO guideline on dengue management in India can be further improved by regular physician training on the guideline. Simultaneously, this educational intervention not only improves patient outcomes but also direct proper resource utilization especially platelet transfusion and antibiotic use. Furthermore, every hospital/institute should have an internal quality improvement program like this to improve the management of dengue patients. Future studies are needed to understand various barriers to 100% implementation of the guideline.

Introduction

Dengue fever is an arboviral disease caused by Flavivirus continues to be one of the commonest tropical diseases. WHO notified it as a major international health concern because of increasing frequency of epidemics, co-circulation of multiple serotypes, and occurrence of dengue hemorrhagic fever in new areas.[1] WHO descriptions of dengue and their guidelines have been started in 1975, followed by revision in 1986, 1997, and 2009. The management comprises nothing but aggressive body fluid balance and continuous monitoring of clinical-laboratory parameters. Various studies from Malaysia, Indonesia, and Thailand to assess the outcome of practicing WHO guideline have shown the reduced rate of the complications, mortality, and costs of the treatment.[2,3] Studies done in Nepal and Puerto Rico show limited knowledge of physicians regarding the management and sub-optimal compliance to the present guideline.[4,5] However, a study from Singapore identifies no major gaps in knowledge but proves wide variations in the management practice.[6]

The development and publication of guidelines often do not lead to changes in clinicians' bedside practices in a timely fashion. Adopting or de-adopting new evidence based practices among health care persons are sometimes found to be delayed, without any clear reasons.[7] Though we have many guidelines describing protocol based management of dengue fever, actual scenario is found to be different from the ideal one. Fear and panic among common people and health communities lead to admission of maximum cases in the hospital, increased prophylactic transfusion of blood components, and improper hydration and unnecessary use of antibiotics which further cause over utilization of resources, burden to health system, iatrogenic complications, and economic losses. Repeated education/training is the only old known method to overcome this hurdle. Hence, learning has to be adopted again and again on a protocol based approach.

There is no data in India with regard

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Received: 09.04.2018; Accepted: 16.11.2018

Table 1: Criteria for dengue case classification and levels of severity (WHO 2009)

Probable dengue	Warning signs	Severe dengue
Live in / travel to dengue endemic area	1. Abdominal pain or tenderness	Severe plasma leakage:
Fever with any 2 of the followings	2. Persistent vomiting	• Shock
1. Nausea, vomiting	3. Clinical fluid accumulation	• Fluid accumulation with respiratory distress
2. Rash	4. Mucosal bleed	Severe bleeding (as evaluated by clinician)
3. Aches and pains	5. Lethargy/restlessness	Severe organ involvement
4. Tourniquet test positive	6. Liver enlargement >2 cm	• Liver: AST or ALT ≥ 1000
5. Leukopenia	7. Increase in haematocrit (Hct) with rapid fall in platelets	• CNS: Impaired consciousness
6. Any warning sign		• Heart and other organs

Confirmed dengue (important when no sign of plasma leakage)

- ✓ Dengue NS1 antigen demonstration (ELISA) or
- ✓ Dengue RNA detection (PCR), or
- ✓ Dengue IgM positive (ELISA), or
- ✓ A fourfold or greater change in reciprocal IgG in paired sera

to the compliance of WHO guideline on management of dengue fever. Assessing the physician's approach to the management and ensuring the compliance to the guideline is the need of the hour to combat dengue fever. We hypothesize that the baseline compliance of the treating physician to WHO-2009 guideline is highly variable at a referral hospital/institution in India.[8] To increase the compliance, we educate them through an interventional program. The study is a pre- and post- interventional study. Primary objective of the study is to determine the guideline compliances by seeing admitted patients' document/file at baseline and at post-intervention phase and compare them. Secondary objective is to determine the outcomes with respect to the mortality and hospital stay.

Methods

Study settings and participants

The prospective interventional quality improvement study (time series design) was conducted in the department of Emergency and Internal medicine at a tertiary level health centre, North India, during September, 2013 to March, 2015. This chosen time period was of importance with respect to the seasonal occurrence of dengue fever. The disease was usually precipitated by rainfall, temperature, and the degree of urbanization.[9] In India, September to February was the peak time for this. Therefore, pre-intervention phase was chosen in one peak season, post-intervention season was in the next peak season, and intervention phase (education phase) was in between. Included patients were admitted ones who fulfilled the criteria for dengue fever as per WHO-2009 guideline.[8] Dengue fever was defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leukopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. Only laboratory confirmed cases were included (Table 1). Excluded patients were children (age of < 12 years), pregnant, co-infected patients, and those had taken partial treatment from other hospital.

Sample size

Target sample had been calculated based on proportion of properly managed dengue patients. Out of the broad four aspects of the management i.e. fluid management, platelet transfusion, proper monitoring, and other medications, it was expected that fluid or platelet transfusion was less properly managed. Assuming that 30% of the patients were properly managed for fluid and blood transfusion separately; to estimate this with an absolute precision of 10% and confidence interval (CI) of 95%, calculated sample size was 84. Thus a maximum of 84 or all the patients admitted with dengue fever during a season, whichever was the least was considered as the required sample size for the study. Same applied to the post-intervention phase also.

Interventions

Study conducted in three phases of equal time period over 18 months: baseline phase, intervention phase, and post-intervention phase. Resident physicians were chosen for intervention/training because of their lead role during the outbreak management among other staffs (e.g. nurses, technicians) involved in the team work. They were post-graduate trainee of the hospital/institution. Every six months, a new batch of 5-10 residents had entered to the post-graduate education of the institution and at one point of time 50-60 residents were there. New residents were not directly managing the patients, usually accompanied with senior residents and consultants. Intervention delivered in the department were educational programs based on the prevalent WHO guideline.[8] Programs aimed to create awareness and inoculate the guideline among the residents through four training sessions. Two open forums on the same were also being conducted for all staffs involved in the management to further increase the efficiency of management. Training were designed and delivered by the investigators. Emphasis was laid on the accuracy, relevance, layout, and technique of presentation. Content of the training material was kept simple, meaningful, and interesting. Different methods were used to deliver the content using appropriate audio-visual aids. Multiple mock sessions of the presentation were held for validation. Residents were not told about the ongoing study to prevent the bias of documenting properly in patient files even if the guideline was not followed. Blinding was possible because of academic interest of the topic and it was part of educational curriculum to be completed in an academic year.

Outcomes

Compliance with each of the components of the guideline was measured in both phases after seeing individual patient file by applying a standardized checklist/questionnaire which included patient demographics, comorbidities, vital signs, laboratory parameters, and 11 quality indicators (admission criteria, dengue classification, triage into correct stage, vitals monitoring, usage of bolus fluids, crystalloid as choice of fluid, correct fluid titration, hematocrit (Hct) monitoring, proper use of platelet transfusion, use of antibiotics, and discharge criteria). Criteria for admission included all severe dengue patients, dengue with warning signs, and dengue with co-morbidities or in social isolation. Dengue was classified into dengue fever with or without warning signs (DW & DF respectively) and severe dengue (SD) (Table 1). Dengue was staged (triaged) into 3 phases- febrile, critical, and recovery phases. Critical phase included the fluid leak phase where aggressive

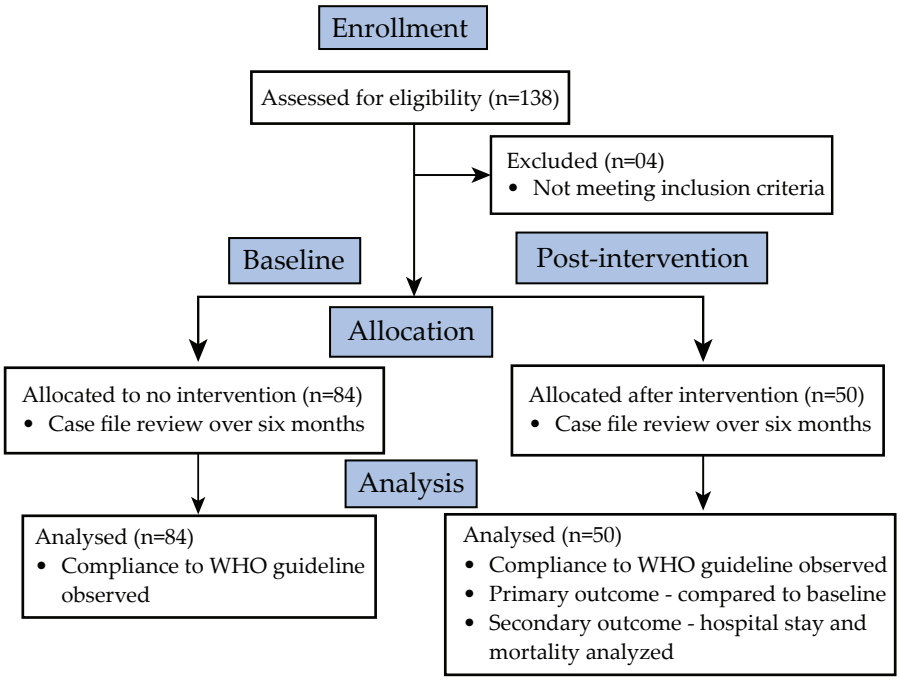

Fig. 1: The study flow details. WHO - World Health Organization

fluid management was required with frequent clinical and Hct monitoring. In the recovery phase patient may develop fluid overload and pulmonary edema if fluid therapy was continued without titration/tapering. Here we assessed how many patients were staged/triaged correctly. Monitoring of vital signs included pulse rate, respiratory rate, blood pressure, pulse pressure, jugular venous pulsations, capillary filling, and urine output. Fluid bolus was defined as 20 mL/kg fluid infused over 30-minutes in critical phase patients. Four hourly monitoring of Hct was assessed. Platelet transfusion was correctly indicated when total platelet count was < 10×10^9/L or there was a major bleed from any body parts. Discharge criterion was fulfilled when patient was afebrile, with subsided warning symptoms, with stable vitals, and with recovered complications.

Statistical Methods

The data storage and analysis were performed using Microsoft excel and STRATA SE 11 respectively. For categorical variables, frequency and percentage were calculated and compared with help of the chi-square test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation (SD) and compared with unpaired student t-test and Mann Whitney test. A p value of less than 0.05 was considered significant.

Ethics approval and consent

The study protocol was approved by the institutional review board. Data collection procedures were completed with ensuring the subject confidentiality. Verbal consent was obtained from all the residents for the educational training.

Results

Participant flow

A total of 138 patients were screened, but 134 patients were assigned, allocated, and analyzed in the study. Four patients were excluded because they had partial treatment from outside hospital and with complications during admission. The study was in two groups; pre-intervention phase of six months having 84 patients and post-intervention phase of six months having 50 patients (Figure 1). The second phase could not reach to the appropriate sample size because of low prevalence of dengue patients in that season.

Baseline data

Baseline characteristics were comparable in the pre- and post-intervention groups (Table 2). Among different categories of dengue, half of cases were DF (n=49/84 [58.3%], n=24/50 [48%] in both groups respectively) followed by DW cases (n=24/84 [28.6%], n=16/50 [32%]) and then SD cases (n=11/84 [13.1%], n=10/50 [20%]). When compliance was expressed in qualitative forms viz. good (> 90%), average (70-90%), poor (50-69%), and very poor (< 50%), at baseline, good compliance was found only in three quality indicators- correct classification, Hct monitoring, and discharge criteria. Very poor compliance was found in four indicators- admission criteria, correct staging of patients, usage of bolus fluid, and correct fluid titration.

Primary outcome variable: compliance with the guideline

When a total score was calculated by giving one point to each of the quality indicators except the discharge criteria and choice of fluids as crystalloid (each 100% in both the groups) and compared, it showed a mean increase from 6.4 in pre-intervention group to 7.9 in post-intervention group. Compliance to major quality indicators improved at post-intervention and four indicators- staging of the patients, adequate usage of bolus fluids, fluid titration, and usage of antibiotics improved to a significant level (Table 3).

Admission criteria was averagely followed in both groups, however, in a subgroup analysis, it was not followed in majority of EHS patients (n=35/52 [67.3%], n=12/16 [75%] respectively). Majority of patients were in either febrile or critical stages in both the groups (febrile stage, n=45/84 [53.6%] and n=23/50 [46%]; critical stage, n=39/84 [46.4%] and n=24/50 [48%]; recovery stage, n=0/84 and n=3/50 [6%] respectively). Choice of fluid was crystalloid in all cases with 0.9% normal saline (90% of total fluids), ringer lactate (7.4% total fluids), and 5% dextrose normal saline (3.6% total fluids). No colloid other than albumin [n=3 (3.6%)] was used in the study. Oral fluids were used in all the patients along with intravenous fluids. Even though the adequacy of oral fluids was low at the time of initiation of fluids, they were monitored well and oral intake was increased with time along with titration of fluid therapy. Compliance to the platelet transfusion showed a downward trend from 65.5% to 58% (p=0.39). In subgroup analysis, excluding the beneficiaries of Employee Health Scheme (EHS) of the hospital, it improved but non-significantly from 56.3% to 58.8% (p=0.83). About other blood component transfusions, packed RBC transfusions were used correctly in 40% cases of severe mucosal bleeding with low or normal Hct (n=6/15) and FFP was correctly in 100% cases of prolonged prothrombin time (n=2/2). Antibiotics were prescribed without

Table 2: Comparison of baseline characteristics in between pre- and post-intervention groups

Parameters	Pre-intervention (n=84)	Post-intervention (n=50)	p value
Age (in years)*	26.7 ± 10.2	30.2 ± 10.6	-
Sex ratio (M:F)	1.6:1	2:1	-
Associated co-morbidities	13.1%	10%	0.06
Pulse rate (per minute)*	89.6 ± 13.6	90 ± 11.8	0.51
Pulse pressure (mm Hg)*	40.1 ± 10.1	37.5 ± 9.4	0.52
Respiratory rate (per min)*	16.1 ± 4.9	15.4 ± 4.1	0.08
Hemoglobin (g/dl)*	13 ± 2.2	12.7 ± 2.3	0.48
Hematocrit (%)*	39.1 ± 7	39.4 ± 6.6	0.77
Total WBC count (x10 ^{6}/L)#	4200 (1200-37400)	4200 (12000-40900)	0.71
Platelet count (x10 ^{6}/L)#	44000 (500-252000)	24500 (5000-195000)	0.10
ESR (mm/ 1st hour)#	8 (2-64)	18 (4-117)	0.40
Prothrombin time (sec)*	13.5 ± 1.9	12.5 ± 2.1	0.10
Blood urea (mg/dl)#	20 (10-116)	22.5 (10-303)	0.99
Serum creatinine (mg/dl)#	0.9 (0.4-7)	0.9 (0.4-10.2)	0.96
Serum sodium (meq/L)*	136 ± 5	137.2 ± 5.1	0.16
Serum potassium (meq/L)*	3.9 ± 0.7	4.3 ± 0.7	0.99
SGOT (IU/L)#	94 (21-1003)	106 (21-3178)	0.09
SGPT (IU/L)#	59 (13-1526)	71 (16-1980)	0.06
ALP (IU/L)#	190 (74-770)	210 (74-1298)	0.51
Total bilirubin (mg/dl)#	0.6 (0.2-2.8)	0.6 (0.2-5.1)	0.08
Serum Albumin (mg/dl)*	3.8 ± 0.5	3.5 ± 0.6	0.31

**Mean ± SD and #Median (Min-Max)*

Table 3: Quality indicators – compliance as per WHO guideline in between pre- and post-intervention groups

Quality indicators checked	Pre-intervention (n=84)	Post-intervention (n=50)	p value
Admission criteria	37 (44%)	26 (52%)	0.37
Classification criteria	77 (91.7%)	48 (96%)	0.33
Correct staging/triage	36 (42.9%)	43 (86%)	<0.01
Vitals* monitoring	72 (85.7%)	46 (92%)	0.28
Correct usage of bolus fluids	11 of 32 (34.3%)	16 of 23 (69.5%)	<0.01
Choice of fluid, crystalloid	84 (100%)	84 (100%)	-
Fluid titration proper	22 (26.2%)	28 (56%)	<0.01
Hematocrit monitoring	80 (95.2%)	49 (98%)	0.42
Platelet transfusion when indicated	36 of 55 (65.5%)	17 of 29 (58%)	0.39
Antibiotic use when required	16 of 26 (61.5%)	12 of 15 (80%)	0.03
Discharge criteria	78 of 78 (100%)	50 of 50 (100%)	-

**Vital signs* include pulse rate, respiratory rate, blood pressure, pulse pressure, jugular venous pulsations, capillary filling, and urine output.

an indication in few patients (n=10/26 [38.4%], n=3/15 [20%] respectively in both groups). In pre-intervention phase, right use of antimicrobials was seen in eight patients having leukocytosis with/without any localized infection sites and another eight co-infections: 4 (15.4) had malaria, 3 (12.5%) had enteric fever, and 1 (3.8%) had scrub typhus (all these were diagnosed by serological tests). Similarly, in post-intervention phase, right use of antimicrobials was seen in six patients having leukocytosis with/without any localized infection sites and another six co-infections: 3 (20.1%) had malaria, 2 (13.4%) had enteric fever, 1 (6.7%) had leptospirosis.

Secondary outcome variables

There were 7.1% (n=6) mortalities in the pre-intervention group compared to no death in post-intervention group, although the number of SD patients were higher in the later. Median duration of hospital stay in both the groups were 6 (3-24) and 5 (4-45) days respectively (CI, 95%).

Discussion

The quality improvement study represents an in-depth document evaluation of WHO-2009 guideline compliance in the management of dengue patients before and after resident physician's educational programs. Compliance, assessed using the quality indicators, improves significantly for the correct staging/triage, use of bolus IV fluids, titration of fluids, and usage of antibiotics. It does not improve for the proper use of platelet transfusion, however, improves non-significantly after excluding the EHS populations. There is non-significant improvement in the remaining indicators such as admission criteria, dengue classification, vitals monitoring, and Hct monitoring. There is 100% compliance in both groups for the choice of fluid usage and the discharge criteria. Mortality and hospital stay improve when guideline compliance increases. The study affirms that the established guideline is yet to be implemented fully (100%) in a research institution/tertiary care hospital. To our knowledge, no studies use similar quality indicators comprising the majority parts of the guideline like the present study in determining the compliance except few studying individual criterion.[3-6,10-14] More importantly, document evaluations guiding an institute for the internal quality improvement program are not studied in previous studies. We will discuss few important indicators in details.

According to the guideline, recommended first-line intravenous fluid is crystalloid which was followed in 100% cases in this study. Although crystalloid is not superior to colloid when blood pressure increment is concerned, but colloid takes longer time to make recover in patients with low pulse pressure.[15] Rate of intravenous fluid administration should be at stepwise increments or decrements with at least 4–6 hourly Hct monitoring during the critical phase. This was performed in > 95% cases in both groups. However, overall fluid titration (that includes clinical monitoring in association with Hct monitoring) was not performed well in all patients. This was only in 1/4th of patients and increased significantly after education programs to more than half of patients. Similarly fluid bolus (20 mL/kg) was very poorly performed in pre-intervention groups (1/3rd patients) and significantly improved after the education programs (2/3rd). Hence, the present study describes very poor compliance of fluid management and compliance improves after the educational training. Rocha et al study studied the impact of an educational program in improving the fluid management of dengue fever and outlined the decrease in the number of days of fluid therapy and the increase in usage of intravenous fluids.[2] This subgroup analysis was not done in this study.

Platelet transfusions did not show much improvement even with education and it showed the possibility of a fear factor among patient populations and treating team in withholding the transfusions in patients with thrombocytopenia without any definitive indications. Studies have showed the futility of prophylactic platelet transfusions. A case control study by Prashantha et al showed that prophylactic platelet transfusion in clinically stable DF patients was associated with significant delay in platelet recovery and increased

duration of hospitalization, although it was not harmful in terms of morbidity or mortality.[16] More importantly platelet as a hospital resource material should not be misutilized considering extra load during a dengue outbreak. Human behavioral factors may have significant role on this; a future study on this is need of the hour.

As dengue is a tropical disease, it can be seen as a co-infection with other tropical diseases and co-infections such as with malaria, enteric fever, scrub typhus, or leptospirosis. These co-infections have been reported in the literature and thus antimicrobials use can be justified in such cases.[17-20] However, prophylactic antibiotics are not advocated. Compliance to the rational antimicrobials use (prescribed when indicated) are not priory studied in dengue cases. The present study showed significant 18.5% absolute improvement in the compliance after the education, but the baseline irrational use of antimicrobials was 38.5% which outlined again the misutilization of resources. Hence barriers to the guideline adoption have to be determined again.

Both morbidity (or hospital stay) and mortality among dengue patients had improved after the educational training on the guideline. There were no deaths in post-intervention group despite of higher number of severe dengue cases compared to the pre-intervention group. Therefore, compliance to the guideline definitely improves the outcome. This has also been studied by Magpusao and Mayurasakorn et al who showed significant improvement of the case fatality ratio of dengue cases after providing the education to the physician.[21,3]

For a training program to be successful, it should be convenient, relevant, focused, and delivered to the target population. We had targeted the relevant population (i.e. resident physicians). The individual duties of treating team members may vary, but the resident is the front runner and backbone of the whole patient management, especially in Indian tertiary care institutions. Henceforth, these facts reinforce the strength of the study design and relevance. Furthermore, we observed other obstacles in providing higher compliance rates among individual quality indicators including lack of adequate man power (resident doctor was the only provider many-a-times), delay in response time by medical personnel in an overcrowded Indian hospital setting, practical limitations in implementing training programs to all physicians at a time, difficulty in monitoring in a busy emergency ward, and lack of appropriate means and devices for continuous and accurate surveillance of compliance to the guidelines. Our institute continues to work towards meeting the goals set for this education programs and overcoming barriers.

This study has notable limitations. First, the study location is a referral hospital. Therefore it is difficult to generalize the findings in the whole country/world where primary care delivering hospitals are much more. However, the success of this program is most likely attributable to its focus on quality indicators of the prevalent guideline and proper documentation of the treatment, which should be independent of medical locations and applicable to all hospital-based responders as well. Hence, implication of this study is widespread. Second, the skill retention is a major question as this will determine the frequency at which doctors should be re-educated. Third, we did not measure other variables as discussed above including the contribution of other medical personnel, training of nursing staff, immediate availability of intensive care, overburdened residents, their behaviour, and other unknown factors. These may have blunted the improvement in individual indicator's compliance post-training. Identifying and rectifying all these variables could have led to a better rate of compliance in the study. Henceforth, this study encourages having a large study/program for each institute to target an adequate compliance (100%) to the guideline.

In conclusion, the study affirms that the education training improves the guideline compliance which should be upto the mark in dengue endemic country like ours. The documentation quality, evaluated after training the medicine residents (who are usually the front runner of the dengue management team), may be used as an assessment tool for the internal quality improvement program to determine the guideline compliance. Furthermore, this study may prevent resource misutilization like the platelet transfusions or antibiotic uses. Future studies should assess the efficacy of these training programs (i.e., skill retention) and find out various barriers for achieving 100% compliance rate of the prevalent guideline.

References

1. Wilder-Smith A, Schwartz E. Dengue in Travelers. *N Engl J Med* 2005; 353:924–32.
2. Rocha C, Silva S, Gordon A, et al. Improvement in hospital indicators after changes in dengue case management in Nicaragua. *Am J Trop Med Hyg* 2009; 81:287–92.
3. Mayurasakorn S, Suttipun N. The impact of a program for strengthening dengue hemorrhagic fever case management on the clinical outcome of dengue hemorrhagic fever patients. *Southeast Asian J Trop Med Public Health* 2010; 41:858–63.
4. Dhimal M, Aryal KK, Dhimal ML, et al. Knowledge, attitude and practice regarding dengue fever among the healthy population of highland and lowland communities in central Nepal. *PloS One* 2014; 9:e102028.
5. Tomashek KM, Biggerstaff BJ, Ramos MM, et al. Physician survey to determine how dengue is diagnosed, treated and reported in puerto rico. *PLoS Negl Trop Dis* 2014; 8:e3192.
6. Lee LK, Thein TL, Kurukularatne C, et al. Dengue knowledge, attitudes, and practices among primary care physicians in Singapore. *Ann Acad Med Singapore* 2011; 40:533–8.
7. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med* 2003; 348:2635–45.
8. WHO Dengue: Guideline for Diagnosis, Treatment, Prevention and control. 2009. http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf. Accessed September 2, 2017.
9. Simmons CP, Farrar JJ, Nguyen van VC, et al. Dengue. *N Engl J Med* 2012; 366:1423–32.
10. Horstick O, Jaenisch T, Martinez E, et al. Comparing the usefulness of the 1997 and 2009 WHO dengue case classification: a systematic literature review. *Am J Trop Med Hyg* 2014; 91:621–34.
11. Kalayanarooj S. Dengue classification: current WHO vs. the newly suggested classification for better clinical application? *J Med Assoc Thail* 2011; 94 Suppl 3:S74–84.
12. Thein T-L, Gan VC, Lye DC, et al. Utilities and limitations of the World Health Organization 2009 warning signs for adult dengue severity. *PLoS Negl Trop Dis* 2013; 7:e2023.
13. Jayaratne SD, Atukorale V, Gomes L, et al. Evaluation of the WHO revised criteria for classification of clinical disease severity in acute adult dengue infection. *BMC Res Notes* 2012; 5:645.
14. Cao XTP, Ngo TN, Wills B, et al. Evaluation of the World Health Organization standard tourniquet test and a modified tourniquet test in the diagnosis of dengue infection in Viet Nam. *Trop Med Int Health* 2002; 7:125–32.
15. Ngo NT, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* 2001; 32:204–13.
16. Prashantha B, Varun S, Sharat D, et al. Prophyactic platelet transfusion in stable dengue Fever patients: is it really necessary? *Indian J Hematol Blood Transfus* 2014; 30:126–9.
17. Pérez Rodríguez NM, Galloway R, Blau DM, et al. Case series of fatal Leptospira spp./dengue virus co-infections-Puerto Rico, 2010-2012. *Am J Trop Med Hyg* 2014; 91:760–5.
18. Magalhães BML, Alexandre MAA, Siqueira AM, et al. Clinical profile of concurrent dengue fever and Plasmodium vivax malaria in the Brazilian Amazon: case series of 11 hospitalized patients. *Am J Trop Med Hyg* 2012; 87:1119-24.
19. Panda PK, Mohta S, Wig N, et al. Dengue Co-infections-An Emerging Entity during the Outbreak. *Journal of Clinical & Diagnostic Research* 2018; 12:OR01 - OR04.
20. Kumar S, Kumar PS, Kaur G, et al. Rare concurrent infection with scrub typhus, dengue and malaria in a young female. *J Vector Borne Dis* 2014; 51:71-2.
21. Magpusao NS, Monteclar A, Deen JL. Slow improvement of clinically-diagnosed dengue haemorrhagic fever case fatality rates. *Trop Doct* 2003; 33:156–9.