Dengue fever: a practical guide

Introduction

Dengue is a flavivirus which is endemic throughout tropical and sub-tropical regions across the globe (*Figure 1*) (Pinheiro and Corber, 1997). Case reports describe dengue-like illnesses dating back to the late 18th century (Rush, 1789). It now causes disease predominantly in children and adolescents who live in the tropics, and in travellers (Gubler, 1997; Wilder-Smith and Schwartz, 2005).

Dengue virus is transmitted from human to human via one of two types of mosquito, *Aedes aegypti* and *Aedes albopictus* (Kuno, 1995). These are day-biting mosquitoes that breed in both clean and stagnant water and are readily adapted to urban environments. They breed in small pools of water in domestic settings be it in house plants, guttering or open water butts. The female mosquitoes preferentially feed and rest indoors (Scott et al, 2000).

Dengue virus was initially spread to new areas from infected mosquitoes travelling on ships and causing epidemics in the ports where the ships docked (Gubler, 1997). However, since the 1970s, spread of *A. aegypti*, increased population migration and urbanization has lead to hyper-endemic transmission (continuous transmission and multiple small scale epidemics) throughout tropical areas. Localized epidemics tend to occur with rainy seasons, but transmission does occur year round (Endy et al, 2002).

The number of dengue virus infections has increased year on year since the 1970s. As a result, a quarter of the world's population is at risk of infection with 50–100 million dengue virus infections worldwide per year (World Health Organization, 2009a). In an endemic area 6–8% of children will be infected every year (Balmaseda et al, 2010; Endy et al, 2010). Details of current outbreaks can be found through CDC-DengueMap (www.healthmap.org/dengue/index.php) and Promed mail (www.promedmail.org). Interestingly, Google has developed software that identifies where people are using the search term 'dengue' as a surrogate for potential new outbreaks (www.google.org/denguetrends/). This has shown to be a useful predictor of an outbreak in areas where internet access is good.

Clinical disease

Classical dengue fever

Many people who are infected with dengue virus will have an asymptomatic infection (5–50%) (Balmaseda et al, 2010; Endy et al, 2010). However, of those who do develop symptoms, most will experience classical dengue fever. Dengue is also known as 'break bone fever', which gives a good description of the illness. The incubation period is between 3 and 14 days. Symptoms begin with fever, retro-orbital headache, arthralgia and generalized myalgia. After a few days of illness a rash develops. It is most commonly an evanescent, generalized flushing rash (*Figure* 2). However, it may be macular, maculopapular, scarlatiniform or petechial (*Figure 3*). The petechiae can be demonstrated after applying a tourniquet to a limb for 5 minutes. The rash occurs over the trunk, inner arms and thighs, and on plantar and palmar surfaces.

The predominant laboratory findings are leukopenia, thrombocytopenia and mild to moderate elevation in the serum transaminase levels (Sharp et al, 1995). The illness usually lasts between 5 and

Figure 1. Map of dengue transmission.

Figure 2. Classical dengue rash.

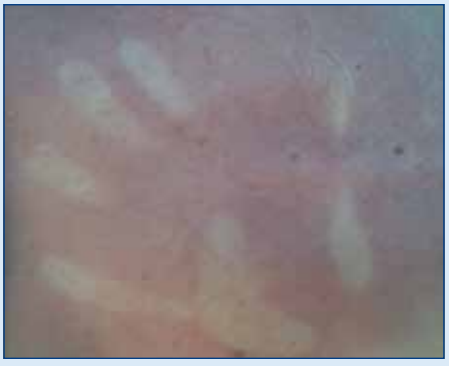
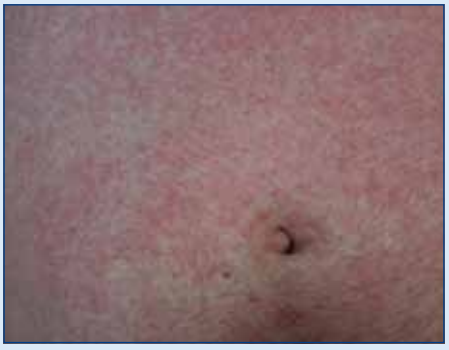


Figure 3. Maculopapular dengue rash.



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10 days. Patients should expect a full recovery, but may experience post-viral fatigue for a few weeks afterwards (Siler et al, 1926; Sabin, 1952; Halstead et al, 1969).

Severe dengue (dengue haemorrhagic fever or dengue shock syndrome)

The more severe forms of dengue disease are known as dengue haemorrhagic fever and dengue shock syndrome. There has been a reclassification combining both dengue haemorrhagic fever and dengue shock syndrome under the common term severe dengue following a major international prospective trial (Alexander et al, 2011). Severe dengue occurs in approximately 5–13% of cases (Schwartz et al, 1996; Kalayanarooj et al, 1997). This syndrome commences with the typical features of dengue fever, but after a few days as the fever abates, the disease progresses to a more severe form.

These disorders are marked by severe capillary leak. In patients, this is heralded by narrowing of the pulse pressure and is followed by rapid and devastating hypovolaemic shock. The hypovolaemia is caused by significant fluid losses to the extravascular space. The shock is short lived, lasting only a few days, if the patient survives (Moxon and Wills, 2008). Capillary fragility causes the haemorrhagic manifestations. These include petechiae, ecchymoses and purpura, and may include mucosal bleeding causing blood loss from the gastrointestinal and respiratory tracts (Díaz et al, 1988).

Patients may not necessarily experience both shock and haemorrhagic manifestations. In the multicentre trial (Alexander et al, 2011), abdominal pain, lethargy, mucosal bleeding and a decreased platelet count were risk factors for progression to severe disease. It can be difficult triaging those who need admission from those who need observational care, and determining the early signs of clinical deterioration. As a result, the World Health Organization (2009b) has published a guideline to help clinicians in assessing patients with dengue and their risk of progression to severe disease (*Table 1*).

Interestingly, these severe manifestations do not represent rampant viral replication. Indeed, viraemia is usually only present for around 2 days before and 2–7 days after the development of symptoms. As the fever resolves, the viraemia disappears and at that point severe features may develop (Vaughn et al, 1997). An aberrant immune response drives dengue haemorrhagic fever and dengue shock syndrome. The details of the immune response are not fully clarified, but it seems to be related to the interplay between antibody-mediated and cytotoxic T cell responses (Murphy and Whitehead, 2011).

There are four serotypes of dengue virus (numbered 1–4) and their genetics differ from each other markedly (approximately 30% of their RNA) (Westaway and Blok, 1997). After infection with one serotype, a person becomes immune to that serotype, but only partially immune to other serotypes. From epidemiological studies, we know that the incidence of severe disease is much higher in secondary infection with second serotype than primary infection. In a Cuban study, 95% of cases of dengue haemorrhagic fever or dengue shock syndrome were from secondary infection and 5% were from primary infection. Infants within the first 6 months of life are at higher risk of severe infection than children older than 6 months of age (Guzmán et al, 1990). It is postulated that infantile infection mimics secondary infection in older children as a result of maternal antibodies and this changes as circulating maternal antibodies wane. Antibody responses therefore seem to play an important role.

Unusual manifestations of dengue virus

A number of neurological symptoms have been noted in association with dengue infection, including encephalopathy, seizures and acute motor weakness (Solomon et al, 2000). Liver failure can also occur, but tends to be a sequela of severe hypotension rather than a direct viral effect. In a small number of predominantly paediatric patients, severe acute abdominal pain can occur, mimicking an acute abdomen (Nimmannitya et al, 1987).

Differential diagnosis

The differential diagnosis of dengue fever is broad. A range of viral illnesses can present with a non-specific febrile illness, transaminitis and rash. Most importantly these include measles, rubella, enterovirus and influenza. In those returning from tropical and subtropical regions malaria, typhoid, leptospirosis and chikungunya should be considered. In data from GeoSentinel Surveillance, 23% of children with an illness following foreign travel had dengue fever, as did 10.4% of all returning travellers with a systemic illness (Wilson et al, 2007).

Diagnosis

Diagnosis is generally made on clinical grounds taking into account relevant travel history, incubation period, clinical and laboratory features. Clearly, for those working in epidemic areas during an epidemic, diagnosis is made solely on clinical grounds. To aid physicians in endemic areas, the World Health Organization (2009b) has produced a clinical case definition (*Table 2*).

In the UK samples can be sent to detect the virus through polymerase chain reaction (Vaughn et al, 1997) during the first few days of illness, and IgM and IgG antibodies (Rigau-Pérez et al, 1994). Both IgM and IgG develop in rapid succession at approximately 4–7 days. IgM lasts several months and IgG several years. In secondary infection, there may not be an IgM response, but IgG levels are usually high. Therefore, lone IgG response may represent either acute secondary infection or previous infection. In these cases, polymerase chain reaction can be helpful to delineate the diagnosis.

As with other flavivirus infections, there is significant cross-reactivity in immunoglobulin responses. Therefore, low-level antibody responses may be seen to, for example, West Nile virus or Japanese encephalitis, in the acute and early convalescent phase of dengue. In the UK it takes approximately 1 week to obtain results for routine samples. However, there is a rapid service available, which can provide results within 24 hours.

A range of commercially available kits is now available to help with rapid, accurate and easy dengue virus detection. These are mostly ELISA tests against the NS1 antigen of the virus. They can be either performed as a standard ELISA or as a dipstick test. These have a sensitivity of 70–90% in acute infection and therefore may become increasingly useful in the future (Nga et al, 2007; Lima et al, 2010).

Treatment

Treatment is currently centred on supportive therapy. In those with classical dengue fever, analgesics and antiemetics along with intravenous rehydration as necessary are the mainstays of treatment. In dengue shock syndrome, careful and appropriate fluid resuscitation is paramount. Overhydration leads to pulmonary oedema and underhydration can give hypotension and subsequent hypoperfusion of the brain, liver and kidneys. Trials have shown that, as the pulse pressure narrows, carefully titrated fluid boluses followed by further fluid boluses to maintain the pulse pressure from further narrowing result in significantly improved outcomes, reducing the mortality rate from 5–30% to <1% (Nimmannitya et al, 1987; Ngo et al, 2001).

Despite the current focus on supportive therapy, considerable research effort is now looking at antiviral compounds. Although many of the severe features of dengue are

Table 1. World Health Organization triaging and management criteria

Group A Can be sent home	Clinical features	Able to tolerate adequate volumes of fluid orally	
		Able to pass urine at least 6-hourly	
		Do not have any warning signs	
	Management/advice	Encourage oral intake with oral rehydration solution or equivalent	
		Paracetamol and/or tepid sponging for fever. Avoid aspirin	
		Encourage to return to hospital if: no clinical improvement, deterioration at defervescence, severe abdominal pain or vomiting, cold peripheries, irritability, bleeding, not passing urine for 6 hours	
		Clinician review daily	
Group B Inpatient management	Clinical features	Patients with warning signs	
		Patients with pre-existing conditions, e.g. pregnancy, infancy, old age, diabetes, renal impairment or haemolytic disease	
		Social reasons discharge would be unsafe	
	Management/advice	Obtain initial haematocrit	
		Give isotonic fluids (Start with 5–7 ml/kg/hour for 1–2 hours, then reduce to 3–5 ml/kg/hr for 2–4 hours, and then reduce to 2–3 ml/kg/hr or less according to the clinical response)	
		Re-measure haematocrit	
		If haematocrit increasing, then increase fluids to increase the rate to 5–10 ml/kg/hour for 1–2 hours and reassess regularly	
		Give the minimum fluids required to maintain haematocrit and urine output	
		If no warning signs, rehydrate with oral rehydration solution	
Group C High dependency management	Clinical features	Severe plasma leak	
		Severe haemorrhage	
		Severe organ dysfunction	
	Management/advice	Compensated shock	Give isotonic fluids at 5–10 ml/kg/hour over 1 hour, then reassess
			If improving, intravenous fluids should be gradually reduced to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, then to 2–3 ml/kg/hr, and then further depending on haemodynamic status
			If vital signs are still unstable, check the haematocrit after the first bolus. If haematocrit high (>50%), repeat a second bolus at 10–20 ml/kg/hr for 1 hour. If there is improvement, reduce the rate to 7–10 ml/kg/hr for 1–2 hours, and then continue to reduce as above
			If haematocrit decreases this indicates bleeding
		Hypotensive shock	Give intravenous fluids at 20 ml/kg as a bolus over 15 minutes
			If improves, give a crystalloid/colloid infusion of 10 ml/kg/hr for 1 hour. Then continue with crystalloid infusion and gradually reduce to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, and then to 2–3 ml/kg/hr or less
			If still unstable (i.e. shock persists), review the initial haematocrit. If the haematocrit was low (<40% in children and adult females, <45% in adult males), this indicates bleeding. If the haematocrit was high, change intravenous fluids to colloid solutions at 10–20 ml/kg as a second bolus over 30 minutes. After the second bolus, reassess the patient. If the condition improves, reduce the rate to 7–10 ml/kg/hr for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above
		Haemorrhage	Give 5–10 ml/kg of fresh-packed red cells or 10–20 ml/kg of fresh whole blood at an appropriate rate and observe the clinical response

From World Health Organization (2009b)

caused by the immune system after the level of viraemia has fallen, a high peak viraemia is more likely to result in severe disease. Therefore, if patients are diagnosed early in disease and given an antiviral to reduce peak viraemia, the chance of developing severe disease may be reduced. Current potential molecular targets are non-structural proteins and virus-specific proteases (World Health Organization, 2009b; Chang, 2011; Schleich et al, 2011).

Infection prevention and vaccines

Between the 1940s and 1970s there were concerted efforts to reduce the transmission of yellow fever in urban environments in the Americas. This involved mosquito surveillance and insecticide spraying with DDT. As a secondary consequence, the transmission of dengue virus reduced. However, as epidemics came under control and concern about the effects of DDT increased, insecticide use tailed off. Following this, there has been a resurgence in dengue transmission (Gubler, 1989). Insecticide spraying during an epidemic has limited effect because of the ability of *A. aegypti* to breed in all types of standing water, including in houses (Halstead, 1984).

To date there are no vaccines that prevent dengue virus infection. There is a conceptual challenge as efficacy of vaccines containing more than one serotype are poor and a person vaccinated against one serotype would be at increased risk of dengue haemorrhagic fever and/or dengue shock syndrome if infected with another serotype (Monath, 2007). However, with an increasing worldwide epidemic, vaccine research continues.

For travellers, the best preventative measure is daytime use of insect repellents containing DEET.

Advice to travellers who have previously had dengue fever

Counselling travellers about dengue virus is difficult. Certainly, for those who have never had dengue fever, it is most appropriate to discuss primary prevention with insect repellent use. However, those who have had dengue fever and will return to a dengue endemic area should be counselled more carefully. They clearly not only remain at risk from further dengue infection, but are also more at risk of severe disease should they contract the infection subsequently. Quantifying this risk is difficult and data relating to this have mostly been derived from epidemiological studies in Cuba. Cuba has experienced infrequent epidemics of dengue, in 1977, 1981, 1997 and 2001. Whether these data are applicable to travellers from the UK who return to endemic areas should be considered. Approximately 90% of patients with severe disease will have secondary infection (Nielsen, 2009). In Cuba, they found that the risk of severe disease in secondary infection was 1 in 79.5 in adults and 1 in 23 in children (Kouri et al, 1989).

Table 2. World Health Organization classification of dengue fever

	Symptoms		Notes
Probable dengue fever	Live in/travel to endemic area		Supportive serology/molecular studies
	Two or more of:	Nausea and vomiting	
		Myalgia/arthralgia	
		Rash	
		Leukopenia	
		Tourniquet test positive	
		Any warning sign	
Warning signs	Any of abdominal pain/tenderness		Requires strict observation and medical intervention
	Persistent vomiting		
	Clinical fluid accumulation		
	Mucosal bleed		
	Lethargy/restlessness		
	Liver enlargement >2 cm		
	Laboratory: increase in haematocrit concurrent with rapid decrease in platelet count		
Severe dengue	Severe plasma leak leading to		Shock (dengue shock syndrome)
			Fluid accumulation with respiratory distress
	Severe bleeding		
	Severe organ involvement		Liver: aspartate transaminase and alanine transaminase >1000 units/ml
			CNS: impaired conciousness
			Other organs

From World Health Organization (2009b)

Conclusions

Dengue virus is transmitted by day-biting mosquitoes and occurs in a large number of tropical and subtropical countries throughout the world. Travellers with a febrile illness within 14 days of returning from an endemic area should have the diagnosis considered. However, care must be taken to rule out differential diagnoses, in particular malaria. The symptoms of dengue fever begin in a non-specific fashion with fever, retro-orbital headache, myalgia and arthralgia, but a classic rash may develop after a few days of illness. The treatment is supportive, but patients should be monitored for the development of severe disease. This classically occurs in those with secondary infection as the fever subsides. Severe dengue haemorrhagic fever and dengue shock syndrome have a high mortality of ~20%, but this can be reduced to <1% with expert fluid resuscitation and intensive care. BJHM

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Balmaseda A, Standish K, Mercado JC et al (2010) Trends in patterns of dengue transmission over 4 years in a pediatric cohort study in Nicaragua. *J*

Infect Dis **201**: 5–14
Chang J (2011) Combination of α-glucosidase inhibitor and ribavirin for the treatment of dengue virus infection in vitro and in vivo. *Antiviral Res* **89**(1): 26–34
Díaz A, Kourí G, Guzmán MG et al (1988) Description of the clinical picture of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) in adults. *Bull Pan Am Health Organ* **22**: 133–44
Endy TP, Nisalak A, Chunsuttiwat S et al (2002) Spatial and temporal circulation of dengue virus serotypes: a prospective study of primary school children in Kamphaeng Phet, Thailand. *Am J Epidemiol* **156**: 52–9
Endy TP, Yoon IK, Mammen MP (2010) Prospective cohort studies of dengue viral transmission and severity of disease. *Curr Top Microbiol Immunol* **338**: 1–13
Gubler DJ (1989) *Aedes aegypti* and *Aedes aegypti*-borne disease control in the 1990s: top down or bottom up. Charles Franklin Craig Lecture. *Am J Trop Med Hyg* **40**: 571–8
Gubler DJ (1997) Dengue and dengue hemorrhagic fever: its history and resurgence as a global public health problem. In: Gubler DJ, Kuno G, eds. *Dengue and Dengue Hemorrhagic Fever.* CAB International, Wallingford: 1
Guzmán MG, Kouri GP, Bravo J, Soler M, Vazquez S, Morier L (1990) Dengue hemorrhagic fever in Cuba, 1981: a retrospective seroepidemiologic study. *Am J Trop Med Hyg* **42**: 179–84
Halstead SB (1984) Selective primary health care: strategies for control of disease in the developing world. XI. Dengue. *Rev Infect Dis* **6**(2): 251–64
Halstead SB, Nimmannitya S, Margiotta MR (1969) Dengue and Chikungunya virus infection in man in Thailand, 1962–1964: II. Observations on disease in outpatients. *Am J Trop Med Hyg* **18**: 972–83
Kalayanarooj S, Vaughn DW, Nimmannitya S et al (1997) Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis* **176**: 313–21
Kouri GP, Guzmán MG, Bravo JR, Triana C (1989) Dengue haemorrhagic fever/dengue shock syndrome: lessons from the Cuban epidemic, 1981. *Bull World Health Organ* **67**(4): 375–80
Kuno G (1995) Review of the factors modulating dengue transmission. *Epidemiol Rev* **17:** 321–5
Lima Mda R, Nogueira RM, Schatzmayr HG, dos Santos FB (2010) Comparison of three commercially available dengue NS1 antigen capture assays for acute diagnosis of dengue in Brazil. *PLoS Negl Trop Dis* **4**(7): e738–46
Monath TP (2007) Dengue and yellow fever--challenges for the development and use of vaccines. *N Engl J Med* **357**(22): 2222–5
Moxon C, Wills B (2008) Management of severe dengue in children. *Adv Exp Med Biol* **609**: 131–44
Murphy R, Whitehead SS (2011) Immune response to dengue virus and prospects for a vaccine. *Annu Rev Immunol* **29**: 587–619
Nga TT, Thai KT, Phuong HL et al (2007) Evaluation of two rapid immunochromatographic assays for diagnosis of dengue among Vietnamese febrile patients. *Clin Vaccine Immunol* **14**(6): 799–801
Ngo NT, Cao XT, Kneen R et al (2001) Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* **32**(2): 204–13
Nielsen DG (2009) The relationship of interacting immunological components in dengue pathogenesis. *Virol J* **6**: 211–18
Nimmannitya S, Thisyakorn U, Hemsrichart V (1987) Dengue haemorrhagic fever with unusual manifestations. *Southeast Asian J Trop Med Public Health* **18**: 398–406
Pinheiro FP, Corber SJ (1997) Global situation of dengue and dengue haemorrhagic fever, and its emergence in the Americas. *World Health Stat Q* **50**: 161–9
Rigau-Pérez JG, Gubler DJ, Vorndam AV, Clark GG (1994) Dengue surveillance--United States, 1986-1992. *MMWR CDC Surveill Summ* **43**: 7–19
Rush AB (1789) An account of the bilious remitting fever, as it appeared in Philadelphia in the summer and autumn of the year 1780. In: *Medical Inquiries and Observations.* Richard & Hall, Philadelphia: 104
Sabin AB (1952) Research on dengue during World War II. *Am J Trop Med Hyg* **1**: 30–50
Schleich K, Nürnberger C, Sobanski A, Efferth T (2011) Vaccination and antiviral treatment of neglected diseases caused by flaviviral infections. *Curr Med Chem* **18**(4): 604–14
Schwartz E, Mendelson E, Sidi Y (1996) Dengue fever among travellers. *Am J Med* **101**: 516–20
Scott TW, Morrison AC, Lorenz LH et al (2000) Longitudinal studies of *Aedes aegypti* (Diptera: Culicidae) in Thailand and Puerto Rico: Population dynamics. *J Med Entomol* **37**: 77–88
Sharp TW, Wallace MR, Hayes CG et al (1995) Dengue fever in U.S. troops during Operation Restore Hope, Somalia, 1992-1993. *Am J Trop Med Hyg* **53**: 89–94
Siler JF, Hall MW, Hitchens AP (1926) Dengue: its history, epidemiology, mechanism of transmission, etiology, clinical manifestations, immunity, and prevention. *Philipp J Sci* **29**: 1–304
Solomon T, Dung NM, Vaughn DW et al (2000) Neurological manifestations of dengue infection. *Lancet* **355**: 1053–9
Vaughn DW, Green S, Kalayanarooj S et al (1997) Dengue in the early febrile phase: viremia and antibody responses. *J Infect Dis* **176**: 322–30
Westaway EG, Blok J (1997) Taxonomy and evolutionary relationships of the flaviviruses. In: Gubler DJ, Kuno G, eds. *Dengue and Dengue Hemorrhagic Fever*. CABI Publishing, Wallingford, Oxfordshire: 147–73
Wilder-Smith A, Schwartz E (2005) Dengue in Travellers. *N Engl J Med* **353**: 924–32
Wilson ME, Weld LH, Boggild A, Keystone JS, Kain KC, von Sonnenburg F, Schwartz E; GeoSentinel Surveillance Network (2007) Fever in returned travellers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis* **44**(12): 1560–8
World Health Organization (2009a) Dengue and dengue haemorrhagic fever. Fact sheet no. 117. www.who.int/mediacentre/factsheets/fs117/en/ (accessed 23 March 2012)
World Health Organization (2009b) *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control.* World Health Organization, Geneva

KEY POINTS

- Dengue is a viral illness transmitted by day-biting mosquitoes in tropical climates throughout the world.
- It has an incubation period of 3–14 days.
- Classical dengue fever presents with fever, retro-orbital headache, arthralgia, myalgia and a rash. The rash classically looks like sunburn.
- Severe dengue, be it dengue haemorrhagic fever or dengue shock syndrome, is more likely to occur in those who have previously had dengue.
- Treatment of dengue fever is symptomatic. In those with shock, careful fluid resuscitation with fluid boluses should be given with the aim of preventing pulse pressure narrowing. Physicians should be wary of the development of pulmonary oedema.

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