Management of dengue in Australian travellers: a retrospective multicentre analysis

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The known The revised WHO guidelines (2009) are a helpful tool for managing patients with dengue, but among Australian medical practitioners there is a lack of awareness of the warning signs of severe dengue in travellers.

The new Two-fifths of Australian travellers hospitalised for dengue presented with warning signs of severe dengue. Many signs were unrecognised as such, and NSAIDs were prescribed for more than 20% of patients, exposing them to unnecessary risk.

The implications Australian clinicians should be familiar with the clinical manifestations of dengue, especially of dengue with warning signs, and with its management.

Abstract

Objectives: To describe the epidemiology, clinical and laboratory features and outcomes of dengue in returned Australian travellers, applying the revised WHO dengue classification (2009) to this population.

Design, setting and participants: Retrospective case series analysis of confirmed dengue cases hospitalised at one of four Australian tertiary hospitals, January 2012 – May 2015.

Main outcome measures: Clinical features, laboratory findings and outcomes of patients with dengue; dengue classification according to 2009 WHO guidelines.

Results: 208 hospitalised patients (median age, 32 years; range, 4–76 years) were included in the study. Dengue was most frequently acquired in Indonesia (94 patients, 45%) and Thailand (40, 19%). The most common clinical features were fever (98% of patients) and headache (76%). 84 patients (40%) met the WHO criteria for dengue with warning signs, and one the criteria for severe dengue; the most common warning signs were mucosal bleeding (45, 22% of all patients) and abdominal pain (43, 21%). Leukopenia (176 patients, 85%), thrombocytopenia (133, 64%), and elevated liver enzyme levels (154, 76%) were the most common laboratory findings. 46 patients (22%) had serological evidence of previous exposure to dengue virus. WHO guidelines were documented as a management benchmark in ten cases (5%); 46 patients (22%) received non-steroidal anti-inflammatory drugs (NSAIDs).

Conclusions: A significant proportion of returning Australian travellers hospitalised for dengue have unrecognised warning signs of severe disease. Many received NSAIDs, which can increase the risk of haemorrhage in dengue. As travel to Asia from Australia continues to increase, it is vital for averting serious outcomes that clinicians can recognise and manage dengue.

Dengue is a mosquito-borne disease caused by infection with one of four serotypes of the dengue virus, a member of the *Flavivirus* genus. An estimated 50–100 million people are infected with the dengue virus each year, and the World Health Organization has designated dengue a neglected tropical disease and major international public health problem.[1,2] Paralleling the increasing numbers of major overseas outbreaks, the number of infections diagnosed in Australian travellers has increased over the past decade;[3] about 1800 cases have been reported each year since 2013.[4] As the frequency of international travel increases, it is vital that Australian clinicians, including general practitioners and hospital clinicians, have a good knowledge of the presentation and management of dengue and other arboviral diseases, including those caused by the yellow fever, chikungunya, and Zika viruses.

The primary vector of the dengue virus is the mosquito *Aedes aegypti*, once found in many Australian states, but now almost exclusively limited to northern Queensland.[5] Dengue is not endemic to Queensland, but several outbreaks initiated by viraemic travellers have occurred over the past decade.[2] Australians are frequent travellers to countries in which dengue is endemic; between July 2014 and June 2015, there were 9.2 million short term departures by Australian residents to such countries, and travel to Indonesia (1.1 million departures), Thailand (550 000 departures) and India (280 000 departures) is increasing.[6] Reported incidence rates of dengue among travellers from various countries range between 10.2 and 30 per 1000 person-months, notably higher than the incidence of other travel-related diseases.[7-10]

The clinical manifestations of dengue range from a mild febrile illness and widespread rash to potentially severe manifestations such as shock or haemorrhage. Dengue has a three-phase course: the febrile phase, usually lasting 2–7 days; the critical phase, when the fever resolves and increased capillary permeability results in plasma leakage; and the recovery phase, during which some patients develop a new rash, often described as "isles of white in a sea of red", typically on their palms and soles. Recognising the different phases and their associated problems is vital for ensuring optimal patient outcomes.

The former WHO classification of the forms of clinical dengue as dengue fever, dengue haemorrhagic fever, and dengue shock syndrome was based on clinical data collected during the 1950s and 1960s in Thailand.[11,12] Diagnosis of dengue haemorrhagic fever was based on four specific criteria being satisfied, and this definition was criticised for failing to capture some patients with severe manifestations.[13,14] The clinical limitations of the definition were evaluated in dengue-endemic countries in South-East Asia and Latin America by the international Dengue Control study (DENCO),[15] which identified warning signs that predicted severe dengue. This led to revision of the WHO guidelines (2009), which now classify symptomatic dengue infection into three categories: probable dengue, dengue with warning signs, and severe dengue.[16] While still not ideal, the guidelines and new

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classification are simpler and more practical with respect to triage and the clinical management of patients.[16-18] This is especially useful in an epidemic setting for deciding which patients need hospital admission and more intensive monitoring.

There have been few published studies of traveller populations using the 2009 WHO classification, and many patients with warning signs for severe disease are probably missed in the Australian setting. All published studies to date have been single centre studies with small case numbers.[19-21] Our recent investigation in a single Melbourne centre found that more than 50% of patients admitted to hospital with dengue presented with warning signs.[21] As travellers tend to seek medical attention soon after developing worrying symptoms, the data they provide uniquely reflect the distribution of clinical dengue types.

We describe the clinical and laboratory features, management and outcomes of returned travellers presenting with dengue to selected Australian hospitals, applying the 2009 WHO dengue classification to this population. The results we report in this article include data from our single centre analysis together with data for a much larger cohort of patients from across four hospital networks.

Methods

We performed a retrospective case series analysis of confirmed cases of dengue, January 2012 – May 2015, across four health care networks: Monash Health, Austin Health, Melbourne Health (all in Victoria), and the Royal Darwin Hospital. Inclusion criteria were detection of dengue virus by polymerase chain reaction (PCR) or of dengue non-structural protein 1 (NS1) antigen in blood, and a clinically compatible illness. We excluded cases where the diagnosis was based on serology alone (ie, dengue virus-specific IgM or IgG without NS1 or PCR confirmation), if there was no documented history of overseas travel, if dengue was locally acquired, or if there was another illness that explained the presentation of the patient to hospital.

We identified cases in the database of the Victorian Infectious Diseases Reference Laboratory, the Northern Territory notifiable disease database, and the Royal Darwin Hospital discharge coding database. Demographic, epidemiological, clinical, laboratory and outcome data were extracted from hospital records. Detection of dengue virus-specific IgM or IgG was regarded as evidence of exposure to dengue virus.

Statistical analysis

Categorical variables are presented as counts and proportions, continuous variables as medians and ranges or interquartile ranges (IQRs). The significance of differences between groups was assessed with Fisher exact or χ^2 tests for binary and nominal covariates, and with Wilcoxon rank sum tests for continuous covariates. $P < 0.05$ (two-sided) was deemed statistically significant. Analyses were conducted in R 0.99.896 (R Foundation).

Ethics approval

Ethics approval was provided by Research Support Services, Monash Health (reference, no. 15274Q), the Office for Research, Austin Health (reference, LNR/15/Austin/315), the Office for Research, Melbourne Health (reference, QA2012129), and the Human Research Ethics Committee of the Northern Territory Health Department and Menzies School of Health Research (reference, EC00153). Local ethics approval was also obtained at each health care site.

Results

Demographic characteristics

A total of 208 patients were included in the study, of whom 96 (46%) were male and 112 (54%) female. The median age was 32 years (IQR, 27–47 years), and most patients had no significant comorbidities. Thirty-one (15%) were born in dengue-endemic countries, and 46 (22%) had serological evidence (IgG) of exposure to dengue virus. The most frequent travel destinations had been Indonesia (94 patients, 45%), Thailand (40, 19%) and East Timor (23, 11%); the main reason for travel was tourism (138 patients, 66%) (Box 1).

Admission and clinical history

The median time from symptom onset to hospital presentation was 4 days (IQR, 3–6 days). Most patients (174, 84%) were admitted to hospital for more than 24 hours, with a median length of stay of 3 days (IQR, 2–4 days). Dengue was documented in the admission differential diagnosis for 128 patients (62%). Only one patient was admitted to an intensive care unit (Box 2).

According to the WHO 2009 criteria, 84 patients (40%) met the criteria for dengue with warning signs, and one patient met the criteria for severe dengue. Most patients presented with fever (204, 98%); other frequently presented symptoms were headache (158 patients, 76%), retro-orbital pain (69, 33%), myalgia (139, 67%) and arthralgia (90, 43%). Gastrointestinal symptoms were also common, with diarrhoea reported for 78 patients (38%) and abdominal pain for 43 (21%). Rash was recorded for 138 patients (66%), petechiae for 29 (14%), and ecchymosis for three patients (1%). Haematuria was reported in 15 cases (7%), bleeding gums in nine (4%), gastrointestinal bleeding in four (2%), and vaginal bleeding in nine (4%). Three patients (1%) had pleural effusions, and one (0.5%) had ascites (Box 2).

Laboratory findings

Common findings included leukopenia (176 patients, 85%), thrombocytopenia (133, 64%) and elevated liver enzyme (alanine transaminase [ALT]) levels (154, 76%); in eight patients (4%) ALT levels exceeded 500 U/L (maximum value, 1112 U/L; reference level, < 45 U/L). Acute renal injury (defined as an increase in serum creatinine concentration of greater than 50% of baseline level) was determined in nine patients (4%; Box 3).

Case management

For only ten cases (5%) was there documented reference to the WHO guidelines as guiding management. Despite the importance of closely monitoring the fluid balance of patients with dengue, there was a complete fluid balance chart for at least one day for only 29 patients (14%). Three patients (1%) received blood products, 56 (27%) initially received antibiotics, 162 (78%) received paracetamol, and 46 (22%) were prescribed non-steroidal anti-inflammatory drugs (NSAIDS) (Box 4).

Dengue with warning signs

A history of diabetes was more common in patients with warning signs than those without (odds ratio [OR], 9.3; 95% CI, 1.1–430; $P = 0.018$), as was thrombocytopenia being noted during the hospital admission (OR, 2.3; 95% CI, 1.2–4.6; $P = 0.008$). Length of stay was longer for patients with warning signs (median, 3.5 days; IQR, 2–5 days) than for patients without warning signs (median, 3 days; IQR, 2–4 days; $P < 0.001$; Box 2). Patients with warning signs received empirical antibiotics more frequently than those who did not (OR, 2.3; 95% CI, 1.2–4.5; $P = 0.01$).

1 Demographic characteristics and travel history of the 208 patients with dengue included in the study

	Clinical dengue classification (WHO, 2009)			
	Dengue	Dengue with warning signs	Severe dengue	All patients
Number of patients	123	84	1	208
Age (years), median (range)	32 (4–69)	35 (6–72)	76	32 (4–76)
Sex				
Male	66 (54%)	29 (34%)	1	96 (46%)
Female	57 (46%)	55 (66%)	0	112 (54%)
Country of birth				
Australia/New Zealand	88 (72%)	52 (62%)	1	141 (68%)
Europe/United States	13 (11%)	11 (13%)	0	24 (12%)
South-East Asia/South Asia	13 (11%)	16 (19%)	0	29 (14%)
Pacific islands	1 (1%)	1 (1%)	0	2 (1%)
Other	3 (2%)	3 (4%)	0	6 (3%)
Unknown	5 (4%)	1 (1%)	0	6 (3%)
Comorbidities				
Pregnancy	3 (2%)	1 (1%)	0	4 (2%)
Diabetes	1 (1%)	6 (7%)	1	8 (4%)
Chronic kidney disease	2 (2%)	2 (2%)	0	4 (2%)
Malignancy	2 (2%)	2 (2%)	0	4 (2%)
Rheumatoid arthritis	1 (1%)	0	0	1 (1%)
Steroid use	1 (1%)	1 (1%)	0	2 (1%)
Serologic evidence of previous exposure to dengue virus*	23 (20%)	22 (28%)	1	46 (22%)
Travel destination				
Indonesia	55 (45%)	38 (45%)	1	94 (45%)
East Timor	11 (9%)	12 (14%)	0	23 (11%)
Thailand	26 (21%)	14 (17%)	0	40 (19%)
Malaysia/Singapore	7 (6%)	4 (5%)	0	11 (5%)
Other South-East Asian country	7 (6%)	7 (8%)	0	14 (7%)
South Asia	11 (9%)	4 (5%)	0	15 (7%)
Pacific islands	5 (4%)	3 (4%)	0	8 (4%)
South America	1 (1%)	0	0	1 (1%)
Unknown	0	2 (2%)	0	2 (1%)
Travel reason				
Visiting friends and relatives	19 (15%)	17 (20%)	0	36 (17%)
Tourism	82 (67%)	55 (66%)	1	138 (66%)
Business/other	18 (15%)	12 (14%)	0	30 (14%)
Unknown	4 (3%)	0	0	4 (2%)

* Seven cases of dengue and four of dengue with warning signs were excluded because serological testing was not performed. ◆

Case of severe dengue

Only one patient fulfilled the criteria for severe dengue (evidence of end organ involvement and severe bleeding).

Discussion

Dengue is an important illness in travellers returning to Australia. Indonesia is the most frequently reported country of acquisition for Australian travellers, reflecting its growth in popularity as a holiday destination,[3] with more than one million short term visits by Australians during 2014–15.[6] The patients in our study were young (median age, 32 years), and most acquired dengue in South-East Asia, consistent with Asia being a major source of dengue importation into Australia.[22] A considerable number of our patients were infected in East Timor, partly reflecting the role that Royal Darwin Hospital plays as a repatriation destination for unwell Australian travellers to East Timor.

In dengue-endemic countries, exposure to multiple viral serotypes results in more severe disease.[23,24] Notably, there were patients with primary dengue in our study who developed haemorrhagic

2 Details of hospital admissions and clinical features for the 208 patients with dengue included in the study

	Clinical dengue classification (WHO, 2009)			
	Dengue fever	Dengue fever with warning signs	Severe dengue fever	All patients
Number of patients	123	84	1	208
Time from symptom onset to hospital presentation (days), median (range)*	4.5 (1–14)	4 (1–13)	4	4 (1–14)
Admission to hospital longer than 24 hours	99 (81%)	74 (88%)	1	174 (84%)
Hospital length of stay (days), median (range)†	3 (1–8)	3.5 (1–115)	9	3 (1–11)
Dengue documented in admission differential diagnosis	71 (58%)	56 (67%)	1	128 (62%)
Intensive care unit admission	0	1 (1%)	0	1 (1%)
Symptoms of classic dengue fever				
Fever	121 (98%)	82 (98%)	1	204 (98%)
Duration of fever (days), range (median)	1–10 (4)	1–13 (5)	4	0–13 (4)
Headache	94 (76%)	63 (75%)	1	158 (76%)
Retro-orbital pain	37 (30%)	32 (38%)	0	69 (33%)
Myalgia	78 (63%)	61 (73%)	0	139 (67%)
Arthralgia	55 (45%)	35 (42%)	0	90 (43%)
Diarrhoea	34 (28%)	44 (52%)	0	78 (38%)
Cough	13 (11%)	10 (12%)	0	23 (11%)
Syncope	3 (2%)	7 (8%)	1	11 (5%)
Dyspnoea	2 (2%)	5 (6%)	0	7 (3%)
Rash	83 (68%)	54 (64%)	1	138 (66%)
Positive tourniquet test	0	2 (2%)	0	2 (1%)
Petechiae	9 (7%)	20 (24%)	0	29 (14%)
Ecchymosis	1 (1%)	2 (2%)	0	3 (1%)
Dengue warning signs				
Haematuria	0	15 (18%)	0	15 (7%)
Bleeding gums	0	8 (10%)	1	9 (4%)
Epistaxis	0	8 (10%)	0	8 (4%)
Vaginal bleeding	0	9 (11%)	0	9 (4%)
Gastrointestinal bleeding (haematemesis/ malaena)	0	4 (5%)	0	4 (2%)
Haematocrit rise > 20%, with concurrent rapid drop in platelet number	0	10 (12%)	0	10 (5%)
Pleural effusion	0	3 (4%)	0	3 (1%)
Ascites	0	1 (1%)	0	1 (1%)
Abdominal pain	0	43 (51%)	0	43 (21%)
Persistent vomiting (more than twice daily)	0	8 (10%)	0	8 (4%)
Hepatomegaly (> 2 cm)	0	5 (6%)	0	5 (2%)
Profound lethargy	0	6 (7%)	0	6 (3%)

* Four patients with dengue were excluded because of conflicting data. † Data for 174 patients who presented to and were admitted to hospital. ◆

manifestations and severe disease. When dengue in travellers was analysed according to the WHO 1997 classification,[12] the reported incidence of dengue haemorrhagic fever in travellers ranged between 0.9% and 3.0%,[25] similar to rates for populations of regions where dengue is endemic.[26] In our study, the proportion of patients who had previously been exposed to dengue (as indicated by positive dengue virus-specific IgG) who developed warning signs was not statistically significantly different from that of patients with primary infections. Clinicians should be mindful that travellers without prior exposure to dengue can also develop severe dengue.

According to the 2009 WHO criteria, 84 patients (40%) who were admitted to hospital presented with warning signs that may predict life-threatening complications, including severe organ dysfunction and refractory shock. Our study included a larger proportion of patients presenting with warning signs than other studies of travellers that have applied the WHO 2009 classification (Box 5). This could indicate selection bias, as our patients were sufficiently ill to present to tertiary centres. Only one patient developed severe dengue, and there were no deaths. This may reflect the quality of supportive care in our institutions, although best practice according to WHO guidelines or another dengue

3 Results of laboratory investigations for the 208 patients with dengue included in the study

	Clinical dengue classification (WHO, 2009)			
	Dengue	Dengue with warning signs	Severe dengue	All patients
Number of patients	123	84	1	208
Leukopenia (< 4.0 × 10^9/L)	107 (87%)	69 (82%)	0	176 (85%)
White blood cell nadir, median	2.7 × 10^9/L	2.3 × 10^9/L	NA	2.55×10^9/L
Thrombocytopenia (< 150 × 10^9/L)	69 (56%)	63 (75%)	1	133 (64%)
Platelet nadir, median	92 × 10^9/L	67 × 10^9/L	5 × 10^9/L	78 × 10^9/L
Renal impairment†	4	5	0	9
Alanine transaminase level > 42 IU/L	87 (73%)*	66 (79%)	1	154 (76%)*
Serum albumin level < 35 g/L	50 (42%)*	60 (71%)	1	111 (53%)*

NA = not available. * Data not available for four dengue patients. † Defined as an increase in serum creatinine concentration of greater than 50% above baseline level. ◆

protocol may not have been followed, as documentation of compliance was noted in only 5% of cases. Further, dengue was not included in the admission differential diagnosis for 27 patients (13%), and these patients were not diagnosed with dengue before they were discharged.

The small patient cohorts in the traveller population[19,27,28] make it difficult to search for predictors of severe disease, as recommended by the WHO for countries with endemic dengue.[16] In the absence of a non-endemic situation protocol for managing dengue, all Australian health professionals should be familiar with the WHO 2009 guidelines and apply them as a tool for triaging and managing returning ill travellers who present to them. The applicability of the WHO guidelines to the traveller population needs further evaluation and validation, as this population is qualitatively different from those in endemic settings.

Managing the patient's fluid balance is vital when treating dengue; hydration and haemodynamic status, especially in those presenting with warning signs or severe dengue, should be assessed frequently. It is concerning that a complete fluid balance chart for at least one day was available for only 14% of our patients. Even more worrying was that NSAIDs were prescribed to treat fever in 22% of cases, exposing patients to risks of further bleeding complications and renal impairment.

In order to prevent deaths from dengue in travellers, it is vital that the disease is suspected and identified early, and then managed correctly with the appropriate monitoring and medical support. The WHO stratifies management into three patient categories, groups A, B and C.[16] Group A comprises patients who do not fulfil hospital admission criteria, although inpatient treatment may be required if the diagnosis has not been confirmed, or if symptomatic management is needed. Group B includes patients who should be referred to hospital (online Appendix), and Group C encompasses patients needing emergency treatment, ideally in an intensive care unit. We propose that GPs and other community health care providers who assess returned travellers with clinical suspicion of dengue contact their local infectious diseases service for assistance, or refer these patients to hospital for further assessment. The main objectives of the referral would be to assess the patient for warning signs of severe dengue, and to decide whether admission for intravenous fluid therapy and biochemical monitoring is appropriate.

Dengue can also be a biphasic illness, with patients seeming to improve around day 5 before quickly relapsing. GPs and travel medicine physicians should provide patients seeking travel advice accurate and up-to-date information on arboviruses such as dengue and Zika, as well as about preventing mosquito bites when travelling in dengue-endemic regions.[29] Resources include the

4 Management of the 208 patients with dengue included in the study

	Clinical dengue classification (WHO, 2009)			
	Dengue fever	Dengue fever with warning signs	Severe dengue fever	All patients
Number of patients	123	84	1	208
Documented reference to WHO protocol	5 (4%)	5 (6%)	0	10 (5%)
Documented assessment of postural blood pressure	1 (1%)	2 (2%)	0	3 (1%)
Central capillary refill time checked and documented	7 (6%)	7 (8%)	0	15 (7%)
Complete fluid balance chart (for at least one day)	14 (17%)	14 (17%)	0	29 (14%)
Blood products received	0	2 (2%)	1	3 (15%)
Antibiotics received	25 (20%)	31 (37%)	0	56 (27%)
Paracetamol received	92 (75%)	69 (43%)	1	162 (78%)
Received non-steroidal anti-inflammatory drugs	26 (21%)	20 (24%)	0	46 (22%)
Intensive care unit review	0	3 (4%)	0	3 (1%)
Dengue fever diagnosed before discharge	71 (58%)	65 (77%)	1	137 (66%)

5 Published studies of dengue in travellers that used the WHO 2009 classification

Country	Study period	Number of travellers	Travellers with warning signs	Travellers with severe dengue
Germany[19]	1996–2010	56	11 (20%)	6 (11%)
Czech Republic[27]	2004–2013	132	Not stated	1 (1%)
Germany[28]	2007–2011	119	13 (11%)	0
Australia (our study)	2012–2015	208	84 (40%)	1 (0.5%)

travel medicine website of the Centers for Disease Control and Prevention (http://wwwnc.cdc.gov/travel) and the ProMED website of the International Society for Infectious Diseases (http://www.promedmail.org).

Limitations of our study include the fact that the study population comprised only patients with a positive NS-1 antigen or dengue virus nucleic acid PCR result, excluding those with only with positive serology (IgG) results; case selection was therefore limited to patients who presented during the first week or so of illness. Repeated serological testing of our patients was not commonly performed, making serological diagnosis difficult. Our study population consisted entirely of people presenting to a tertiary hospital, which may account for the high proportion with warning signs; this selection bias means our results may not be generalisable to patients with dengue treated in the community. Finally, although our sample of travellers was the largest to have been studied with the 2009 WHO classification, it was still too small to include more than one case of severe dengue, so we could not examine predictors of severe disease.

Conclusions

Our study highlights the wide range of clinical presentation of dengue by travellers, and calls attention to the significant proportion of hospitalised travellers who have warning signs for severe disease that are not always recognised. There were no deaths and only one case of severe dengue among our patients, but optimal case management is important, and treatment errors, including the prescription of NSAIDs, must be avoided. Australian GPs and hospital clinicians should be familiar with the clinical manifestations of dengue, and ensure that their knowledge of the diagnosis, classification and management of dengue is up to date.

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