Health
Hunter New England
Local Health District

Case presentation: Severe Dengue

Infectious Diseases / Immunology Clinical Meeting

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BPT Medical Registrar

September 2016

Case presentation: 47-year-old woman

- Returned traveller
  - 10 days in Bali
  - Returned on 23rd July
- Referred 10th August 2016 to John Hunter Hospital from a local private facility
- Was well prior to and during holiday

- 5 days after return
  - Myalgia and arthralgias
  - Lethargy
  - Rhinorrhoea
  - Dry cough
  - Mild headache and mid-back pain
  - No neck stiffness, abdominal, or urinary symptoms
- Reviewed by LMO who noted microhaematuria
- Symptoms appeared to be resolving after a week

- 8th August (16 days after return) symptoms returned
  - Severe lumbar back pain, rigors, chills, night sweats, and anorexia
  - Some increased stool frequency (×3/day) but no other abdominal symptoms
- Admitted to private facility
  - 5 litres IV fluid over 36 hours
  - Initially flucloxacillin 2 g, gentamicin 280 mg
  - Later given benzylpenicillin, doxycycline

- Nil specific travel immunisations or prophylaxis taken
- Stayed in resorts, ate mostly in hotels, nil street food
- Bathed in the ocean but not in freshwater lakes
- No animal contacts, no visits to forest areas
- No mosquito nets but used deterrent coils; no obvious bites
- Denied any risky sexual activity
- Travelled with husband and 17-year-old child who were both well

Background

- Melanoma: right arm, three excisions, sentinel node negative, no chemotherapy (2008)
- Hemithyroidectomy : not requiring thyroxine
- Hysterectomy: for menorrhagia
- Nil regular medications

- Works in an office at the university
- Non-smoker
- Social drinker
- Denies other drug use

On examination

- Looked unwell, having rigors
- Temp 37.4 °C, HR 73 bpm, BP 106/58, RR 20, normal O2 saturation on room air
- Hands and ankles mildly oedematous
- Normal cardiorespiratory examination
- No hepatosplenomegaly. Suprapubic tenderness. Abdomen otherwise unremarkable
- Tender T12/L1 on palpation
- Neurologically unremarkable
- Urinalysis haematuria, nil leukocytes, nil casts, nil growth

ALL OBSERVATIONS MUST BE GRAPHED | COMPLETE ALL DETAILS OR AFFIX PATIENT LABEL HERE

Date / Time

AIRWAY/BREATHING

Respiratory Rate

SpO_2%

Oxygen — O_2 Lpm / Device / mode

Key: RA = Room Air, NP = Nasal Prongs, FM = Simple facemask, NRB = Non Re-breather, VM = Venturi Mask

CIRCULATION

Blood Pressure (mmHg) SBP is trigger > <

Heart Rate •

Rhythm

DISABILITY

Neurological

A
V
P
U

Enter appropriate letter. A= Alert, V= Rousable by voice (conduct GCS), P= Rousable only by pain (conduct GCS), U= Unresponsive

Initials

ALL OBSERVATIONS MUST BE GRAPHED | COMPLETE ALL DETAILS OR AFFIX PATIENT LABEL HERE

Date / Time

EXPOSURE

Temperature (°C) •

Pain

Assess pain level at rest and with movement. Enter R for at rest, M for movement

Severe (7-10)
Moderate (4-6)
Mild (1-3)
Nil

Initials

Blood Glucose

Date
Time
BGL

Bowels

Date

Weight

Date
☐ Daily

Urinalysis

Date
Time
SG
pH
Leuk
Blood
Nitrite
Ketones
Bilirubin
U/Bil
Protein
Glucose

Haematology: progressive neutropenia and thrombocytopenia

Date Time	16Aug16 c06:00	15Aug16 c04:45	14Aug16 c06:40	14Aug16 c05:30	13Aug16 c07:25	12Aug16 c08:00	12Aug16 c07:00	11Aug16 c08:00	10Aug16 c??:??	Units	Range
White Ce*	2.1 L	1.8 L		1.3 L	1.4 L	1.4 L	1.5 L	2.3 L	2.0 L	10^9/L	(4.0 - 11.0)
Red Cell*	3.26 L	3.77 L		3.52 L	3.56 L	3.77 L	3.83	3.64 L	3.27 L	10^12/L	(3.80 - 5.80)
Hb (Haem*	100 L	115		107 L	108 L	115	116	111 L	99 L	g/L	(115 - 165)
Haematoc*	0.287 L	0.333		0.310 L	0.317 L	0.332	0.341	0.328	0.289 L	L/L	(0.320 - 0.460
MCV	88	88		88	89	88	89	90	88	fl	(80 - 100)
Platelets	78 L	65 L		53 L	54 D	73 L	77 L	87 L	99 L	10^9/L	(150 - 400)
Neutroph*	1.0 L	1.2 L		0.9 L	0.7 D	1.1 L	1.1 L	1.8 L	1.8 L	10^9/L	(2.0 - 8.0)
Lymphocy*	0.7 D	0.4 L		0.3 L	0.3 D	0.2 L	0.3 L	0.2 D	0.2 L	10^9/L	(1.0 - 4.0)
Monocytes	0.3	0.1 L		0.1 L	0.0 L	0.0 L	0.0 L	0.1 L	0.1 L	10^9/L	(0.2 - 1.0)
Eosinoph*	0.0	0.0		0.1	0.0	0.0	0.1	0.0	0.0	10^9/L	(< 0.5)

Film 10/8/16: Anaemia. Elliptocytes. Neutrophil morphology normal. Note history indicates

Biochemistry: maker hepatitis with decline in albumin

Date Time	18Aug16 c10:40	17Aug16 c11:15	16Aug16 c06:00	15Aug16 c04:45	14Aug16 c05:30	13Aug16 c07:25	12Aug16 c08:00	12Aug16 c07:00	11Aug16 c08:00	Units	Range
Calcium			1.90 L	1.88 L	1.94 L	1.85 L	1.87 L			mmol/L	
Calc.Ion*			1.02	0.99 L	1.10	1.04	1.04			mmol/L	
Correcte*			2.12	2.08 L	2.22	2.11	2.03 L			mmol/L	
Phosphate			0.67 L	0.57 L	0.81 D	< 0.30 C	0.41 L			mmol/L	
Protein *	56 L	57 L	50 L	52 L	45 L	44 L	49 L		55 L	g/L	(60 - 80)
Albumin	32 L	33 L	29 L	30 L	26 L	27 D	32 L		36	g/L	(35 - 52)
Bilirubi*	13	16	17	23 H		11	6		4	umol/L	(3 - 20)
GGT	562 H	561 D	333 D	222 H		119 D	25 D		17	U/L	(9 - 36)
Alkaline*	563 H	586 D	386 D	280 H		113 D	66		65	U/L	(30 - 110)
ALT	264 H	298 H	328 H	315 H		188 D	63 D		26	U/L	(< 55)
AST	589 H	762 H	1189 H	1094 H		738 D	231 D		108 H	U/L	(12 - 36)

Investigations

- Blood cultures : negative
- Coagulation – APPT and INR normal
- Malaria : negative
- CXR: clear
- CT abdomen/pelvis, mild R ureteric dilatation, no lithiasis, 11 mm left inguinal lymph node

Management

- IV fluid
- Paracetamol
- Differential diagnosis:
  - Leptospirosis (due to haematuria) + drug rash
  - Typhoid fever
  - Dengue (from the very first symptoms)

Dengue results

VIROLOGY - ARBOVIRUS-ZOONOSIS SEROLOGY (VZOONC)

Flavivirus Total Ab	Not Detected
Dengue IgG Ab	Negative
Dengue IgM Ab	Weak positive
Dengue NS1 Ag	Weak positive

COMMENT:
Dengue Ab Confirmation : Not Detected
Dengue IgM Confirmation: Not tested

Progress

- 12/8/16 (day 3 JHH) - Dengue NS1 Ag +ve
  - Rising Hb despite aggressive IV fluid resuscitation
    - Hb 99 → 116 over two days (in spite of IVF)
    - Additional 3 L fluid given
  - *Dengue haemorrhagic fever with shock syndrome*
- 13/8/16 - Admitted to ICU following RRT for hypotension
  - metaraminol, phosphate replacement

Final diagnosis : Severe Dengue presenting as biphasic illness; primary presentation

Convalescent serology:

VIROLOGY - ARBOVIRUS-ZOONOSIS SEROLOGY (VZOONC)

Flavivirus Total Ab	
Dengue IgG Ab	POSITIVE
Dengue IgM Ab	POSITIVE
Dengue NS1 Ag	Negative

DENGUE

NSW GOVERNMENT Health
Hunter New England
Local Health District

Dengue

- Arthropod-borne Flavivirus (*Aedes* mosquito)
- Four serotypes, DENV 1 – 4
- Endemic in over 100 countries
  - 390 million infected
  - 96 million worldwide incidence (2013 estimate)
  - Travellers an important role in global epidemiology
- Primary infection provides lifelong immunity against the infecting serotype

Guzman and Harris 2015

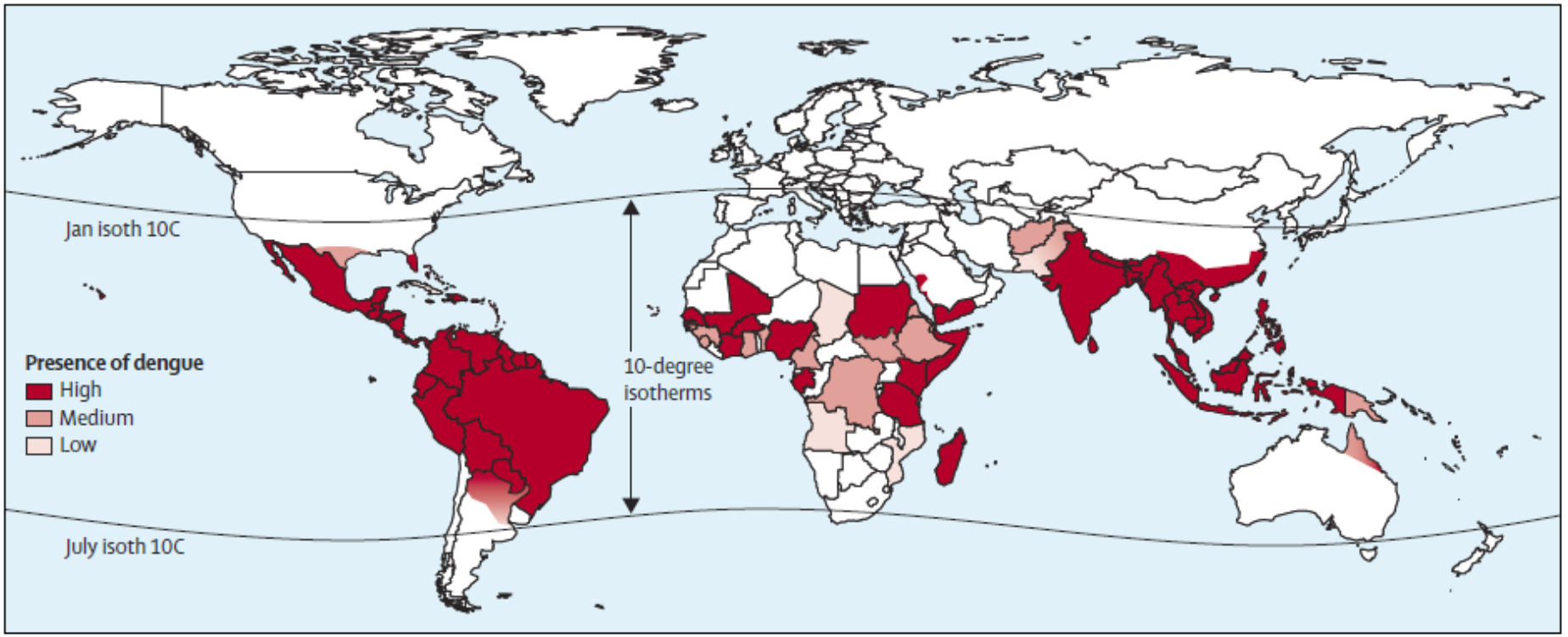


***Figure 1*: Global dengue burden, 2014**
Data from Bhatt and colleagues,[1] Healthmap,[2] and WHO[3] were integrated to indicate the relative amount of dengue globally according to best estimates.

- Incubation period typically 4 – 8 days (3 – 14)
- Wide clinical spectrum, often subclinical
- Triphasic illness
  - febrile, critical, recovery
    - Persistent symptoms in 57%, lasting up to 2 years

- Classic dengue fever
    - Headache, retro-orbital pain, myalgia, arthralgia (“breakbone”)
    - Fever for 5 – 7 days
    - Some cases biphasic (“saddleback fever”)
    - Macular/maculopapular rash in about 60% cases

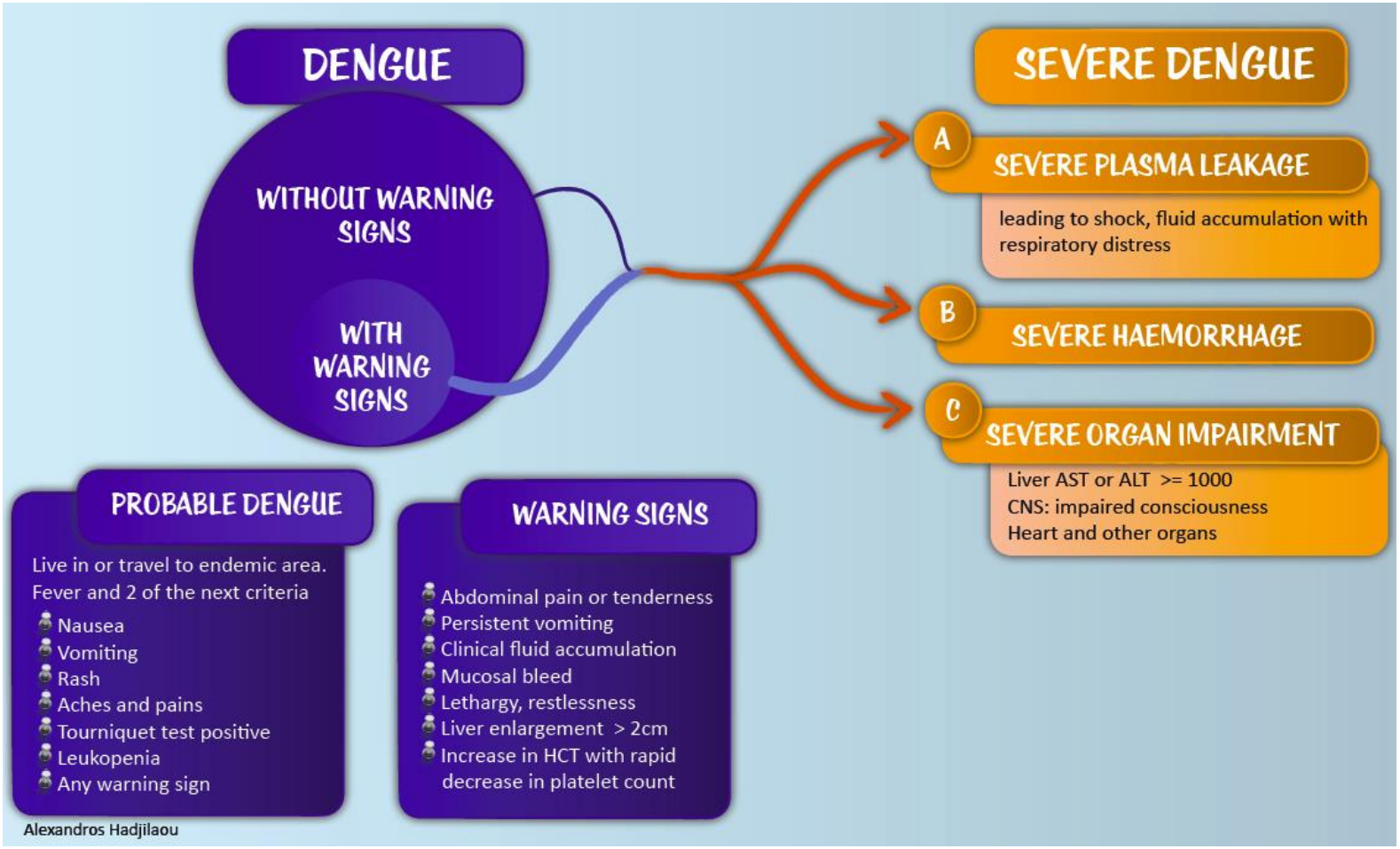
Dengue haemorrhagic fever

- Four cardinal features:
  - Increased vascular permeability (↑ Hct, effusion/ascites)
  - Marked thrombocytopenia (< 100,000)
  - High fever 2 – 7 days (up to 10 days)
  - Haemorrhagic tendency (tourniquet test, spontaneous haemorrhage)
- 500,000 cases annually
  - Case fatality rate of 15%, especially children
  - Shock syndrome in 7-10% of these

Dengue shock syndrome

- Dengue shock syndrome
  - When shock results in addition to the above criteria
  - Mainly due to extensive plasma leakage
  - Fatality rate may reach 12% with treatment (50% without)
- Critical phase is at time of defervescence
  - associated with increased capillary permeability
  - intravascular volume depletion and shock
  - organ dysfunction
  - metabolic acidosis
  - disseminated intravascular coagulation
  - haemorrhage

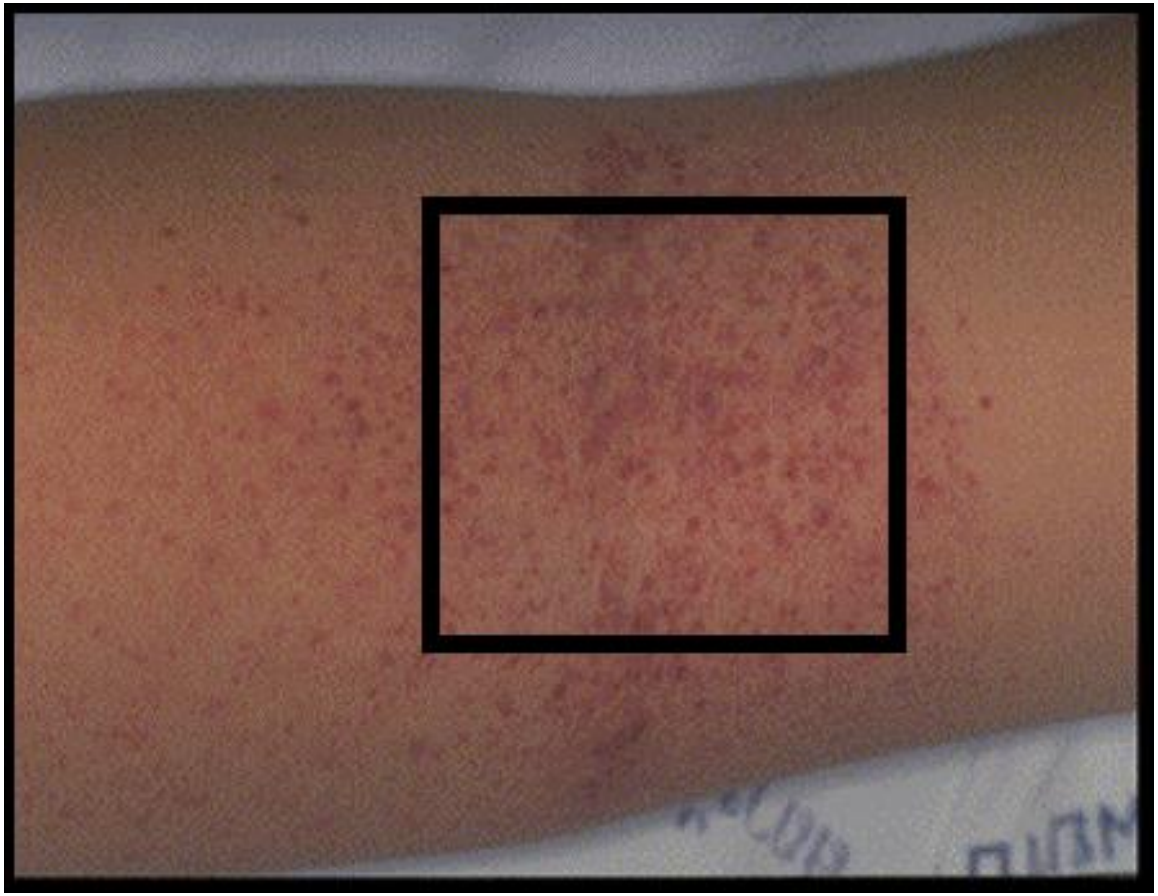
2009 WHO case classification



Diagnosis

- IgM from 5 days after fever onset
  - Risk of false negative in first 6 days of illness
  - Persists for 2 – 3 months
  - Convalescent phase serum 10 – 14 days after acute
    - Gold standard: ≥4 rise in haemagglutination inhibition titre
- NS1 antigen (dengue non-structural protein)
- IgG with low titres at 8 – 10 days after onset
  - Faster IgG in secondary infection
- PCR assays exist

Tourniquet test



CDC (http://www.cdc.gov/dengue/training/cme/ccm/page73112.html)

Pathophysiology

- Antibody-dependent enhancement
  - In secondary infection: pre-existing antibodies bind to DENV virions
  - Can lead to suppression of interferon-mediated antiviral responses in the host and facilitate cellular viral update
- High serotype cross-reactivity
- Complement activation
  - High complement activation with accelerated consumption and depletion
  - Inflammatory cytokines trigger local and systemic effects in intravascular coagulation
  - Theory that anti-NS1 protein antibodies associated with increased severity, and cross-react with liver, endothelial cells, and platelets leading to apoptosis

- Host risk factors for DHF/DSS
  - During secondary infection with a different serotype to the original infection
  - Infected infants born to immune mothers
  - Increased interval between infections associated with greater severity and fatality
  - Associations with asthma, diabetes, sickle-cell disease, and white>black ethnicity, child>adult

Treatment

- Largely supportive
- No drugs are approved for anti-dengue therapy
- Prednisone has not been shown to improve clinical or virological endpoints
- Potential role for anti-inflammatory effect of statins at endothelial level

Dengue vaccine?

- Ideal to have a tetravalent vaccine which produces balanced host immune response to each
- Risk that vaccine may lead to antibody-dependent enhancement and therefore could cause more severe illness
- Numerous vaccines in various phases of trials
- Sanofi-Pasteur has a phase 3 trial vaccine
- Vector control remains important

Key points

- Dengue is a common cause of fever in returned travellers from south-east Asia (32%)
- Essential to identify patients with plasma leakage, the most specific and potentially fatal consequence of dengue haemorrhagic fever
- Diagnosis often clinical with serum NS1 antigen is test of choice
- Treatment is supportive

References

Guzman, M. and Harris, E., “Dengue”, in *Lancet* (2015) 385:453-65.

Rothman, A. *et al.*, “Clinical manifestations and diagnosis of dengue virus infection”, in *UpToDate* (accessed online, 2016).

Greenwood, D. *et al.*, *Medical microbiology*, 17th ed., London: Churchill Livingstone (2007).