Clinical Management of Patients with Dengue Infection in Japan: Results from National Database of Health Insurance Claims

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Abstract. Dengue guidelines for diagnosis, treatment, prevention, and control (WHO, 2011) recommend acetaminophen and isotonic fluid for patients with dengue infection but do not recommend nonsteroidal anti-inflammatory drugs (NSAIDs) and hypotonic fluid. Other research showed no evidence of efficacy of platelet infusion in prophylactic. This research aims to clarify to what extent dengue patients were managed in accordance with the guidelines in Japan. We extracted claim data of patients with either dengue fever (DF) or dengue hemorrhagic fever (DHF) from the National Database of Health Insurance Claims and Specific Health Checkups of Japan between 2011 and 2015. The total number of patients was 1,370, which consisted of 1,306 DF patients and 64 DHF patients; 185 patients were younger than (<) 20 years and 1,185 patients were aged 20 years or older (≥). Among them, 24.5% of DF patients and 48.4% of DHF patients received hypotonic intravenous fluid, 12.9% and 18.8% NSAIDs, and 1.3% and 17.2% platelet transfusion, respectively. Comparing patients aged <20 years with patients aged ≥20 years, 57.8% and 54.5% received acetaminophen, 6.5% and 14.3% received NSAIDs, 40.0% and 38.3% received isotonic fluid, and 37.8% and 23.7% received hypotonic fluid, respectively. Platelet transfusion was used for 1.3% of DF and 17.2% of DHF patients. The study indicated that dengue patients in Japan might have increased risks of developing adverse events because of receiving the treatment that the guidelines do not recommend. More effort is needed to facilitate medical practitioners to follow the guidelines.

INTRODUCTION

Dengue fever (DF) is spread over 128 countries, with 390 million infections per year, but only 96 million manifest clinically.^{1,2} Its common symptoms are high fever, headache, vomiting, rash, and leucopenia.³ According to the dengue guidelines of the WHO and International Classification of Diseases (ICD)-11, dengue cases are classified into three categories by severity: dengue without warning signs, dengue with warning signs, and severe dengue. Warning signs include clinical fluid accumulation, mucosal bleed, and an increase in hematocrit (HCT) concurrent with a rapid decrease in the platelet count. The criteria for severe dengue are severe plasma leakage, severe bleeding, and severe organ involvement.³ In Japan, dengue is predominantly an imported disease mainly from Southeast Asia. Dengue fever is designated as a category IV infectious disease, in which every new case needs to be reported to the nearest public health center under the act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases in Japan.⁴ Under the act, dengue infection was reported as either DF or dengue hemorrhagic fever (DHF) as of 2018 in accordance with ICD-10. The Japanese Ministry of Health, Labour, and Welfare explains that dengue patients with the following four criteria are classified as DHF in the infection report under the act: 1) fever continuing for 2–7 days, 2) one or more symptoms of HCT increased, shock, and serum protein decreased/presence of pleural effusion or ascites, 3) platelet decreased (< 100,000/mm³), 4) one or more symptoms are positive for tourniquet test, petechiae bleeding/patchy ecchymoses/purpura, mucosal or gastrointestinal bleeding/bleeding at injection site or any other site, or blood in stool. The number of reported dengue cases under the act gradually increased from 18 cases in 2000 to 74 in 2005 and 244 in 2010.⁵ No

domestically infected dengue cases had been reported for 69 years after World War II. However, in 2014, there were 162 such domestically infected cases, from whom several genotypes of dengue virus (DENV)-1 strains were isolated.^{6–8} About 80% of the domestic cases in 2014 were infected in and around Yoyogi Park during the summer season. Mosquitos captured in the Yoyogi Park on September 3, 2014, had dengue virus, and, then, a mosquito with dengue virus has not been found since September 25, 2014.⁹

The WHO published the clinical guideline for dengue in 2009,³ and the Japanese guideline was published in 2014.¹⁰ Both guidelines recommend to use isotonic intravenous (IV) fluid and acetaminophen and not hypotonic IV fluid and nonsteroidal anti-inflammatory drugs (NSAIDs). Dengue fever patients often need isotonic IV fluid because of volume depletion. Because NSAID increases vascular permeability and bleeding tendency, the use of NSAIDs may cause progression of their symptoms. There is no efficacy for platelet transfusion in prophylactic use.¹¹ There is a scarcity of information about which type of medication was prescribed to the dengue patients in Japan.

Thus, this research aims to investigate the clinical management of dengue patients in Japan to confirm whether they received appropriate treatment in accordance with the dengue clinical guidelines.

METHODS

Data source and procedure. We extracted claim data having DF or DHF from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) between 2011 and 2015. The NDB covered 99.9% of claims from hospitals and pharmacies and 97.9% from clinics as of May 2015.¹² The NDB has two categories for dengue infection, which are DF and DHF, the same as the Japanese act of infection report because the NDB used ICD-10 version 2003 as disease name between 2011 and 2015. Dengue fever is diagnosed by detecting dengue nonstructural protein 1 (NS1) antigen ELISA, or immunochromatographic dengue

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NS1 antigen and IgM antibody test. reverse transcription polymerase chain reaction (RT-PCR) or IgM ELISA can also be used for diagnosis of dengue. The NDB has “suspicious flag” function for unconfirmed cases. It was considered that dengue with the suspicious flag was not diagnosed by the confirmation test. We excluded the extracted DF and DHF with the suspicion flag to include only the confirmed dengue patients into our analysis.

Statistical analysis. The extracted data included gender, age, diagnosis of either DF or DHF, diseases other than dengue, inpatient or outpatient, and prescribed drugs. We categorized prescribed drugs into isotonic fluid infusion including saline, hypotonic fluid infusion, acetaminophen, NSAIDs, the other analgesic-antipyretics, and platelet transfusion. Then, we calculated the proportion of the patients by the category of drugs prescribed. We analyzed slopes of the change in the percentage and their Spearman’s correlation coefficient for each categorized drug from 2011 to 2015. We used R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) for statistical analysis.

Ethical considerations. The ethics committee of Kyorin University and the expert panel at the Japanese Ministry of Health, Labour, and Welfare approved this research. Informed consent was not obtained from patients. Although the NDB data do not have personal information such as patient’s name, address, and telephone number, we treated the NDB data as strictly as the personal information in accordance with the Act on the Protection of Personal Information and guidelines for the provision of claims data and special health checkup result. The guideline prohibits from displaying summary statistics of less than 10 cases.¹³

RESULTS

The number of DF and DHF patients between 2011 and 2015 was 1,306 (95.3%) and 64 (4.7%), of which 801 and 41 were male, and 557 and 45 inpatients, respectively (Table 1). The number of patients with DHF aged < 20 years and in each

TABLE 1

Descriptive characteristics of dengue patients in the National Database of Health Insurance Claims and Specific Health Checkups of Japan from 2011 to 2015

Year	2011	2012	2013	2014	2015	Total
Number of patients	193	230	293	353	301	1,370
Gender						
Male	123	155	169	203	192	842
Female	70	75	124	150	109	528
Age (years)			*			
< 10						52
10–19						133
20–29						373
30–39						324
40–49						243
50–59						120
60–69						96
< 69						29
Disease name			*			
Dengue fever						1,306
Dengue hemorrhage fever						64
Inpatient/outpatient						
Inpatient	64	103	130	162	143	602
Outpatient only	129	127	163	191	158	768

* Less than 10 patients are not allowed to be shown according to the guideline of using the NDB, guidelines for provision of claims data and special health checkup result.

year cannot be shown because there were less than 10 such patients.

Other diseases, which more than 5% of the patients had, without a suspicion flag on the claims data categorized into ICD-10 version 2003 were general symptoms and signs ($n = 494$), metabolic disorders ($n = 449$), acute upper respiratory infections ($n = 339$), diseases of esophagus, stomach, and duodenum ($n = 297$), coagulation defects, purpura and other haemorrhagic conditions ($n = 294$), intestinal infectious diseases ($n = 271$), diseases of liver ($n = 269$), dermatitis and eczema ($n = 246$), symptoms and signs involving the digestive system and abdomen ($n = 126$), dorsopathies ($n = 102$), other bacterial diseases ($n = 101$), other viral diseases ($n = 96$), episodic and paroxysmal disorders ($n = 96$), urticaria and erythema ($n = 93$), other diseases of blood and blood-forming organs ($n = 92$), other diseases of upper respiratory tract ($n = 78$), and chronic lower respiratory diseases ($n = 71$).

Figure 1 shows the annual change in the percentage of patients prescribed the isotonic fluid infusion including saline, hypotonic fluid infusion, acetaminophen, and NSAIDs. The other analgesic-antipyretics and platelet transfusion were not analyzed because there were less than 10 such cases. The slope of annual change was 6.1% increase for isotonic fluid infusion ($R^2 = 0.84$), 0.7% increase for hypotonic fluid infusion ($R^2 = 0.14$), 4.2% increase for acetaminophen ($R^2 = 0.68$), and 0.8% increase for NSAIDs ($R^2 = 0.42$), respectively. For analgesic-antipyretic, NSAIDs were used for 181 (13.2%) of all the dengue patients, 169 (12.9%) of DF, and 12 (79.2%) of DHF (Table 2). Isotonic and/or hypotonic fluid infusion was used for 631 (46.1%) patients, which consisted of 439

FIGURE 1. Annual changes in percentage of dengue patients prescribed fluid infusion (isotonic/hypotonic) and analgesic-antipyretics (acetaminophen/NSAIDs) from 2011 to 2015. (A) Fluid infusions, (B) analgesic antipyretics. NSAIDs = non-steroidal anti-inflammatory drugs.

TABLE 2
Percentages of DF and DHF patients who were prescribed fluid infusions, analgesic-antipyretics, and/or platelet transfusions

	Fluid infusion			Analgesic-antipyretics				Platelet transfusion
	Isotonic (no hypotonic)	Hypotonic (no isotonic)	Both isotonic and hypotonic	Acetaminophen (no NSAIDs)	NSAIDs (no acetaminophen)	Both acetaminophen and NSAIDs	Others	
Total (n = 1,370)	280 (20.4%)	103 (7.5%)	248 (18.1%)	645 (47.1%)	73 (5.3%)	108 (7.9%)	14 (1.0%)	28 (2.0%)
DF (n = 1,306)	268 (20.5%)	*	221 (16.9%)	620 (47.5%)	*	*	*	17 (1.3%)
DHF (n = 64)	12 (18.8%)	*	27 (42.2%)	25 (39.1%)	*	*	*	11 (17.2%)

DF = dengue fever; DHF = dengue hemorrhage fever; NSAIDs = nonsteroidal anti-inflammatory drugs.

* Less than 10 patients are not allowed to be shown according to the guidelines for provision of claims data and special health checkup result.

inpatients (79.2%) and 89 outpatients (11.6%). Comparing the patients aged < 20 years (n = 185) with those aged ≥ 20 years (n = 1,185), 107 (57.8%) and 646 (54.5%) received acetaminophen, 12 (6.5%) and 169 (14.3%) received NSAIDs, 30 (16.2%) and 250 (21.1%) received isotonic fluid without hypotonic fluid, 26 (14.1%) and 77 (6.5%) received hypotonic fluid without isotonic fluid, and 44 (23.8%) and 204 (17.2%) received both isotonic and hypotonic fluid, respectively. The number of patients aged < 20 years who received platelet transfusion was not shown because there were less than 10 such patients.

DISCUSSION

Dengue patients in Japan were imported cases, except those in 2014. The number of DHF cases aged < 20 years were less than 10 patients. Considering that the total number of DHF patients from 2011 to 2015 was 64, this number was much lesser than that found in dengue-epidemic countries such as Brazil.¹⁴ People who had been to dengue-epidemic countries or Yoyogi park could have dengue infection. Therefore, patient characteristics were considered to be different from the general population. As Japan is an aging society, the age distribution of the Japanese population is also different from that of dengue-epidemic countries. And, 64 DHF cases are too small a population to assess the age distribution of dengue cases. Further research will be needed to clarify the difference.

The study showed that the proportion of dengue patients who were prescribed isotonic fluid and acetaminophen had increased from 2011 to 2015 in Japan. The main reasons for the upward trend in proportions toward 2015 were because the WHO guidelines for dengue was published in 2009 and domestic infection of dengue in 2014 promoted medical doctors to follow the Japanese clinical guidelines for dengue, which was published in 2014.

Most inpatient dengue cases received IV fluid, but outpatient cases did not. In Japanese clinical situations, it is common for inpatients to receive IV fluid. Outpatients receive IV fluid less frequently because they can take water orally. However, isotonic IV fluid is recommended for some outpatients to prevent fluid overload, hyponatremia, and acid-base imbalances instead of hypotonic fluid.^{3,15} Infusion control is an important element to prevent excessive IV fluid, which causes iatrogenic pulmonary edema even if isotonic fluid is used. About 50% of dengue patients received isotonic fluid in 2014 and 2015 in accordance with the guidelines. However, still, more than 20% received hypotonic fluid, which might have been needed depending on the patient's condition. According to Leroy and Hoorn, hypotonic fluid therapy causes less fluid overload and saline caused hyperchloremic

acidosis.¹⁶ It is worth noting that the choice of fluid replacement is still controversial among researchers.

Isotonic fluid, hypotonic fluid, and platelet transfusion were used more for DHF than for DF. These results can be explained because DHF has more severe symptoms, such as sweating, vomiting, and decreasing platelet, than DF. The use of NSAIDs for more than 13% of dengue patients is a huge concern. And, it should be noted that 18.8% of DHF patients used NSAIDs compared with 12.9% of DF patients. Nonsteroidal anti-inflammatory drugs are associated with gastrointestinal bleeding.¹⁷ It has been established that NSAIDs and aspirin increase the risk of colonic diverticular bleeding (RR = 3.08) in the Asian population.¹⁸ Because this research used the data of all dengue patients in Japan during the study period, it is plausible to say that the use of NSAIDs had exposed 169 DF patients and 12 DHF patients to a high risk of bleeding and might have caused bleeding among them from 2011 to 2015. It is important to emphasize the use of acetaminophen over NSAIDs in dengue patients and suspected dengue patients.

Platelet transfusion is not only ineffective for preventing bleeding but also increases risks of adverse events.^{3,10,11} Japanese dengue guidelines also mention that platelet transfusion is not necessary for severe dengue cases with platelet count decreased.⁹ However, 17.2% of DHF patients in our study received platelet transfusion. Most frequently used platelet transfusion was Irradiated Platelet Concentrate, Leukocytes Reduced, NISSEKI (Ir-PC-LR)® (The Japanese Red Cross Society, Tokyo, Japan), and the cost for 10 units (about 200 mL) was \$775.11 as of July 1, 2018 (USD 1 = JPY 103.05).^{19,20} Even for the patient with thrombocytopenia, platelet transfusion should be used more carefully with consideration of its efficacy, safety, and high cost.

Patients aged < 20 years were prescribed few NSAIDs and tend to use more IV fluid than adults. Acetaminophen is the first choice of analgesic-antipyretic for children, the same as in dengue treatment. Children are affected by dehydration more than adults. The results do not contradict usual clinical situations.

The limitation of this research is that the provided claim data do not have details of patients' clinical information such as diagnosed test, other prescribed drugs, and conditions. It is possible that hypotonic IV fluid might have been needed for dehydration, NSAIDs for the patient with an allergy for acetaminophen, and platelet transfusion for comorbidities such as cancer or surgery. The information from the medical records can compensate for the limitation and improve the accuracy of this result. Further research incorporating such information is needed. Another limitation of using the NDB is that less than 10 patients cannot be shown under the guidelines for provision of claims data and special health checkup result. Details of data of less than 10 patients must be very important, such as those categorized as children, infants, severe dengue, and patients with comorbidity or using other drugs.

CONCLUSION

In accordance with the guidelines for dengue, acetaminophen was used more than NSAIDs and more isotonic fluid was administered than hypotonic fluid. Because the proportion of DHF patients who received NSAIDs was higher than that of DF patients, the use of NSAIDs might have caused progression of the symptoms to dengue patients. Despite a dearth of evidence for its efficacy and its high cost in therapeutic use and no efficacy in prophylactic use, as many as 17.2% of DHF patients received the platelet transfusion. More effort is needed to appropriately treat dengue patients in accordance with the guideline.

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