Dengue viral infections

衛福部 疾病管制署
中區傳染病防治醫療網
王任賢 指揮官

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Dengue viruses

- Flavivirus
- Four serotypes: DEN-1, -2, -3, -4
  (distinguished by neutralization test)
- In vivo cross protection (-)

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Host range of dengue virus

- Primary vertebrate host: humans
- Primary mosquito vectors: *Ae. aegypti*
  Ae. albopictus
  Ae. polynesiensis
- Enzootic forest cycles: nonhuman primates
- Experimental: neonatal mice, challenged IC
  Vero, LLC-MK2,
  C6/36 *Ae. albopictus*

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Dengue virus in vector

- No pathogenic effect on vectors
- Site of infection:
  midgut – hemocele – salivary gland
  genital tract – egg
- Extrinsic incubation period:
  8 – 12 days

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Life cycle of dengue virus

- Jungle cycle
  Aedes spp. -- monkey -- *Aedes spp.*
  Aedes spp. -- ova -- *Aedes spp.*
- Urban cycle
  Aedes aegypti -- human -- *Aedes aegypti*
  Aedes aegypti -- ova -- *Aedes aegypti*

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Vector of dengue virus: *Aedes aegypti*

- Low susceptibility to oral infection with virus
- Highly domesticated habits
- Day-biting
- Breeding in fresh water
- Short flight range
- Easily interrupted feeding & repeated probing of one or several hosts

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Aedes aegypti Mosquito

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Aedes aegypti Mosquito

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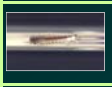
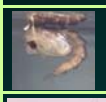
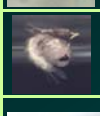
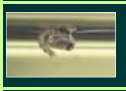
台灣常見蚊蟲各蟲期之區別

蚊種	斑蚊屬	家蚊屬	瘧蚊屬
卵期	 卵粒單產於水邊上，可耐旱最長達1年	 卵粒結成卵塊，產於水面上	 卵兩側邊具有浮囊，單產於水面上
幼蟲期	 呼吸管短，身體常垂懸於水中	 呼吸管長，身體與水平面成一角度	 沒有呼吸管，具掌肢，身體與水平面平行
蛹期	 呼吸管介於家蚊屬及瘧蚊屬(以肉眼較難分)	 呼吸管較狹長(以肉眼較難分)	 呼吸管短而開闊(以肉眼較難分)
成蟲期	 停息時，與平面成平行白天吸血活動，身體及腳具黑白斑	 停息時，與平面成平行，晚上吸血活動	 停息時，成45角度，晚上吸血活動

台灣傳播登革熱的病媒蚊

- 埃及斑蚊
- 白線斑蚊

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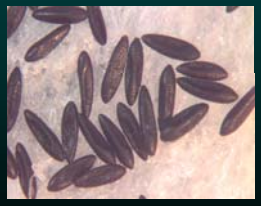
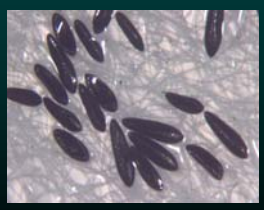
卵黑色，可耐旱產於容器水面邊緣的器壁

- 埃及斑蚊
- 白線斑蚊





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俗稱孑孓或水蟲，生活於水，以水中的微生物、有機顆粒等為食，脫皮四次，分為四齡

- 埃及斑蚊
- 白線斑蚊 (6-8天)

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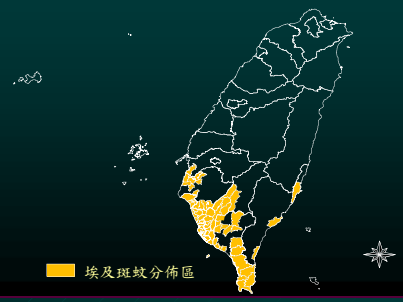
白線斑蚊分布於全台灣1500公尺以下的平地及山區，埃及斑蚊在台灣之分布(下圖)



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斑蚊棲息場所及吸血習性

- 埃及斑蚊
  喜歡棲息於室內，尤其是深色之窗簾、衣服、布幔及其他陰暗處所
- 白線斑蚊
  喜歡棲息於室外草生棲所附近之植物及戶外之陰涼處所
- 吸血高峰
  斑蚊在白天吸血，以早上9-10時及下午 4-5時為吸血高峰

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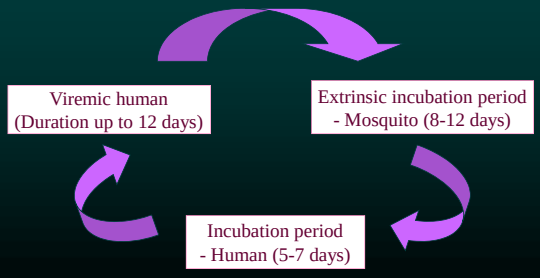
Transmission of dengue virus



Am J Trop Med Hyg 1999;62:720-5

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Dengue virus in human body

- Dengue virus antigen (by RT-PCR): monocyte-macrophage lineage in lymphoid, lungs, and liver
- Dengue virus could only be isolated from liver in DHF
- Dengue virus can infect but not replicate in human Kupffer cells

J Trop Med Public Hlth 1993;24:467-71
Am J Trop Med Hyg 1999;62:720-5
J Virol 1999;73:5201-6

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Epidemiology

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流行病學

- 登革熱的分佈取決於埃及斑蚊的分佈
  熱帶：全年都有，尤其是雨季
  溫帶：夏季
- 登革熱的流行區
  東南亞、印度、中國、臺灣、大洋洲、澳洲、非洲、沙烏地、葉門、中南美洲
- 全世界每年有一億人感染登革熱
- 高流行地區每年有10-20%的人口感染登革熱

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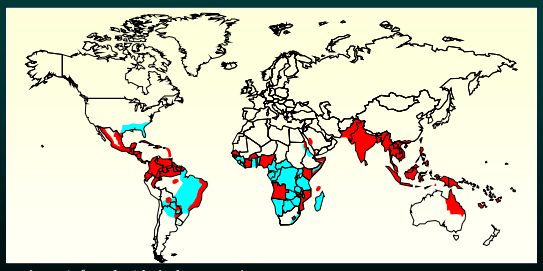
World Distribution of Dengue 1999



Areas infested with *Aedes aegypti*
Areas with *Aedes aegypti* and recent epidemic dengue

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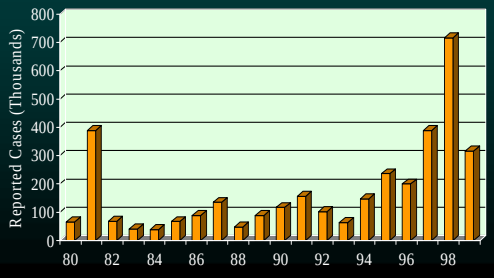
Reported Cases of Dengue in the Americas, 1980 - 1999



* Provisional data for 1999

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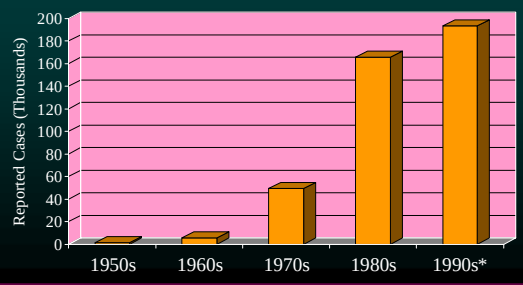
Mean annual number of DHF cases

Thailand, Indonesia and Vietnam, by decade



* Provisional data through 1998

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Disease Pathogenesis

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Clinical presentations of dengue virus infection

- Classical dengue fever
  - recognized before 1800
  - "breakbone fever"
  - an acute, self-limited febrile illness
- Dengue hemorrhagic fever (DHF)
  - recognized in Southeast Asia in the 1950s
  - capillary leak syndrome
  - an acute, potentially life-threatening illness

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Risk factors for DHF

- Virus strain
- Pre-existing anti-dengue antibody
  - – previous infection
  - – maternal antibodies in infants
  - – hyperendemic area with two or more serotypes
- Host genetics
- Age

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Increased Probability of DHF

Hyperendemicity

Increased circulation of viruses → Increased probability of occurrence of virulent strains

Increased probability of secondary infection → Increased probability of immune enhancement

Increased probability of DHF

Gubler & Trent, 1994

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Pathogenesis of DHF

Antibody-dependent enhancement (ADE)

Anamnestic sensitisation

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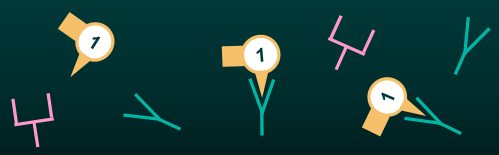
Homologous antibodies



Dengue 1 virus

Neutralizing antibody to Dengue 1 virus

Non-neutralizing antibody

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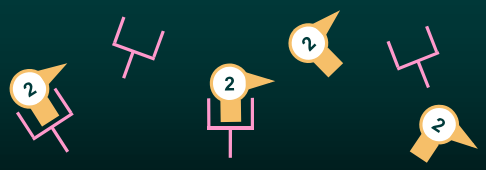
Heterologous antibodies



Dengue 2 virus

Non-neutralizing antibody to Dengue 1 virus

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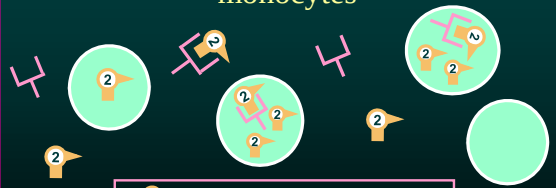
Heterologous complexes enter more monocytes



Dengue 2 virus

Non-neutralizing antibody

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Viral risk factors for DHF

- Virus strain (genotype)
  - Epidemic potential: viremia level, infectivity
- Virus serotype
  - DHF risk is greatest for DEN-2, followed by DEN-3, DEN-4 and DEN-1

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Clinical manifestations

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Dengue Clinical Syndromes

- Undifferentiated fever
- Classic dengue fever
- Dengue hemorrhagic fever
- Dengue shock syndrome

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Undifferentiated Fever

- The most common manifestation of dengue
- Prospective study found that 87% of students infected were either asymptomatic or only mildly symptomatic
- Other prospective studies including all age-groups also demonstrate silent transmission

Am J Trop Med Hyg 1988; 38:172-80.

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Clinical presentations of dengue fever

- Fever
- Headache
- Muscle and joint pain
- Nausea/vomiting
- Rash
- Hemorrhagic manifestations

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Dengue fever: clinical manifestations

- fever, chillness
- headache
- retrobulbar pain
- lumbosacral pain
- conjunctiva congestion
- eyelids puffiness
- facial flushing
- myalgia
- arthralgia
- respiratory symptoms
- maculopapular rash
- generalized LNE
- leukopenia
- thrombocytopenia
- CNS & PNS symptoms
- minor hemorrhage

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Unusual presentations of severe dengue fever

- Encephalopathy
- Hepatic damage
- Cardiomyopathy
- Severe gastrointestinal hemorrhage

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Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS)

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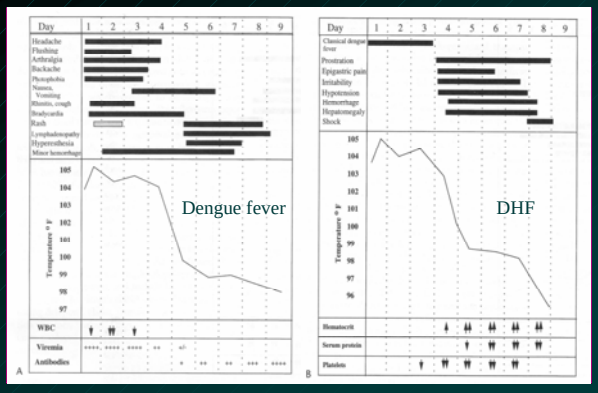

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Virology of DHF/DSS

- All 4 dengue viruses cause DHF/DSS
- DEN-2, 3 are the most important
- DEN-1 is rare
- Risk factors
  - sequence of infecting serotypes
  - interval between infections
  - strain differences in virulence

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Clinical & pathologic findings in DHF

- Plasma leakage
  - hemoconcentration, pleural effusion, ascites
  - at the time of dengue recovery
  - no evidence of endothelial cell destruction
- Bleeding tendency
  - capillary fragility + marked thrombocytopenia
- Liver involvement
  - hepatomegaly, elevated liver enzymes

Virology 1999;257:1-6

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Characteristics of DHF/DSS

- Diffuse capillary plasma leakage
  - hemoconcentration, decreased effective blood volume, tissue hypoxia, lactic acidosis, shock
- Hemorrhage
- Immunopathologic diseases
  - 3% after secondary dengue infection
  - 0.2% after primary dengue infection
  - Infant may develop DHF after primary infection

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Hemorrhagic manifestations of dengue

- Skin hemorrhages: petechiae, purpura, ecchymoses
- Gingival bleeding
- Nasal bleeding
- Gastro-intestinal bleeding
- Hematuria
- Increased menstrual flow

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Clinical manifestations of DHF/DSS

DHF
- classic dengue fever
- thrombocytopenia (platelet < 100 K)
- hemoconcentration (Hct increase by 20%)

DSS
- DHF
- hypotension pulse pressure < 20 cold clammy skin or profound shock

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Classification of dengue fever, DHF/DSS

Dengue fever
- fever, arthralgia, rash
- no or minor hemorrhage
- normal Hct
- normal platelet count
- normal pulse pressure

DHF grade I
- fever, GI, resp. symptoms
- no or minor hemorrhage
- Hct increase > 20%
- platelet < 100 K
- normal pulse pressure

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Classification of dengue fever, DHF/DSS

DHF grade II
- fever, GI, resp. symptoms
- spontaneous hemorrhage
- Hct increase > 20%
- platelet < 100 K
- normal pulse pressure

DHF grade III
- fever, GI, resp. symptoms + hypotension
- none or spontaneous hemorrhage
- Hct increase > 20%
- platelet < 100 K
- pulse pressure < 20 mmHg

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Classification of dengue fever, DHF/DSS

DHF grade IV
- profound shock
- none or spontaneous hemorrhage
- Hct increase > 20%
- platelet < 100 K
- pulse pressure < 20 mmHg

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Clinical parameters predictive of DHF

- Facial flushing
- Conjunctival injection
- Hepatomegaly with tenderness
- Positive tourniquet test

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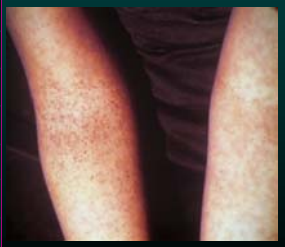
Tourniquet test



Method:
Inflate blood pressure cuff to a point midway between systolic and diastolic pressure for 5 minutes
Positive result:
> 20 petechiae/inch^2

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Danger signs in DHF

- Abdominal pain - intense and sustained
- Persistent vomiting
- Abrupt change from fever to hypothermia, with sweating and prostration
- Restlessness or somnolence

Salud Pública Mex 37 (supl):29-44, 1995.

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Clinical presentations of DHF, Puerto Rico, 1990 - 1991

Signs/symptoms	Case No.	%
Fever	57	100
Rash	27	47.4
Hepatomegaly	6	10.5
Effusions	3	5.3
Frank shock	3	5.3
Coma	2	3.5
Any hemorrhage	57	100

Only 2 (3.5%) cases had severe hemorrhagic manifestations

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Hemorrhagic types of DHF, Puerto Rico, 1990 - 1991

Signs/symptoms	Case No.	%
Microscopic hematuria	28	51.9
Petechiae	26	45.6
Epistaxis	13	22.8
Gingival hemorrhage	8	14.0
Blood in stools	8	14.0
Positive tourniquet test	5	31.3

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Hemorrhagic presentations of DHF, Puerto Rico, 1990 - 1991

Signs/symptoms	Case No.	%
Blood in vomitus	4	7.0
Bleeding at venipuncture	4	7.0
Hemoptysis	3	5.3
Vaginal hemorrhage	2	3.5
Gross hematuria	2	3.5
Other hemorrhage	2	3.5

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Laboratory findings of DHF, Puerto Rico, 1990 - 1991

Test with Abnormal Result	Frequency*	Mean Result (Range)
Thrombocytopenia		
Platelet count	57/57 (100%)	45,980 (9 - 99,000)
Increased Capillary Permeability		
Hemoconcentration	34/57 (59.6%)	0.26 (0 - 1.0)
Low serum protein	18/51 (35.3%)	6.3 (3.8 - 8.3)
Low serum albumin	35/52 (67.3%)	3.5 (2.3 - 4.9)

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Dengue in pregnant women

- Increase miscarriage (-)
- Increase birth defects (-)
- Maternal infection near parturation
  transplacental infection (+)
  severe dengue in neonate (+)

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Laboratory diagnosis of dengue viral infections

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Laboratory diagnosis: I

- Isolation of virus
  - IT injection of blood into *Toxorhynchites spp.*
  - TRA-284 (*Toxorhynchites amboinensis*)
  - C6/36 (*Aedes albopictus*)
  - AP-61 (*Aedes pseudoscutellaris*)
  - detection method: DFA
- Antigen detection
  - DFA of acute phase PB mononuclear cells
  - (not reliable, only to primary infection)

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Laboratory diagnosis: II

- RT-PCR
  - rapid, reliable diagnostic test
- Serologic diagnosis
  - IgM antibody-capture ELISA
  - plaque-reduction neutralization test
  - hemagglutination inhibition
  - complement fixation
  - neutralization test
  - ELISA

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Serologic diagnosis of dengue fever

- IgM antibody-capture ELISA
  - persist for 1-2 months
  - positive provide a presumptive diagnosis
  - found both in primary and secondary infection
- Plaque-reduction neutralization test
  - for type-specific diagnosis
- IgM/IgG ratio determined by ELISA
  - primary infection: IgM/IgG > 1.5

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Treatment

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Treatment of dengue fever: I

- Bed rest
- Fluid replacement
- Antipyretics
- Analgesics
- Avoid aspirin
  - hemorrhage diathesis
  - Reye's syndrome

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Outpatient Triage

- Home treatment
  no hemorrhagic manifestations and patient is well-hydrated
- Outpatient observation center or hospitalization
  hemorrhagic manifestations or hydration borderline
- Hospitalized
  warning signs (even without profound shock) or DSS

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Patient Follow-Up

- Patients treated at home
  - Instruction regarding danger signs
  - Consider repeat clinical evaluation
- Patients with bleeding manifestations
  - Serial hematocrits and platelets at least daily until temperature normal for 1 to 2 days
- All patients
  - Check convalescent sera

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Treatment of Dengue Fever: II

- Continue monitoring after defervescence
- If any doubt, provide intravenous fluids, guided by serial hematocrits, blood pressure, and urine output
- The volume of fluid needed is similar to the treatment of diarrhea with mild to moderate isotonic dehydration (5%-8% deficit)

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Treatment of DHF/DSS

- Aggressive fluid therapy
  Ringer's lactate or isotonic saline
  plasma or dextran solution for profound shock
  DC fluid as shock is controlled
  whole blood transfusion if severe hemorrhage
- Avoid aspirin & hepatotoxic drugs
- Oxygen, monitor BP, pulse pressure, urine output, Hct, & serum albumin, platelet, level of consciousness

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Treatment of Dengue Fever: III

- Avoid invasive procedures when possible
- Unknown if the use of steroids, IVIG, or platelet transfusions to shorten the duration or decrease the severity of thrombocytopenia is effective
- Patients in shock may require treatment in an intensive care unit

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Indications for Hospital Discharge

- Absence of fever for 24 hours (without anti-fever therapy) and return of appetite
- Visible improvement in clinical pictures
- Stable hematocrit
- 3 days after recovery from shock
- Platelets $\geq 50{,}000/mm^3$
- No respiratory distress from pleural effusions/ascites

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Mosquito Barriers

- Only needed until fever subsides, to prevent *Aedes aegypti* mosquitoes from biting patients and acquiring virus
- Keep patient in screened sickroom or under a mosquito net

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Common Misconceptions about DHF

- Dengue + bleeding = DHF
  - Need 4 WHO criteria, capillary permeability
- DHF kills only by hemorrhage
  - Patient dies as a result of shock
- Poor management turns dengue into DHF
  - Poorly managed dengue can be more severe, but DHF is a distinct condition, which even well-treated patients may develop
- Positive tourniquet test = DHF
  - Tourniquet test is a nonspecific indicator of capillary fragility

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More Common Misconceptions about DHF

- DHF is a pediatric disease
  - All age groups are involved in the Americas
- DHF is a problem of low income families
  - All socioeconomic groups are affected
- Tourists will certainly get DHF with a second infection
  - Tourists are at low risk to acquire DHF

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Dengue Vaccine?

- No licensed vaccine at present
- Effective vaccine must be tetravalent
- Field testing of an attenuated tetravalent vaccine currently underway
- Effective, safe and affordable vaccine will not be available in the immediate future

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新版「登革熱」病例通報定義

- 突發發燒≧38℃並伴隨下列任二（含）項以上症狀：
  - （一）頭痛/後眼窩痛/肌肉痛/關節痛/骨頭痛
  - （二）出疹
  - （三）白血球減少（leukopenia）
  - （四）噁心/嘔吐
  - （五）血壓帶試驗陽性
  - （六）任一警示徵象

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Thank you for your attention

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