Clinical manifestations and diagnosis of dengue virus infection  
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INTRODUCTION — Dengue is the most prevalent mosquito-borne viral disease; it is estimated that over 390 million dengue virus infections occur each year throughout the world, including 96 million that produce illness [1]. Symptomatic dengue virus infections can present with a wide range of clinical manifestations, from mild febrile illness to a life-threatening shock syndrome or organ dysfunction [2,3]. Both viral and host factors are thought to contribute to the manifestations of disease in each infected individual.

The various clinical features and the available methods for the diagnosis of dengue virus infections will be reviewed here. The pathogenesis and measures to prevent and treat the disease are discussed separately. (See “Pathogenesis of dengue virus infection” and “Prevention and treatment of dengue virus infection” and “Epidemiology of dengue virus infections”.)

VIROLOGY — There are four closely related but serologically distinct dengue viruses, called DENV-1, DENV-2, DENV-3, and DENV-4, of the genus Flavivirus. There is only transient and weak cross-protection among the four serotypes; therefore, individuals living in an area of endemic dengue can be infected with up to four dengue serotypes in a lifetime. Multiple virus serotypes often co-circulate within the same region (hyperendemicity), causing periodic epidemics.

CLINICAL MANIFESTATIONS — The typical clinical manifestations of dengue range from self-limited dengue fever (DF) to dengue hemorrhagic fever with shock syndrome [4]. With wider availability of laboratory testing, there are increasing reports of unusual clinical manifestations, as discussed below [3]. The risk of severe disease is much higher in repeat infection than primary infection [5]. (See “Pathogenesis of dengue virus infection”.)

Asymptomatic infection — Most dengue virus infections in adults are symptomatic [6]. For example, in a survey of 44 military personnel with serologic evidence of dengue virus, approximately 86 percent of infections were symptomatic [7]. In contrast, most infections among children under age 15 years are asymptomatic or minimally symptomatic. In one study of schoolchildren in rural Thailand, 53 percent of dengue virus infections were not associated with a recognized febrile illness despite intense active surveillance [8].

Classic dengue fever — Classic dengue fever is an acute febrile illness accompanied by headache, retroorbital pain, and marked muscle and joint pains, which evoked the term “break-bone fever” [9]. Symptoms typically develop between 4 and 7 days after the bite of an infected mosquito; the incubation period may range from 3 to 14 days. Dengue can essentially be excluded as the cause of symptoms in a traveler who develops illness more than 14 days after returning from a dengue-endemic country [10].

Fever typically lasts for five to seven days [11]. Some patients have a biphasic (“saddleback”) fever curve, with the second febrile phase lasting one to two days; this has been described in approximately 5 percent of patients [7,11]. The febrile period may also be followed by a period of marked fatigue that can last for days to weeks, especially in adults.

In a study including more than 3900 patients with dengue in Puerto Rico, the frequency of symptoms was influenced by the patient's age and sex and differed in patients with primary versus secondary dengue virus infection [12]. All symptoms were less frequent in patients ≤19 years of age. Joint pain, body aches, and rash were more common in females. Constitutional symptoms and gastrointestinal symptoms were
more common in patients experiencing a second infection, whereas rash was more commonly noted during primary infection.

High frequencies of myalgia, headache, and retroorbital pain among dengue cases in the studies listed above may represent overestimates due to selection bias. Several studies of travelers or military personnel have reported these “classic” symptoms of DF in 15 to 60 percent of patients [7,10,11,13]. Fever and extreme fatigue have been the predominant symptoms of patients in these series. When a rash occurred, it appeared between two and five days after the onset of fever.

**Hemorrhagic manifestations** — Hemorrhagic manifestations occur commonly in patients with DF and, in rare cases, can be life threatening. In a large study in Thailand, spontaneous bleeding occurred in 68 percent of children with DF [14]. The main bleeding sites were the skin (58 percent) and nose (19 percent); gastrointestinal bleeding was less common (4 percent). In another series of 18 adults who acquired DF during travel, hemorrhagic phenomena were noted in 22 percent; two patients had purpura and two had melena [11]. This clinical presentation needs to be differentiated from dengue hemorrhagic fever, described below. (See ‘Dengue hemorrhagic fever’ below.)

**Other symptoms** — Acute dengue virus infection often presents without the full picture of classical DF, especially in children. Gastrointestinal or respiratory tract symptoms may dominate the clinical picture in some patients. Among 3926 patients with laboratory-diagnosed dengue virus infections in Puerto Rico during 1990 and 1991 (one-third of whom were <15 years of age), the frequency of specific symptoms was as follows [12]:

- Constitutional symptoms, including fever (90 percent)
- Headache, eye pain, body pain, and joint pain (63 to 78 percent)
- Rash (slightly more than 50 percent)
- Gastrointestinal symptoms including nausea or vomiting (more than 50 percent) and diarrhea (30 percent)
- Respiratory tract symptoms including cough, sore throat, and nasal congestion (each observed in approximately one-third of patients)

**Physical examination** — The physical examination in patients with DF is generally nonspecific. Conjunctival injection, pharyngeal erythema, lymphadenopathy, and hepatomegaly are observed in 20 to 50 percent of patients [13]. The rash is typically macular or maculopapular and may be associated with pruritus (picture 1).

**Laboratory findings** — Laboratory findings typical of DF include the following:

- Leukopenia is common in both adults and children with DF and is a useful diagnostic feature [13,15,16].
- Thrombocytopenia is noted in most patients with DF [17]. In several studies, platelet counts <100,000 cells/mm$^3$ were observed in 16 to 55 percent of patients [11,15].
- Serum aspartate transaminase (AST) levels are frequently elevated in both adults and children with DF; the elevations are usually modest (2 to 5 times the upper limit of normal values), but marked elevations (5 to 15 times the upper limit of normal) are occasionally noted [11,15].

**Dengue hemorrhagic fever** — Dengue hemorrhagic fever (DHF) is the most serious manifestation of dengue virus infection and can be associated with circulatory failure and shock. The four cardinal features of DHF, as defined by the World Health Organization (WHO), include [3,5,18]:

1. Hemorrhagic manifestations
2. Hypotension
3. Alterations in clotting factors
4. Evidence of plasma leakage
Increased vascular permeability (plasma leakage syndrome) evidenced by hemoconcentration (20 percent or greater rise in hematocrit above baseline value), pleural effusion, or ascites [15]

Marked thrombocytopenia (100,000 cells/mm$^3$ or lower)

Fever lasting two to seven days

A hemorrhagic tendency (as demonstrated by a positive tourniquet test) or spontaneous bleeding (see 'Hemorrhagic manifestations' below)

The term dengue shock syndrome (DSS) is used when shock is present along with these four criteria [15].

Although DF and DHF are frequently considered different diseases, physicians should recognize that the criteria listed above define DHF narrowly. This definition highlights the importance of plasma leakage as a pathophysiologic feature of severe dengue but does not encompass all patients with clinically severe or complicated dengue infections [5,19]. Therefore, the case definition should not supplant good clinical judgment in the management of patients with suspected dengue. (See 'Classification controversies' below.)

Plasma leakage — Plasma leakage is the most specific and life-threatening feature of DHF. The increase in vascular permeability develops over a period of 24 to 48 hours. Shock may develop in patients with marked plasma leakage, especially if supportive treatment is delayed. This clinical presentation is referred to as "dengue shock syndrome" (DSS) and is associated with a case-fatality rate as high as 12 percent in some studies, even with aggressive therapy [20].

Plasma leakage usually occurs between three and seven days after the onset of illness. This coincides with defervescence, severe thrombocytopenia, and elevation of aminotransferases [15]. Abdominal pain is also reported to precede the onset of plasma leakage in approximately 60 percent of patients with DHF [21-23]. The presence of intense abdominal pain, persistent vomiting, and marked restlessness or lethargy, especially coinciding with defervescence, should alert the clinician to possible impending dengue shock syndrome [24].

Chest radiography and chest/abdominal ultrasound are the imaging modalities useful for detection of plasma leakage in DHF. In one study of 158 suspected cases in Thailand [25], right lateral decubitus chest radiograph was sensitive for detection of pleural effusion, but ultrasound was useful for detecting larger effusions and also had the advantages of evaluating for presence of peritoneal fluid. Plasma leakage was detected by ultrasound as early as three days after the onset of fever; pleural effusions were more common than ascites or edema of the gallbladder wall.

Hemorrhagic manifestations — The severity of hemorrhagic manifestations is quite variable among patients with DHF. Spontaneous petechiae or ecchymoses were noted in approximately one-half of adults and children with DHF in Cuba [21,22]. Other less-frequent hemorrhagic manifestations reported in these studies included: hematemesis (15 to 30 percent of subjects), menorrhagia (40 percent of adult women), melena (5 to 10 percent), and epistaxis (10 percent).

Microvascular fragility may be demonstrated by a positive "tourniquet test"; this test is performed by inflating a blood pressure cuff on the arm to midway between systolic and diastolic blood pressures for five minutes [26]. The pressure is released for at least one minute and the skin below the cuff is examined for petechiae. A finding of 10 or more petechiae in a one square inch area is considered positive (picture 2).
Hemorrhagic manifestations are also common in dengue fever [14,27]; this can be severe, requiring hospitalization and transfusion in rare cases [19]. (See ‘Classic dengue fever’ above.)

**Other manifestations** — In some cases, liver failure, central nervous system (CNS) dysfunction, and/or myocardial dysfunction occur in the setting of acute dengue virus infection [28-31]. Liver failure has been documented particularly after resuscitation from profound shock, and, in many cases, may be caused by prolonged hypoperfusion or hypoxia rather than a direct viral effect.

Neurological manifestations that have been associated with dengue virus infection include encephalopathy and seizures [29,30,32-34]. In case series, the frequency of such manifestations has been approximately 1 percent [35]. Symptoms include fever, headache, and lethargy; some patients may have no characteristic features of dengue fever or dengue hemorrhagic fever on admission [30]. The diagnosis of dengue virus infection has been supported by either serologic testing or viral isolation or detection by polymerase chain reaction in cerebrospinal fluid [30]. Permanent neurologic sequelae have been described [30,32].

Reye syndrome has been noted in children but may be associated with use of salicylate-containing medications rather than dengue virus infection per se. Other neurologic syndromes that have been reported to be potentially associated with dengue virus infection include acute pure motor weakness, mononeuropathies, polynuropathies, Guillain-Barré syndrome, and transverse myelitis [30,31].

Clinical and echocardiographic evidence of myocardial dysfunction has been described in hospitalized patients with dengue [36]. Cardiac dysfunction does not appear to be the major cause of shock in most patients with DSS but may reflect clinical response to intravenous fluid therapy. Histologic findings of myocarditis at autopsy have been described in case reports; one noted positive staining for dengue viral antigens in cardiomyocytes [37]. A study of 81 hospitalized patients with dengue in Brazil described elevated levels of troponin-I or the N terminal fragment of B-type natriuretic peptide in 15 percent of cases [38]. Two patients developed cardiogenic shock and died; dengue viral antigen was detected in infiltrating inflammatory cells at autopsy. Echocardiography demonstrated abnormal wall motion in three patients, one of whom had abnormal left ventricular ejection fraction.

Abdominal pain has been described as the predominant clinical feature in a small number of patients with dengue, mimicking an acute abdomen. Acute kidney injury (AKI) has been reported in up to 3 percent of dengue cases in several hospital-based case series [39-41]. Some cases may reflect complications of shock, but other mechanisms include rhabdomyolysis, glomerulonephritis, and acute tubular necrosis. In a retrospective study of 1076 adult dengue patients hospitalized at one center in Taiwan, rhabdomyolysis was noted in 9 cases (0.8 percent) [42]. Other disease syndromes, including cholecystitis and retinal vasculitis [43], have been reported in patients in endemic countries with serologic evidence of acute dengue; however, subclinical dengue infections are common in these areas, and dengue virus infection has not been definitively established as the cause of these unusual manifestations.

Hemophagocytic lymphohistiocytosis has been described in association with dengue fever [44,45]. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis".)

**CLASSIFICATION CONTROVERSIES** — For several decades prior to 2009, the World Health Organization (WHO) classified symptomatic dengue virus infections into three categories: undifferentiated fever, classic dengue fever (DF), and dengue hemorrhagic fever (DHF). Subsequently, these categories have been criticized for several reasons [46]:
Confusion arises because the term DHF suggests that hemorrhage is the cardinal manifestation, whereas plasma leakage leading to shock is the most specific feature of severe dengue and is most important for clinical management.

Some patients with severe clinical syndromes requiring medical intervention do not meet all the criteria for DHF.

Classification is difficult when patients meet some but not all four diagnostic criteria, especially if pivotal clinical laboratory data are unavailable.

The diagnostic criteria for DHF have been inconsistently applied in epidemiologic and scientific reports.

Reporting that is limited to DHF according to the WHO classification scheme underestimates the disease burden of dengue illness [47].

These issues have been illustrated in studies among travelers and patients with documented dengue infection in endemic areas [14,48]. In one study of travelers, two patients (0.9 percent) fulfilled the WHO case definition for DHF, although 23 (11 percent) had what were considered severe clinical manifestations including internal hemorrhage, plasma leakage, shock, or marked thrombocytopenia [48]. A secondary immune response was associated with both spontaneous hemorrhage and other severe manifestations of disease.

As a result of these concerns, revised classification systems have been adopted [3,49], albeit with significant areas of divergence:

- The WHO Special Program for Research and Training in Tropical Diseases and Pan-American Health Organization have adopted a revised classification of “dengue” and “severe dengue”; “severe dengue” is applied to patients who show severe plasma leakage (ie, leading to shock or fluid accumulation with respiratory distress), severe hemorrhage (as defined by the treating physician), or severe organ impairment (defined as aspartate transaminase [AST] or alanine transaminase [ALT] ≥1000, impaired consciousness, or severe involvement of the heart or other organs) [49]. The revised classification further divides nonsevere dengue into dengue with or without “warning signs” (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement >2 cm, or increase in hematocrit concurrent with rapid decrease in platelet count). Given the limited experience with this revised classification scheme, its sensitivity and specificity for guiding management of patients in general practice are not known. Therefore, these revised guidelines recommend laboratory confirmation of dengue virus infection when plasma leakage is absent.
- The WHO Regional Office for South-East Asia (SEARO) adopted a more modest revision of the older dengue classification scheme [3]. The three categories of undifferentiated fever, DF, and DHF were retained, with the addition of a fourth category of expanded dengue syndrome, encompassing those patients who present with any of the unusual features described above in association with dengue virus infection, including those with isolated severe organ dysfunction.

DIFFERENTIAL DIAGNOSIS — Dengue virus infection should be considered in the differential diagnosis of a febrile illness in any patient who has resided in or traveled to an appropriate region in the two weeks before the onset of illness. Malaria, chikungunya, rickettsial infections, and leptospirosis are the travel-related illnesses that can be mistaken for dengue fever.
Analysis of data from over 17,000 ill travelers in the GeoSentinel Surveillance Network found that dengue accounted for 10 percent of post-travel systemic febrile illnesses, second only to malaria [50]. Mononucleosis related to Epstein-Barr virus or cytomegalovirus, rickettsial infections, and typhoid or paratyphoid fever were the next most common defined causes of systemic febrile illnesses in this study. Dengue was the most frequently identified cause of systemic febrile illness among travelers returning from Southeast Asia (32 percent), the Caribbean (24 percent), South Central Asia (14 percent), and South America (14 percent) and was only slightly less common than malaria among travelers returning from Central America (12 percent of cases). (See "Evaluation of fever in the returning traveler" and "Clinical manifestations of malaria" and "Epidemiology, microbiology, clinical manifestations, and diagnosis of typhoid fever".)

Chikungunya virus, the causative agent of chikungunya fever, is an increasing problem in differential diagnosis of travel-related febrile illness. Chikungunya is also transmitted by Aedes aegypti mosquitoes and has recently been associated with widespread and often explosive outbreaks in areas infested by this mosquito [51]. Clinical features of chikungunya fever overlap considerably with those of dengue fever. In several studies comparing the two diseases, joint pain was reported somewhat more often by patients with chikungunya, whereas abdominal pain and leukopenia were more common in those with dengue [52-54]. Joint swelling is highly specific for chikungunya, having been reported by 85 (65 percent) of 131 patients with chikungunya versus 4 (4 percent) of 104 patients with dengue in one study [52]. Conversely, bleeding manifestations and severe thrombocytopenia are relatively specific for dengue.

In patients with fever and maculopapular rash, other viral exanthems should be considered, including measles and rubella. Other RNA viruses associated with hemorrhagic fever syndrome include filoviruses (Ebola and Marburg), arenaviruses (eg, Lassa fever, Junin), bunyaviruses (eg, hemorrhagic fever with renal syndrome, Rift Valley fever, severe fever with thrombocytopenia syndrome), and flaviviruses (yellow fever, Kyasanur Forest disease); these are mostly highly restricted in their geographic distribution. Severe illness with fluid accumulation or organ involvement that is uncommon in dengue hemorrhagic fever (eg, peripheral or pulmonary edema, severe renal dysfunction) should increase suspicion of these alternative diagnoses in the setting of a compatible exposure history.

**DIAGNOSIS** — The diagnosis of acute dengue virus infection is mainly clinical. In developing countries, laboratory confirmation is typically not available. In developed countries, laboratory confirmation is usually available only in specialized reference laboratories and is often not sufficiently timely to assist in the management of the illness. (See "Prevention and treatment of dengue virus infection".)

**Clinical diagnosis** — The clinical manifestations of dengue fever (DF) or dengue hemorrhagic fever (DHF) with or without shock can be helpful in making a provisional diagnosis:

- One study of children with febrile illnesses in Thailand reported that some clinical features, such as a positive tourniquet test, leukopenia, thrombocytopenia, and increased serum aspartate transaminase (AST) levels, were more frequent in patients with dengue than in those with other febrile illnesses [15]. However, none of these features of classic DF is sufficiently sensitive or specific to permit a reliable diagnosis.
- A systematic review of the English language literature from 1990 to 2007 identified 15 studies that evaluated the usefulness of clinical criteria to distinguish dengue from other febrile illnesses among populations living in dengue-endemic areas [16]. Low platelets, white blood cell and neutrophil counts, elevated hepatic transaminases, and the presence of petechiae were associated with a confirmed diagnosis of dengue across multiple studies.
One study applied decision tree classification analysis to clinical, hematological, and virological data from 1200 patients presenting within the first 72 hours of an acute febrile illness [55]. Of these, 364 were dengue reverse transcriptase-polymerase chain reaction (RT-PCR) positive; 173 had DF, 171 had dengue hemorrhagic fever, and 20 had dengue shock syndrome. The diagnostic algorithm utilized platelet count, white blood cell, neutrophil and lymphocyte counts, hematocrit, and body temperature and noted an accuracy of 85 percent for classification of patients with dengue versus non-dengue illnesses.

In developing countries, dengue hemorrhagic fever is frequently diagnosed based upon the clinical case definition established by the World Health Organization (WHO) [3,18]. In regions (and seasons) with a high incidence of DHF, the positive predictive value of the case definition is high. Laboratory tests confirm dengue virus infection in as many as 90 percent of such cases [56,57]. However, malaria, leptospirosis, or typhoid fever must be considered in the differential diagnosis of DHF. (See ‘Differential diagnosis’ above.)

When dengue virus infection (DF or DHF) is suspected on clinical grounds, the patient should be treated empirically as appropriate for the symptoms and signs present. (See “Prevention and treatment of dengue virus infection”.)

**Laboratory testing** — Confirmation of acute dengue virus infection is most frequently accomplished using serology [18,58]. Tests for detection of viral RNA or NS1 antigen are commercially available and more successful than serology in detecting dengue virus infection in the early stages [59]. We favor the following diagnostic approach to the patient with suspected dengue if laboratory support is available [18,58]:

- An acute phase serum or plasma sample should be obtained. If the acute phase sample is obtained ≥3 days after the onset of illness, the IgM immunoassay (MAC-ELISA or equivalent) is the procedure of choice for rapid confirmation of the diagnosis. The potential for a false-negative result remains elevated within the first six days of illness. (See ‘Serologic testing’ below.)
- If the acute phase sample is obtained within the first three days after the onset of illness or if the sample is obtained within the first six days of illness and there is a negative IgM assay result, testing for the presence of the dengue viral RNA or NS1 antigen has the highest diagnostic yield. (See ‘Virus detection’ below.)
- To confirm a positive IgM result or if initial testing is negative in a patient with suspected dengue virus infection, a convalescent phase serum sample should be obtained at least 10 to 14 days after the acute phase serum. The acute and convalescent specimens should be analyzed together by a hemagglutination inhibition (HI) or enzyme immunoassay to provide definitive serologic testing for acute dengue virus infection. These tests are not licensed for use in the United States, however, and results do not affect clinical management.

A more detailed discussion of serologic testing and viral detection methods follows.

**Serologic testing** — The most frequently used serologic tests for the diagnosis of acute dengue virus infection are the HI assay and IgG or IgM enzyme immunoassays. Complement fixation and neutralizing antibody assays are more technically demanding and are used in specialized laboratories only. Thus far, the US Food and Drug Administration (FDA) has approved the IgM capture enzyme-linked immunosorbent assay (ELISA) for use in the United States.
The HI assay remains the gold standard for serologic testing for dengue virus-specific antibodies [18]. Analysis of paired acute and convalescent serum samples is essential; a fourfold or greater rise in HI antibody titer between acute and convalescent samples defines acute infection.

The antibody response depends on whether the patient has primary or secondary dengue virus infection. In primary infection, HI antibodies develop relatively late (after the fifth day of illness) and reach titers of less than 1:1250 in the convalescent phase. In secondary infection, HI antibodies rise early and reach titers above 1:1250 (often 1:10,240 or higher) in the convalescent phase.

Immunoassays for the detection of dengue virus-specific IgG antibodies have demonstrated sensitivity and specificity of approximately 99 percent and 96 percent, respectively, compared with the HI assay [60]. As with the HI assay, diagnosis of acute dengue virus infection using the IgG ELISA requires testing of paired acute and convalescent serum samples, showing a greater than fourfold rise in antibody titer.

One assay that can use a single blood specimen for diagnosis of dengue infection is the IgM antibody capture ELISA or MAC-ELISA [58]. Dengue virus-specific IgM antibodies are typically detected by the MAC-ELISA by about the sixth day of illness and persist for 30 to 90 days. If positive, this test can assist in rapid diagnosis of the patient with dengue infection. However, the sensitivity and specificity of this assay is much lower than the HI assay. In one study of Thai children with predominantly secondary dengue virus infections, only 29 percent of subjects had a positive result in the MAC-ELISA by the time of defervescence [61]. Factors that reduce the sensitivity or specificity of the MAC-ELISA include occasional blunting of the IgM antibody response in secondary dengue virus infections and the potential for positive results to reflect recent rather than acute dengue virus infection.

The development of rapid diagnostic tests using immunochromatographic or immunoblot technologies has provided a mechanism for bedside serological testing. However, in one report, diagnostic accuracy fell below the manufacturer's claims; when eight of these available assays were tested in the field, only two had sensitivities of >50 percent and, of these, one assay also had low specificity [62].

A component of the antibody response is dengue virus serotype-specific; a substantial portion of the antibody response has cross-reactivity with other dengue virus serotypes and even other flaviviruses. Cross-reactivity is more problematic in secondary dengue virus infection and also in individuals who have been immunized with vaccines against other flaviviruses such as Japanese encephalitis virus [63]. Although neutralizing antibody assays have greater specificity than HI or ELISA assays, serologic assays cannot be relied on for identification of the infecting dengue virus serotype [64]. (See "Pathogenesis of dengue virus infection" and "Yellow fever".)

**Virus detection** — Isolation of dengue virus or detection of dengue viral RNA or protein in an acute phase serum or tissue specimen provides the most definitive confirmation of infection. However, the importance of specimen timing and quality and the technical demands of these assays limits their clinical applications. As mentioned above, when laboratory confirmation of illness is obtained, it is typically with serology.

In the United States, most diagnostic laboratory testing for dengue virus infection has been performed by the Dengue Branch of the Centers for Disease Control and Prevention (CDC) [58]. Serum samples must be submitted with appropriate clinical and epidemiologic information through state health department laboratories. A real-time RT-PCR assay kit developed by the CDC was approved by the FDA in 2012 for diagnostic use in the United States [65]. In both prospective and retrospective testing, the sensitivity and specificity of the test were ≥98 percent compared with a reference method [66]. The CDC DENV-1-4 Real
Time RT PCR Assay was designed to be performed on equipment already in use in many clinical and public health laboratories in the United States, and it should expand the availability of early diagnostic testing.

Virus isolation is generally performed only for epidemiologic or research purposes. Serum and plasma are the preferred specimens for virus isolation, although virus can occasionally be isolated from liver tissues after clearance of virus from the serum [67]. Regardless of the specific method used, optimal detection is achieved when specimens are obtained early after the onset of symptoms, during the febrile period. In one study of children in Thailand, dengue viruses could be isolated from all plasma samples obtained at least two days before defervescence but from no samples obtained two or more days after fevers resolved [61]. Virus isolation typically requires one to two weeks [68].

RT-PCR has comparable sensitivity to viral isolation [69,70]. Although technically demanding and not widely available, RT-PCR is the only method that can detect virus within a clinically meaningful time frame (one to two days or less) [71-73].

Dengue viral proteins can be detected in tissue samples using immunohistochemical staining [74]. Liver tissues appear to have the highest yield. However, since liver biopsy is rarely indicated in patients with suspected dengue virus infection, this method is generally only used for postmortem diagnosis.

The dengue viral nonstructural protein 1 (NS1) can be detected in plasma, especially during the first five to six days of illness. In one study, high levels early in infection were associated with DHF [75]. Two assays have become commercially available outside the United States. The sensitivity of these assays for diagnosis of acute dengue infection at the time of hospital admission is 50 to 70 percent, with specificity >95 percent [76,77]. However, neither assay is formulated to provide either identification of the specific DENV serotype or quantitative measurement of soluble NS1 protein levels.

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● Basics topic (see "Patient information: Dengue fever (The Basics)"

SUMMARY AND RECOMMENDATIONS

● The clinical manifestations of dengue range from self-limited dengue fever to dengue hemorrhagic fever with shock syndrome, which carries a significant mortality rate. The risk of severe disease is much higher in secondary rather than primary dengue infection. There is also an increasing recognition of atypical syndromes associated with acute dengue virus infection, some of which can be severe. (See ‘Clinical manifestations’ above.)

● Classic dengue fever is an acute febrile illness accompanied by headache, retroorbital pain, and marked muscle and joint pains. Fever typically lasts for five to seven days. Hemorrhagic
manifestations and thrombocytopenia can also occur. Physical examination is nonspecific but may include a macular or maculopapular rash in approximately half of cases. (See ‘Classic dengue fever’ above.)

- Dengue hemorrhagic fever is the most serious manifestation of dengue virus infection and can be associated with shock. The four cardinal features of dengue hemorrhagic fever include increased vascular permeability, fever, hemorrhage, and marked thrombocytopenia (100,000 cells/mm³ or lower). (See ‘Dengue hemorrhagic fever’ above.)

- Plasma leakage is the most specific and life-threatening feature of dengue hemorrhagic fever and usually occurs over a period of 24 to 48 hours, typically coincident with defervescence. Severe plasma leakage can occur in patients with minimal hemorrhagic manifestations. (See ‘Dengue hemorrhagic fever’ above.)

- Hemorrhagic manifestations of dengue virus infection can range from spontaneous petechiae to profuse bleeding. Severe bleeding sometimes occurs in the absence of plasma leakage. (See ‘Classic dengue fever’ above and ‘Dengue hemorrhagic fever’ above.)

- The diagnosis of acute dengue virus infection is based mainly on clinical signs and symptoms in endemic countries. In settings where serologic assays are available, we favor use of an acute phase serum sample for use in an IgM immunoassay (MAC-ELISA or equivalent) as the laboratory test of choice. If the IgM immunoassay is negative and the serum was obtained within the first six days after onset of illness, we favor testing the sample for dengue viral NS1 antigen by enzyme-linked immunosorbent assay (ELISA). (See ‘Diagnosis’ above.)

- If the clinical suspicion of dengue virus infection is high and the assay results on the acute phase sample are negative, we favor testing paired acute and convalescent sera for antibodies to dengue virus by hemagglutination inhibition assay or IgG ELISA. (See ‘Serologic testing’ above.)

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