Dengue: A Growing Public Health Problem in Europe with Potential Severe Renal Involvement

In depth review

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ABSTRACT
Dengue is an arboviral infection transmitted by the mosquito of the Aedes genus, widespread especially in tropical and subtropical regions but now with worldwide involvement. Cases of contagion are also progressively increasing in Europe, and the differential diagnosis with other infections is not always easy. Renal involvement with acute renal failure is possible and caused by the direct action of the virus, hemodynamic instability, rhabdomyolysis, or acute glomerular damage. In patients most at risk of renal involvement, there is high morbidity and mortality, with more extended hospital stays and follow-ups over time, which increases the burden on healthcare systems. Knowledge of this infection by nephrologists is essential for reducing morbidity, mortality, and, therefore, healthcare costs.

KEYWORDS: Acute kidney failure, Arbovirus, classical Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome, early diagnosis

Introduction

The dengue virus, responsible for the disease, is an arbovirus with four antigenically and genetically distinct DENV serotypes (DENV1–4). It is an important mosquito-borne viral infection, once confined to tropical and subtropical regions but now it is a growing global public health concern.
DENV has a single-stranded RNA genome composed of three structural protein genes: core protein (C), a membrane-associated protein (M), an envelope protein (E) and seven nonstructural protein (NS) genes, and glycoprotein NS1 has diagnostic importance. Infection with any serotype confers lifelong immunity to that viral serotype. However, in cross immunity for the other serotypes, the recovery is only partial, and temporary. Genetic variation within each serotype is called “subtypes” or “genotypes”. Currently, three subtypes are identified for DENV-1, six for DENV-2, four for DENV-3, and four for DENV-4. Any change in the serotype of DENV is associated with severe forms of the disease and can lead to high mortality. The female Aedes aegypti mosquito is the primary vector for transmission of dengue viruses to humans; it arrived in the Americas during the slave trade in the 1600s [1] and spread worldwide via ships. The life of the female mosquito is about 1 week, although some can live for up to two weeks. Aedes albopictus, commonly called the “tiger mosquito”, is also a carrier of Dengue disease, it is present in temperate regions (Figure 1). It is responsible for spreading the virus in Asia, Africa, and Europe, preferably developed in highly anthropised environments, is active during daylight hours, and preferentially stings humans with uncommon aggressiveness [1]. Aedes albopictus thrives in a broader range of sites than Aedes aegypti, including coconut shells, cocoa pods, bamboo stumps, tree cavities, and natural or artificial water surfaces, such as vehicle tyres, flowerpot saucers of plants, fresh cut flowers, ornamental plants and trunks of exotic wood, where even minimal quantities of water can support mosquito survival and reproduction. In Africa, several other mosquitoes can be potential vectors for the dengue virus. Aedes aegypti and Aedes albopictus mosquitoes adapt quickly to different environments. Therefore dengue is also recorded in Europe and North America, particularly during summer. In September 1990, Aedes albopictus [2], known as the “tiger mosquito,” a non-indigenous species of Asian origin, was reported in Italy for the first time. Some infected adults have been identified in the city of Genoa, and during the following summer, numerous larval outbreaks of the species were found in the province of Padua [3]. The mosquito could overcome the harsh winter seasons of northern Italy, and numerous insect populations were already strongly rooted in the territory of various Italian areas [4]. The distribution in Northern Italy was linked to the importation of tyres infested with eggs from the southern United States by some large manufacturing companies in the Veneto region when appropriate legislation was lacking. The Aedes mosquito, unlike the Anopheles mosquitoes which carry malaria, also bites during daylight hours, with peaks of activity in the early morning and in the late afternoon, before sunset, in environments indoors or outdoors.

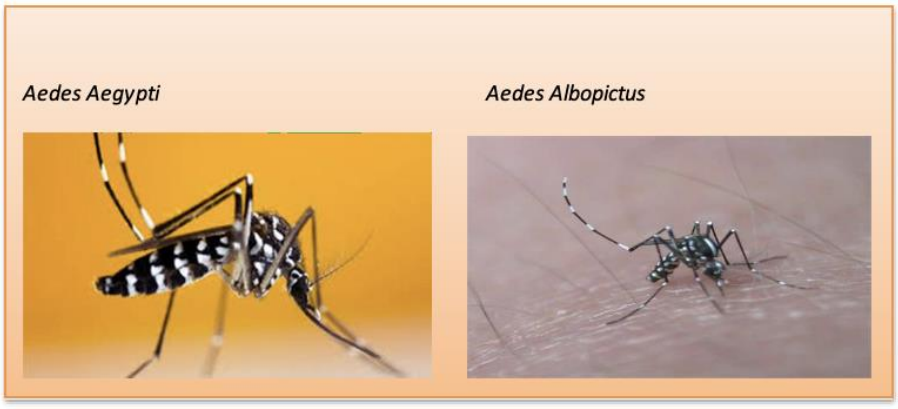

Figure 1. Aedes mosquitoes have striking white stripes on their black bodies and legs. These mosquitoes also transmit other viral infections, including chikungunya and yellow fever.

Epidemiology

The first confirmed epidemic of DHF was recorded in the Philippines in 1953-1954 [1] and in Thailand in 1958. About two-fifths of the world's population in tropical and subtropical countries are at risk, with an estimated 100/400 million infections occurring each year around the world. Dengue fever (DF) and Dengue hemorrhagic fever (DHF) are endemic in more than 100 countries in the WHO, including the African regions, Americas, Eastern Mediterranean, Southeast Asia, and Western Pacific [1]. The Southeast Asia and Western Pacific regions are the most severely affected; imported cases are common, and the co-circulation of multiple serotypes/genotypes is evident. In recent years, dengue has spread to new areas, including Europe. Local transmission was first reported in France and Croatia in 2010, and imported cases have been detected in three other European countries. An unprecedented number of dengue cases was reported globally in 2019.

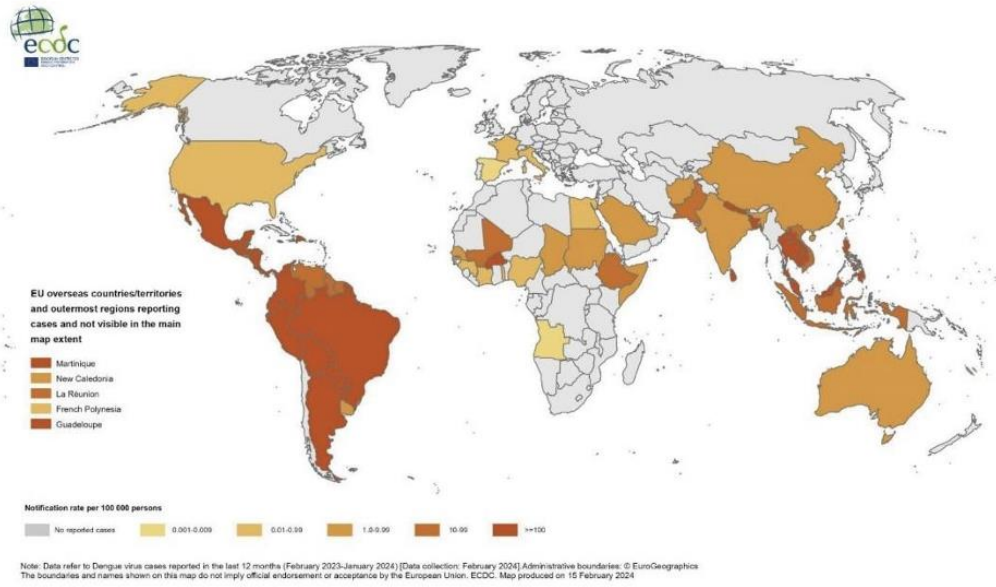

Figure 2. Cases of dengue virus from December 2023 to February 2024 [5].

Transmission

Dengue disease is transmitted to humans through the bite of an infected female mosquito, primarily by the bite of the *Aedes aegypti* mosquito. Other species of Aedes can infect humans but with less severity. The virus replicates in the mosquito's midgut before spreading to secondary tissues, including the salivary glands. The time between ingestion of the virus and actual transmission to a new host lasts approximately 7 – 12 days when the temperature is between 25 and 28°C; it may also vary due to fluctuations in daily temperature, initial viral concentration and virus genotype. This time interval is called the EIP (extrinsic incubation period), which can change the time it takes for a mosquito to transmit the virus [6].

Human-to-mosquito transmission can occur 2 days before someone shows symptoms, or up to 2 days after fever resolves. The duration of viremia is generally 4-5 days but can last up to 12 days. Today we know that, although it is very rare, DENV can transfer the infection between humans. One possibility is vertical transmission from a pregnant mother to her baby. The infection in a pregnant woman may cause fetal distress, preterm birth, and low birth weight. Cases of transmission via blood products, organ donations, and transfusions have also been reported, although this is very rare. After 4-10 days of incubation, the infected insect can transmit the viral agent for the rest of its life. The infection/transmission cycle that sustains epidemic is human-mosquito-human [6].

Clinical manifestations

Dengue infection is a systemic disease, with a broad spectrum of symptoms ranging from asymptomatic to mild clinical manifestations, to severe. After incubation, there are three phases: febrile, critical, and recovery. Despite being a complex disease, its management can be simple, but only with an early diagnosis and correct intervention, understanding the problems that develop in each phase of the disease.

Overlap between clinical presentations has been observed in dengue patients grouped using the WHO's earlier classification of dengue infection: dengue fever (DF), DHF, and dengue shock syndrome (DSS) (Table 1) [7].

The 2009 WHO's reclassification of dengue infection into dengue without warning signs, dengue with warning signs, and severe dengue has allowed us to recognize better patients with atypical manifestations or organ involvement who did not fit into any disease groups.

In the 1997 WHO dengue classification (Figure 3) [7].

Dengue Fever	DHF(Grade 1, 2)	DSS (Grade 3,4)
Acute febrile illness with ≥ 2 of the following symptoms: Headache Retro-orbital pain Myalgia Arthralgia Rash Haemorrhage manifestations	The following must be all present: Fever or history of fever Haemorrhage tendencies (as manifested by a positive tourniquet test, petechiae/purpura/ecchymoses, mucosal bleeding) Thrombocytopenia Plasma leakage (a rise in the haematocrit, pleural effusion, ascites)	All four criteria of DHF plus evidence of circulatory failure evidenced by: Rapid and weak pulse Narrow pulse pressure (< 20 mm Hg) Hypotension Cold clammy skin and restlessness

Table 1. 1997 WHO classification [7]. DHF: Dengue hemorrhagic fever; DSS: Dengue shock syndrome.

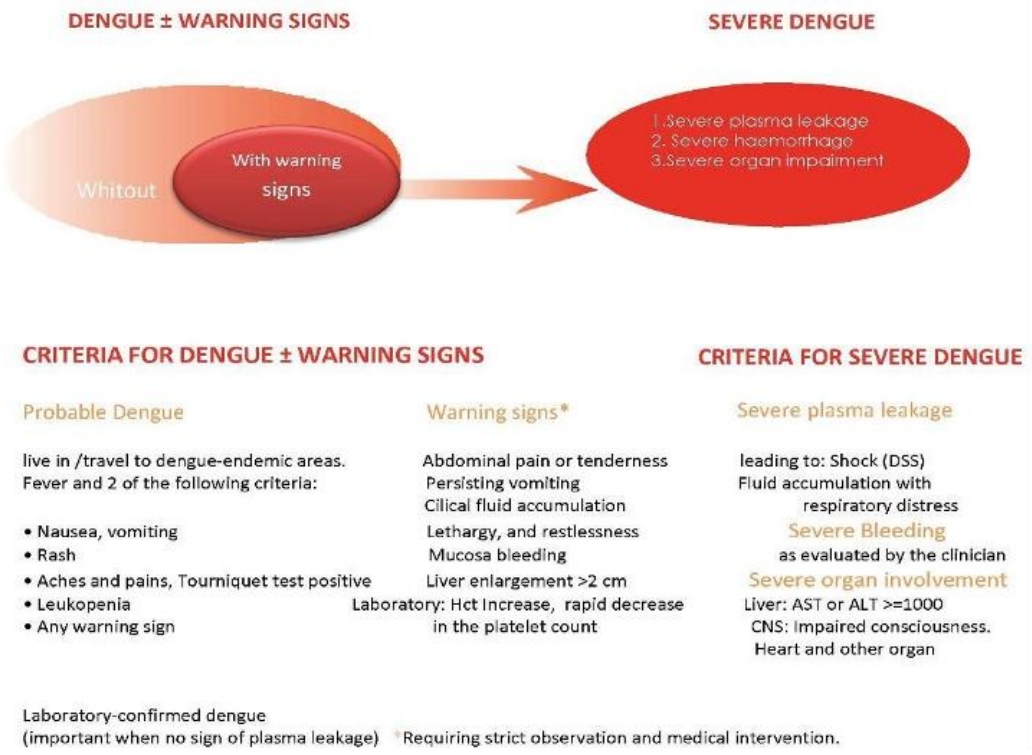

Figure 3. Inspired by WHO 2009: Suggested dengue case classification and levels of severity [8].

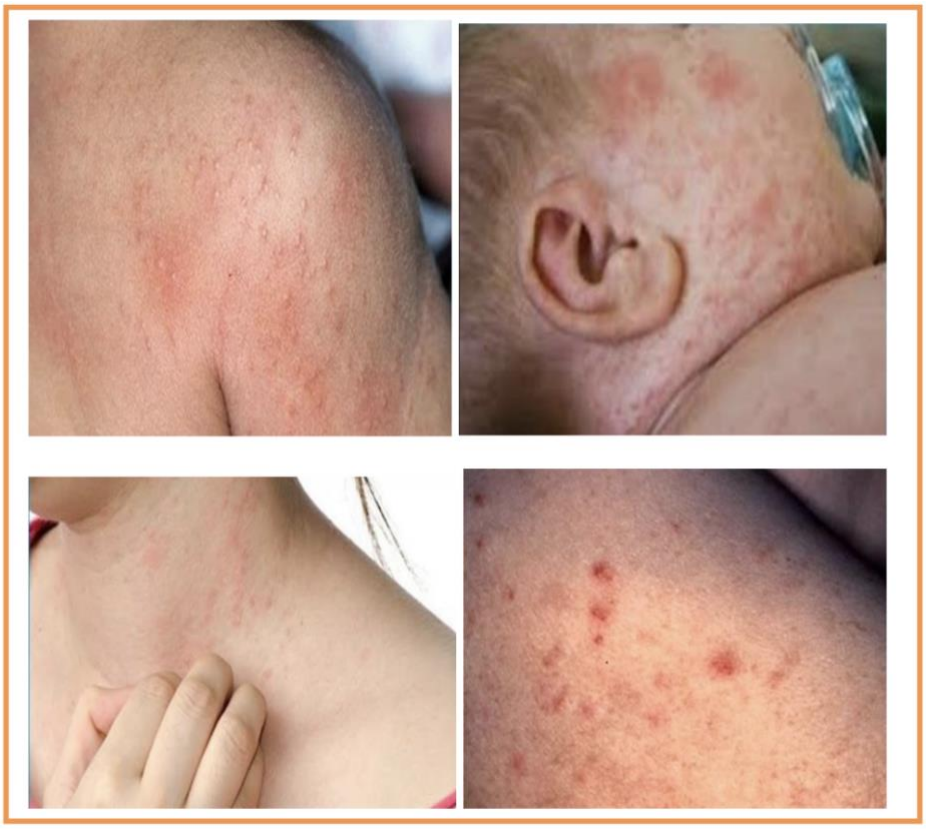

Figure 4. Dengue fever rashes.

Dengue virus can infect all organs, and DENV RNA has been detected in most body tissues in post-mortem studies. Prolonged hepatic ischemia leads to shock and secondary bacterial sepsis can progress to fulminant hepatic failure. Hemorrhagic necrosis of the liver has a poor prognosis. Myocarditis can also be severe enough to lead to death [9]. In severe cases, all organs may be involved to varying degrees, a condition termed “expanded dengue syndrome”, and acute kidney injury (AKI) is one of the atypical manifestations of this syndrome (Box 1) [10].

Neurological: Encephalitis, encephalopathy, neuropathies, Guillain–Barré S.

Gastrointestinal: Hepatitis, cholecystitis, pancreatitis, hemorrhagic liver necrosis.

Renal: Nephritis, AKI

Cardiac: Myocarditis, pericarditis.

Hematological: Haemophagocytic lymphohistiocytosis, Immune thrombocytopenia.

Musculoskeletal – Myositis

Box 1. Expanded dengue syndrome [10].

Kidney involvement

Renal involvement covers a broad spectrum of manifestations, from AKI to glomerular injury with nephritic/nephrotic syndrome in dengue disease, with a reported incidence of approximately 14.2% [11, 12]. The majority of cases remain symptom-free and show full recovery.

AKI can present as damage secondary to rhabdomyolysis or occur without rhabdomyolysis. Over time, Dengue can cause hematuria and or proteinuria, an acute glomerulopathy that can occur during and after the acute infection; AKI due to acute tubular necrosis associated with rhabdomyolysis is well-known, but in literature, there are also reports of cases of rhabdomyolysis related to dengue, with myalgia, dark urine and very high creatine kinase levels in the blood without the development of AKI [12, 13]. Other factors must also contribute to myoglobinuria causing AKI, such as hypovolemia, dehydration, and acidosis. AKI can be a condition of hemodynamic stability in DF, DHF, and DSS; in these cases, the damage could be a direct action of the virus on the renal tissue. Therefore, the pathogenetic mechanism that causes myositis and rhabdomyolysis is unknown. In general, the increased release of cytokines causes muscle damage, which often leads to an increase in CK; hence, monitoring closely to prevent AKI is essential. Retrospective studies highlight how AKI increases morbidity, mortality, and healthcare costs.
Even today, histopathological data from renal biopsies are scarce, and many histopathological observations are made by autopsy.
Dengue causes kidney damage with several mechanisms, but there is no clear understanding of whether one prevails over the others. However, likely, multiple mechanisms are often involved:

1. Hemodynamic instability: is by the inflammatory process that the viral infection causes, with a cytokine storm, with consequent activation of complement, platelets, endothelial damage, increased vascular permeability, and loss of fluids, hemodynamic instability, which can lead to shock, with damage to the perfusion of the kidney, therefore ischemia of the tubules and AKI.
2. Rhabdomyolysis: an increase in ionized calcium within cells leads to the loss of the transcellular calcium gradient; after this, a series of events responsible for cell death and the release of toxic substances damage the capillaries, resulting in local oedema and increased compartmental pressure. Leukocytes are activated and move to the injured muscles, releasing proteolytic enzymes. This inflammatory process causes renal vasoconstriction, therefore ischemia, obstruction by cylinders in the distal convoluted tubule, and direct cytotoxic effect of myoglobin on the epithelial cells of the proximal convoluted tubule. The depletion of ATP, in turn, causes necrosis of the tubular cells, accumulation and precipitation inside the tubular lumen of myoglobin, and formation of cylinders. The formation of cylinders with consequent obstruction of the distal tubules causes a reduction in blood flow and glomerular filtration fraction, therefore, AKI.
3. Direct action of the virus: the virus antigen was also found in the kidney during autopsy, particularly in the tubular epithelial cells; however, no viral RNA has been detected. Therefore, unlike other organs, the kidney is not a site of viral replication. The direct renal damage of the virus would occur through a cytopathic effect caused by the viral protein on the glomerular and tubular structures, with an in situ immune-mediated mechanism: the binding of the viral antigens to the glomerular structures would cause tissue lesions, as well as the production of compound immune complexes by antiviral antigens and antibodies against antiviral antigens, with the release of inflammatory mediators.

Therefore, AKI in dengue infection can also result from hemolytic uremic syndrome, with evidence of hemolytic anaemia and thrombocytopenia [19]. Renal biopsy reports in dengue are rare; however, renal histology has described acute tubular necrosis (ATN) cases [12, 13]. Thin fibrosis lines and oedema may also be evident [12, 13]. In the interstitial area, it is possible to find immunostaining for myoglobin in the cytoplasm of the tubular cells in patients with dengue-associated rhabdomyolysis. Mesangial proliferation and immune complex deposition are the dominant histologic features of dengue-associated glomerulonephritis [15]. In 2010, a previously unreported

case of glomerulonephritis associated with IgA nephropathy [14] in dengue virus infection was also reported in a 15-year-old boy hospitalized for dengue fever complicated by AKI and requiring urgent dialysis treatment. Urinalysis showed microscopic glomerular hematuria and proteinuria. The first renal biopsy showed mesangial proliferation with dominant mesangial immune complex IgA deposits and acute tubular necrosis, a second biopsy was repeated 6 weeks after clinical recovery and showed recovery of mesangial damage and disappearance of mesangial IgA deposits. Similarly, a case of membranoproliferative glomerulonephritis type 1 (MPGN-l) reported dengue virus is yet another viral cause of MPGN-l [15]. On rare occasions, dengue infection is also associated with systemic autoimmune disorders involving the kidneys.

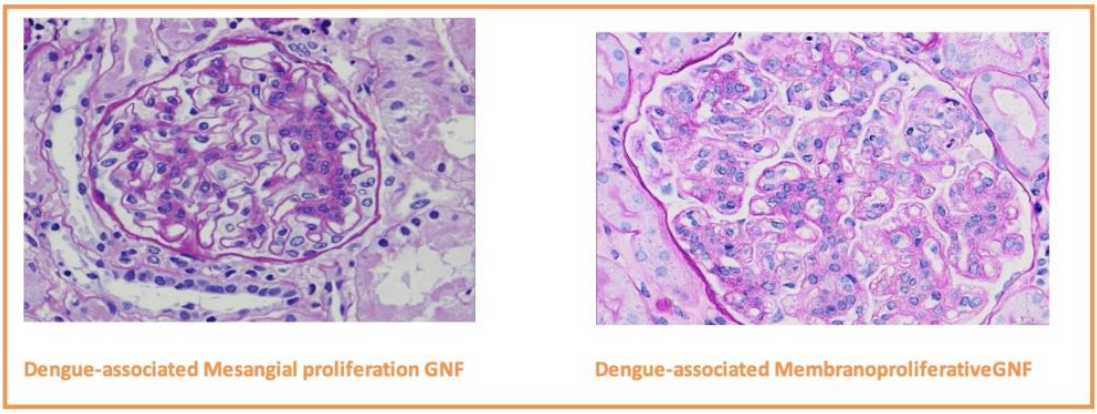

Figure 5. Dengue kidney histopathology.

Diagnostic Laboratory Test

There are rapid diagnostic tests (RDTs) (NS1/IgM/IgG) that can provide results after only 15 minutes, but they have poor sensitivity and specificity, therefore they are not considered confirmatory tests for dengue. The rapid test is an initial screening, which requires confirmation with ELISA. The ELISA-based NS1 antigen test is used for early diagnosis, as it becomes detectable from the first day and remains detectable for up to 5-6 days. It is positive in patients with primary disease and those with secondary dengue infection up to 6 days after illness.
Serological tests are:

- IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA): Anti-dengue IgM antibodies are developed before IgG antibodies, usually detectable by the 5th day of illness. IgM can persist for more than 90 days, disappearing more often after 60 days of illness.
- IgG ELISA: the positivity of anti-dengue IgG antibodies appears shortly after compared to IgM antibodies. IgG can test positive after the seventh day of illness. This positivity helps to differentiate primary and secondary dengue infection. Seroconversion of IgG in paired sera or a fourfold increase in paired IgG titer is diagnostic for dengue infection.
- IgM/IgG ratio: It helps to distinguish the primary infection from the secondary one. If the ratio is greater than 1.2, a primary infection is suspected and if the ratio is less than 2, has to be considered a secondary infection.
- Neutralization test: it is the most sensitive and specific for the diagnosis of dengue infection, but it is an expensive test, which also requires more time, therefore, it is not a routinely used.
- The Complement Fixation Test is also not commonly used for the diagnosis of dengue because it is a complex test; it is not suitable for seroepidemiology studies, although it is useful for patients with active infection.

- Haemagglutination inhibition test: It is not a test to diagnose dengue but for seroepidemiological studies.

Laboratory tests that help support the diagnosis of dengue hemorrhagic fever are the CBC, coagulation profile (the result of thrombocytopenia, leukopenia), serum complement levels (C3, C4), aPTT, PT, D-Dimer and fibrinogen level; markers of inflammation (ESR and Ferritin, CRP); laboratory tests that may demonstrate the involvement of organs (liver, kidneys, lungs and central nervous system), e.g.: blood gases, electrolytes, kidney function, liver function tests. It is also possible to isolate the dengue virus during the febrile (viraemic) phase, before the 5th day of illness, using samples collected during the acute phase including serum, plasma, washed buffy coat, and tissues collected from the liver, thymus spleen, lymph node; time virus isolation is from 7 to 10 days.

1. Radiological Investigations. A chest X-ray is essential to rule out pleural effusions and bronchopneumonia. Right pleural effusion is typical; bilateral pleural effusions are joint in patients with dengue shock syndrome. In patients with neurological symptoms, brain CT helps to exclude intracranial haemorrhage or brain oedema, which is possible in dengue hemorrhagic fever.
2. Histopathology. Skin biopsy in areas of rash in non-fatal and uncomplicated dengue fever detects minor blood vessel abnormality, endothelial swelling, perivascular oedema, and mononuclear cell infiltration. Muscle biopsies in patients with myalgia have shown perivascular muscular infiltrate of variable size, proliferation of mitochondria, and few areas of myonecrosis, but the critical correlation with myalgia seems to be the accumulation of lipids and the mononuclear perivascular infiltrate.

Differential Diagnosis

The differential diagnosis is not always simple, particularly in Western countries where it is mistakenly considered a rare infection and often unknown even to specialists. Depending on the phase of the disease, it can mimic many other types of infections: in the febrile phase it mimics the most common viral ones, influenza, adenovirus, measles, rubella, and enterovirus but also COVID-19 and bacterial ones such as rickettsiae, typhoid, leptospirosis; it can also mimic autoimmune diseases such as Still's disease or SLE, or acute leukaemias. Medical history is of fundamental help in the differential diagnosis, investigating the patient's origin, recent trips to risk areas and carefully evaluating the progression of the symptoms.

Chikungunya virus *	**Adenovirus**	**COVID-19**
Influenza virus	**Rubella**	**Scarlet fever**
Morbillivirus	**Enterovirus**	Meningococcaemia
Rickettsiae	**Typhoid fever**	Epstein-Barr Virus
Leptospirosis	**Yellow fever**	Malaria
Ebola Virus	ITP	Zika Virus
Still Disease	**SLE**	**Acute Leukemia**

Box 2. Differential diagnosis of dengue disease. * Chikungunya disease has often been mistaken for dengue in South-East Asia.

Vaccine

To date, no perfect vaccine can be administered to people of all ages and confer permanent immunity to all subgroups of the virus (DENV-1, DENV-2, DENV-3, and DENV-4).

- QDENGA, marketed in Italy and Europe, is used in travel medicine; it is a live attenuated vaccine that induces an effective immune response against the four serotypes of the virus (DENV-1, DENV-2, DENV-3, and DENV-4). It is administered under the skin in two doses, 3 months apart, to subjects aged 4 years or older, regardless of previous exposure to the dengue virus (it is therefore not necessary to undergo serological tests before vaccination). It is authorized for use from 4 years of age both in subjects never exposed to the virus and in subjects with previous infection with DENV.
- DENGVAXIA is distributed only in some countries where the disease is endemic; it is administered to people aged 6-45 years, and it has low efficacy in children and dengue-naïve individuals. It can prevent the disease caused by all four serotypes but is authorized only in subjects with previous DENV infection certified by a laboratory or an adequately validated serological test because it also increases the risk of severe dengue in people who have not been exposed to dengue [18].
- Butantan-DV: a vaccine, developed in Brazil, is being tested and directed to people between 2 and 59 years old. Its advantage is that it works for those with no previous infection and those with a history of dengue virus infection.

Therapy

There is no therapy to prevent dengue disease or kidney involvement, but early diagnosis is crucial. Acetylsalicylic acid and Ibuprofen should be carefully avoided, as they could favour the appearance of hemorrhagic manifestations. Paracetamol can be taken to reduce fever and joint pain. The use of steroids, immunoglobulins, and N-acetylcysteine is still controversial, and there is no indication of the use of steroids for the prevention of AKI. Hemodialysis replacement therapy may be necessary for hemodynamically stable patients and continuous dialysis treatment in hemodynamically unstable patients. Early detection of severe dengue patients is crucial. The timely and careful medical evaluation of severe dengue patients, blood volume evaluation, serum creatine phosphokinase (CPK) levels monitoring, and electrolyte rebalancing are fundamental to preventing AKI. Must avoid nephrotoxic drugs. Close monitoring of laboratory and clinical parameters can identify and deter AKI early. It is also essential in post-discharge, close follow-up in patients who developed AKI. Patients who have acute kidney disease during dengue may develop chronic kidney disease, even if they previously had normal kidney function. Patients with chronic kidney failure who contract dengue disease and AKI progress more quickly to advanced stages of CKD [11, 16, 17]. There is no indication of the routine use of antibiotics in dengue disease. However, the infection can be complicated by bacterial sepsis, due to severe leukopenia and a state of immunosuppression up to septic shock, in which case appropriate antibiotics must be used.
There is an indication for platelet infusion in patients with severe bleeding and thrombocytopenia or in patients requiring emergency surgery. The use of blood transfusion, however, in dengue complicated by severe bleeding, may cause liver involvement or refractory acidosis.

Conclusion

Dengue is a growing public health problem in Europe, and renal involvement, even with acute kidney injury (AKI), is one of the frequent but least considered complications of dengue virus infection, hence the importance of knowledge of the disease and its early diagnosis. Patients with dengue hemorrhagic fever, male sex, presence of multiorgan dysfunction, rhabdomyolysis, diabetes mellitus, late hospitalization, and use of nephrotoxic drugs appear to increase the incidence of AKI. These patients have more significant morbidity and mortality, with more extended hospital stays, and require follow-up over time, which increases the burden on healthcare systems. Early diagnosis, correct monitoring and knowledge of this infection by the nephrologist are very important to prevent complications.

Abbreviations:

DHF: dengue hemorrhagic fever; DF: classical dengue fever; DSS: dengue shock syndrome; AKI: acute kidney injury; ITP: immune thrombocytopenia; ATN: acute tubular necrosis; EIP: extrinsic incubation period; DENV: Dengue virus.

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