Dengue and dengue haemorrhagic fever

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The incidence and geographical distribution of dengue have greatly increased in recent years. Dengue is an acute mosquito-transmitted viral disease characterised by fever, headache, muscle and joint pains, rash, nausea, and vomiting. Some infections result in dengue haemorrhagic fever (DHF), a syndrome that in its most severe form can threaten the patient’s life, primarily through increased vascular permeability and shock. The case fatality rate in patients with dengue shock syndrome can be as high as 44%. For decades, two distinct hypotheses to explain the mechanism of DHF have been debated—secondary infection or viral virulence. However, a combination of both now seems to be the plausible explanation. The geographical expansion of DHF presents the need for well-documented clinical, epidemiological, and virological descriptions of the syndrome in the Americas. Biological and social research are essential to develop effective mosquito control, medications to reduce capillary leakage, and a safe tetravalent vaccine.

Dengue is the most important human viral disease transmitted by arthropod vectors. Annually there are an estimated 50–100 million cases of dengue fever (DF), and 250 000 to 500 000 cases of dengue haemorrhagic fever (DHF) in the world. Over half of the world’s population live in areas at risk of infection, and these are popular tourist destinations too.1,2 (figure 1). DF and DHF are live in areas at risk of infection, and these are popular DF/DHF epidemics. The changes in disease pattern have been most dramatic in the American region. In the 1950s and 1960s, through the efforts of a programme coordinated by the Pan American Health Organization, most countries in central and south America were certified to have eradicated Aedes aegypti. The programme was terminated in the early 1970s. By the late 1970s Aedes aegypti had reinfested many locations. The number of countries with epidemic dengue increased sharply during the 1980s and 1990s as new virus strains and serotypes were introduced. In 1980, severe disease was rare, but by 1997 DHF had emerged as a disease entity in several major and many minor epidemics in tropical and subtropical countries of the Americas. The factors responsible for this global resurgence of DF and the emergence of DHF include unprecedented population growth, unplanned and uncontrolled urbanisation, increased air travel, the lack of effective mosquito control, and the deterioration, during the past 30 years, of public-health infrastructure.1,2,5

Epidemiology

Epidemics of an illness compatible with DF were first reported in the medical literature in 1779 and 1780, and until the 1939–45 war pandemics of DF occurred every 10–30 years. Nevertheless, recurrence of epidemic DF at any one location was infrequent. During the second world war south-east Asia experienced the co-circulation of multiple dengue virus serotypes and epidemic activity increased. With the subsequent uncontrolled growth of cities, epidemic DHF emerged as a major public-health problem in most countries of south-east Asia. The first epidemic of DHF was in 1953 (Manila) and the disease remained localised in south-east Asia through the 1970s. In the 1980s and 1990s, however, epidemic DHF spread west into India, Pakistan, Sri Lanka, and the Maldives and east into China.1 DHF and dengue shock syndrome (DSS) are now a leading cause of hospital admission and death among children in Asia.1,4 Except for a small DEN-3 outbreak in Tahiti in 1965, epidemic DF was absent from the south Pacific for 25 years. In 1971, DEN-2 was introduced, and several islands had major DF/DHF epidemics.

Clinical manifestations

Dengue

Dengue virus infections may be asymptomatic or lead to a range of clinical presentations, even death. The incubation period is 4–7 days (range 3–14). Typically, DF is an acute febrile illness characterised by frontal headache, retro-ocular pain, muscle and joint pain, nausea, vomiting, and rash.6 The febrile, painful period of DF lasts 5–7 days, and may leave the patient feeling tired for several more days. A biphasic or “saddleback” fever curve is not the norm. Dengue virus disappears from the blood after an average of 5 days, closely correlated with the disappearance of fever, and no carrier state ensues.8,9

The vast majority of infections, especially in children under age 15 years, are asymptomatic or minimally symptomatic.8 Population-based studies have shown increasing severity in the clinical features of DF with increasing age of the patient and with repeated...
DHF commonly begins with a sudden rise in temperature and other symptoms resembling DF. The temperature is typically high (38–40°C) and continues for 2–7 days. DHF and dengue shock usually develop around the third to seventh day of illness. The most common hemorrhagic feature is a positive tourniquet test (over 50% of patients). Petechiae, easily bruised skin, and subcutaneous bleeding at venepuncture sites are present in most cases. Transudate due to excessive capillary permeability collects at the pleural and abdominal cavities. A prospective study recorded pleural effusions in 84% (22/26) of DHF cases and the mean pleural effusion index (the proportion of the width of the right hemithorax occupied by a pleural effusion in the right lateral decubitus chest radiograph) was 14-1%. The development of DHF provides warnings of an increased probability of shock (figure 2). The first (and easiest information) to ascertain is the time elapsed since onset of illness. DHF/DSS usually develop around day 3–7 of illness, at the time of defervescence, which is an indication for intensified observation. A progressively decreasing platelet count and a rising haematocrit (signalling abnormal capillary permeability) indicate increased probability of impending shock. When all four criteria for DHF are fulfilled, intravenous fluids (see below) may be all that is required for treatment. Nevertheless all DHF patients need good nursing care and observation because the above changes may happen very quickly or the patient may present in a critical condition.

Dengue shock syndrome
DSS is defined as DHF with signs of circulatory failure, including narrow pulse pressure (<20 mm Hg), hypotension, or frank shock. The liver may be palpable and tender; and liver enzymes are usually mildly abnormal but jaundice is rare. The four warning signs for impending shock are intense, sustained abdominal pain; persistent vomiting; restlessness or lethargy; and a sudden change from fever to hypothermia with sweating and prostration. The development of any of these signs or any suggestion of hypotension are indications for hospital admission and management to prevent shock. The patient may recover rapidly after volume replacement but shock may recur during the period of excessive capillary permeability. The prognosis in DHF/DSS depends on prevention or early recognition and treatment of shock. In hospitals with long experience of DSS the case fatality rate in DHF can be as low as 0-2%. Once shock has set in the fatality rate may be high (12% to 44%).

Other severe dengue syndromes
There are some unusual but well-described manifestations of dengue infection where the risk of death is high. These are DF with massive hemorrhage, cardiomyopathy, and encephalopathy. Neurological manifestations such as altered consciousness, convulsions, and coma have been ascribed to an encephalopathy secondary to prolonged DHF/DSS, resulting from the leakage of plasma into serious spaces, haemorrhage, shock,

DHF has been most extensively studied in south-east Asia, where it first appeared and where it is primarily a children’s disease. In the tropical Americas it is seen in all age groups, and the basic clinical manifestations are similar throughout the age spectrum. DHF is defined as an acute febrile illness with minor or major bleeding, thrombocytopenia (≤100×10⁹/L), and evidence of plasma leakage documented by haemoconcentration (haematocrit increased by at least one-fifth or decreased by the same amount after intravenous fluid therapy), pleural or other effusions, or hypoalbuminaemia or hypoproteinaemia. The major pathophysiological change that determines the severity of disease in DHF and differentiates it from DF is the leakage of plasma. Extravasation occurs through endothelial gaps, without necrosis or inflammation of the capillary endothelium. Nevertheless, a recent clinical trial showed that a drug that counteracts capillary permeability induced by histamine or hyaluronidase, and is currently marketed in Asia (carbazochrome sodium sulphonate) did not prevent dengue vascular permeability or shock.

Figure 1: World distribution of dengue
Figure 2: Warning signs for dengue shock

and metabolic disturbances. However, invasion of the central nervous system (viral encephalitis) is a recently documented possibility.

Vertical transmission of dengue virus has been recorded in a small number of cases, leading to neonatal DF or even DSS. One case of nosocomial transmission from a patient, and the physician must adjust treatment using monitoring of blood pressure, haematocrit, platelet count, haemorrhagic manifestations, urinary output, and level of consciousness is important. Plasma leakage in DHF is very rapid and the haematocrit may continue to rise even while intravenous fluids are being administered; however, the ‘leaky capillary’ period is short and intravenous fluids are usually required for only 1–2 days. There is great variability from patient to patient, and the physician must adjust treatment using serial haematocrit, blood pressure, and urinary output data.

Insufficient volume replacement will allow worsening shock, acidosis, and disseminated intravascular coagulation, while fluid overload will produce massive effusions, respiratory compromise, and congestive heart failure. Because patients have loss of plasma (through increased vascular permeability into the serous spaces) they must be given isotonic solutions and plasma expanders, such as Ringer’s acetate or Ringer’s lactate, plasma protein fraction, and dextran 40. The recommended amount of total fluid replacement in 24 h is approximately the volume required for maintenance, plus replacement of 5% of bodyweight deficit, but this volume is not administered uniformly throughout the 24 h. A bolus of 10–20 mL of an isotonic solution per kg bodyweight is given in case of shock, and repeated every 30 min until circulation improves and urinary output is adequate. Vital signs should be measured every 30–60 min and haematocrit every 2–4 h, then less frequently as the patient’s condition stabilises.

Placement of a central-venous-pressure line is hazardous in patients with haemorrhagic tendencies but may be necessary, especially when more than 60 mL/kg of fluids has been given without improvement. The line should be inserted by an expert in a special care area. It is used to estimate filling pressures and to guide further intravenous fluid administration. An arterial line will help in the assessment of arterial blood gases, acid–base status, coagulation profiles, and electrolytes in the haemodynamically unstable patient, helping to identify early respiratory compromise.

Monitoring should be continued for at least a day after defervescence. Once the patient begins to recover, extravasated fluid is rapidly resorbed, causing a drop in haematocrit. Before discharge, the patient should meet the following criteria: absence of fever for 24 h (without antipyretics) and a return of appetite; improvement in the clinical picture; hospital care for at least 3 days after recovery from shock; no respiratory distress from pleural effusion or ascites; stable haematocrit; and platelet count greater than 50 000/μL. Because convalescent-phase diagnostic samples are often difficult to obtain, a second blood sample should always be taken on the day of discharge.

**Laboratory diagnosis**

Dengue viruses belong to the Flaviviridae, a family which contains almost 70 viruses, including those causing yellow fever and several encephalitides (eg, Japanese, St Louis, West Nile, and tick-borne). All these flaviviruses share group antigens that can cross-react in serological tests, complicating diagnosis. Serum is the specimen of choice for both virological and serological studies. Circulating virus remains detectable in the blood during the febrile period (for an average of 5 days after onset of symptoms), and is then rapidly cleared with the appearance of specific antibody. The virus is stable in diagnostic samples up to 5 days at 4°C. If longer storage is needed, the sample should be frozen at −60°C or lower. Most laboratories attempting virus isolation utilise an established cell culture line of *Ae albopictus* cells. After a week of incubation, the cells are stained with fluorescein-conjugated polyclonal antibodies to detect virus isolates, which are then serotyped with monoclonal antibodies in an indirect fluorescent antibody test. Use of the polymerase chain reaction (PCR) may shorten the time required for result. PCR can also detect viruses inactivated by improper storage or by complexing with neutralising antibody. However, the PCR test is experimental and no commercial products are available.

Serological diagnosis depends on the presence of IgM antibody or a rise in IgG antibody titre in paired acute and convalescent phase sera. IgM antibody becomes detectable during the acute phase of the illness and 90% of patients are IgM positive by the sixth day after onset of symptoms. This antibody may be detectable for a median of about 60 days. Currently, the most widely used IgM assay is a capture ELISA (enzyme-linked immunosorbent assay). Where two flaviviruses cocirculate, such as dengue and Japanese encephalitis in Asia, a differential diagnosis can be made by measurement of antibody titres against these antigens separately, but this technique cannot reliably differentiate among the four dengue serotypes. Commercial kits for the measurement of antibodies to dengue viruses include the standard ELISA-
format microtiter test, a dipstick test, and a rapid dot-blot test. These kits do not require specialised training but their sensitivity and specificity are still being evaluated.

In primary dengue, IgG antibody begins to appear by the fifth day after onset of symptoms. Titres rise slowly for some weeks and then remain detectable for many years. In secondary (ie, repeat) infections, IgG antibody is generally already present in early acute serum samples and titres rise rapidly over a few days. IgG antibody is usually measured by the haemagglutination inhibition test or ELISA. The high rate of IgG positivity in people who have lived in the tropics makes analysis of paired acute and convalescent serum samples critical for such situations because the presence of IgG antibody in a single serum sample has no clinical significance.

In interpreting laboratory results, it is important to consider the limitations of the tests. With acute-phase samples, isolation of virus in tissue culture is 50% sensitive and the serology may be negative because of insufficient time for antibody development. Thus, negative results on acute-phase samples cannot exclude the diagnosis of dengue and convalescent samples should be taken. With samples from the convalescent phase, the IgM ELISA is 90% sensitive but IgM antibody may be due to infection up to 3 months earlier. Moreover, the ELISA cross-reacts with other flaviviruses. Samples positive for IgM antibody alone are thus not confirmatory for current infection, and are reported only as “probable” dengue. For a diagnosis of “confirmed” dengue, dengue virus should be identified by isolation, immunohistochemistry in necropsy tissue, or there should be a four-fold rise in antibody titre using a type-specific plaque reduction neutralisation test. Virus isolation from acute-phase samples requires a week of incubation and in most laboratories, the cross-reactions with other flaviviruses, samples positive for IgM antibody alone are thus not confirmatory for current infection, and are reported only as “probable” dengue. For a diagnosis of “confirmed” dengue, dengue virus should be identified by isolation, immunohistochemistry in necropsy tissue, or there should be a four-fold rise in antibody titre using a type-specific plaque reduction neutralisation test.6,7 Virus isolation from acute-phase samples requires a week of incubation and in most patients antibody will not be detectable earlier than 5 days after onset of symptoms. Laboratory confirmation of the diagnosis may be necessary for the patient’s medical record and for public-health surveillance but the high rate of false-negative results on acute sera means that serological tests should not be depended upon to guide management.

Disease transmission

*Aedes aegypti* is closely associated with human habitation. Larvae are mostly found in artificial containers that may hold water, such as discarded tyres, buckets, flowerpots, wading pools, and blocked rain gutters, but they can also be found in natural sites such as bromeliads, treeholes, and discarded coconut shells. The adult mosquito usually rests in dark indoor sites such as closets and under beds. The species is day-active, with most biting activity occurring in the early morning or late afternoon. The mosquito becomes infected by a blood meal from a viraemic person and becomes infective after an obligatory extrinsic incubation period of 10–12 days. After the mosquito becomes infective, it may transmit dengue by taking a blood meal, or by simply probing the skin of a susceptible person.8,9

Risk factors for infection and severe disease

The reinfection of a region with *Aedes aegypti* or the introduction of a new serotype where the population’s immunity is low are clear harbinger of increased transmission. The introduction of DEN-3 in central America in 1994 (after an absence of almost 20 years) produced widespread epidemics in 1995. The specific effect of other factors is much more difficult to judge. Dengue incidence fluctuates with the seasons and is usually associated with warmer, more humid weather. Temperature, humidity, mosquito population densities and survival, type and productivity of containers that hold larvae, adult flight range, human population density, virus strain, immunity for specific virus serotypes, human behaviour, and housing characteristics, all interact in a manner that may prove different in risk analyses done in different outbreak investigations. The risk of dengue for residents in an endemic area will vary with local conditions, and may approach 100% in outbreaks among susceptible, if infection rather than clinical expression is measured. Several mathematical models have recently explored the interactions of multiple factors that give rise to epidemic transmission in a community.10,11

Travel

What is the risk for travellers? Case-reports of dengue imported into non-endemic countries, although frequent, do not allow an estimation of the risk of illness for the short-term traveller. An estimate may be derived from three studies of non-tourists. Despite high concurrent infection rates in Thais, not more than 1% of 627 American residents in Bangkok in 1962–63 were infected with dengue or chikungunya viruses. In over 30 000 United States troops in Somalia for three months (1993–94), only 289 (0.96%) developed a sustained fever over 38.3°C, and of these, 59 were diagnosed as dengue. In over 20 000 troops in Haiti for six weeks in 1994, 112 patients (about 0.1%) were evaluated for a temperature higher than 38.1°C without focal clinical findings, and only 30 had confirmed dengue. Although we have no data on the dengue incidence rate in the local populations, neither Somalia nor Haiti have reported epidemic dengue in recent years. Soldiers in the campaigns lived in austere locations, exposure to mosquitoes was common, and insect repellent and bednets were not always used.

These data allow for an estimate of roughly 1 illness per 1000 travellers. This may overestimate the risk for tourists who will have less contact with the vector, staying a few days in air-conditioned hotels with well-kept grounds. This 1 per 1000 figure is only an average, and other types of travel accommodation in locations with intense disease transmission have produced outbreaks with high attack rates. Travellers to dengue-endemic areas can reduce the probability of mosquito bites by wearing clothes that reduce the amount of exposed skin and using mosquito repellent and, if necessary, aerosol insecticides in rooms. Healthcare providers should consider dengue in the differential diagnosis of all patients who have symptoms compatible with a systemic viral infection, and who reside in or have recently visited tropical areas.

Other risk factors

The risk for DHF is higher where two or more virus serotypes are circulating simultaneously, and the syndrome seems to occur at epidemic proportions only when the second infecting serotype is of south-east Asian origin.11 The presence of circulating dengue antibodies, acquired actively by prior infection or passively by heterotypic maternal dengue IgG antibody in infants with primary infection is the most frequently reported of the probably multiple contributory causes of altered response to dengue.12,13 Two cohort studies in Thailand found DHF
rates of zero among children with primary infections and 1·8% and 12·5% among children with secondary infections. The most widely accepted hypothesis for the pathogenesis of DHF in secondary infections is immune enhancement. Antibody-dependent enhancement of dengue viruses, it is suggested, is a process in which the infecting virus is complexed with non-neutralising antibodies, thus enhancing phagocytosis by mononuclear cells (the primary site of virus replication in man). Virus replication induces infected monocytes to release vasoactive mediators, which result in the vascular permeability and haemorrhagic manifestations that characterise DHF and DSS. It should be pointed out, however, that antibody-dependent enhancement has never been demonstrated in vivo in dengue-infected patients.

Epidemiological and laboratory evidence suggests that virus strain and perhaps serotype may also be important as a risk factor for DHF. DHF and DSS with fatalities have been documented in adults and children with primary dengue infection. Although not well understood, other risk factors for individual susceptibility to DHF have been suggested. Ironically, undernourished infants seem to have a lower risk of DHF than infants with good nutritional status. A study in Cuba in 1981 found that DHF and DSS seemed to be more frequent in whites (than in blacks) and among those with a history of asthma, diabetes, and sickle-cell anaemia.

Prospects for control

Vaccine development

An effective vaccine will have to be tetravalent because pre-existing heterotypic dengue antibody is a risk factor for DHF. Candidate attenuated virus vaccines have been evaluated in phase I and II trials in Thailand, and a tetravalent formulation is currently undergoing repeat phase I and II trials. Advances have also been made with second-generation recombinant dengue vaccines. A cDNA infectious clone of the DEN-2 PDK-53 vaccine candidate virus has been constructed, and work is in progress to construct chimaeric viruses by inserting the capsid, premembrane, and envelope genes of DEN 1, 3, and 4 into the DEN-2 PDK-53 backbone. These recombinants, through genetic manipulation, may be made to replicate faster, be more immunogenic, and safer. However, an effective, safe and affordable vaccine is not an immediate prospect.

Vector control

At present dengue transmission can only be reduced by mosquito control. The task might seem a simple matter of the treatment or elimination of infested containers. Source (container) reduction campaigns have been very successful but they are hard to sustain, mainly because they are labour intensive, require discipline and diligence, and are plagued by diminishing returns. Emphasis has shifted first to organochlorine insecticides and later to organophosphorus larvicides, and aerosols targeted at adult mosquitoes and mostly applied outdoors as ultra-low volume (ULV) concentrates. The aerosols are principally recommended for emergency control during epidemic transmission as part of an integrated vector elimination effort, including environmental management, source reduction, and larvicides. Nevertheless, their routine use as the principal response even before and after dengue epidemics has become widespread. This is regrettable, because ULV aerosols have very limited impact on adult female Aedes aegypti and no impact on the immature stages. Not surprisingly, therefore, there is no well-documented example of interruption of a dengue epidemic by outdoor ULV treatments. Indoor treatments are probably much more effective but are very labour-intensive and intrusive.

Community participation

In recent years there has been increased focus on the community’s role in Aedes aegypti control. Programmes sponsored by the Rotary Foundation and the Rockefeller Foundation, and a project between the Government of Italy and the Pan American Health Organization in the Caribbean have focused on particular segments of the community, while promoting the involvement of anthropologists, sociologists, and health communications specialists as members of the modern vector control team. Great emphasis has been placed on defining the function of the water-holding container within the family’s daily activities. These containers come in all shapes and sizes; anything that will retain water in the tropics can be transformed into a developmental site for Aedes aegypti. The vast majority of these sites are present in the domestic environment as the result of human action. The promotion of community participation requires an understanding of the knowledge, attitudes and practices of community members about or toward the vector species and the disease. This information can then be discussed with the community members to define technical solutions that are effective, economical, easy to perform and, most of all, acceptable to the family member “responsible” for the container type. To be effective, prevention-oriented messages containing specific actions for specific mosquito production sites must be pretested, disseminated through the appropriate channels of communication, and evaluated.

Effective and sustainable prevention of dengue outbreaks must include the individual community’s participation in dengue control; government participation for the elimination of mosquito production sites when legal or large-scale action is necessary; and some, though limited, use of larvicides and adulticides. Vector control should be regarded in the same way as refuse disposal—a job that can never be finished. Laboratory-based surveillance is indispensable to guide recurrent and emergency interventions, while accurate diagnosis and prompt treatment have a crucial role in the prevention of suffering and death due to dengue. When set against the large human and economic costs of recurrent dengue and DHF epidemics, the benefits of effective prevention are clear.

References


Further reading

General
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