Dengue Infection in Adults: Information for the Unwary

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Dengue infection is commonest arthropod borne viral infection affecting humans. It affects about 100 million persons yearly. Dengue infection is caused by Dengue virus which is a RNA virus with four serotypes. Bite of female Aedes mosquito primarily transmits the infection. Infection with one serotype confers life long immunity against it and short term against the other serotypes. Infection with other serotypes after the variable immune period causes immune enhancement. T lymphocyte activation, production of cytokine, mainly tumour necrosis factor alpha (TNF-α) and activation of complement system results from immune enhancement. These along with viral factors are considered responsible for the development of bleeding and capillary leakage.

During last few years dengue infection has become serious health care issue in Pakistani scenario. Dengue is now endemic in Pakistan. In 2011, 252935 Pakistanis were suspected to be suffering from dengue infection, of these 219 died. Swat district of Khyber Pakthunkhwa province and Rawalpindi city in Punjab province have been recently hit by dengue epidemic. Main reason for spread of dengue infection in Pakistan as in other countries are unplanned urbanization, changing demographics, environmental factors including change in climate, lack of awareness about disease spread modes, traveling, and poor socioeconomic conditions. Although Government and public are doing best to control current dengue epidemic, it seems that we will have to live with dengue till arrival of effective vaccination. This review was done to provide concise and focused information about dengue infection in adults based on recent experience of managing dengue infected patients.

Dengue Fever and Dengue Hemorrhagic Fever

Dengue infection can be divided in to dengue fever (DF) and dengue hemorrhagic fever (DHF). First infection can be asymptomatic in up to 90% of the infected persons in rest it is associated with development of classical dengue fever. Classical DF is a short duration, self limiting illness characterized by high grade fever, aches, headache, retro orbital pain, nausea, vomiting, rash, hemorrhagic tendencies, and sore throat. The term bone breaking fever is used to point towards severe aches and pains associated with dengue infection.

Table I. Dengue case definitions

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<th>Case Definition</th>
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<td><strong>Dengue Fever (DF)</strong></td>
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<td>DF is most commonly an acute febrile illness defined by the presence of fever and two or more of the following; retro orbital or ocular pain, headache, rash, myalgias, arthralgia, leucopenia, and hemorrhagic manifestations (positive tourniquet test, petechia, purpura/ecchymosis, gum bleeding, blood in vomitus urine or stools, and vaginal bleeding). Anorexia, nausea, abdominal pain, and persistent vomiting are not case defining criteria.</td>
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<th><strong>Dengue Hemorrhagic Fever (DHF)</strong></th>
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<td>DHF is characterized by plasma leakage as shown by hemoconcentration (an increase in hematocrit ≥20% above average for age or decrease in hematocrit ≥20% of baseline following fluid replacement therapy), or pleural effusion, or ascites, or hypoproteinemia plus one of the following: Febrile illness of 2-7 days duration, Hemorrhagic manifestations or positive tourniquet test, Thrombocytopenia ≤100000/mm³</td>
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<th><strong>Dengue Shock Syndrome (DSS)</strong></th>
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<td>DSS has all the features of DHF plus circulatory failure evidenced by rapid, weak pulse, and narrow pulse pressure (20 mm Hg) OR Age specific hypotension and cold, clammy skin, and restlessness.</td>
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DHF on the other hand is problematic version of dengue infection. It is additionally characterized by short term capillary leakage due to endothelial dysfunction which is caused by immune and viral mechanisms. Hemoconcentration results from capillary leakage and if this stage is not managed appropriately shock ensues. Compared to classical dengue fever, hemorrhagic manifestations are severe in DHF. Up to 5% mortality can be encountered in DHF cases, this figure may rise if management is inadequate. Target mortality in DHF is <1%. Dengue shock syndrome (DSS) is the worse form of DHF. Dengue Expert Advisory Group (DEAG) diagnostic criteria of DF, DHF, and DSS are detailed in Table I.

Phases of Illness

Human incubation period of dengue infection is 4-7 days. Dengue infection is divisible in three stages; febrile, critical, and convalescent/recovery phases.
Febrile phase is present in DF and DHF, critical phase in DHF only, and convalescent/recovery phase in both DF and DHF.

**Febrile phase:** Febrile phase is characterized by viremia. It is of 2-7 days duration. Symptoms suggestive of dengue infection are noted in this phase.

**Critical Phase:** Following febrile phase critical phase occurs in DHF patients. It is of 24-48 hours duration and occurs generally between days 3-7 of illness. Cytokine storm due to immune enhancement that occurs in secondary dengue infections is considered responsible for the development of this phase. It is the phase of leakage which needs to be identified and managed efficiently. A number of features point to onset of this phase. These are settling of fever, worsening of thrombocytopenia, rising hematocrit, and improvement in leukocyte count. Details regarding critical period of DHF adopted from WHO guidelines are given in Figure 1.13

### Warning features

Warning features suggestive of critical phase include; abdominal pain, persistent vomiting, irritability, confusion, decreased urinary output, marked hemorrhagic manifestations, tachycardia, pulse pressure <30, cold peripheries, tender hepatomegaly, and ultrasonographic evidence of ascites/pleural effusion.12,14,15 This phase is also characterized by hypocholesterolemia (<100mg%, or 20mg% decrease compared to base line level), and hypoalbuminemia (<3.5g%). A lateral decubitus CXR may show pleural effusion much later and in less number of patients compared to ultrasonographic examination.16

### Convalescent/Recovery phase

Convalescent/recovery phase follows febrile phase in dengue fever and critical phase in DHF. It is stage of recovery. Its duration is 1-2 days. Leakage abates if this phase follows critical period. Clinical improvement is noted in terms of settlement of symptoms. Improvement in well being and appetite occurs in this phase. Pruritis, erythematous rash with normal skin islands (Figure 2), bradycardia, and diuresis due to resorption of fluid in DHF cases.9,11,12 Platelets count and total leukocyte count improves and hematocrit stabilizes.

### How to Diagnose Dengue Infection

Diagnosis of suspected case of dengue infection is made if patient has febrile illness of 2-10 days and fulfills DF case defining criteria.12 Serial complete blood counts are done at day 3, 4, and 5 of fever. If total leukocyte count is <3000 mm$^3$, and platelet count <100000/mm$^3$ or the platelets are rapidly falling diagnosis of probable dengue infection is made.12

### Dengue Markers

#### Table 2. Dengue Markers

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<th>Test</th>
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<td>NS1</td>
<td>Non structural 1 viral antigen detected during viremic phase;Classically present between days 2-5 of illness.</td>
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<tr>
<td>PCR for Dengue virus</td>
<td>Corresponds with viremic phase;</td>
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<td>IgM</td>
<td>Generally positive after 5th day of illness;If negative initially will become positive in convalescent phase;Can be negative in some cases of secondary infections May remain positive for few months.</td>
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<tr>
<td>IgG</td>
<td>Mere positivity doesn’t signify acute dengue infection;There should be &gt;4 time rise in paired samples during or after convalescence if IgM and NS1 are negative;In secondary dengue infection ratio of quantititative of IgG and IgM is &gt;1.8,17</td>
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Confirmation of dengue infection can be done by getting NS1 antigen, PCR for the virus, specific IgM and IgG markers depending upon the duration of illness (Table 2). Patients with positive dengue markers are termed as confirmed cases of dengue infection.12

![Figure 2. Convalescent/recovery rash](image-url)
Dengue markers have inherent limitations i.e., 1) these should be interpreted in clinical context, 2) ELISA technique tests are more reliable rather than rapid tests, 3) IgM and IgG may be false positive in other infections like malaria, syphilis, leptospirosis, Japanese encephalitis and rheumatologic diseases like rheumatoid arthritis.12

**Differential Diagnosis**

Other viral illnesses, malaria, typhoid fever, leptospirosis are important differential diagnosis. It should however be noted that thrombocytopenia, hemoconcentration and leakage will differentiate these from dengue infection.9,11,12

**Treatment**

The art of dengue management is earliest identification of dengue infected patients who are in or may end up in critical phase. Depending on clinical scenario the dengue infected patients may need to be admitted or can be managed on outpatient basis.

**When and Whom to Admit**

Patients should be admitted if; 1) they fulfill probable dengue infection criteria and are in later part of febrile phase, 2) DF defining clinical features are not improving or worsening, 3) warning features mentioned in critical period are present, 4) co-morbidities like diabetes mellitus, ischemic heart disease, renal disease, chronic liver disease, and chronic pulmonary diseases etc are noted, 5) pregnant, 6) are at extremes of age, and 7) have social issues.

**Fluid Regimen and Monitoring**
There is no viricidal medication for dengue infection. Untreated, inefficiently managed shock complicating DHF is associated with multi organ failure and high mortality. Over treated patients on the other hand, may develop fluid overload, and increase in ascites and pleural effusion etc. Meticulous monitoring and fluid regimen meant to maintain vital organ functions are thus the mainstay of therapy in critical phase of DHF. Shock in DHF is consequence of plasma leakage in critical period. This short term leakage is taking place inside the body not outside, so the leaked fluid will be reabsorbed if the patient is kept stabilized during critical phase. The other point is that body’s plasma and albumin are oozing out of the damaged capillaries so infusion of fresh frozen plasma and albumin will be potentially useless.

For the typical 24-48 hours critical phase in an adult ≥50 Kg, 4600ml fluid quota is used based on the formula, maintainence + 5% body weight.\textsuperscript{10,12} Fluid quota includes total (intravenous plus oral) fluid administration during specified period. Normal saline, and Ringer lactate are mainstays of fluid regimen used in management of DHF; if hemodynamic stability cannot be achieved with their infusion Dextran 40, or HES (hydroxyl ethyl starch) can be used.\textsuperscript{9,10,12,18} Fresh blood or red cell concentrates are used to manage bleeding depending on the status whether patient is under or overloaded.\textsuperscript{10,12} By clinical evaluation and investigations the phase of illness (febrile/critical/convalescent or recovery), hemodynamic and hydration status (pulse, blood pressure, pulse pressure, capillary refill time, urine output, and temperature of extremities) be assessed at admission urgently. Timing of start of critical phase can be estimated based on clinical scenario and serial blood complete examinations as detailed in Figure 1. Keeping in mind dynamicity of illness, 15 minutes to 1 Hourly monitoring of vitals, and urinary output may be required. Pulse pressure (≥230 mm) and urine

![Figure 4. Decompensated shock management in DHF.](image)
output (≥ 0.5 ml/kg/hr or 25ml/hr) are targets in this regard. In addition to clinical parameters, frequent hematocrit monitoring may also be required to guide adequacy of fluid regimen. Baseline investigations should be sought to look for additional illnesses and complication of dengue infections.

Generally fluid regimen with normal saline is started at rate of 1.5-7ml/kg/hour for 1 hour. It is then adjusted based on monitoring of pulse pressure, urine output, and hematocrit. Algorithms showing management protocols adopted from DEAG are given in Figure 2, and 3.12

Acidosis, hypocalcaemia, hypoglycemia, bleeding, and myocardial involvement should be sought when patients are not improving. Discharge criteria adopted from DEAG are given in Table III.12 Many of the admitted patients will not require aggressive management; problems may be encountered if they are not managed well.

Table 3. Discharge criteria12

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<td>Must be afebrile for 48 hours (without antipyretics)</td>
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<td>Stable general condition</td>
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<td>Recovery of appetite</td>
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<tr>
<td>Stable hematocrit for at least 24 hours</td>
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<tr>
<td>Rising trend in platelet count (minimum 40,000)</td>
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<tr>
<td>No dyspnea or respiratory distress attributable to pleural effusion or ascites</td>
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<tr>
<td>No or minimal visible bleeding</td>
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<td>Fully recovered organ dysfunction</td>
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Outpatient Management

Patients who don’t require admission can be managed at home. They should come for regular follow up so that they can be admitted if they don’t improve or develop warning features. Stress should be given to hydration. Paracetamol (maximum 4 gram for adults/day) should be prescribed.9 Tap water sponging advice should be given if fever doesn’t settle. Use of aspirin, mefenamic acid, NSAIDS, steroids, antibiotics, and steroids should be avoided.12,19 Avoidance of red/brown color fluids should be explained, as vomiting may be interpreted as hematemesis. Focus should be given to personal protective measures against mosquito bites and warning features.

Bleeding, Thrombocytopenia, Platelet Transfusions, and Colony Stimulating Factors (CSF)

Bleeding manifestations are noted in DF as well as DHF. These may vary from petechial hemorrhage and positive tourniquet to frank mucocutaneous bleeding leading to hypovolemia. Thrombocytopenia (due to increased destruction, decreased production, increased utilization), disseminated intravascular, NSAID use, and mucosal injury due to shock are contributory.10,12,17 Proton pump inhibitors, H2 blockers are used in patients with gastrointestinal bleeding. Fresh blood or red cell concentrates are employed for bleeding and hypovolemia. Vitamin K can be administered to patients with marked hepatic dysfunction/deranged prothrombin time. Platelet transfusions are not required even in the settings of severe thrombocytopenia when patient is not bleeding.12 Fancy medications like granulocyte monocyte (GM) CSF are not required as already body is facing short term cytokine storm.

Ascites, Pleural, Pericardial Effusions and Ultrasonography in DHF

Leakage is responsible for the development of ascites and pleural effusion in DHF.20 Ascitic and pleural fluids are thus exudative.21 Diagnostic taps are not required. Therapeutic tap can be done in case of mechanical problems i.e., marked abdominal distension, respiratory embarrassment. Development of gall bladder wall edema or collection of fluid in pericholystic area may be earliest ultrasonographic manifestation. Presence of left pleural effusion only and pericardial effusion alone should hint towards alternative causes. 22 Cautious interpretation of presence of pelvic ascites alone should made.

Diet and Activity

Dengue infected patients don’t require specific diet. Dehydration can develop because of fever, anorexia and vomiting. Patients who can tolerate orals can take water, fruit juices, and oral hydration salt. Improvement of appetite is recovery feature in dengue infection. Dengue related infection is a short term problem unless complicated, various natural remedies like papaya extract and juices are considered beneficial in improving thrombocytopenia encountered in dengue infection.23 There is no definite evidence to support their use as platelets start improving with the course of illness. Bed rest is advised for dengue infected patients. Gradual resumption of activities should be advised to patents after convalescent/recovery phase.9

Pitfalls

Diseases don’t comply with the literature as a readymade suit doesn’t fit all persons. A patient who is afebrile and thrombocytopenic may be in critical phase of DHF. Elevated hematocrit and other evidence
of leak may point towards diagnosis. As baseline hematocrit of most of the patients will be unknown, one should be alarmed in related scenario when hematocrit of male patients is ≥46, and of female patients ≥40. Management decisions based on only platelet count may prove disastrous. A patient in critical period may come after taking most of the quota intravenously or orally. Improperly instituted fluid regimen in this patient may lead to fluid overload and aggravate severity of illness. Patients in DHF critical phase don’t have facial or peripheral edema unless overloaded by fluid administration. Ultrasonographic detection of bilateral pleural effusion and ascites may precede such circumstances and should be kept in mind. Malaria and other illnesses may coexist with dengue infection. In suggestive scenario these should be evaluated and treated.

**Recommendations**

It is to be clearly understood that dengue is a newer problem hitting Pakistani health care system. Capacity building is required to combat the problem at health care facilities. This includes; 1) training of doctors, nurses, other health care workers and administrators relating to disease management as improperly managed patients will have high mortality, and 2) resource provision in terms of high dependency unit facilities, laboratory facilities, and adequate staffing etc. Resource deficient Pakistani public sector hospitals cannot manage loads of patient from a disease which is preventable. Until the availability of effective vaccination, the government and public should implement preventative steps with zeal and dedication in order to decrease morbidity and mortality caused by dengue infection.

**References**

2. WHO. Dengue and severe dengue. Fact sheet N°117. Updated September 2013